



Rheumatoid Arthritis Pathophysiology, Animal Models and Herbal Potential In It's Treatment: A Comprehensive Overview

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ABSTRACT

Rheumatoid arthritis is a major ailment among rheumatic disorders. There are various types of arthritis. The rheumatoid joint contains a various pro-inflammatory cytokines besides IL-1 and TNF- α , which include IL-6, IL-15, IL-16, IL-17, IL-18, IFN- γ , granulocyte macrophage-colony stimulating factor, and chemokines such as IL-8, macrophage inflammatory protein-1 and monocyte chemo attractant protein-1. TNF- α blockade, IL-1 blockade, B cells therapy, IL-6 blockade and Angiogenesis blockade these are therapeutic target for its treatment. Complete Freund's Adjuvant (CFA) induced arthritis in rats, Collagen type II induced arthritis in rats, Carrageenan induced paw edema in rats, Formaldehyde induced arthritis in rats are some of the animal models performed to see the anti-arthritis potential of plants. Research in this area has explored the potential of various plants for their anti-arthritis activity.

Keywords: Anti- arthritis potential, Complete Freund's Adjuvant, Pro-inflammatory cytokines, Rheumatoid Arthritis, Therapeutic target.

INTRODUCTION

Rheumatoid arthritis (RA) is chronic, relapsing inflammatory, autoimmune disease that affects the joints. It involves numerous cell types, including macrophages, T cells, B cells, fibroblasts, chondrocytes, and dendritic cells.¹ It is characterized by inflammation of the synovial membrane, cartilage and bone destruction, pain and restricted joint movement. It is a most common inflammatory arthritis affecting approximately 1-2 % of the general population worldwide. Incidences increases with age, women being affected three times more than men.^{2,3} It often starts between ages 25 and 55. The disease is characterized by aggressive synovial hyperplasia (pannus formation) and inflammation (synovitis) results from immune response and non-antigen specific innate inflammatory process. That are untreated, leads to destruction of joint cartilage and bone.³ Expansion of the synovial lining of joints and the subsequent invasion due to pannus underlying the bone and cartilage occurs in RA. To cope the increased oxygen and nutrient requirement requires an increase in the vascular supply to the synovium. RA usually affects joints on both sides of the body equally. There are different types of arthritis. Morning stiffness, joint pain etc are some of the symptoms of the RA. Risk factors for RA are age, gender, family history etc. There are various advance techniques for diagnosis of RA. There are two important components of the immune system that play a role in the inflammation associated with rheumatoid arthritis are B cells and T cells and other pro-inflammatory cytokines, chemokines and nitric oxide are also responsible for pathogenesis of RA. There are different targets for treatment of RA. Complete Freund's adjuvant induced arthritis, Collagen type II induced arthritis are commonly used animal models to see anti-arthritis activity of a drug. There are various plants showing anti-arthritis potential

due to their phytoconstituents. Many studies are also carried out to find the exact phytoconstituents responsible for anti-arthritis activity of a plant.

GENERAL CONSIDERATION OF ARTHRITIS

RA can be classified as⁴

Palindromic rheumatoid arthritis

In which periodic monoarticular and polyarticular joint swelling occurs.

Juvenile rheumatoid arthritis

In this type of arthritis oligoarthritis are more common, systemic onset is more frequent, large joints are more affected than small, rheumatism nodules & rheumatoid factor are absent, antinuclear antibody, and seropositivity is common. It is acute and occurs at age of 2 and 4 years.

Rheumatoid spondylitis

It is a chronic inflammatory disease that affects the joints between the vertebrae of the spine, and the joints between the spine and the pelvis.

Other types of arthritis⁴

Osteoarthritis

In this type of arthritis, cartilage consists of two major components that are collagen type II and proteoglycans which are secreted by chondrocytes. Chondrocytes are synthesizing matrix and also secretes matrix degrading enzyme. In addition there is increase in water, decrease concentration of proteoglycan, decrease local synthesis of type II collagen, decrease breakdown of preexisting collagen. Increase in IL-1, TNF and nitric oxide, decrease in chondrocytes.



There are two types of osteoarthritis –

- a) Primary osteoarthritis - It occurs in elderly.
- b) Secondary osteoarthritis- It occurs at any stage.

