CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.7433597

Available online at: http://www.iajps.com *Review Article*

REVIEW ON: PATHOPHYSIOLOGY OF ARTHRITIS AND DRUGS USED IN THE MANAGEMENT OF ARTHRITIS

Anisha A Kohale[1], Priya N Kothari[1], Anuj A Deshmukh[2], Amol V Sawale[3], Kiran L Humbarde[4], Shirin S Bhuyar[4], Riya S Bhendkar[5]

Vidyabharti college of Pharmacy, Naidu marg Camp, Amravati MH INDIA 444-602.

Article Received: October 2022 **Accepted:** November 2022 **Published:** November 2022

Abstract:

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.

Keywords: *Joint Inflammation, osteoarthritis, gouty arthritis, rheumatoid arthritis, natural therapeutics.*

Corresponding author:

Anisha A Kohale,

Vidyabharti college of Pharmacy, Naidu Marg Camp,
Amravati MH INDIA 444-602.

QR code

Please cite this article in press ***Anisha A Kohale*** *et al,* ***Review On: Pathophysiology Of Arthritis And Drugs Used In The Management Of Arthritis.,*** *Indo Am. J. P. Sci, 2022; 09(11).*

INTRODUCTION:

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.

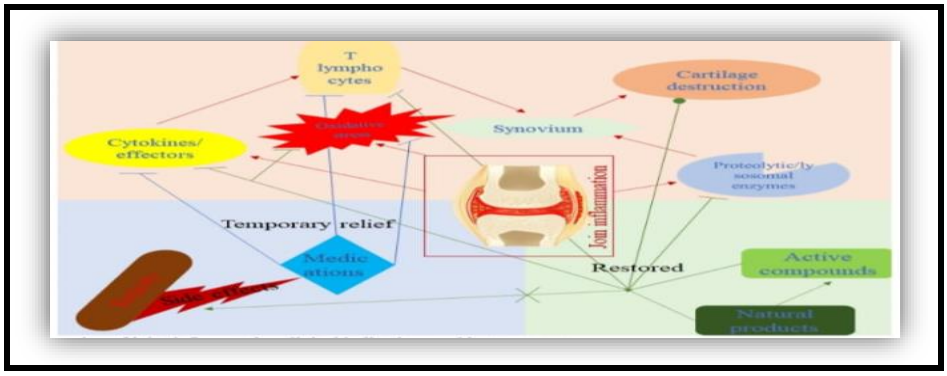

Fig. 1: Overview of joint inflammation clinical indications and its treatments

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,

Prevalence:

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.

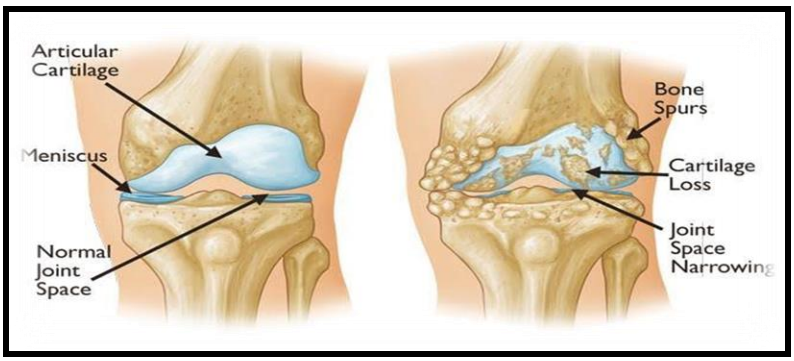

Fig. 2. Osteoarthiritis

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-statin-M will also generate Reactive Oxygen Species (ROS) such as Nitric oxide (NO), Oxygen (O2), Hydrogen peroxide (H2 O2) 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[16].

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[17]. 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 [18]. 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[19]. NSAIDs have analgesic, antipyretic and antiinflammatory 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[20]. 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[21,22]. Certain research has reported that corticosteroids have many side effects, such asskin disease, cushing syndrome, ophthalmologic, cardiovascular disease, neurotoxicity, gastro toxicity and poor growth[23]. 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[24]. This medication also shows the side effect, for example, gastrointestinal diseases, skin diseases, neurotoxicity and autonomic nervous system disorder[25].

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[26]. 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[27]. 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[28,29]. There are some diseases associated with gout are type-2 diabetes, hyperuricemia, hypertension and Cardiovascular Disease (CVD)[30]. 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[31].

