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SUPERIORITY OF NATURAL PRODUCTS IN THE TREATMENT OF ARTHRITIS

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ABSTRACT:

Rheumatoid arthritis (RA) is chronic autoimmune disease which mainly affects the joints of the hands and feet. This disease is caused by dysregulation of pro-inflammatory cytokines (e.g. tumour necrosis factor and interleukin1-b) and pro-inflammatory enzymes that mediates the production of prostaglandins (e.g. cycloxygenase-2) and leucotriens (e.g. lipoxygenase). Also the expression of adhesion molecules i.e. leucotriens & prostaglandins and matrix metalloproteinases, and hyperproliferation of synovial fibroblasts. All of these factors regulated by the activation of transcription factor i.e. nuclear factor-kB. Thus, agents which suppress the expression of tumour necrosis factor-a, interleukin-1b, cycloxygenase-2, lipoxygenase, matrix metalloproteinases or adhesion molecules or suppress the activation of nuclear factor-kB are believed to have potential for the treatment of arthritis. Generally four different classes of drugs, namely nonsteroid anti-inflammatory drugs (NSAIDs), analgesics, glucocorticoids and disease-modifying antirheumatic drugs (DMARDs) are used for treatment. Several natural products obtained from plants which can suppress these cell signaling intermediates, including curcumin (turmeric), resveratrol (red grapes, cranberries and peanuts), tea polyphenols, genistein (soy), quercetin (onions/squill), silymarin (artichoke), guggulosterone (guggul), boswellic acid (salai guggul), and withanolides (ashwagandha). In this review, information about all the drugs and natural products describe in brief including their advantages, mechanism and limitation.

KEYWORDS:

DMARDs, natural products, RA, NSAIDs.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease in which there is joint inflammation, synovial proliferation and destruction of articular cartilage[1]. Rheumatoid arthritis (RA) is a chronic symmetric polyarticular arthritis that mainly affects the small diarthrodial joints of the hands and feet[3]. It is a fairly common disorder and occurs in 0.5–1% of the adult population, in a female/male ratio of 2.5:1 worldwide[3, 4]. Although the precise etiology remains unknown, RA is thought of as an autoimmune disease[5,6]. The inflamed synovium is central to the pathogenesis of RA[3,4] and formation of tumor-like synovial tissue, the so called 'pannus' is a characteristic feature of RA[3]. Apart from destroying the affected joints, RA also has extra-articular effects in the body and osteoporosis is commonly associated with RA. As a relapsing systemic disease, RA affects the physical functioning of patients, their psychological and social health eventually progresses to substantial disability[3, 5].

RA patients have a significantly higher incidence of fatality from cardiovascular diseases, infections and cancers than the general population[2, 5].

Although there are more than 100 different kinds of arthritides, the three most common in the Western world are gout, osteoarthritis (OA) and rheumatoid arthritis (RA).

Gout occurs in response to the presence of monosodium urate (MSU) crystals in joints, bones and soft tissues, and is usually treated by non-steroidal anti-inflammatory drugs (NSAIDs), oral or intravenous colchicines, and oral, intravenous or intrarticular glucocorticoids. All can abort acute attacks, but may have severe side effects.

OA results from articular cartilage failure induced by a combination of genetic, metabolic, biochemical and

biomechanical factors. OA is normally treated with analgesics such as acetaminophen and opioids, NSAIDs, and intraarticular therapies such as glucocorticoids and hyaluronans[6].

Arthritis, an inflammation of the joints, is usually a chronic disease that results from dysregulation of pro-inflammatory cytokines (e.g. tumour necrosis factor and interleukin-1b) and pro-inflammatory enzymes that mediate the production of prostaglandins (e.g. cyclooxygenase-2) and leukotrienes (e.g. lipooxygenase), together with the expression of adhesion molecules and matrix metalloproteinases, and hyperproliferation of synovial fibroblasts. All of these factors are regulated by the activation of the transcription factor nuclear factor-kB. Thus, agents that suppress the expression of tumour necrosis factor-a, interleukin-1b, cyclooxygenase-2, lipooxygenase, matrix metalloproteinases or adhesion molecules, or suppress the activation of NF-kB, all have potential for the treatment of arthritis[6].