Ankylosing spondyloarthritis

It is an inflammatory joint disease of axial especially the sacroiliac joints. Ankylosing Spondylitis is Arthritis involving the spine. It eventually causes the affected vertebrae to fuse or grow together forming vertical bony outgrowths called syndesmophytes.

Reactive arthritis

It is an episode of noninfectious arthritis of appendicular skeletal. Occurs within one month after primary infection

Psoriatic arthritis

It occurs at age between 30 and 50. It is affected to patient with psoriasis. Similar to that of RA

Infectious arthritis

This type of arthritis is serious because of rapid destruction of the joint and produces permanent deformities further it can be classified as follows-

- a) *Supportive arthritis*: It occurs because of bacterial infection-gonococcus, staphylococcus, streptococcus, haemophilus, influenza and gram negative bacilli (E. coli, S. pseudomonas)
- b) *Tuberculous arthritis*: It is chronic progressive monoarticular disease occurs in all age group.
- c) *Lyme arthritis*: This type of arthritis caused due to the infection with Borrelia burgdorferi transmitted by the ticks of the Ixodes ricinus complex.
- d) *Viral arthritis*: It generally occurs in setting of a variety of viral infection i.e. parvovirus B₁₉, rubella, hepatitis C.

Gout and gouty arthritis

It involves articular crystal deposits which are associated with a variety of acute and chronic joint disorder.

Signs and Symptoms^{5,6}

Symptoms of arthritis are gradually developed. The first symptoms are often felt in small joints, i.e. fingers and toes, although shoulders and knees can be affected early, and muscle stiffness can be a prominent early feature.

Symptoms of RA include-

- Morning stiffness that last for at least 1 hr.
- Joint pain with warmth, swelling, tenderness and stiffness of the joint after resting
- Limited range of motion in the affected joints
- Fatigue and chest pain.
- Lack of appetite leads to the weight loss
- Weakness and muscle ache.

- Low-grade fever.
- Inflammation of small blood vessels can cause small nodules under the skin, but they are generally painless.

Risk Factors⁶

Age

Since rheumatoid arthritis can occur at any age from childhood to old age, generally it occurs at older age.

Gender

RA is more commonly develop in women than men due to hormonal or reproductive influences.

Family History

Some people may inherit genes that make them more susceptible to developing RA. Peoples with specific human leukocyte antigen (HLA) gene have greater chances of developing rheumatoid arthritis. Not everyone with a HLA gene develops RA.

Smoking

Heavy long-term smoking may increase the risk of RA.

Diagnosis⁶

Rheumatoid arthritis can be difficult to diagnose. Generally laboratory testing and imaging techniques may used for diagnosis. Even after diagnosis, it is very important to determine progress of the disease i.e. benign (type 1) or aggressive (type 2) in order to treat the problem appropriately.

Blood Tests

Various blood tests can be used to diagnose RA, to determine its severity, and to detect complications of the disease.

- Rheumatoid Factor.
- Erythrocyte Sedimentation Rate Test.
- C - reactive protein (CRP).
- Anti- cyclic citrullinated peptide (anti-CCP) antibody Test.
- Anti-nuclear antibody (ANA) test.
- Tests for Anemia (low red blood cell count).

Possible RA Markers in Synovial Fluid

Analyzing the synovial fluid for the presence of type I collagen, type II collagen, matrix metalloproteinase (MMPs), Hyluronidase (HAase) are markers of joint destruction, but this is not commonly performed.

Imaging Techniques

X-Rays, Dexa scan, Ultrasound scanning, Magnetic Resonance Imaging (MRI).

PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS

The pathogenesis process may develop in the following way:-

RA starts in synovium, the membrane produces sac surrounding the joint. This sac containing synovial fluid which lubricating and cushioning joints along with that supplies nutrients and oxygen to cartilage which coats the end of bones. Cartilage is made of collagen and gives support and flexibility to joints. In rheumatoid arthritis, destructive molecules produced by an abnormal immune system response which is responsible for continuous inflammation of the synovium. Collagen is gradually destroyed, narrowing the joint space and finally damaging bone. In a progressive rheumatoid arthritis, destruction of the cartilage accelerates. Further pannus (thickened synovial tissue) formation occurs due to the accumulation of fluid and immune system cells in the synovium. The pannus produces more enzymes which destroy nearby cartilage, worsening the area and attracting more inflammatory white cells as shown in Figure 1.

