Joint Inflammation: Insights of Osteoarthritis, Gouty and Rheumatoid Arthritis and its Prevalence, Mechanism, Medications and Remedies

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Katturajan et al.: Joint Inflammation Factors and Remedies

Arthritis is a chronic inflammation in joints, which mostly affects the bones. In the global prevalence of joint inflammation, it’s means to be taken it as potential issues. Current treatments mostly targeting the inflammatory cytokines or effector molecules and oxidative stress involved in arthritis as pain relief temporarily. This review has mechanistically demonstrated the type of joint inflammation insights in to arthritis, such as osteoarthritis, gouty arthritis and rheumatoid arthritis to understand the clear background. This review has also highlighted the prevalence, mechanism and mediations used for arthritis, in which various causative agents are used to induce arthritis in preclinical studies that has been collectively elucidated. This review is first to be reported the mechanism of various arthritis causative agents. It pointed out the side effects of clinical medicine used for arthritis and suggested the natural products involved in medication for above-listed conditions. As comparatively natural products are low cost, easily available and beneficial than modern medicines with minimal side effects.

Key words: Joint inflammation, osteoarthritis, gouty arthritis, rheumatoid arthritis, natural therapeutics

Arthritis is an inflammation in joints; this term includes over 100 disorders related to the bones and its joints. It is associated with the joint in fingers, hips, wrists and knees[1]. The rate of this condition is increasing due to lifestyles and prominent to the aged people. Thus 1 out of 5 mankind was found to be in this disease. It can be caused due to age, genes, gender, injuries in joints and obesity. Some of the rare types of arthritis inflammation can be seen in organs, connective tissues and skins[2]. To overcome this condition as a primary defense the medications such as acetophenone, Nonsteroidal Antiinflammatory Drugs (NSAIDs), corticosteroids and anti-rheumatic agents are prescribing for temporary relief as well these agents reported to have various side effects[3-5]. Therapeutics to get rid of joint inflammation with minimal or no side effects are to be discovered.

Few standard organizations have proved that many countries have been following their ancient traditional ways as natural therapeutics and treating many diseases including joint inflammation[6]. Natural therapeutics of preclinical experiments on various joint inflammation conditions such as osteoarthritis, gouty and rheumatoid arthritis have also been discussed in this review.

In summary, fig. 1 describing the overview of joint inflammation clinical indications and their treatments. In brief, the occurrence of joint inflammation leading to cartilage destruction and synovium stimulation. As well, oxidative stress and inflammatory system are playing a significant role in this condition by activating T cells and inflammatory mediators such as cytokines and chemokines. Several medications are prescribed to inhibit T cell and oxidative stress from reducing inflammation. However, prolonged exposure leads to adverse effects, so present research on reducing inflammation without side effects with natural products is studying preclinically. This is the review of various agents to induce joint inflammation and protocol and mechanism collectively in preclinical studies and natural remedies against it.

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OSTEOARTHRITIS

Osteoarthritis is generally an articular cartilage disease found in articulation organ systems like a capsule, ligaments, menisci, periarticular muscle and synovium[7]. Joint in our body can be classified into patellofemoral and tibiofemoral, where osteoarthritis occurs either of this joint, but most of the research has been studied in the patellofemoral joint because it is highly observed[8]. It causes joint inflammation, changes in cartilage structure and alters the anti-inflammatory and pro-inflammatory mechanisms[9]. The risk factors include age, weight, gender, muscle weakness, obesity and repetitive movement of joints leads to trauma[10]. The disease such as cancer, cardiovascular disease and diabetes are also associated with osteoarthritis.

Prevalence:

A recent study has been reported that the National Health Interview Survey appraised approximately 1.4 crore people in the United States of America who were found to have an osteoarthritis symptom. Where 0.7 crore of the affected people seemed to be less than 65 y [11]. In Greece, it was found that the prevalence rose up to 6 %. In osteoarthritis, women are more prominent than man where prevalence has raised from 3.7 % to 26.7 % around the globe[10]. Prevalence in India has reported that the rate of osteoarthritis raised to 39 %, where 45 % of the women in India have this symptom over 65 y of age[12]. The Johnston country osteoarthritis project has reported that the African-American population and the other people such as Irish, Italian, Lebanese, German, Moroccan and Asian have an osteoarthritis prevalence of 28 %[13].