The goals of drug therapy in RA are-

- Ameliorate pain, swelling and joint stiffness
- Prevent articular cartilage damage and bony erosions
- Prevent deformity and preserve joint function[1].

Arthritis, a disease of the joints, is primarily a pro inflammatory disease. As such, a better understanding of the pro-inflammatory nature of arthritis is essential if new therapies are to succeed[6]. The cell signalling network that mediates the inflammatory response during arthritis is depicted in **Figure 1**.

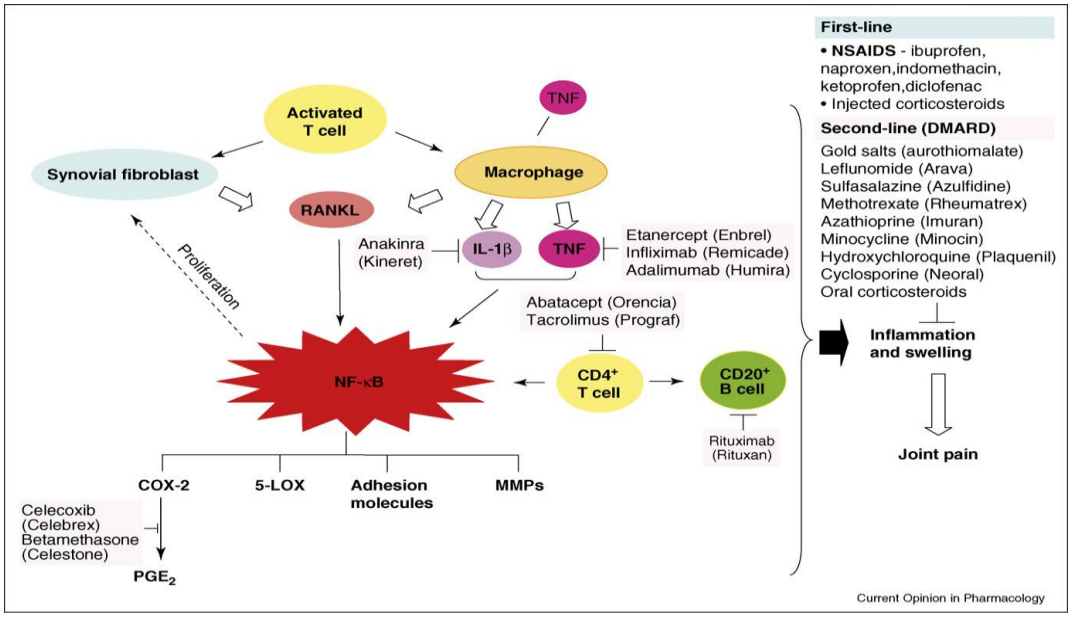

Figure 1: Pathophysiology of inflammatory arthritis.

The figure shows current therapeutic targets and their sites of action.

RA is an incurable disease therefore life-long therapy is required[2,3]. Generally four different classes of drugs, namely nonsteroid anti-inflammatory drugs (NSAIDs), analgesics, glucocorticoids and disease-modifying antirheumatic drugs (DMARDs) are used clinically[5]. Though mild/early cases are still mostly treated only with NSAIDs, the current recommendation is to add DMARDs as soon as the diagnosis of RA is confirmed. However, use of DMARDs in early/mild RA should be weighed against their potential adverse effects, which may be serious. More than one DMARD may be used concurrently; advance cases may require 2/3 drugs together, because all DMARDs tend to lose effectiveness with time.