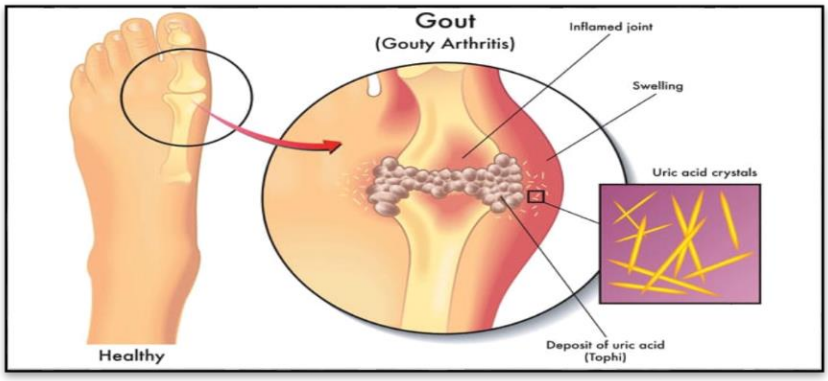

Fig. 3. Gouty Arthritis.

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[32]. 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[33].

Mechanism:

Gouty arthritis can be caused by various factors wherethe 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[34]. 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[35]. 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[35].

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[36]. As a result of structural changes in joints it causes erosions in bone and degradation of cartilage[37]. 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[38]. It also causes the reduction of red blood cells in the blood, inflammation in the

lungs and heart[39]. Common factors causing rheumatoid arthritis are age, sex, race, poverty, chain-smoking, alcohol consumption and obesity, where the diseases associate with rheumatoid arthritis are CVD, atrial fibrillation, stroke and autoimmune diseases[40,41]

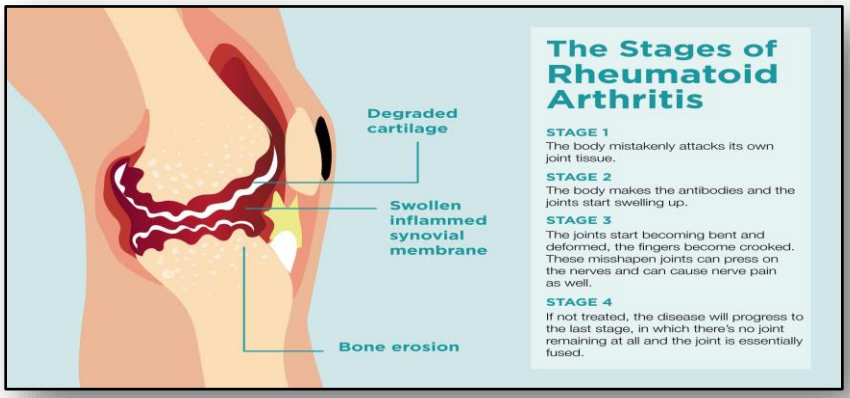

Fig. 4.Rheumetoide Arthritis

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[42]. 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 [43,44]. 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[45].

Mechanism:

The people with rheumatoid arthritis seem to have an increased C-Reactive Peptide (CRP) in the. Anticitrul blood[46]linated-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[47]. 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 histocompatbility complex-2 molecules expression, which stimulates the immune response in the joint tissues[48,49]. 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[50]. 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[51].

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[52]. 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, antihypertensive, renal toxicity, hepatotoxicity and . 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[53]. 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[54]. Where corticosteroids are also not advisable to take due to its major side effects like vaso constrictive effects, asthma, nausea, pulmonary edema and autoimmune diseases were also causes Sjogren syndrome, graves ophthalmopathy and osteoarthritis while consuming long – term [55]. 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[56]. It also reduces the level of pro-inflammatory cytokines such as IL-1, IL-6, IL-8 and inhibited the collagenase expression in synovium to terminate inflammation in joints [57]. In addition, it inhibits autoimmune responses like malfunction of lymphocytes, T-cell activation and B-cell activators[58]. DMARD are powerful drugs it causes side effects like stomach upset, gastro-toxicity, bone marrow erosion, lung disease, hepatotoxicity, neurotoxicity and liver disease[59], 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. These medicines have been followed as more than 1000 y due to its beneficial role and treatment against diverse disorders in humans and animals[60,61]

