

This review article described on various medical strategies against Arthritis

Piyush Mukati, Mrs. Anjula Patidar, Mr. D.S. BELE

Charak Institute of Pharmacy, Mandleshwar

Submitted: 02-01-2023

Accepted: 10-01-2023

ABSTRACT: Arthritis is an chronic, inflammatory, systemic autoimmune disease characterized by pain, swelling and stiffness. Allopathic medications have been prescribed to alleviate symptoms of this disease which results into associated side effects like gastrointestinal bleeding and bone loss (osteoporosis). Rheumatoid arthritis (RA) is a systemic inflammatory arthritis in which primary prevention is key. The use of herbal medicine becoming popular due to toxicity and side effects of allopathic medicines. Rheumatoid arthritis (RA) is a systemic inflammatory arthritis in which primary. The risk factors include age, gender, genetics, and environmental exposure (cigarette smoking, air pollutants, and occupational). Many complications can follow, such as permanent joint damage requiring arthroplasty, rheumatoid vasculitis, and Felty syndrome requiring splenectomy if it remains unaddressed. Typically, it is a collection of diseases together nomenclatured as "Arthritis". Nearly 47 million people in the US alone are suffering from this disease. Globally, it imposes a huge financial burden. Considering medical condition, the disease exerts medium to severe problem at various bone-joints displaying inflammation as a common symptom which often turns serious, incapacitating the individuals through pain, swelling and inflexibility at those affected joints. Joint destruction progresses soon after the onset, and once the affected joints are deformed, the development of irreversible physical dysfunction is noted. Thus, proper diagnosis and treatment are required from the early stages of the disease. Although palliative therapy with glucocorticoids and anti-inflammatory drugs had been used, disease-modifying antirheumatic drugs (DMARDs) are currently used to suppress immune abnormalities and to control disease activity. The advent of molecular-targeted therapies has allowed for the use of treatments based on pathological mechanisms, and such therapeutic strategies have also been applied to the treatment of various autoimmune inflammatory diseases. In the future,

safer and more effective treatments, therapeutic strategies aimed at drug holidays or cure, and the introduction of precision medicine are expected. Significant reduction in WOMAC pain scores from baseline were observed in topical Curcumin 5% gel -2.47 compared to the control -0.70 for OA of the knee at week one, with the p-value being 0.03. No side effects were seen. Administration of topical Curcumin 5% gel 2 ml twice daily resulted in significantly greater improvement in pain reduction at week one versus control.

Keywords: Arthritis, Rheumatoid Arthritis, Osteoarthritis, Inflammatory, Joints.

I. INTRODUCTION:

"Arthritis" is a combinatorial word originated by the mixing of Latin and Greek. In Greek, "Arthron" signifies joint and in Latin "Itis" specifies inflammation. Thus arthritis is normally viewed as a disease caused as a result of inflamed joints. The disease can incapacitate permanently if proper treatments are not provided in time. Globally, it imposes a huge financial burden through wage loss along with the cost of medications. Several treatment pathways are now available just to control the disease but no imminent cure is found yet. Arthritis is most common in the following areas of the body: Feet, Hands, Hips, Knees.[1] "Arthritis" literally means joint inflammation. Although joint inflammation is a symptom or sign rather than a specific diagnosis, the term arthritis is often used to refer to any disorder that affects the joints. Joints are places in the body where bones come together, such as the knees, wrists, fingers, toes, and hips. These disorders fall within the broad category of rheumatic diseases. These are diseases characterised by inflammation (signs include redness or heat, swelling, and symptoms such as pain) and loss of function of one or more connecting or supporting structures of the body. They especially affect joints, tendons, ligaments, bones, and muscles. Common signs and symptoms are pain, swelling, and stiffness. Some rheumatic