Classification of Antirheumatoid drugs[1]:

1. Disease modifying antirheumatic drugs (DMARDs)

a) Immunosuppressants: Methotrexate, Azathioprine, Cyclosporine
b) Sulfasalazine
c) Chloroquine
d) Leflunomide
e) Gold sod.thiomalate, Auranofin
f) d-Penicillamine

2. NSAIDs
3. Biologic response modifiers(BRMs)
   a) TNFα inhibitors: Etanercept, Infliximab, Adalimumab
   b) IL-1 antagonist: Anakinra
4. Adjuvant drugs
   Corticosteroids: Prednisolone and others.

DMARDs:

DMARDs are the mainstay of pharmacologic treatment for RA[8,9,10]. These agents consist of agents with nonbiologic or biologic activity. Based on severity of the disease, particular DMARDs may be recommended and prescribed for an individual or specific patient. DMARDs without biologic activity include methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide. These agents do not target a specific component of the immune system involved in the pathophysiology of RA but these nonbiologic agents have been shown to improve clinical outcomes. Due to an enhanced understanding in the pathophysiology of RA, therapies with biologic activity have been developed to target a specific component of the immune system. DMARDs with biologic activity include TNF antagonists, IL antagonists, T-cell modulator, and B-cell modulator[8-12].

Methotrexate (Mtx): This dihydrofolate reductase inhibitor has prominent immunosuppressant and anti-inflammatory property. Beneficial effects in RA are related to inhibition of cytokine production, chemotaxis and cell-mediated immune reaction. Mtx is now the DMARD of first choise and standard treatment of most patients, including cases of juvenile RA. Response is more predictable and sustained over long term[1].

Disadvantages:

- Oral bioavailability of Mtx is variable and may be affected by food.
- It is not recommended for the patients having the renal disease.
- Nodulosis, oral ulceration and g.i. upset are the major side effects with low dose Mtx regimen. With prolonged therapy, dose dependent progressive liver damage leading to cirrhosis occurs in some patients.
- Incidence of chest infection is increased.
- Mtx is contraindicated in pregnancy, breast feeding, liver disease, active infection, leucopenia and peptic ulcer.

Methotrexate or leflunomide is recommended for most patients with RA. Both agents have documented improvement in objective assessment of the disease and reduction in radiographic progression. Combination therapy of a TNF antagonist and methotrexate can be used for patients with newly diagnosed or early RA. If a patient fails a particular TNF antagonist with or without methotrexate, another DMARD with biologic activity can be initiated as long as the patient does not have any contraindications. Choice of any DMARD with BRMs will be based on the severity of the disease, previous response with an agent, and cost.[8,9,10].

Sulfasalazine: It is compound of sulfapyridine and 5-amino salicylic acid(5-ASA) has anti-inflammatory activity and it suppresses the disease in significant number of RA patients. The mechanism of action is not known. Efficacy of sulfasalazine in RA is modest and side effects are few but neutropenia/ thrombocytopenia occurs in about 10% patients.

NSAIDs: NSAIDs have been used in the management of RA for several decades. NSAIDs inhibit COX to prevent further formation of prostaglandins and other related inflammatory

mediators. Based on its mechanism of action, NSAIDs are useful adjuvant therapy for the symptomatic management of RA, as this class of medications can reduce joint swelling, tenderness, and pain.[10,11,12] . All NSAIDs pose anti-inflammatory properties when prescribed at high doses, are equally effective.

Disadvantage:

- Main disadvantages of NSAIDs includes the safety profile (ie, gastrointestinal [GI], nephrotoxicity, and cardiovascular).
- In addition, it is difficult to predict an individual's response with a particular NSAID.
- Compared to more-specific agents (ie, COX-2 inhibitor), there is no superior evidence between these therapeutic classifications of medications.[6,7]

Therefore, celecoxib is the only COX-2 inhibitor that can be an alternative agent for an individual prone to GI bleeding or ulcers.