TABLE 1: ANTIARTHRITIC ACTIVITY OF NATURAL THERAPEUTICS ON OSTEOARTHRITIS AT CLINICAL/ PRECLINICAL STUDIES

Therapeutics	Source	Formulation	Causative agent/Model	Therapeutic effects	Reference
Honokiol	Magnolia officanalis	Aqueous solution	NA/Patients	Inhibition of COX2, PGE2 and IL Signalling	[62]
Curcumin	Etlingera elatior	Curcuminin aqueous phophatidycholine	NA/Patients	Protects the degradation of chondrocytes and proteoglycan and prevents (AP)-1, IL-1β and NF-K	[63]
SKI-306X	Clematis mandshurica; Prunella vulgaris; Trichosanthes kirilowii	Aqueous with the ratio of 1:2:1	Collagenas/ Rabbit	Inhibited proteoglycan degradation, glycosaminoglycan releases and structural changes in cartilage	[64]
Carbopol,aerosol, veegum and charcoal	Mud of Lake of Urmia in Iran	Ointment	NA/Patients	Pain relieved and decreased hs-CRP and TNF-α	[65]

Epigallocatechin-3-gallate, gallic acid, agallin and methylxanthines	Camelliasinensis is	Aqueous solution	NA/Patients	Inhibited leukocytes, myeloperoxidase, chondrocyte and ROS ,protects DNA damage and restores cartilage	[66]
Naringin	Skimmiajaponica	Aqueous solution	Surgical/ Rats	Decreased IL-1β, TNF-α, matrix-metalloproteinase-13, free radicals (NO) and ADAMTS-5 antibody	[67]
Alpha-mangostinis	Garcinia mangostana	Aqueous solution	IL-1β/Rats	Prevents NO, PG-E2, COX2 and metalloproteinases-(3,9 and 13) as well inhibited NF-kB and p65 nuclear translocation pathways	[68]
Aucubin	Aucuba japonica	Aqueous solution	NA/Patients	Prevents NO, COX2 and metalloproteinases-(3,9 and 13) as well inhibited p65 nuclear translocation pathway	[69,70]
Anemonin	Ranunculus eschscholtzii	Aqueous solution	Surgical/ Mouse	Cartilage regeneration and decreases metalloproteinase-13, ADAMTS-5, PG and collagen X as well inhibitedNF-KB pathway	[71]
Salvianolic acid-Bis	Salvia miltiorrhiza	Intraperitoneal saline solution	MIA/Mouse	Inhibits NO, COX2, metalloproteinases-13 and ADAMTS5 and suppressed NK-KB and P65 nuclear translocation pathways	[72]

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

Therapeutics	Source	Formulation	Causative agent/Model	Therapeutic effects	Reference
Curcuminoids	Curcuma longa	Aqueous solution	MSU/Mice	Reduces paw edema, normalizes lipid peroxidation and renal markers. Inhibited cytokines, purine metabolism and enhances xanthine oxidase inhibitor	[73]
Leaves	Pistacia Integerrima	Aqueous leaf extract	Fructose/Mice	Reduced uric acid level and promoted antioxidants as well inhibits xanthine oxidase	[74]
Leaves	Sparattosperma leucanthum	Ethyl acetate/ methyl/aqueous leaf extract	MSU/Mice	Protects synovial cells damage, inhibits xanthine oxidase and reduces uric acid level	[75]
Leaves/α and B Amyrins	Tabebuia roseoalba	Ethanolic leaves extract	MSU/Rats	Reduces uric acid level, paw volume, IL-1, IL-6, IL-8 and TNF-α. Suppressed NF-KB and COX2 pathway	[76]
Flower head	Helianthus annuus	Aqueous extract of head powder	MSU/Rats	Reduces Paw edema, IL-10 and restored cartilage, synovium deformation and cell infiltration	[77]
Piperine	Piper nigrum	Aqueous solution	MSU/Rats	Restores the level of uric acid, lipid peroxidation, lysosomal enzymes and TNF-α	[78]
Root powder	Withania somnifera	Gum acacia with root powder	MSU/Rats	Reduces the paw inflammation, lipid peroxidation, lysosomal enzymes and cytokines	[79]
Triphala	Emblica officinalis Terminalia chebula; Terminalia belliricain the ratio of 1:1:1	Aqueous solution	MSU/Rats	Reduces the paw edema, lipid peroxidation, lysosomal enzymes and TNF-α as well cartilage regneration	[80]
Quercetin	Beverages vegetables and fruits	Aqueous solution	MSU/Rats	Reduces lysosomal enzymes and lipid peroxidation in joints tissues. Also, inhibited COX2, IL–1b, TNF-α, PGE2 and NO and restored leukocyte infiltration in joints	[81]
Seed powder	Cyamopsis tetragonoloba	Aqueous seed extract	MSU/Rats	Reduces renal markers and oxidative stress in spleen and joint homogenate. Importantly, protects bone erosion in articular cartilage	[82]