Mechanism:

In a normal joint, the bones are enclosed or covered by cartilage shielded by capsules associated with a synovial membrane that generates synovium[14]. The integration of the capsule and synovium protects the cartilage and connective tissues in the bone. In case of aged or aberrant mechanical force that induce a chondrocyte from a lower metabolic activity which stimulates inflammatory mediators that produce macrophages during inflammation which includes cytokines and chemokines like Interleukins (IL) such as IL-1, IL-6, IL-8, IL-17 and IL-18, Monocyte Chemotactic Protein 1 (MCP-1), Differentiation-Inducing Factor (DIA),
growth-related oncogene and onco-statins will also generate Reactive Oxygen Species (ROS) such as Nitric oxide (NO), Oxygen (O₂), Hydrogen peroxide (H₂O₂) and Peroxynitrite (ONOO⁻)\[^{[15]}\]. In addition, lipid inflammatory mediators like Prostaglandin (PG) and Leukotrienes (LT) rise due to the chondrocyte metabolism that leads to the release of proteolytic enzymes that alters the normal structural formation of joints by increasing the synovium and fragmentation of cartilage that lead to pain and immobility in osteoarthritis condition\[^{[10]}\].

**Chemical induced osteoarthritis:**

**Papain:** It is a proteolytic enzyme that is commercially available. It is used as osteoarthritis-inducing agent papain that needs to be injected with cysteine to cause osteoarthritis. The cysteine act as a papain activator. To cause osteoarthritis, 4 % of the papain prepared with 0.03 M of cysteine and can be injected in intra-articular joint\[^{[17]}\]. Inducing papain in an intra-articular joint increases the joint volume and knee distension. When papain administrated into the cartilage, it releases chondroitin sulphate which breakdown and induces the production of inflammatory cytokines such as IL-beta (β) and Tumor Necrosis Factor Alpha (TNF-α) as well as LT; these cytokines increase the matrix metalloproteinases level\[^{[18,19]}\]. The role of the matrix metalloproteinases is to degrade matrix protein in organogenesis, but in osteoarthritis condition, it increases the level of degradation of matrix protein, leading to the formation of a ROS such as NO\[^{[20]}\]. These all together show a symptom of osteoarthritis.

**Monosodium Iodoacetate (MIA):** It is a commercially available product. To cause an osteoarthritis, 3 mg/kg body weight of MIA can be dissolved in the sterile saline and injected into the articular cartilage of the joint\[^{[21,22]}\]. Inducing MIA in articular space in animal causes joint inflammation, which is similar to the human osteoarthritis. Where full mechanism of MIA-induced osteoarthritis yet to be studied but when MIA is induced, an inflammation will form, which leads to degenerative structural changes in articular cartilage, decrease the weight, increases the pro-inflammatory cytokines like IL-1, IL-6, TNF-α, Prostaglandin-E2 (PGE2) and genetic erosion of Transient Receptor Potential Ankyrin 1 (TRPA1)\[^{[9,23,24]}\]. One of MIA’s actions has been found that it inhibits the glyceraldehyde-3-phosphate dehydrogenase by inducing the formation of ROS and caspase stimulation\[^{[25]}\]. Caspase belongs to the family of a proteolytic enzyme, which is responsible for inflammation\[^{[26]}\].

**Collagenase type 2:** It is commercially available, which was dissolved in sterile saline. It can be injected intra-articularly to the leg joint to cause osteoarthritis. Collagenase can be injected twice in a day\[^{[27]}\]. Collagenase is a protein degradation enzyme that degrades the protein called collagen. When collagenase is injected to intra-articular space, it leads to the degradation of the collagen layer which is surrounded around cartilage. Due to the collagen layer's degradation, the cartilage structure will be changed that also increase the levels of synovium and degrade the proteoglycan of the cellular matrix\[^{[28]}\]. Proteoglycans consist of protein that cores with glycosaminoglycan chains, whereas glycosaminoglycan can be found in synovium in osteoarthritis condition\[^{[29]}\].

**Medication for osteoarthritis:**

The first line of medication prescribing for osteoarthritis is acetaminophen, which is also known as paracetamol; at a mild stage due to its antipyretics and analgesic properties\[^{[30]}\]. The mechanism of this drug against osteoarthritis is yet to be studied. Due to the absence of anti-inflammatory activity and also it causes hepatotoxicity\[^{[31]}\]. NSAIDs such as diclofenac, celecoxib, ibuprofen, ketoprofen and naproxen were used to prescribe. The NSAID mechanism against osteoarthritis is to inhibit the prostaglandin isoenzymes like Cyclooxygenase 1 (COX1) and COX2 where COX1 inhibition causes gastro-toxicity so COX2 selective NSAID were used. COX2 enzyme are used to be highly expressed in inflammation conditions\[^{[32]}\]. NSAIDs have analgesic, antipyretic and anti-inflammatory activity with the COX2 inhibition ability which is used against osteoarthritis. Even though NSAIDs reduce the osteoarthritis inflammation, it is not advisable to take due to its severe side-effects like hepatotoxicity, renal-toxicity, gastrointestinal-toxicity and cardiovascular disorders consuming for long term or on overdosage\[^{[33]}\].