Corticosteroids: Corticosteroids possess anti-inflammatory and immunosuppressive properties through an unknown specific mechanism. However, it is suspected that these agents have inhibitory properties on the generation and migration of immune system mediators. Similar to NSAIDs, corticosteroids are commonly used for symptomatic management[10,15]. The advantage of corticosteroids is the availability in oral and intra-articular formulations for the treatment of RA. Therefore, a patient can receive systemic or localized corticosteroid treatment based on clinical presentation, particularly with joint involvement. Intra-articular injections are useful when large joint is involved in the clinical presentation. Specific instructions, however, should be provided to the patient regarding intra-articular injections. Corticosteroids may be used as bridge therapy with DMARDs to avoid long-term adverse events. Some patients also will require continuous therapy to maintain remission of the disease. With continuous therapy, ACR recommends the lowest dose of corticosteroid (eg, prednisone <10 mg daily/d) to control symptoms and reduce the risk of adverse events[10]. High doses of corticosteroids also may need to be prescribed as "burst" therapy during exacerbations.

Natural agents against arthritis:

Agents derived from plants that can modulate the expression of pro-inflammatory signals clearly have potential against arthritis. These include flavonoids, terpenes, quinones, catechins, alkaloids, anthocyanins and anthoxanthins, all of which are known to have anti-inflammatory effects. Some of these polyphenols, which have been tested for the treatment of arthritis, are discussed below:

Table 1:

Molecular targets of natural products that exhibit anti-arthritic potential.

Compounds	Sources	Molecular Targets
Boswellic acid	Boswellia serrata (Salai guggul)	NF-kB, COX-2, 5-LOX, MMP-9, ICAM-1
Berberine	Berberis vulgaris (barberry)	NF-kB, COX-2, TNF-a, IL-1b, IL-6
Celastrol	Tripterygium wilfordii	NF-kB, COX-2, MMP-9, TNF-a, AMs
Cucurbitacin R	Cayaponia tayuya	NF-kB, COX-2, TNF-a
Curcumin	*Curcuma longa* (turmeric)	NF-kB, COX-2, 5-LOX, TNF-a, IL-1b, IL-6, IL-8, MMPs, AMs
Eugenol	Syzygium aromaticum (cloves)	NF-kB, COX-2, 5-LOX, TNF-a, IL-1b
Guggulsterone	Commiphora mukul (guggul)	NF-kB, COX-2, MMP-9

Genistein	Glycine max (soybeans)	NF-kB, TNF-a, IL-1b, IL-6
Luteolin	Thymus vulgaris (thyme)	NF-kB, COX-2, TNF-a
Morin	Chlorophora tinctoria (fustic)	NF-kB, COX-2, 5-LOX, MMP-9, TNF-a, IL-1b, IL-6
Quercetin	Allium cepa (onions)	NF-kB, COX-2, TNF-a, 5-LOX, TNF-a, IL-1b, AMs
Resveratrol	Vitis vinifera (red grapes)	NF-kB, COX-2, TNF-a, 5-LOX, AMs
Rosmarinic acid	Rosmarinus officinalis (rosemary)	NF-kB, COX-2, TNF-a, AMs
Silymarin	Silybum marianum (milk thistle)	NF-kB, COX-2, TNF-a, 5-LOX, AMs
Statins	Aspergillus terreus (yeast)	NF-kB, COX-2, MMP-9, AMs
Tea polyphenols	Camellia sinensis (black tea)	NF-kB, COX-2, TNF-a, 5-LOX, AMs, MMPs
Ursolic acid	Ocimum sanctum (holy basil)	NF-kB, COX-2, MMP-9
Withanolides	Withania somnifera (Ashwagandha)	NF-kB, COX-2, MMP-9, ICAM-1

1. Curcumin (Curcuma longa):

Curcumin (diferuloylmethane) is a yellow colouring agent present in turmeric (Curcuma longa, Family-Zingiberaceae) that has been used for centuries as a spice in the Indian subcontinent [13]. Curcumin has been well documented in Ayurveda, as an anti-inflammatory agent. Both in vitro and in vivo study suggest that curcumin may have potential against arthritis.