TABLE 3: ACTIVITY OF NATURAL THERAPEUTICS ON RHEUMATOID ARTHRITIS ANTIARTHRITIC AT CLINICAL/PRECLINICAL STUDIE

Therapeutics	Source	Formulation	Causative agent/Model	Therapeutic effects	Reference
Root	Withania somnifera	Aqueous root extract	Collagen and adjuvant/Rats	Reduces ankylosis,lipid peroxidation,glycoprotein and cartilage regeneration	[83,84]
Rutin	Eucalyptus tereticornis	Aqueous solution	Adjuvant/Rats	Reduces joint erosion, cartilage degradation, TNF-α and IL-1β in NF-KB pathway	[85]
Total flavonoids	Astragalus propinquus	Aqueous solution	Adjuvant/Rats	Reduces joint swelling and arthritic index, restored BAX and BCL-2 and inhibited PGE2, NF-KB and osteoprotegerin	[86]
Root	Tripterygium wilfordii	Aqueous root extract	Collagen/Mice	Reduces joint swelling, arthritic score and antibody titers and restored cartilage destruction	[87]
Leaves	Calotropis procera	Methanol leaf extract	Adjuvant/Rats	Increases antioxidants, decreases PGE2, TNF-α and lipid peroxidation and cartilage regeneration	[88]
Tamarixinin-A	Tamaricaceae	Aqueous solution	Collagen and Adjuvant/Rats	Restores synovium hyperplasia, bone erosion and cartilage degradation, decreases TNF-α, IL-6 and IL1-βand inhibited p38 and NF-KB pathway	[89]
Leaves	Ziziphora clinopodioides	Aqueous leaf extract	Xylene and carrageenan/Rats	Reduces paw volume, pannus formation and cartilage joint erosion and inhibited autacoids	[90]
Seeds	Abrus precatorius seed	Ethanolic extract	Adjuvant/Rats	Prevents pannus formation, joint inflammation and cartilage degradation and inhibits cytokines and the COX2 pathway	[91]
Leaves	Baccharis genistelloides	Aqueous leaves extract	Collagen/Rats	Prevents antigen presenting cells, decreases cytokines, DNA damage and articular cartilage degradation	[92]
Bark	Semecarpus anacardiumis	Aqueous bark extract	Adjuvant/Rats	Reduces lipid peroxidation, macrophages, cytokines and restores joint damages	[93]

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 trails, which can be further study to understand its clear therapeutic mechanism against arthritis.This could be studied through invivo, insilico and in vitro approaches.

REFERENCES:

1. Arthritis. National Institute of Arthritis and Musculoskeletal and Skin Diseases2019.
2. K.D.Tripathi, Essentials of Medical Pharmacology ,8th edition, page no.1467.
3. F.S.K.Barar ,Essentials of Pharmacotherapeutics, page no.117.
4. Gary C. Yee ,Joseph T. DiPiro ,Gary R.Matzke, Barbar G. Wells, L. Micheal Posey, Parmacotherapy A Pathophysiologic Approach, 9th edition, page no.1437.
5. Cronstein BN, Sunkureddi P. Mechanistic Aspects of Inflammation and Clinical Management of Inflammation in Acute Gouty Arthritis. J Clin Rheumatol 2013;19(1):19-29.
6. Dar RA, Shahnawaz M, Rasool S Qazi PH. Natural product medicines: A literature update. J Phytopharm 2016;6(6):340-2.
7. Hunter DJ, Felson DT .Osteoarthritis. BMJ 2006;332(7542):63t9- 42.
8. Takahashi I, Matsuzaki T, Kuroki H, Hoso M. Induction of osteoarthritis by injecting monosodium iodoacetate into the patellofemoral joint of an experimental rat model. PLoS one 2018;13.
9. Xu Q, Zhang Z, Sun W. Effect of Naringin on Monosodium Iodoacetate-Induced Osteoarthritis Pain in Rats. Med Sci Monit 2017;23:3746-51.
10. Heidari B. Knee osteoarthritis prevalence, risk factors, pathogenesis and features: Part I. Casp J Intern Med 2011;2(2):205-12.
11. Vina ER, Kwoh CK. Epidemiology of osteoarthritis:literature update. Curr Opin Rheumatol 2018;30(2):160-7.
12. Pal CP, Singh P, Chaturvedi S, Pruthi KK,Vi jA.Epidemiology of knee osteoarthritis in India and related factors. Indian J Orthop2016;50(5):518-22.
13. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. Best Pract Res Clin Rheumatol 2014;28(1):5-15.
14. Yasuda T. Cartilage destruction by matrix degradation products. Mod Rheumatol2006;16(4):197-205.
15. Attur MG, Dave M, Akamatsu M, Katoh M, Amin AR. Osteoarthritis or osteoarthrosis: the definition of inflammation becomes a semantic issue in the genomic era of molecular medicine. Osteoarthritis Cartilage 2002;10(1):1-4.
16. Loeser RF. Molecular Mechanisms of Cartilage Destruction: Mechanics, Inflammatory Mediators and Aging Collide. Arthritis Rheum2006;54(5):1357-60.
17. Zhang W, Jones A, Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis?: A meta- analysis of randomised controlled trials. Ann Rheum Dis 2004;63(8):901-7.
18. Yoon E, Babar A, Choudhary M, Kutner M, Pyrsopoulos N. Acetaminophen-Induced Hepatotoxicity: A Comprehensive Update. J ClinTranslHepatol2016;4(2):131-42.
19. Fokunang CN, Fokunang ET, Frederick K, Ngameni B, Ngadjui B. Overview of non-steroidal anti-inflammatory drugs (nsaids) in resource limited countries. MOJ Toxicol2018;4(1):5-13.
20. Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A Comprehensive Review of Non-Steroidal Anti-Inflammatory Drug Use in the Elderly. Aging Dis 2018;9(1):143-50.
21. Ayhan E, Kesmezacar H, Akgun I. Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. World J Orthop2014;5(3):351-61.
22. Yavuz U, Sökücü S, Albayrak A, Oztürk K. Efficacy comparisons of the intra articular steroidal agents in the patients with knee osteoarthritis. Rheumatol Int 2012;32(11):3391-6.
23. Stein C, Baerwald C. Opioids for the treatment of arthritis pain. Expert Opin Pharmacother 2014;15(2):193-202.
24. Nakatani T. Opioid therapy and management of side effects associated with opioids. Gan To Kagaku Ryoho 2017;44(4):294-7.
25. Rymal E, Rizzolo D. Gout: A comprehensive review. JAAPA 2014;27(9):26-31.
26. Richette P, Bardin T. Gout. Lancet 2010;375(9711):318-28.
27. Sabina EP, Nagar S, Rasool M .A role of piperine on monosodium urate crystal-induced inflammation-an experimental model of gouty arthritis. Inflammation2011;34(3):184-92.
28. An J, Yang HJ, Park K, Lee J, Kim BW. Reparatory and preventive effects of oriental herb extract mixture (OHEM) on hyperuricemia and gout. Food Sci Biotechnol 2010;19:517-24.
29. Harris MD, Siegel LB, Alloway JA. Gout and Hyperuricemia. Am Fam