Corticosteroids also suggested for the treatment of osteoarthritis because of its immunosuppressive and anti-inflammatory properties. Betamethasone, dexamethasone, methylprednisolone and triamcinolone were used for the treatment. The mechanism is to act on steroid hormone receptor to inhibit the inflammation by the reduction of microvascular permeability to prevent the inflammatory cells from accumulation and stimulation of neutrophils to inhibit the production of PG and LT\[^{[34,35]}\]. Certain research has reported that corticosteroids have many side effects, such as
skin disease, cushing syndrome, ophthalmologic, cardiovascular disease, neurotoxicity, gastro toxicity and poor growth[3,4].

In addition, opioid analgesics like tramadol and oxycodone were commonly used for treating osteoarthritis. When the patient takes opioid analgesics, it binds with the opioid receptor in the central and peripheral nervous system, which inhibits the nociceptive pathway of pain[36]. This medication also shows the side effect, for example, gastrointestinal diseases, skin diseases, neurotoxicity and autonomic nervous system disorder[37].

**GOUTY ARTHRITIS**

Gouty arthritis is a disorder called as unwalkable disease where the uric acid level in the serum seems to be increased in this condition[38]. Gout is a type of arthritis that causes inflammation in joints of the toe, elbow, ankles, fingers and knees with indications of tender, hot, red and swollen in joints. Which is due to the diet, heredity combinations and raised level of urate in serum[39,40]. Risk factors that cause gout are age (40-50 y), medications (such as aspirin, levodopa, niacin, etc.,) alcohol intake, lead exposure, obesity, high blood pressure, diabetes, hypothyroidism, hypertension, cancer and kidney diseases[41,42]. There are some diseases associated with gout are type-2 diabetes, hyperuricemia, hypertension and Cardiovascular Disease (CVD) [43]. Reasons behind the gout increase are the lacking of common habits like diet, exercises, obesity and metabolic syndromes such as cardiovascular disease, diabetes and ischemic stroke[44].

**Prevalence:**

A recent study has reported that 4-6 % of men and approximately 2 % of women are affected by gouty arthritis in western countries such as Europe, United States, Canada, Australia and England. Commonly it occurs 1-3 % of the common people and men are more frequently affected than women. It is evident from the recent literature which an increase in prevalence in that the percentage exceeded up to 10 % for males and 6 % for females in many countries[44]. Other countries like Germany, USA, Europe, Switzer land, Australia, Israel, South Korea, Japan and Canada it ranges from 6 % to 10 %. This is because of less diet, food habitat, obesity due to no utilization of exercises and syndrome X[44].

**Mechanism:**

Gouty arthritis can be caused by various factors where the mechanism is when the uric acid level in our blood increased due to the obesity of other factors that is need to be filtered and excreted through the kidney by the enzyme called uricase[46]. The excess level of uric acid in the blood cannot be completely excreted; in that case, the uric acid further increases and settles in renal tissues and joints and later forms a crystal called uric acid. That crystal interacts with the phagocytic cells and induces pro-inflammatory cytokines release, which will release macrophages[47]. Microcrystal infiltration in synovial membrane will also induce leukocytes to lyse the lysosomal membrane and oozed out of lysosomal enzymes into the blood. PG and LT get raised and lead to the formation of ROS[40].

**Chemical induced gouty arthritis:**

**Monosodium urate (MSU):** MSU crystals can be synthesized by mixing with the 4 g of uric acid in 800 ml of water and 9 ml of 0.5 N sodium hydroxide. The mixture should be adjusted to a pH of 8.9 and heated in a water bath at 60°; later it should be cooled overnight under cold temperature, then washed and dried the mixture compounds[48]. At last, needle-like MSU crystals can be seen under the microscope that can be used to induce gouty arthritis. When MSU is injected into the paw, it simulates the neutrophils and macrophages and produces cytokines such as IL-1β, IL-6, IL-8, IL-18 and TNF-α[49]. Increased levels of neutrophils will influx into synovial fluids. Accumulation of a large amount of synovial fluid will lead to ROS formation and lyse lysosomal membrane to release lysosomal enzymes[50]. Thus, in gouty arthritis patients, the lysosomal enzymes are found to be excess levels.