Mechanism of action:

Curcumin can downregulate activation of the transcription factor NF-kB[14], thus leading to downregulation of the expression of TNF-a[15], adhesion molecules [16], MMPs[17], COX-2[17], 5 –LOX [18] and other inflammatory intermediates[19], all of which are associated with arthritis. Neutral matrix MMPs are responsible for the pathological features of RA such as degradation of cartilage; however, the upregulation of MMP mRNA associated with arthritis was inhibited by curcumin [20]. This polyphenol has also been shown to suppress the expression of TNF-a-induced MMP-13 in primary chondrocytes[21].

Jackson et al. [22] found that curcumin inhibited neutrophil activation, synoviocyte proliferation, angiogenesis, and collagenase and stromelysin expression, thus suggesting that curcumin has therapeutic potential in arthritis. It has also been reported to potentiate the growth-inhibitory and pro-apoptotic effects of the COX-2 inhibitor celecoxib in osteoarthritis synovial adherent cells [23].

Indeed, a recent study showed that the suppression of NF-kB activation by curcumin leads to inhibition of the expression of COX- 2 and MMP-9 in human articular chondrocytes [24].

Funk et al.[25] determined the in vivo efficacy of curcumin in the prevention or treatment of arthritis using streptococcal cell wall-induced arthritis, a model of RA. In this model, curcumin prevented joint inflammation when treatment was started before, but not after, the onset of joint inflammation.

The chemical structures of some agents are shown in **Figure 2.**

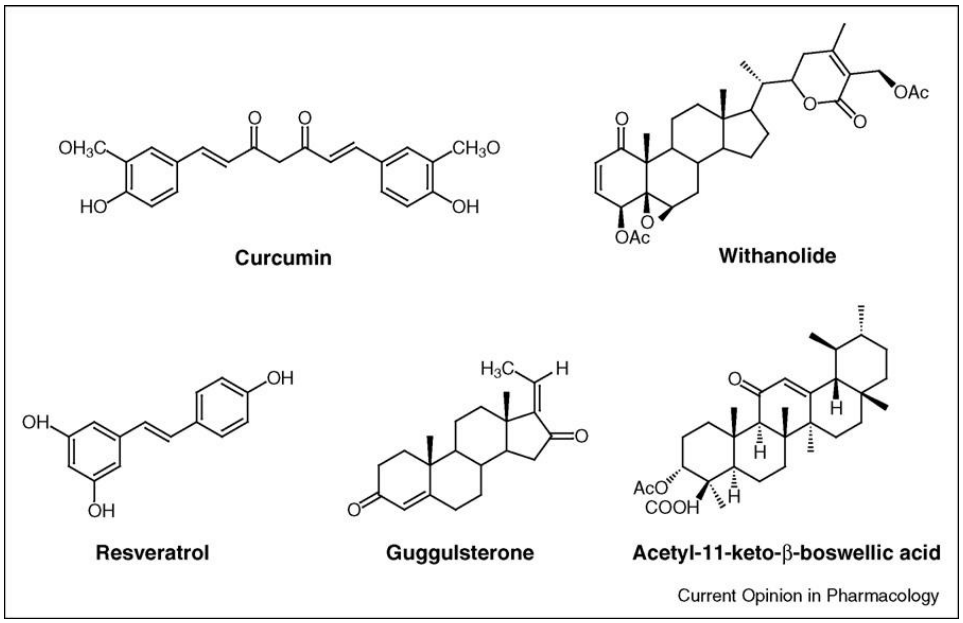

Figure 2: Chemical structure of some natural products

2. Resveratrol (*Vitis vinifera*):

Resveratrol (or trans-3,5,40-trihydroxystibene) is a constituent of the roots of white hellebore (Veratrum grandiflorum O. Loes), but also found in various plants including grapes, berries and peanuts[26].