Physician1999;59(4):925-34.
30. Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: Prevalence, incidence and risk factors. Nat Rev Rheumatol2015;11(11):649-62.
31. Saigal R, Agrawal A. Pathogenesis and Clinical Management of Gouty Arthritis. J Assoc Physicians India 2015;63(12):56- 63.
32. Busso N, So A. Mechanisms of inflammation in gout. Arthritis Res Ther2010;12(2):206.
33. Ong KL, Wu BJ, Cheung BMY, Barter PJ, Rye KA. Arthritis: its prevalence, risk factors and association with cardio vascular diseases in the United States, 1999 to 2008. Ann Epidemiol 2013;23(2):80-6.
34. Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. Lancet 2017;389 (10086):2338-48.
35. Dinesh P, Rasool M. uPA/uPAR signaling in rheumatoid arthritis: Shedding light on its mechanism of action. Pharmacol Res 2018;134:31-9.
36. MajithiaV, Geraci SA. Rheumatoid Arthritis: Diagnosis and Management. Am J Med2007;120(11):936-9.
37. Gibof sky A. Overview of epidemiology, pathophysiology and diagnosis of rheumatoid arthritis. Am J Manag Care 2012;18:S295-302.
38. Xu B, Lin J. Characteristics and risk factors of rheumatoid arthritis in the United States: an NHANES analysis. PeerJ 2017;5:e4035.
39. Hunter TM, Boytsov NN, Zhang X, Schroeder K, Michaud K, Araujo AB. Prevalence of rheumatoid arthritis in the United States adult population in healthcare claims databases, 2004-2014. Rheumatol Int 2017;37(9):1551-7
40. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising? Results from Olmsted County,Minnesota,1955-2007.Arthritis Rheum 2010;62(6):1576-82.
41. Yamanaka H, Sugiyama N, Inoue E, Taniguchi A, Momohara S. Estimates of the prevalence of and current treatment practices for rheumatoid arthritis in Japan using reimbursement data from health insurance societies and the IORRA cohort(I). Mod Rheumatol 2014;24(1):33-40.
42. Fazal SA, Khan M, Nishi SE, Alam F, Zarin N, Bari MT, *et al*. A clinical update and global economic burden of rheumatoid arthritis.Endocr Metab Immune Disord Drug Targets 2018;18(2):98-109.
43. Orr CK, Najm A, Young F, Mc Garry T, Biniecka M, Fearon U, *et al*.The utility and limitations of CRP, ESR and DAS28-CRP in appraising disease activity in rheumatoid arthritis. Front Med2018;5.
44. Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone Res 2018;6:15.
45. Firestein GS, Mc Innes IB. Immuno pathogenesis of Rheumatoid Arthritis. Immunity 2017;46(2):183-96.
46. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet 2016;388(10055):2023-2038.
47. Gaffen SL. The role of interleukin-17 in the pathogenesis of rheumatoid arthritis.CurrRheumatol Rep2009;11(5):365-70.
48. Udhaya Lavinya B, Sangeetha N, Manisha P, Ramkumar K, Kavitha M, Evan Prince Sabina. Virtual screening of peptidyl arginine deiminase type 4 inhibiting potential of chosen flavonoids. Res J Pharm Technol 2018;11:753-7.
49. Crofford LJ. Use of NSAIDs in treating patients with arthritis. Arthritis Res Ther2013;15:S2.
50. Clarke L, Kirwan J. Efficacy, safety and mechanism ofaction of modified-release prednisone in rheumatoid arthritis. Ther Adv Musculoskelet Dis 2012;4(3):159-66.
51. Haraoui B, Jovaisas A, Bensen WG ,Faraawi R ,Kelsall J, Dixit S, *et al*. Use of corticosteroids in patients with rheumatoid arthritis treated with infliximab: Treatment implications based on a real-world Canadian population. RMD Open 2015;1(1):e000078.
52. Satyanarayanasetty D, Pawar K, Nadig P, Haran A. Multiple adverse effects of systemic corticosteroids: A case report. J Clin Diagn Res 2015;9(5):FD01-2.
53. Benjamin O, Lappin SL. Disease Modifying Anti-Rheumatic Drugs (DMARD). StatPearls2018.
54. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: A review. JAMA 2018;320(13):1360-72.
55. Wang W, Zhou H, Liu L. Side effects of methotrexate therapy for rheumatoid arthritis: Asystematic review. Eur J Med Chem 2018;158:502-16.
56. Joshi P, Dhaneshwar SS. An update on disease modifying antirheumatic drugs.Inflamm Allergy Drug Targets 2014;13(4):249-61.
57. Okoronkwo I, Onyia-pat JL, Okpala P, Agbo MA, Ndu A. Patterns of complementary and alternative medicine use, perceived benefits and adverse effects among adult users in Enugu Urban, Southeast Nigeria. Evid Based Complement Altern Med2014;2014.
58. Poivre M, Duez P. Biological activity and toxicity of the Chinese herb *Magnolia officinalis* Rehder & E.Wilson(Houpo) and its constituents.