**Medication for gouty arthritis:**

The most common drugs prescribed for gouty arthritis are in their following ways against the inflammation like Colchicine block the generation of LTB4, Corticosteroids drug acts against inflammation through Adrenocorticotropic Hormone (ACTH) and NSAID such as indomethacin, ibuprofen, naproxen and sulindac has analgesic, antipyretic and anti-inflammatory medical property[5]. Even though these drugs are used to treat gouty arthritis, it also has severe side effects such as chronic kidney diseases, gastrointestinal toxicity and high Blood Pressure (BP) upon abiding consumption[51]. Allopurinol, febuxostat, probenecid and benz bromaron are the xanthine oxidase inhibitors which have the property of uricosuric agent and used as a treatment for gouty arthritis. These drugs are also reported to have
side effects such as hypersensitivity arthralgia, nausea, diarrhea, gastric-ulcer and gastrointestinal-toxicity[^49,52].

### RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a disease associated with joints commonly called an autoimmune inflammatory disease that leads to structural changes in multiple joints where the feet and hand joints are the first affected part and later other parts of the body are affected, resulting in severe pain and immobility[^53]. As a result of structural changes in joints it causes erosions in bone and degradation of cartilage[^54]. This induces macrophages and neutrophils to release cytokines like IL-1β, IL-6, IL-17 and TNF-α, leading to the destruction of joints' pleiotropic traits rheumatoid arthritis[^55]. It also causes the reduction of red blood cells in the blood, inflammation in the lungs and heart[^50]. Common factors causing rheumatoid arthritis are age, sex, race, poverty, chain-smoking, alcohol consumption and obesity, where the diseases associated with rheumatoid arthritis are CVD, atrial fibrillation, stroke and autoimmune diseases[^57,58].

#### Prevalence:

The report of the Rochester Epidemiology Project has said that the prevalence rate of rheumatoid arthritis has increased from 4 % to 5.3 % in the United States. Where also, among the 1 million people, 531 women and 277 men are affected by this disorder. People above 65 y old are more prominent than the adults, where 894 aged people are affected in 1 million population[^59]. The rate of rheumatoid prevalence is increasing every year of 2.5 % of women and 2 % of men. Other countries like Denmark, Finland, Sweden and Norway the prevalence rate of rheumatoid arthritis has been increased from 200 to 500 people in 1 million population[^60,61]. In addition, the Global Burden of the disease has also reported that the prevalence of rheumatoid arthritis that been increased from 0.5 % to 1.1 % globally. In Southern European countries, the prevalence rate increases from 0.3 % to 0.7 % and in many developing countries, prevalence is not exact but approximately increased from 0.1 % to 0.5 % reported by the American College of rheumatology[^62].

#### Mechanism:

The people with rheumatoid arthritis seem to have an increased C-Reactive Peptide (CRP) in the blood[^63]. Anticitrullinated-Protein Antibodies (ACPA) and Peptidyl-Arginine-Deiminase (PAD) enzyme are responsible for causing rheumatoid arthritis. Among that ACPA, it is associated with the genetics where abnormal antibody glycosylation can be found in rheumatoid arthritis condition that induces the inflammation in joints[^64]. During inflammation, activated T-lymphocytes enter into synovium, leading to aggregation of CD4 and infiltration of CD8 cells. These induce the dendritic cells by major histocompatibility complex-2 molecules expression, which stimulates the immune response in the joint tissues[^65,66]. This leads to thickening of the synovium, erosion of cartilage, the disintegration of bone and joint. The TRANCE receptor induces the production of osteoclast in the inflammation responsible for joint degradation. TNF-α is a major factor in rheumatoid arthritis where it is released when rheumatoid factor (ACPA) is formed were also TNF is stimulated by IL-17 in the hypersensitivity condition[^67]. The role of PAD is to convert arginine to citrulline where type 4 PAD inhibition was encoded by a gene called PADI-4 which is also responsible for the rheumatoid arthritis[^68].

#### Chemical induced rheumatoid arthritis:

**Collagen type-2:** Collagen type-2 and Incomplete Freund’s adjuvant (IFA) are commercially available. Collagen type-2 should be dissolved in 0.05 M acetic acid and mixed with IFA. Here IFA is used to stabilize the collagen. As administrated to rats, the mixture can be injected intradermally at the rat’s tail. This admiration causes rheumatoid arthritis, which can be boosted up on the 10th d by the mixture administration subcutaneously in the tail[^69,70]. Collagen mixture is injected; it initiates the immune response against collagen with T and B-cells' activation that produces antibodies (predominately IgG2). This antibody targets the collagen and stimulates the autoimmune response against collagen by producing macrophages, neutrophils and lymphocytes to the joint[^71]. In addition, the immune response leads to the activation of inflammatory mediators and cytokines such as TNF-α, IL-10 and IL-23 and Th-17[^70].