diseases also can involve internal organs. There are more than 100 rheumatic diseases that collectively affect more than millions of people world wide . Arthritis affects 15% of the Indian population (about 180 million people). There are several diseases where joint pain is primary, and is considered the main feature. Generally when a person has "arthritis" it means that they have one of these diseases, which include: Osteoarthritis, rheumatoid arthritis, gout and pseudogout, septic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and still's disease. Joint pain can also be a symptom of other diseases. In this case, the arthritis is considered to be secondary to the main disease; these include: Psoriasis (Psoriatic arthritis), reactive arthritis, etc.[2] Around 10 million people in the UK are thought to have arthritis .It can affect people of all ages – even children and teenagers. Some forms of arthritis are more common in older people. Although there's no cure for arthritis, treatments have improved greatly in recent years and, for many types of arthritis, particularly inflammatory arthritis, there's a clear benefit in starting treatment at an early stage. Arthritis can make life tough by causing pain and making it harder to get about. The symptoms of arthritis can vary from week to week, and even from day to day. Many types, such as osteoarthritis and rheumatoid arthritis, are long-term conditions.[3] Arthritis occurs when the joints in the body are inflamed or there is a breakdown of cartilage in the joints. Cartilage is the cushion in the joints that protects them from pressure and makes movements smooth. When cartilage breaks down in a joint, the bones rub together.[4]

TYPES OF ARTHRITIS: Some of the more common types of arthritis are:

1. Osteoarthritis
2. Rheumatoid arthritis
3. Gout
4. Lupus arthritis (LA)
5. Childhood arthritis
6. Ankylosing Spondylitis (AS)
7. Psoriatic arthritis (PA)
8. Infectious arthritis (IA)

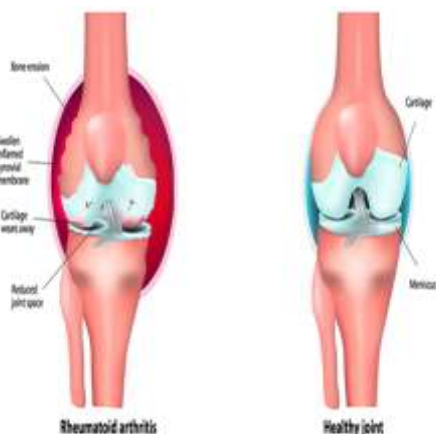
OSTEOARTHRITIS:- This is the most common type. It causes the cartilage on the ends of your bones to wear away. That makes the bones rub against each other. The cartilage breakdown, or degeneration, of osteoarthritis often happens with age. This is why osteoarthritis is sometimes called degenerative joint disease. But if there are other causes, it can begin much sooner. For example, an athletic injury like a torn anterior cruciate ligament (ACL) or a fracture near a joint can lead to arthritis. It can happen in any joint but most often affects the

hands and weight-bearing joints such as the knee, hip, and facet joints (in the spine). Being overweight can make you more likely to get osteoarthritis and can make it worse. Taking painkillers, such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen can help reduce your symptoms and allow you to stay active. Keeping active will also reduce pain, stiffness and swelling. There are NSAID creams that you can rub into the affected area . It might be an idea to try these first. There is a range of pain relief options available.^[3]



Osteoarthritis

RHEUMATOID ARTHRITIS:- This is a widely known inflammatory disease. In RA, the synovium is inflamed owing to auto-immune attack producing stiffness, swelling, pain and deformity at the later stage. RA occurs three times more within women than men at ages ranging from 40 – 60 but rarely, children are the victims. The affected joints are arms, fingers, wrists, knees or legs. The joints are swollen due to inflammation thus felt stiffness especially after waking up in the morning. If touched, patients feel tenderness showing red or puffy colours at the affected areas. Patients often feel tired and experience weight losses. The disease can strike at several places simultaneously spreading from smaller to the larger joints; like wrists, ankles and feet to elbows, knees, hips, necks or shoulders.[1]



Rheumatoid Arthritis

GOUT ARTHRITIS:- This is a painful condition that happens when the body can't get rid of a natural substance called uric acid. The excess uric acid forms needle-like crystals in the joints that cause marked inflammation with swelling and severe pain. Gout is a type of inflammatory arthritis that can cause painful swelling in joints. It typically affects the big toe, but it can also affect other joints in the body. Joints affected by gout can become red and hot. The skin may also look shiny and can peel. It's caused by having too much urate, otherwise known as uric acid, in the body. We all have a certain amount of urate in our body. However, being overweight or eating and drinking too much of certain types of food and alcoholic drinks can cause some people to have more urate in their bodies. The genes you inherit can make you more likely to develop gout. If it reaches a high level, urate can form into crystals that remain in and around the joint.[3]