J Zhejiang Univ Sci B.2017;18(3):194-214.
59. Chen YJ, Tsai KS, Chan DC, Lan KC, Chen CF, Yang RS, *et al.* Honokiol, a low molecular weight natural product, prevents inflammatory response and cartilage matrix degradation in human osteoarthritis chondrocytes. J Orthop Res 2014;32(4):573-80.
60. Belcaro G, Cesarone MR, Dugall M, Pellegrini L, Ledda A, Grossi MG, *et al.* Product-evaluation registry of Meriva®, a curcumin-phosphatidylcholine complex, for the complementary management of osteoarthritis. Panminerva Med2010;52:55-62.
61. Choi JH, Choi JH, Kim DY, Yoon JH, Youn HY, Yi JB, *et al.* Effects of SKI 306X, a new herbal agent, on proteoglycan degradation in cartilage explant culture and collagenase- induced rabbit osteoarthritis model. Osteoarthritis Cartilage 2002;10(6):471-8.
62. Mahboob N, Sousan K, Shirzad A, Amir G, Mohammad V,Reza M, *et al.* The efficacy of a topical gel prepared using lake urmia mud in patients with knee osteoarthritis. JAltern Complement Med 2009;15(11):1239-42.
63. Hashempur MH, Sadrneshin S, Mosavat SH, Ashraf A. Green tea (*Camellia sinensis*) for patients with knee osteoarthritis: A randomized open-label active-controlled clinical trial. ClinNutr2018;37(1):85-90.
64. Zhao Y, Li Z, Wang W, Zhang H, Chen J, Su P, *et al*. Naringin protects against cartilage destruction in osteoarthritis through repression of NF-κB signaling pathway. Inflammation 2016;39(1):385-92.
65. Pan T,Wu D,Cai N,Chen R,Shi X, LiB, *et al.* Alpha-Mangostin protects rat articular chondrocytes against IL-1β-induced inflammation and slows the progression of osteoarthritis in a rat model. Int Immunopharmacol 2017;52:34-43.
66. Wang SN, XieGP, Qin CH, Chen YR, Zhang KR, Li X, *et al*. Aucubin prevents interleukin-1beta induced inflammation and cartilage matrix degradation via inhibition of NF-κBsignaling pathway in rat articular chondrocytes. Int Immunopharmacol 2015;24(2):408-15.
67. Wang Z, Huang J, Zhou S, Luo F, Xu W, Wang Q, *et al*. Anemonin attenuates osteoarthritis progression through inhibiting the activation of IL-1β/NF-κB pathway. J Cell Mol Med 2017;21(12):3231-43.
68. Lou Y, Wang C, ZhengW, Tang Q, Chen Y, Zhang X, *et al.* Salvianolic acid B inhibits IL-1β-induced inflammatory cytokine production in human osteoarthritis chondrocytes and has a protective effect in a mouse osteoarthritis model. Int Immunopharmacol 2017;46:31-7.
69. Kiyani MM, Sohail MF, Shahnaz G, Rehman H, Akhtar MF, Nawaz I, *et al.* Evaluation of turmeric nanoparticles as anti- gout agent: Modernization of a traditional drug. Medicina 2019;55(1):10.
70. Yin J, RenW, Huang X, Deng J, Li T, Yin Y. Potential mechanisms connecting purine metabolism and cancer therapy. Front Immunol2018;9:1697.
71. Ferraz-Filha ZS, Michel Araújo MC de P, Ferrari FC, Dutra IPAR, Saúde-Guimarães DA. *Tabebuiaroseoalba*: *In vivo* hypouricemic and anti-inflammatory effects of its ethanolic extract and constituents. Planta Med2016;82(16):1395-402.
72. Li L, TengM, Liu Y, QuY, Zhang Y, Lin F, *et al.* Anti- Gouty arthritis and antihyperuricemia effects of sunflower (*Helianthus annuus*) head extract in gouty and hyperuricemia animal models. BioMed Res Int 2017;2017:5852076.
73. Sabina EP, Rasool M. An *invivo* and *invitro* potential of Indian ayurvedic herbal formulation Triphala on experimental gouty arthritis in mice.Vascul Pharmacol2008;48(1):14-20.
74. Huang J, Zhu M, Tao Y, Wang S, Chen J, Sun W, *et al.* Therapeutic properties of quercetin on monosodium urate crystal-induced inflammation in rat. J Pharm Pharmacol 2012;64(8):1119-27.
75. Peter SJ, Katturaja R, Namachivayam A, Nithyanandham S, Parthasarathy M, Sabina EP. Anti-inflammatory potential of the aqueous extract of *Cyamopsis tetragonoloba* against the MSU-induced arthritis in female Wistar albino rats. Asian Pac J Mol Biol Biotechnol 2020;28:1-12.
76. Rasool M, VaralakshmiP. Protective effect of *Withania somnifera* root powder in relation to lipid peroxidation, antioxidant status, glycoproteins and bone collagen on adjuvant-induced arthritis in rats. Fundam Clin Pharmacol 2007;21(2):157-64.
77. Gupta A, Singh S. Evaluation of anti-inflammatory effect of *Withania somnifera* root on collagen-induced arthritis in rats. Pharm Biol 2014;52(3):308-20.
78. Sun CL, Wei J, Bi LQ. Rutin attenuates oxidative stress and proinflammatory cytokine level in adjuvant induced rheumatoid arthritis via inhibition of NF-κB. Pharmacology 2017;100:40-9.
79. Liu XY, Xu L, Wang Y, Li JX, Zhang Y, Zhang C, *et al.* Protective effects of total flavonoids of Astragalus against adjuvant-induced arthritis in rats by regulating OPG/RANKL/ NF-κB pathway. Int Immunopharmacol2017;44:105-14.