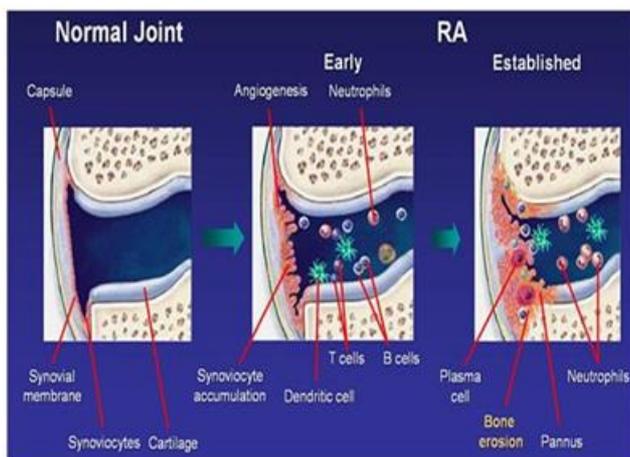


Figure 1: It shows Inflammation of Synovium in Rheumatoid arthritis.

There are two most important components of immune system i.e. B cells and T cells lymphocytes that play important role in inflammation associated with rheumatoid arthritis. This inflammatory process not only affects cartilage and bones but can also harm organs in other parts of the body.

If the T cell recognizes an antigen as "non-self," it will produce chemicals (cytokines) which cause B cells to multiply and release antibodies circulate largely in the bloodstream, recognizing the foreign particles and triggering inflammation in order to rid the body of the invasion.⁶ There are various steps involved in inflammatory responses in RA disease in Figure 2.⁷

The rheumatoid joint contains a various pro-inflammatory cytokines IL-1, IL-6, IL-8, IL-15, IL-16, IL-17, IL-18, IL-23, IFN- γ TNF- α , granulocyte macrophage-colony stimulating factor, macrophage inflammatory protein-1 and monocyte chemo attractant protein-1.