Gout Arthritis

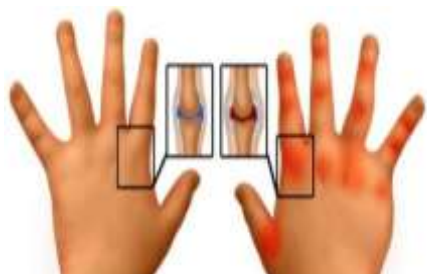
LUPUS ARTHRITIS (LA):- It is a systemic autoimmune disorder affecting nearly 1.5 million people in the US alone. Almost 90% of the lupus patients suffer from joint and muscle pain and about 35% of them bear LA. Occasionally fluid accumulates at the swelled joints. Besides serious damages, LA creates deformities and discomforts but does not attack the neck or spine. Areas far away from the body are mostly affected eg, fingers, wrists, knees, feet, toes, elbows and hands. The effect of LA is symmetrical, for example, attacking identical joints on both sides of the body. There can be many symptoms of lupus. It's possible for the heart, lungs and other organs of the body to be affected.[1] Joint pain in lupus can move around from one joint to another. Lupus can be difficult to diagnose, as it can cause many different symptoms which often appear like other conditions.[3]



Lupus Arthritis

CHILDHOOD ARTHRITIS / JUVENILE ARTHRITIS:- Arthritis in childhood can cause permanent damage to joints, and there is no cure. However, remission is possible, during which time the disease remains inactive. It may be due to immune system problems.[6] Arthritis in children is called childhood arthritis or juvenile arthritis. The most common type of childhood arthritis is juvenile idiopathic arthritis (JIA), also known as juvenile rheumatoid arthritis. Childhood arthritis can cause permanent physical damage to joints. This damage can make it hard for the child to do everyday things like walking or dressing and can result in disability. Although there is no cure, some children with arthritis achieve permanent remission, which means the disease is no longer active. Any physical damage to the joint will remain. Signs and symptoms include: Joint pain, Swelling, Fever, Stiffness, Rash, Fatigue (tiredness), Loss of

appetite, Inflammation of the eye, Difficulty with daily living activities such as walking, dressing, and playing.



Juvenile Arthritis

ANKYLOSING SPONDYLITIS (AS):- It is also regarded as an inflammatory autoimmune disease of the spinal joints or between spine and pelvis. The inflamed joints perpetuate excruciating pain that increases with time. Along that course, the spine experiences stiffness due to the fusion of bones. The exact cause remains unidentified but suspicion points it to be genetic. The disease affects more male than females and often starts at the ages of 20 – 40. The pain and stiffness are severe at night or morning but subsides during the day with the start of physical activities. Patients lose mobility of the lower spine and cannot expand their chest properly for taking a full breath.[1] In this condition, in response to inflammation around the spine, the body can create more of the mineral calcium. This mineral is normally used by the body to make bones strong. However, in ankylosing spondylitis the extra calcium can make new bits of bone grow in the spine, and this will cause pain and stiffness.[3]



Ankylosing spondylitis

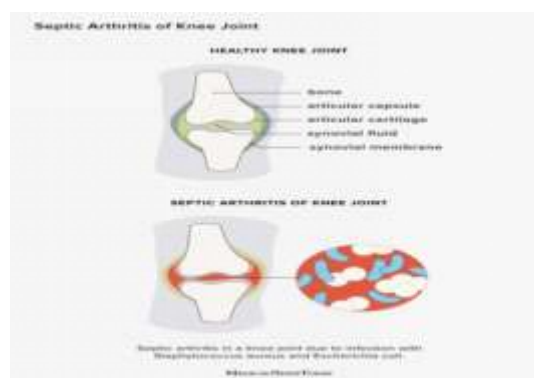
PSORIATIC ARTHRITIS (PA):- Psoriatic arthritis is an auto-immune condition. It is also a type of spondyloarthritis. The body's immune system can cause painful swelling and stiffness within and around joints, as well as a red scaly skin rash called psoriasis. The rash can affect several

places in the body, including the elbows, knees, back, buttocks and scalp. It is also common to have severe tiredness, otherwise known as fatigue. Disease modifying anti-rheumatic drugs (DMARDs) and biological therapies can treat the cause of the inflammation in joints. There is also a variety of treatments, such as creams and medications, for psoriasis. Psoriatic arthritis usually affects people who already have psoriasis. However, some people develop arthritis before the psoriasis. It's possible to have arthritis but no psoriasis at all. This condition can affect people of any age, but tends to affect adults.[3]