**Freund's complete adjuvant (FCA):** It is commercially available where adjuvant contains heat-killed *Mycoplasma tuberculosis*, which was suspended in paraffin oil. As administration in rats, the adjuvants can be injected intradermally on the rat’s paw. Rheumatoid arthritis are caused by the adjuvant in 18 d[^72,73]. Adjuvant is injected intradermally; it causes inflammation in joints with the generation of synovial cells that induces the immunoinflammatory cells to cartilage destruction in joints. Due to the increased level of synovial cells, the neutrophils and macrophages stimulated that lead
to the formation of ROS like O$_2$, H$_2$O$_2$ and OH$^-$. ROS generally damage the tissues and protein membranes; when it is damaged, the lipid membrane will result in lipid peroxidation and initiates NO that destruct the joints$^{[74]}$. As pro-inflammatory cytokines have been released during joint destruction, the increased levels of cytokines are responsible for inflammation such as TNF-$\alpha$ and IL-6 released in joints, leading to the initiation of the leukocytes ROS formation, that result in cartilage damage$^{[75,76]}$. In addition, inflammatory mediators like PG and LT are generated.

**Pristane oil:** It is commercially available, which also can be used to cause rheumatoid arthritis. Pristane can be injected via intraperitoneally. On the 7th d, pristane can be again injected to increase the inflammation$^{[77,78]}$. Mechanisms of pristane inducing rheumatoid arthritis are not known, but the pristane initiates an autoimmune response by activating immune to antigens to prevent microbes. Antibodies and collagens are used to detect rheumatoid arthritis, which is similar to pristane-induced arthritis. Thus, rheumatoid arthritis represents bone erosion, cartilage damage and joint inflammation. These factors were confirmed in the pristane induction in model$^{[79]}$.

**Peptidoglycan-polysaccharides:** Peptidoglycan-polysaccharides of the *Streptococcus* Cell Wall (SCW) are commercially available where the peptidoglycan-polysaccharides were from *Streptococcus pyogenes*. SCW can be dissolved in PBS and injected intra-articularly on the ankle joint to induce rheumatoid arthritis$^{[80,81]}$. SCW-induced arthritis is a state of rheumatoid arthritis with the infiltration of granulocyte, CD4-T cells and macrophages in the synovium, which leads to cartilage erosion and bone disintegrations. It also induces cytokines and chemokines like TNF-$\alpha$, IL-4, IL-1$\alpha$, Vascular Cell Adhesion Molecule-1 (VAM-1) and MCP-1. In addition, it is involved in NOS and COX in the SCW-induced arthritis development has been reported$^{[82]}$.

**Medication for rheumatoid arthritis:**

NSAIDs like ibuprofen and naproxen are used to treat rheumatoid arthritis due to its anti-inflammatory and analgesic properties. Mechanisms of NSAIDs against rheumatoid arthritis have the ability to prevent the PG production and mainly inhibition of COX$^{[83]}$. Even though it has anti-inflammatory activities, it is not advisable to take due to its severe side effects such as gastrointestinal bleeding, high blood pressure, anti-hypertensive, renal toxicity, hepatotoxicity and CDV$^{[33]}$. Corticosteroids like prednisone, triamcinolone and dexamethasone were used to reduce the joints pain. Cortisol is a hormone produced in our body in the adrenal gland where the role corticosteroids is to reduce the immune response that results in an inflammation reduction$^{[84]}$. In addition, steroid hormones are administrated to reduce rheumatoid arthritis that acts as immune-modulators to suppress the formation of antibodies during inflammation. Immune modulators are the inhibitors of the immune system$^{[85]}$. Where corticosteroids are also not advisable to take due to its major side effects like vasoconstrictive effects, asthma, nausea, pulmonary edema and autoimmune diseases were also causes Sjogren syndrome, graves ophthalmopathy and osteoarthritis while consuming long-term$^{[3,86]}$.