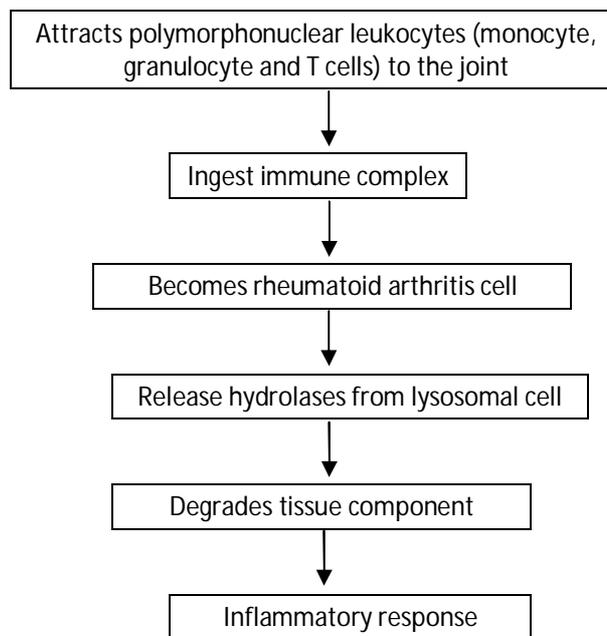


Figure 2: Steps involved in inflammation of RA

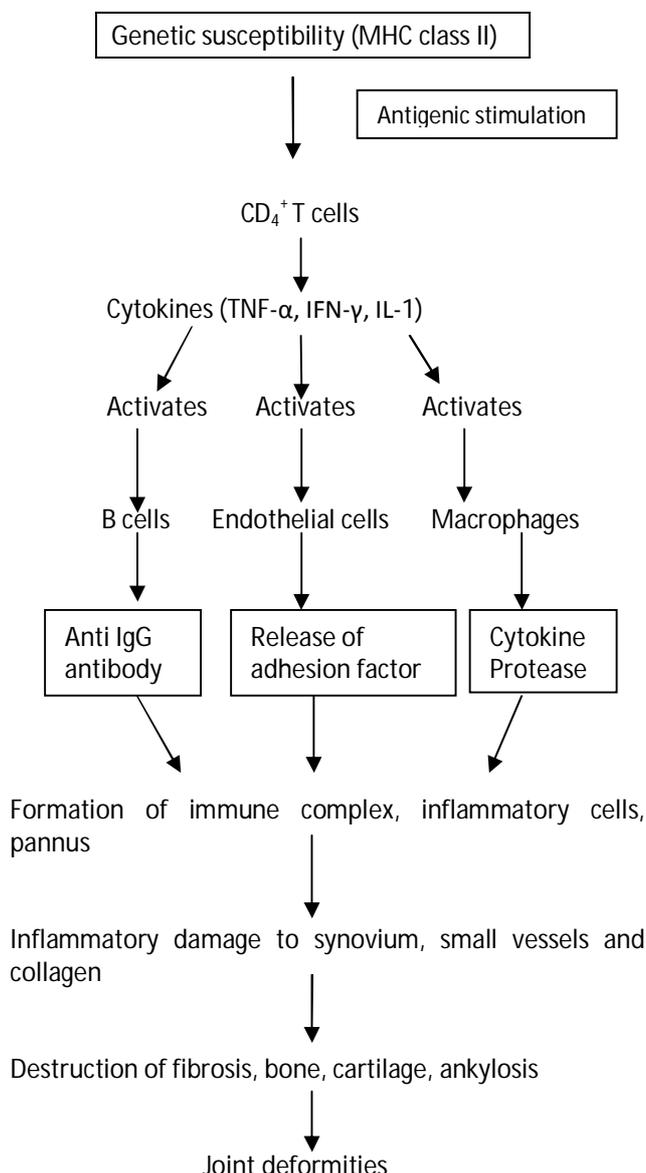


Figure 3: Steps involved in pathogenesis of RA

Anti-inflammatory cytokines, such as IL-4, IL-10, IL-11, and IL-13, and natural cytokine antagonists, including IL-1 receptor antagonist (IL-1ra), soluble type 2 IL-1 receptor, soluble TNF receptor (TNF-RI), and IL-18 binding protein are responsible for maintenance of balanced action of these pro-inflammatory cytokines, in normal physiological condition. In the rheumatoid joint, the balance swings towards the pro-inflammatory cytokines.⁸

The recruitment of inflammatory cells to the inflammatory site can be up regulated by the expression of cell adhesion molecules on endothelial cells with the help of IL-1 and TNF- α . Both IL-1 and TNF- α activate a variety of inflammatory cell types found in the synovial, including macrophages, fibroblast, mast cell, neutrophils, chondrocytes, dendritic cells and osteoclasts, resulting in the release of other pro-inflammatory mediators and degradative enzymes. Both stimulate proliferation of synovial cells leading to pannus formation. Both cytokines influence immunological activity by causing T cell and B cell activation.⁹

Step by step process in the pathogenesis of RA including various factors viz B cells, T cells, cytokines etc. which is shown in Figure 3.⁵⁻⁹

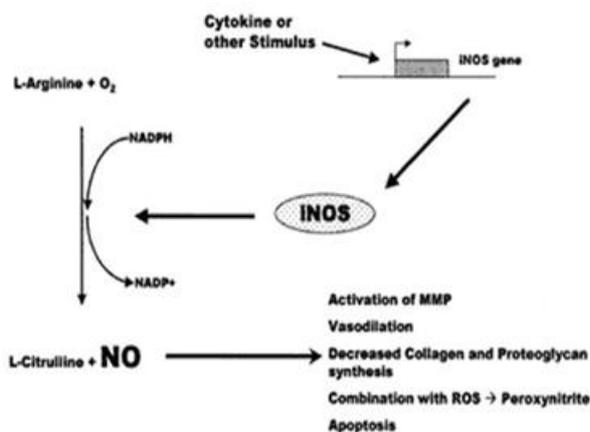


Figure 4: Nitric oxide induction by cytokines and other stimuli

Targets in Arthritis Treatment

Following sites of attacks are likely to bear therapeutic importance -

Nitric oxide

Nitric oxide (NO) has been shown to regulate T cell functions under physiological conditions, but overproduction of NO may contribute to T lymphocyte dysfunction.^{9,10}

TNF- α blockade

TNF- α spontaneously develops RA – lesion in the joints with a progressive inflammation, cellular proliferation and bone destruction. It has the capability to induce the expression of other proinflammatory cytokines i.e. (IL-1) and chemo tactic cytokines (chemokines). TNF- α

expression in the synovial contributes to disease progression.¹¹

IL-1 blockade

IL-1 is proinflammatory cytokine play a critical role in the pathogenesis of RA. IL-1 promoted cartilage and bone destruction. IL-1 blockade could be used to reduce joint inflammation and prevent progressive joint damage in RA. IL-1 is most important cytokine in joint destruction more than TNF is suggested from animal data.¹²