Psoriatic Arthritis

INFECTIOUS ARTHRITIS (IA) :- IA arises due to infection inside the synovium caused by bacteria, fungi or viruses. If patients are already suffering from any arthritis, they would be prone to it which then synergizes the sufferings further. It might be the cause why patients with arthritis often become the prey to infection thus worsening the situation more. But IA affects single joint only. [1] Infectious arthritides are a set of arthritic conditions caused by exposure to certain microorganisms. In some instances the microorganisms infiltrate the joint space and cause destruction, whereas in others an infection stimulates an inappropriate immune response leading to reactive arthritis. Typically caused by bacterial infections, infectious arthritis may also result from fungal and viral infections.



Infectious arthritis

CAUSES OF ARTHRITIS:- Different types of arthritis have different causes. For instance, gout is the result of too much uric acid in your body. But for other types of arthritis, the exact cause is unknown. You may develop arthritis if you:

- Have a family history of arthritis.
- Have a job or play a sport that puts repeated stress on your joints.
- Have certain autoimmune diseases or viral infections.
- An injury, which can lead to degenerative arthritis.
- An abnormal metabolism, which can cause gout and calcium pyrophosphate deposition disease (CPPD).
- A genetic inheritance, which can lead to developing osteoarthritis.
- An infection such as Lyme disease, which can trigger arthritis symptoms, Autoimmune Disorders
- Muscle Weakness.[9]

RISK FACTORS FOR ARTHRITIS: Some factors make you more likely to develop arthritis, including:

- **Age:** The risk of arthritis increases as you get older. Over time, your joints tend to get worn down. That's why the risk of developing arthritis, especially osteoarthritis, goes up with age.
- **Family history:** Some types of arthritis run in families, so you may be more likely to develop arthritis if your parents or siblings have the disorder.
- **Lifestyle:** Smoking or a lack of exercise can increase your risk of arthritis.
- **Sex:** Most types of arthritis are more common in women.
- **Weight:** Obesity puts extra strain on your joints, which can lead to arthritis.
- **Injuries:** They can cause joint damage that can bring on some types of the condition.
- **Obesity:** Obesity is a relevant comorbidity with the potential to contribute to chronic inflammation, as a result of the accumulation in adipose tissue of pro-inflammatory immune cells such as M1 macrophages, mast cells, neutrophils and CD4+ and CD8+ T cells^[10]
- **Smoking:** The relationship between smoking and HLA-DRB1 SE alleles is a well-described gene-environment interaction with regard to the development of ACPA-positive RA.[10]

SYMPTOMS OF ARTHRITIS:- Different types of arthritis have different symptoms. They can be mild in some people and severe in others.

Joint discomfort might come and go, or it could stay constant. Common symptoms include:

- **Pain:** Pain from arthritis can be constant, or it may come and go. It may affect only one part or be felt in many parts of the body.
- **Stiffness:** Stiffness is a typical symptom. With some types, this is most likely upon waking up in the morning, after sitting at a desk, or after sitting in a car for a long time. With other types, stiffness may occur after exercise, or it may be persistent.
- **Swelling:** In some types of arthritis, the skin over the affected joint becomes red and swollen and feels warm to the touch.
- **Difficulty moving a joint:** If moving a joint or getting up from a chair is hard or painful, this could indicate arthritis or another joint problem.
- Tenderness
- Warmth
- Redness
- Decreased range of motion

About 40% of people who have rheumatoid arthritis also experience signs and symptoms that don't involve the joints. Areas that may be affected include:

- Skin, Eyes, Lungs, Heart, Kidneys, Salivary glands, Nerve tissue, Bone marrow, Blood vessels [11]

DIAGNOSIS: If you think you may have arthritis, see your healthcare provider. The provider will ask about your symptoms and learn how joint pain affects your life. Your provider will perform a physical exam, which may include:

- Assessing mobility and range of motion in your joints.
- Checking for areas of tenderness or swelling around your joints.
- Evaluating your overall health to determine if a different condition could be causing your symptoms.