Disease-Modifying Antirheumatic Drugs (DMARDs) like methotrexate, leflunomide, hydroxychloroquine and sulfasalazine were used to treat rheumatoid arthritis. The mechanism of DMARD is to initiate the adenosine hormone to neutrophil reduction, LTB4 inhibition produced by neutrophils$^{[87]}$. It also reduces the levels of pro-inflammatory cytokines such as IL-1, IL-6, IL-8 and inhibited the collagenase expression in synovium to terminate inflammation in joints$^{[88]}$. In addition, it inhibits autoimmune responses like malfunction of lymphocytes, T-cell activation and B-cell activators$^{[89]}$. DMARD are powerful drugs it causes side effects like stomach upset, gastro-toxicity, bone marrow erosion, lung disease, hepatotoxicity, neurotoxicity and liver disease$^{[90]}$, so it’s better to stop consuming this drug.

**NATURAL PRODUCTS**

World Health Organization (WHO) has been reported that 75 % of people in global of developing countries are dependent on ancient traditional medicines like Ayurveda, Ebers Papyrus, Hippocrates and Chinese herbal medicine$^{[90]}$. These medicines have been followed as more than 1000 y due to its beneficial role and treatment against diverse disorders in humans and animals$^{[91,92]}$. Natural therapies are treating the diseases based on their bioactive compounds in it. That is also called as flavonoids or phytochemicals or polyphenols$^{[93]}$. Polyphenols are the naturally derived-valuable compounds that have been reported that it has wide medicinal properties like antioxidant, antimicrobial and anti-inflammatory abilities$^{[94,95]}$. ROS is the formation of a group of free radicals, which plays a serious role in inflammation or diseases, by scavenging the free radicals can prevent ROS. To scavenge the free radicals, antioxidants need to be high where herbal
products with polyphenols have been reported to be rich in antioxidants[96]. As comparatively natural products are less costly and beneficial than modern medicines with lots of side effects[97]. Moreover, a mechanism of actions of some of natural therapeutics on joint inflammation conditions such as osteoarthritis, gouty and rheumatoid arthritis are listed in Table 1-Table 3. Reports from the previous experimental studies show natural products against osteoarthritis, gouty and rheumatoid arthritis are potent to have beneficial effects. The effect of natural therapeutics against osteoarthritis includes Honokiol, a compound of Magnolia officanalis barks, which has antiarthritic activity by inhibiting T cell production and preventing NO production protects chondrocytes[98]. Curcumin has low solubility, so phosphatidycholine has been mixed in the ratio of 1:2, Anemonin, a compound of Ranunculus eschscholtzii Alpha-mangosteen, had restored inflammation by Nuclear Factor-κB (NF-κB) pathway[99-101]. SKI-306X, a combination of Clematis mandshurica, Prunella vulgaris, Trichosanthes kirilowii in the ratio of 1:2:1 and mud of Lake Urmia found to have a better effect on arthritis patients[102,103]. A dietary supplement has scavenged the free radicals and protects Deoxyribonucleic acid (DNA) by joints restoration[104]. Aucubin and Salvianolic acid-Bis shows good anti-inflammatory by inhibiting the p65 nuclear translocation-signaling pathway[105-107].

The effect of natural therapeutics against gouty arthritis as follows, an effective antioxidant and antibiotic product, turmeric and Pistacia integerrima leaf extract, has restored MSU-induced gout in mice, enhancing xanthine oxidase inhibitor or inhibited purine metabolism[108]. Sparattosperma leucanthum and Tabebuia roseoalba have proven a paw volume reduction in 72 h, protected the synovial cell from the damage and reduces the serum uric acid level in gout mice[109,110]. Sunflower head powder recovered the synovium deformation and cell