B cells therapy

B cells in RA synovial membrane may also secrete proinflammatory cytokines such as TNF- α and chemokines. Rheumatoid synovial membrane contains an abundance of B cells that produce the rheumatoid factor (RF) antibody. RF positive (seropositive) RA is associated with more aggressive articular disease, a higher prevalence of extra-articular manifestations, T cell activation is considered to be a key component of the pathogenesis of RA. Recent evidence indicates that this activation is critically dependent on the presence of B cells.¹³

IL-6 blockade

Among the major proinflammatory cytokines, IL-6 plays a pleiotropic role both in terms of activating the inflammatory response and osteoclastogenesis. IL-6 is expressed in a large proportion of cells in rheumatoid synovial tissue. IL-6 is an important proinflammatory cytokine and is importantly involved in the pathogenesis of RA. Significant improvement in signs and symptoms are due to blocking of IL-6 receptor.¹⁴

Angiogenesis blockade

Angiogenesis is a formation of new blood vessels. It considered as key factor in the formation and maintenance of the pannus in RA to cope up with the increased requirement of oxygen and nutrients. Targeting blood vessels in RA may be an effective therapeutic strategy. Disruption of the formation of new blood vessel is not only to prevent delivery of nutrients to the inflammatory sites but also lead to vessel regression and reversal of disease. Vascular endothelial cells (VEGF) are a pro-angiogenic factor has central involvement in the angiogenic process in RA.¹⁵

Antiosteoclastogenesis

The melanocortin-receptor type 3 (MC3) pathways, involved in antiosteoclastogenesis, hence this receptor is a novel target for the development of therapeutics for arthritis.¹⁶

Tyrosine kinase

In RA, macrophages, neutrophils, T cells and B cells infiltrate the synovium and produce cytokines, chemokines and degradative enzymes that promote inflammation and joint destruction. The synovial lining expands owing to the proliferation of synoviocytes and

infiltration of inflammatory cells to form a pannus, which invades the surrounding bone and cartilage. Many of these cell responses are regulated by tyrosine kinases which operate in specific signaling pathways, and inhibition of a number of these kinases might be expected to provide benefit in RA.¹⁷

Animal Models

Collagen Type II Induced Arthritis (CIA) In Rats

Principle

CIA model is standard animal model of RA. It is a complement dependent. There are three different cartilage-derived proteins are responsible for induction of arthritis in rats i.e. collagen type II, collagen type XI, and cartilage oligomeric matrix protein. To study mechanism of immune response to auto antigen which are generally involved in human disease, it is an excellent model. Induction of collagen arthritis in many strains of rats by immunizing them with type II collagen emulsified in Incomplete Freund's Adjuvant (IFA). After the induction of disease there is development of both cellular and humoral immune response to type II collagen, which can be passively transferred by sensitized spleen and lymph node cells as well as IgG antibodies to type II collagen. Collagen arthritis is an immunologic hypersensitivity to type II collagen. After introduction of collagen type II into the dermis, immediately captured by antigen presenting cells (APCs). In this type of disease activation of both T & B cells are antigen-specific & auto reactive. T cell and T cell-derived cytokines promote differentiation and activation of macrophages, osteoclasts and fibroblast causes development of an aggressive erosive arthritis.¹⁸ CIA is genetically controlled by expression of Class II major histocompatibility complex (MHC) molecules, specifically I-A_q and I-A_r in the mouse.¹⁹

Procedure

Type II collagen is dissolved in a 10 mM (4 mg/ml) acetic acid overnight at 4°C. After that solution is emulsified in an equal volume of chilled Complete Freund's adjuvant and mixed for 30 minutes at 1000 rpm with homogenizer. Induction of arthritis is done by a subcutaneous injection of 100 µl of emulsion (Bn CII 100 mg + CFA 100 mg) into the plantar surface of paw. On day 7 after the first adjuvant injection, rats are boosted intradermally into the base of tail with a same volume of the emulsion. Animals are dividing into 3 groups of 6 rats each. Control animals receive only the Complete Freund's adjuvant diluted with 10mM acetic acid. Standard group receive Indomethacin (10 mg/ kg) orally. Drug treatment to standard and test group started from the 18th day after chronic infection of disease and continued till 36th day. The volume of both hind paws is measured plethysmographically.¹⁸⁻²⁰