Imaging exams can help your healthcare provider get a clear picture of your bones, joints and soft tissues. An X-ray, MRI or ultrasound can reveal:

- Bone fractures or dislocations that may be causing you joint pain.
- Cartilage breakdown around your joints.
- Muscle, ligament or tendon injuries near your joints.
- Soft tissue inflammation.[12]

TREATMENT: Conservative (nonsurgical) treatments include:

1. MEDICATION: Anti-inflammatory and pain medications may help relieve your arthritis symptoms. Some medications, called biologics, target your immune system's inflammatory response. A healthcare provider may recommend biologics for your rheumatoid or psoriatic arthritis. A number of different types of medication treat arthritis:

- **Analgesics**, such as hydrocodone (Vicodin) or acetaminophen (Tylenol), are effective for pain management, but do not help decrease inflammation.
- **Nonsteroidal anti-inflammatory drugs (NSAIDs)**, such as ibuprofen (Advil) and salicylates, help manage pain and inflammation. Salicylates can thin the blood, so they should not be used with additional blood thinning medications.
- **Menthol or capsaicin creams.** These creams block the transmission of pain signals from your joints.
- **Steroids**, like prednisone, help reduce inflammation but should be used cautiously and for brief periods of time.

2. NEWER MEDICATIONS

• **Leflunomide**

- It is approved for the treatment of RA. • It can be used as monotherapy or in combination with methotrexate
- MOA: (after biotransformation) Inhibitor of dihydroorotate dehydrogenase (DHODH).
- Side effects: headache, diarrhea, nausea, weight loss, allergic reactions (flu-like syndrome, skin rash), alopecia, and hypokalemia. It is not recommended in patients with liver disease (risk of hepatotoxicity)

• **Biologics**

- IL-1 and TNF- α are proinflammatory cytokines involved in the pathogenesis of RA.
 - When secreted by synovial macrophages, IL-1 and TNF- α stimulate synovial cells to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption, and inhibiting proteoglycan synthesis.
- Biologic agents can work on: TNF- α , IL-1, T-cell, B-cell, JAK

• **Tumour necrosis factor (TNF)**

- The TNF- α inhibitors (adalimumab, certolizumab, etanercept, golimumab, and infliximab) have been

shown to decrease signs and symptoms of RA, reduce progression of structural damage, and improve physical function.

- Clinical response can be seen within 2 weeks of therapy.

• **Anakinra (Kineret)**

- It is used in moderate to severe RA in patients who have failed one or more DMARDs (leads to a modest reduction in the signs and symptoms)
- MOA: is an IL-1 receptor antagonist.
- Adverse effects: it is associated with neutropenia and is infrequently used in the treatment of RA.

• **Tocilizumab (Actemra)**

- It can be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs for patients with moderate to severe RA.
- MOA: It is a monoclonal antibody that inhibits the actions of IL-6 by blocking the IL-6 receptor.
- Administration: IV infusion every 4 weeks.[13]

3. PHYSICAL THERAPY: Rehabilitation can help improve strength, range of motion and overall mobility. Therapists can teach you how to adjust your daily activities to lessen arthritis pain. It has been found that, in contrast to suggestions in the past, there are no specific foods that patients with RA should avoid. The idea that diet can "aggravate" symptoms is no longer accepted as true. Home remedies have been proven to be helpful for patients suffering from RA, although they are not as effective as DMARDs. Fish oils and omega-3 fatty acid supplements are beneficial for the short-term symptoms of RA. Cumin has been shown to have anti-inflammatory effects in patients with this disease. Calcium and vitamin D supplementation can be helpful in preventing osteoporosis.[13]

Use hot and cold therapy: Heat and cold treatments can help relieve arthritis pain and inflammation.