<table>
<thead>
<tr>
<th>Therapeutics</th>
<th>Source</th>
<th>Therapeutic effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honokiol</td>
<td>Magnolia officanalis</td>
<td>Inhibition of COX2, PGE2 and IL signaling</td>
<td>[98]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Etlingera elatior</td>
<td>Protects the degradation of chondrocytes and proteoglycan and prevents (AP)-1, IL-18 and NF-K</td>
<td>[99]</td>
</tr>
<tr>
<td>SKI-306X</td>
<td>Due to the combination of two plants</td>
<td>Inhibited proteoglycan degradation, glycosaminoglycan releases and structural changes in cartilage</td>
<td>[100]</td>
</tr>
<tr>
<td>Carbol, aerosol,</td>
<td>Mud of Lake Urmia in Iran</td>
<td>Pain relieved and decreased hs-CRP and TNF-α</td>
<td>[101]</td>
</tr>
<tr>
<td>Epigallocatechin-3-gallate</td>
<td>Camellia sinensis</td>
<td>Inhibited leukocytes, myeloperoxidase, chondrocyte and ROS, protects DNA damage and restores cartilage</td>
<td>[102]</td>
</tr>
<tr>
<td>Naringin</td>
<td>Skimmia japonica</td>
<td>Decreased IL-18, TNF-α, matrix-metalloproteinase-13, free radicals (NO) and ADAMTS-5 antibody</td>
<td>[103]</td>
</tr>
<tr>
<td>Alpha-mangostinin</td>
<td>Garcinia mangostana</td>
<td>Prevents NO, PG-E2, COX2 and metalloproteinases-(3, 9 and 13) as well inhibited NF-KB and p65 nuclear translocation pathways</td>
<td>[104]</td>
</tr>
<tr>
<td>Aucubin</td>
<td>Aucuba japonica</td>
<td>Prevents NO, COX2 and metalloproteinases-(3, 9 and 13) as well as well inhibited p65 nuclear translocation pathway</td>
<td>[105,106]</td>
</tr>
<tr>
<td>Anemonin</td>
<td>Ranunculus eschscholtzii</td>
<td>Cartilage regeneration and decreases metalloproteinase-13, ADAMTS-5, PG and collagen X as well inhibited NF-KB pathway</td>
<td>[107]</td>
</tr>
<tr>
<td>Salvianolic acid-Bis</td>
<td>Salvia miltiorrhiza</td>
<td>Inhibits NO, COX2, metalloproteinases-13 and ADAMTS5 and suppressed NK-KB and P65 nuclear translocation pathways</td>
<td>[108]</td>
</tr>
</tbody>
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TABLE 1: ANTIARTHRITIC ACTIVITY OF NATURAL THERAPEUTICS ON OSTEOARTHRITIS AT CLINICAL/ PRECLINICAL STUDIES

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infiltration in MSU-induced rats\textsuperscript{[111]}. The plasma level of TNF-\(\alpha\) is also reduced by piperine administration, whereas, \textit{in vitro} study Polymorphonuclear Leucocyte (PNL) cell interaction is reduced by the piperine \textsuperscript{[40]}. \textit{Withania somnifera} root powder reduced the paw inflammation, lipid peroxidation, lysosomal enzymes and inflammatory responses in MSU-induced rats\textsuperscript{[50]}. Triphala and Trikatu are made up of combinations of 3 different pants, which have been reported to increase the antioxidant level and paw histopathological analysis to restore joint erosion\textsuperscript{[112,113]}. The quercetin decreased the pro-inflammatory mediators such as COX2, IL–1\(\beta\), TNF-\(\alpha\), PGE2 and NO. The study has reported that quercetin administration in MSU-induced rats has restored polymorphonuclear infiltration in the synovial layer, infiltration of leucocyte with vascular thrombosis and tissue necrosis in the joint histopathology\textsuperscript{[114]}. The therapeutic effect of natural products against rheumatoid arthritis includes, \textit{Withania somnifera} has reduced the ankylosis and radiology score due to the cytokine (TNF-\(\alpha\)) inhibition that protects from disability\textsuperscript{[115]}. Vitamin P has increased the antioxidant levels and reduced joint erosion and cartilage degradation, suppressing the NF-\(\kappa\)B pathway\textsuperscript{[116]}. Milkvetch is proven to have antirheumatic activity by inhibiting serum osteoprotegerin in adjuvant-induced rats, which has also been reported to have suppressed NF-\(\kappa\)B p65 synovial by the immune-histochemical analysis\textsuperscript{[117,118]}. Tripterygium wilfordii root has been reported to reduce swelling, arthritic score and antibody titers in 3 w\textsuperscript{[119,120]}. \textit{Calotropis procera} and \textit{Tamarixinin-A} have restored the synovium hyperplasia, bone erosion and joint cartilage degradation in adjuvant and chemical-induced arthritis by inhibiting the NF-\(\kappa\)B signaling pathway\textsuperscript{[121,122]}. \textit{Abrus precatorius} recovered joint inflammation by blocked the COX2 pathway\textsuperscript{[123]}.