80. Ushiro S, Ono M, Nakayama J, FugiwaraT, Komatsu Y, Sugimachi K, *et al.* New nortriterpenoid isolated from anti-rheumatoid arthritic plant, *Tripterygium wilfordii*, modulates tumor growth and neovascularization. Int J Cancer 1997;72(4):657-63.
81. Kumar VL, Roy S. *Calotropis procera* latex extract affords protection against inflammation and oxidative stress in freund's complete adjuvant-induced monoarthritis in rats. Mediators Inflamm 2007;2007:47523.
82. Zhuang Y, Liu J, Ma P, Bai J, Ding Y, Yang H, *et al.* Tamarixinin A alleviates joint destruction of rheumatoid arthritis by blockade of MAPK and NF-κB activation. Front Pharmacol 2017;8.
83. Shabbir A, Batool SA, Basheer MI, Shahzad M, Sultana K, Tareen RB, *et al. Ziziphora clinopodioides* ameliorated rheumatoid arthritis and inflammatory paw edema in different models of acute and chronic inflammation. Biomed Pharmacother2018;97:1710-21.
84. Sudaroli M, Chatterjee TK. Evaluation of red and white seed extracts of *Abrus precatorius* Linn. Against freunds complete adjuvant induced arthritis in rats.J Med Plants Res 2007;1:086- 94.
85. Coelho MGP, Reis PA, Gava VB ,Marques PR, Gayer CR, Laranja GAT, *et al.* Anti-arthritic effect and subacute toxicological evaluation of *Baccharis genistelloides* aqueous extract. Toxicol Lett 2004;154:69-80.
86. Semalty M, Semalty A, Badola A, Joshi GP, Rawat MSM. *Semecarpus anacardium* Linn: A review. Pharmacogn Rev 2010;4:88-94.
87. Zhao Y, Li Z, Wang W, Zhang H, Chen J, Su P, *et al.* Naringin protects against cartilage destruction in osteoarthritis through repression of NF-κB signaling pathway. Inflammation 2016;39(1):385-92.
88. Pan T, Wu D, Cai N, Chen R, Shi X, Li B, *et al.* Alpha-Mangostin protects rat articular chondrocytes against IL-1β-induced inflammation and slows the progression of osteoarthritis in a rat model. Int Immunopharmacol 2017;52:34-43.
89. Wang Z, Huang J, Zhou S, Luo F, Xu W, Wang Q, *et al.* Anemonin attenuates osteoarthritis progression through inhibiting the activation of IL-1β/NF-κB pathway. J Cell Mol Med2017;21:3231-43.
90. Lou Y, Wang C, Zheng W, Tang Q, Chen Y, Zhang X, *et al.* Salvianolic acid B inhibits IL-1β-induced inflammatory cytokine production in human osteoarthritis chondrocytes and has a protective effect in a mouse osteoarthritis model. Int Immunopharmacol 2017;46:31-7.
91. Yin J, Ren W, Huang X, Deng J, Li T, Yin Y. Potential mechanisms connecting purine metabolism and cancer therapy. Front Immunol 2018;9:1697.
92. Peter SJ, Katturaja R, Namachivayam A, Nithyanandham S, Parthasarathy M, Sabina EP. Anti-inflammatory potential of the aqueous extract of *Cyamopsis tetragonoloba* against the MSU-induced arthritis in female Wistar albino rats J.AsianPac J Mol Biol Biotechnol 2020;28(3):1-12.
93. Rasool M, VaralakshmiP. Protective effect of *Withania somnifera* root powder in relation to lipid peroxidation, antioxidant status, glycoproteins and bone collagen on adjuvant-induced arthritis in rats. Fundam Clin Pharmacol 2007;21(2):157-64.