- Heat treatments can include taking a long, warm shower or bath in the morning to help ease stiffness and using an electric blanket or moist heating pad to reduce discomfort overnight.
- Cold treatments can help relieve joint pain, swelling, and inflammation. Wrap a gel ice pack or a bag of frozen vegetables in a towel and apply it to painful joints for quick relief. Never apply ice directly to the skin.
- Capsaicin, which comes from chilli peppers, is a component of some topical ointments and creams that you can buy over the counter.

These products provide warmth that can soothe joint pain.[14]

4. THERAPEUTIC INJECTIONS

Cortisone shots may help temporarily relieve pain and inflammation in your joints. Arthritis in certain joints, such as your knee, may improve with a treatment called viscosupplementation. It injects lubricant to help joints move smoothly.

5. NATURAL REMEDIES

- **Manage your weight:** Reducing the stress on your joints by losing weight can help:
 - improve your mobility, decrease pain, prevent future damage to your joints
- **Get enough exercise:** If you have arthritis, exercise can help you:
 - manage your weight, keep your joints flexible, strengthen muscles around your joints, which offers more support.

Good options include low-impact exercises, such as:

- Walking, Cycling, water activities, Swimming
- **Get a massage:** Massage can provide an overall sense of well-being. It may also help manage joint pain and discomfort.
- **Yoga:** For those with arthritis, yoga can help to:
 - improve physical function, improve flexibility and range of motion, help people to relax
- **Mindfulness meditation:** Mindfulness meditation involves training the mind to pay nonjudgmental attention to thoughts, emotions, and feelings in the body. This may reduce the pain that results from chronic symptoms.

6. DIET: Eating some types of food may help reduce inflammation.

- Fish, Nuts and Seeds, Fruits and Vegetables, Beans, Olive Oil, Whole Grains
- On the other hand, people living with arthritis should avoid or limit eating processed foods, foods that contain added sugar, and refined carbohydrates. These foods may actually make arthritis inflammation worse.[15]

7. SURGERY FOR ARTHRITIS: Healthcare providers usually only recommend surgery for certain severe cases of arthritis. These are cases that haven't improved with conservative treatments. Surgical options include:

- **Fusion:** Two or more bones are permanently fused together. Fusion immobilises a joint and reduces pain caused by movement.

- **Joint replacement:** A damaged, arthritic joint gets replaced with an artificial joint. Joint replacement preserves joint function and movement. Examples include ankle replacement, hip replacement, knee replacement and shoulder replacement.[13]

8. TESTS:

BLOOD TEST FOR ARTHRITIS: There is no blood test that can directly detect arthritis. But if your healthcare provider suspects gout or rheumatoid arthritis, they may order blood work. It looks for uric acid or inflammatory proteins

PREVENTION

You can lower your chances of developing arthritis by:

- Avoiding tobacco products.
- Doing low-impact, non-weight bearing exercise.
- Maintaining a healthy body weight.
- Reducing your risk of joint injuries.
- Exercise to improve movement and joint strength. Good choices include walking, swimming, bike riding, dancing, strength training and gentle stretching exercises.
- Use hot or cold treatments to control pain and swelling.
- Avoid positions or movements that put extra stress on your painful joints.
- Avoid staying in a position too long. [16]

II. CONCLUSION:-

Arthritis is a common disease and it expresses in several different forms. Among the major varieties OA and RA is seen much abundant whereas, the rests are considerably less prevalent. Concerning the pathophysiology, the disease falls into two main categories; one is mechanically driven and thus possibly arises due to wear and tear of the cartilage tissue as being the initiator which afterward creates serious inflammation inflicting a major problem at the joint. Whereas the other one, RA starts by the inherent autoimmune disorder. For treating the OA, anti-inflammatory and pain killer medications are often prescribed at higher doses. Surgery is also recommended as an ultimate option. In case of RA or other autoimmune arthritis besides relief by the pain-killers or anti-inflammatory medicines, the antibody therapy is now successfully introduced. In that course, the monoclonal antibodies raised against a peptide epitope following the sequence of docking region of TNF- α or its receptor TNF- α -R are used.

Notably, by neutralizing the cytokine's action can efficiently arrest the progress of RA.