\textbf{TABLE 2: ANTIARTHRITIC ACTIVITY OF NATURAL THERAPEUTICS ON GOUTY ARTHRITIS AT CLINICAL/PRECLINICAL STUDIES}

<table>
<thead>
<tr>
<th>Therapeutics</th>
<th>Source</th>
<th>Formulation</th>
<th>Causative agent/Model</th>
<th>Therapeutic effects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcuminoids</td>
<td>\textit{Curcuma longa}</td>
<td>Aqueous solutions</td>
<td>MSU/Mice</td>
<td>Reduces paw edema, normalizes lipid peroxidation and renal markers. Inhibited cytokines, purine metabolism and enhances xanthine oxidase inhibitor</td>
<td></td>
</tr>
<tr>
<td>Leaves</td>
<td>\textit{Pistacia integerrima}</td>
<td>Aqueous leaf extract</td>
<td>Fructose/Mice</td>
<td>Reduced uric acid level and promoted antioxidants as well inhibits xanthine oxidase</td>
<td></td>
</tr>
<tr>
<td>Leaves</td>
<td>\textit{Sparattosperma leucanthum}</td>
<td>Ethyl acetate/methyl/aqueous leaf extract</td>
<td>MSU/Mice</td>
<td>Protects synovial cells damage, inhibits xanthine oxidase and reduces uric acid level</td>
<td></td>
</tr>
<tr>
<td>Leaves/(\alpha) and B Amyrins</td>
<td>\textit{Tabebuia roseaolba}</td>
<td>Ethanolic leaves extract</td>
<td>MSU/Rats</td>
<td>Reduces uric acid level, paw volume, IL-1, IL-6, IL-8 and TNF-(\alpha). Suppressed NF-KB and COX2 pathway</td>
<td></td>
</tr>
<tr>
<td>Flower head</td>
<td>\textit{Helianthus annuus}</td>
<td>Aqueous extract of head powder</td>
<td>MSU/Rats</td>
<td>Reduces Paw edema, IL-10 and restored cartilage, synovium deformation and cell infiltration</td>
<td></td>
</tr>
<tr>
<td>Piperine</td>
<td>\textit{Piper nigrum}</td>
<td>Aqueous solution</td>
<td>MSU/Rats</td>
<td>Restores the level of uric acid, lipid peroxidation, lysosomal enzymes and TNF-(\alpha)</td>
<td></td>
</tr>
<tr>
<td>Root powder</td>
<td>\textit{Withania somnifera}</td>
<td>Gum acacia with root powder</td>
<td>MSU/Rats</td>
<td>Reduces the paw inflammation, lipid peroxidation, lysosomal enzymes and cytokines</td>
<td></td>
</tr>
<tr>
<td>Triphala</td>
<td>\textit{Emblica officinalis; Terminalia chebula; Terminalia bellirica} in the ratio of 1:1:1</td>
<td>Aqueous solutions</td>
<td>MSU/Rats</td>
<td>Reduces the paw edema, lipid peroxidation, lysosomal enzymes and TNF-(\alpha) as well cartilage regeneration</td>
<td></td>
</tr>
<tr>
<td>Quercetin</td>
<td>Beverages; vegetables and fruits</td>
<td>Aqueous solutions</td>
<td>MSU/Rats</td>
<td>Reduces lysosomal enzymes and lipid peroxidation in joints tissues. Also, inhibited COX2, IL–1(\beta), TNF-(\alpha), PGE2 and NO and restored leukocyte infiltration in joints</td>
<td></td>
</tr>
<tr>
<td>Seed powder</td>
<td>\textit{Cyamopsis tetragonoloba}</td>
<td>Aqueous seed extract</td>
<td>MSU/Rats</td>
<td>Reduces renal markers and oxidative stress in spleen and joint homogenate. Importantly, protects bone erosion in articular cartilage</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{[109]} [109]
Aqueous extract of *Semecarpus anacardium* treated adjuvant-induced arthritis by inhibiting macrophages initiation and neutrophil infiltration. Collagen-induced arthritis found to have reduced the paw edema, antigen-presenting cells and DNA damage by the treatment of *Baccharis genistelloides* [124-135].

**CONCLUSION**

Traditional medicine or natural therapeutics has been proved their potential antiarthritic activities to recover joint inflammation in various clinical and preclinical studies. Natural products and its active compounds are found to have significant activity when compared with chemical medications with no side effects. Our review has collectively covered the various factors/agents causing or to induce joint inflammation such as osteoarthritis, gouty and rheumatoid arthritis. The chemicals that are used to cause arthritis and their mode of action have been discussed based on the report presented by researchers. Various researches have suggested that the natural product is beneficial compounds which treat arthritis without any side effects in preclinical studies. Many of the natural products with the essential ability against arthritis were not yet experimented and trials, which can be further study to understand its clear therapeutic mechanism against arthritis. This could be studied through *in vivo*, *in silico* and *in vitro* approaches.

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**Conflict of interests:**

The authors declared no conflicts of interest.

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