Mechanism of action: resveratrol can suppress the activation of NF-kB[27] and downregulate inflammatory gene products such as COX-2, 5-LOX, IL-1b, and IL-6 [28], all of which play a crucial role in arthritis.

In vivo effects in an experimental OA model in rabbits [29,30] indicate that resveratrol significantly reduced cartilage tissue destruction, and hence concluded that resveratrol could protect cartilage against the development of experimentally induced OA.

3.Guggulsterone (*Commiphora mukul*)

Guggulsterone [4,17(20)-pregnadiene-3,16-dione] is a plant sterol derived from the gum resin (guggulu) of the tree Commiphora mukul.

Mechanism of action: This sterol can inhibit NF-kB activation and downregulate the expression of inflammatory gene products such as COX-2 and MMP-9, which are major players in the development of arthritis[31]. Guggulsterone can also suppress osteoclastogenesis induced by RANKL (receptor activator of NF-kB ligand), a bone-resorbing cytokine[32]. The anti-inflammatory activity of C. mukul (guggul) has been compared with that of NSAIDs, namely phenylbutazone and ibuprofen[33].

Experimental study of an inflammatory syndrome resembling RA in humans was induced in the right hock joint of albino rabbits by intra-articular injection of mycobacterial adjuvant in liquid paraffin. All these drugs decreased joint swelling. These results highlight the beneficial role of phenylbutazone, ibuprofen and fraction 'A' of gum-guggul in experimental arthritis

There were no side effects reported during the trial. Therefore, guggul appears to be a relatively safe and effective supplement to reduce symptoms of OA.

4. Withanolide (*Withania sominifera*):

Withanolides, which are extracted from Withania somnifera, are employed in the treatment of arthritis and are known to be potent inhibitors of angiogenesis, inflammation and oxidative stress.

Mechanism of action: withanolides can indeed inhibit the activation of NF-kB and NF-kB-regulated gene expression[34], which could explain their anti-arthritic actions.

Begum and Sadique[35] showed the effect of W. somnifera on adjuvant-induced arthritis in rats.

More recently, Rasool and Varalakshmi[36] investigated the effect of W. somnifera root powder on paw volume and serum lysosomal enzyme activities in rats in which

arthritis was induced with MSU crystal. The NSAID indomethacin was used as a standard. These results provide evidence for the suppressive effect of W. somnifera root powder on arthritis by reducing amplification and propagation of the inflammatory response, without causing any gastric damage.

5. Boswellic acid (*Boswellia serrata*)

Boswellic acid (BA) is an active component of Boswellia serrata (also known as Salai guggul). The active component of this resin is BA (a pentacyclic triterpenic acid) and its derivatives (acetyl-b-boswellic acid, 11-keto-b-boswellic acid and acetyl-11-keto-b-boswellic acid).

Mechanism of action: The anti-arthritic potential of BA is a result of its anti-inflammatory activity, mediated through inhibition of NF-kB, COX-2 and 5-LOX [37,38].

In animal models of inflammation, BA has been shown to be an effective adjuvant mitigating bovine serum albumin-induced arthritis[39, 40] and OA[41].

CONCLUSION

Arthritis is the inflammation of joints, which is chronic disease caused by dysregulation of pro-inflammatory cytokines (e.g. tumour necrosis factor and interleukin1-b) and pro-inflammatory enzymes that mediates the production of prostaglandins (e.g. cycloxygenase-2) and leucotriens (e.g. lipoxygenase). As this is incurable chronic disease, lifelong therapy is required. Various types of drugs are available to treat the RA but these drugs have numerous side effect and adverse effect and these drugs give symptomatic relief only. Natural products can modulate the anti-inflammatory response in arthritis which have been proved from several preclinical and clinical study. These agents have advantages like effectiveness, cost effective and lack of side effect. So, Natural products are the Gold mine for treatment of Arthritis.

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