REFERENCES

- [1]. Sankar P. Mitra Ph.D. Arthritis : Classification, nature and causes - A Review. AJBBL, Published: 2013; 2(3); 01-19.
- [2]. Liana Fraenkel, Joan M. Bathon, Bryant R. England, E. William St.Clair, Thurayya Arayssi, Kristine Carandang, Kevin D. Deane, Kent Kwas Huston, Gail Kerr, Iris Navarro-Millán, Reza Mirza, Pascale Schwab, Namrata Singh, Marat Turgunbaev, Amy S. Turner, Sally Yaacoub,et.al. American College of Rheumatology guideline for the treatment of rheumatoid arthritis, arthritis care and research. 2021; 73(7); 924–939.
- [3]. Gupta BM, Mueen Ahmed KK, Ritu Gupta. Arthritis Research in India:A Scientometric Assessment of publications output during 2007-16. SciFed Journal of Orthopedics & Rheumatology, 2017; 1(1); 1- 10.
- [4]. Jacqueline Bullocka Syed A.A. Rizvib Ayman M. Salehc Sultan S. Ahmedd Duc P. Doe Rais A. Ansarid Jasmin Ahmed. Rheumatoid Arthritis: A brief overview of the treatment. Mini review.2018; 27; 501–507.
- [5]. Vikrant Arya, Vivek Kumar Gupta, Ranjeet Kaur. A review on plants hasving anti-arthritic potential. International Journal of Pharmaceutical Sciences Review and Research. 2011; 7 (2); 131-134.
- [6]. Yannick Degboe , Sebastiaan J. Vastert , Berent J. Prakken and Iain B. McInnes. How does age determine the development of human immune-mediated arthritis.Nature Reviews Rheumatology. 2022; 18; 501-512.
- [7]. Yoshiya Tanaka. Rheumatoid Arthritis.Inflammation and Regeneration. 2020;1-8.
- [8]. Soumya G Rao, Pranav Bantval and Rishi Chiniga. The efficacy of topical curcumin5% gel for knee Osteoarthritis. American Journal of arthritis.2021; 5(1); 1-6.
- [9]. JunSoo Ro , Se Hee Kim , Hae-Rim Kim , Sang-Heon Lee & Hong Ki Min. Impact of lifestyle and comorbidities on seropositive rheumatoid arthritis risk from Korean health insurance data. Scientific Reports. 2022; 1-8.
- [10]. Sharon L. Kolasinski, Tuhina Neogi, Marc C. Hochberg, Carol Oatis, Gordon Guyatt, Joel Block, Leigh Callahan,et.al. 2019 American College of Rheumatology /arthritis foundation guideline for the management osteoarthritis of the hand,hip and knee. American College of Rheumatology. 2020; 72(2);220–233.
- [11]. Jaana T. Joensuu, Saara Huoponen , Kalle J. Aaltonen , Yrjö T. Kontinen, Dan Nordström, Marja Blom. The cost effectiveness of biologic for the treatment of Rheumatoid Arthritis : A systamatic review.PLOS ONE. 2015; 1-27.
- [12]. Howard Birnbaum, Crystal Pike, Rebecca Kaufman, Maryna Maynchenko, Yohanne Kidolezi & Mary Cifald. Societal cost of rheumatoid arthritis patients in the US. 2009; 26 (1); 77-90.
- [13]. Thomas Christian Keller Dino Samartzis Francis H. Shen C arthritis. Encyclopaedia Britannica. 2022; 1-9.
- [14]. Nancy Carteron, M.D., FACR. What are the causes and types of arthritis? Medical News Today. 2022; 1-17.
- [15]. Gabriel SE, Crowson CS, Campion ME, Direct medical costs unique to people with arthritis. J. Rheumatol. 1997; p719 – 725 Vol. 24 (4).
- [16]. Grossman JM. Lupus arthritis. Best Pract. & Res. Clin Rheumatol. 2009; p495 – 506 Vol. 23.
- [17]. Lee JE, Kim IJ, Cho MS, Lee J. A Case of Rheumatoid Vasculitis Involving Hepatic Artery in Early Rheumatoid Arthritis. J Korean Med Sci. 2017 Jul; 32(7): 1207–10.
- [18]. Sabatini M, Rolland G, Leonce S et al. Effects of Ceramide on apoptosis, proteoglycan degradation and matrix metalloproteinase expression in rabbit articular cartilage. Biochem. Biophys. Res. Comm. 2000; p438 – 444 Vol. 267.
- [19]. Loeser RF, Shankar G, Carlson CS et al. Reduction in the chondrocyte response to Insulin like growth factor – 1 in aging and osteoarthritis. Arthritis Rheum. 2000; p2110 – 2120: Vol. 43.
- [20]. Rose NR, Bona C. Defining criteria for autoimmune diseases. Immunol. Today. 1993; p426 – 430 Vol. 14 (9).

- [21]. Jaakkola E, Herzberg I, Laiho K et al. Finnish HLA studies confirm the increased risk conferred by HLA– B27 homozygosity in Ankylosing Spondylitis. *Ann. Rheum Dis.* 2006; p 775 – 780 Vol. 65(6).
- [22]. Calin A, Garrett S, Whitelock H, Kennedy L et al. A new approach to defining disease status in Ankylosing Spondylitis. *Curr. Opin. Rheumatol.* 1994; p384 -391 Vol. 20(4).
- [23]. Mela, Giuseppe S, Cimmino, et al. (1988) an overview of rheumatological research in the European Union. *Annals of the Rheumatic Diseases* 57: 47-643.
- [24]. McGonagle D, Hermann KG, Tan AL. Differentiation between osteoarthritis and psoriatic arthritis: implications for pathogenesis and treatment in the biologic therapy era. *Rheumatology (Oxford)*. 2015 Jan;54(1):29–38.
- [25]. Piyarulli D, Koolae RM. A 22-Year-Old Female With Joint Pain. In: Piyarulli D, Koolae RM, editors. *Medicine Morning Report: Beyond the Pearls*. Philadelphia: Elsevier; 2016. pp. 65–77.
- [26]. Staheli LT. Lower extremity management. In: Staheli LT, Hall JG, Jaffe KM, Paholke DO, editors. *Arthrogyrosis: A Text Atlas*. Cambridge: Cambridge University Press; 1998. pp. 55–73.
- [27]. Louie GH, Ward MM. Changes in the rates of joint surgery among patients with rheumatoid arthritis in California, 1983-2007. *Ann Rheum Dis.* 2010 May;69(5):868–71.
- [28]. Chung KC, Pushman AG. Current concepts in the management of the rheumatoid hand. *J Hand Surg Am.* 2011 Apr;36(4):736–47.
- [29]. Smolen JS, Aletaha D, Barton A, et al. Rheumatoid arthritis. *Nat Rev Dis Primers.* 2018 8;4:18001.
- [30]. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet.* 2016;388: 2023–38.
- [31]. McInnes IB, Schett G. Pathogenetic insights from the treatment of rheumatoid arthritis. *Lancet.* 2017;389:2328–37.
- [32]. Tanaka Y, Ohira T. Mechanisms and therapeutic targets for bone damage in rheumatoid arthritis, in particular the RANK-RANKL system. *Curr Opin Pharmacol.* 2018;40:110–9.
- [33]. Tanaka Y. Clinical immunity in bone and joint. *J Bone Miner Metabolism.* 2019;37:2–8.
- [34]. Aletaha D, Neogi T, et al. 2010 rheumatoid arthritis classification criteria. *Arthritis Rheum.* 2010;62:2569–81.
- [35]. Bandyopadhyay D. Farmer to pharmacist: Curcumin as an anti-invasive and antimetastatic agent for the treatment of cancer. *Front Chem.* 2014;2:113.
- [36]. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. *Clin Geriatr Med.* 2010;26(3):355-69.
- [37]. Verbrugge LM, Gates DM, Ike RW. Risk factors for disability among U.S. adults with arthritis. *J Clin Epidemiol.* 1991;44(2):167-82.
- [38]. Eyre, S., Orozco, G. & Worthington, J. The genetics revolution in rheumatology: large scale genomic arrays and genetic mapping. *Nat. Rev. Rheumatol.* 13, 421–432 (2017).