Complete Freund's Adjuvant Induced (CFA) Arthritis In Rats

Principle

Freund's complete adjuvant induced arthritis in rat model is the best and most widely used experimental model for arthritis. Both MHC-I and non-MHC II are contribute to susceptibility to CFA induced arthritis. It is a T cell and neutrophil dependent and complement independent helper (Th) 1 and (Th) 17 inflammatory cytokines are associated CFA induced arthritis. Increased levels of TNF α , interferon γ (INF γ), IL1, IL6 and IL17A mRNA have been detected in this type of model. This model is sensitive to anti inflammatory and immune inhibiting medicines and best for the study of pathophysiological and pharmacological control of inflammation process as well as for the evaluation of anti-nociceptive potential of drug. CIA is not joint-specific but is associated with granuloma formation in various organs and tissues, such as the spleen, liver, bone marrow, skin and eyes.^{18, 19}

Procedure

Animals are randomly divided into five groups of six animals. Group I served as controlled received normal saline. Standard and test groups are further divide into two sections of treatment i.e. Prophylactic (P) group (before induction of disease) and therapeutic (T) group (after induction of disease). Group II (P) and Group III (T) are standard group received Indomethacin (10mg/kg p.o.) , Group IV(P) and group V (T) are test group received the test drug¹⁶. On day zero animals are injected into the sub plantar region of the left hind paw with 0.1 ml of complete Freund's adjuvant (FA). This consists of 6mg Mycobacterium butyricum suspended in heavy paraffin oil by through grinding with mortar and pestle to give a concentration of 6mg/ml. Drug treatment is started from the 14th day i.e. from the day of adjuvant injection and continued till 28th day. The paw edema and joint thickness is measured on 7th, 14th, 21st and 28th day by using digital vernier caliper or plethysmometer. The mean changes in injected paw edema and joint thickness with respect to initial paw volume and joint thickness, are calculated on respective days and % inhibition of paw edema and joint thickness with respect to untreated group are calculated using following formula.

Inhibition in paw edema / joint thickness= $100 \times (1 - V_t / V_c)$

V_c = Mean paw edema volume/ joint thickness in control group

V_t = Mean paw edema volume/ joint thickness in the drug treated group

In radiological analysis, radiographs are taken by using X-ray apparatus. X-rays are taken at the joint of hind paw of the animal for evaluating the bone damage before sacrificing the animal. In histopathological analysis, the ankle joint of rats are removed and separated from the surrounding tissues. To examine the histopathological



changes during the experimental period in all the groups under the light microscope, the joints are fixed in 10 % formalin and decalcified, sectioned and finally stained with eosin and hematoxyline.²¹⁻²³

Carrageenan Induced Paw Edema In Rats

Principle

Carrageenan (CRR), a sulphated polysaccharide, is most commonly used in pain models. CRR produces acute and chronic inflammatory responses. The acute response appears to be similar to rheumatoid arthritis lesions, which are characterized by sustained cellular emigration. Hydrolyzed carrageenan induces inflammation by inhibiting deoxyribonucleic acid synthesis it also effects on chromium release, and cell morphology retarded cell growth and eventually caused cell death.¹⁸

Procedure

Acute inflammation is produce in all animals by sub plantar injection of freshly prepared suspension of 1% carrageenan an in 0.9 % normal saline on the left hind paw of rats. The paw volume of the tibio-tarsal articulation is measured by using plethysmometer. Increase in paw volume is determined at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6 h.²⁴ The % inhibition in paw volume is calculated by using following formula:

$$\% \text{ inhibition in paw volume} = 100 \times (1 - V_t/V_c)$$

V_t: mean paw volume in control group

V_c: mean paw volume in drug treated group.

Formaldehyde Induced Arthritis

Principle

Swelling around the ankle joint and paw of arthritic rat is considered to be due to the edema of particular tissue

such as ligament and capsule.²⁴ The development of edema in the paw of the rat after injection of formaldehyde is due to the release of histamine, serotonin and the prostaglandin like substances at the site of injection.²⁸ Formaldehyde induces arthritis by denaturing protein at the site of administration, which produces immunological reaction against the degraded product.³⁴

Procedure

Animals are divided into four groups of six animals, Group I served as controlled received 0.5% CMC, Group II received Indomethacin (10mg/kg p.o.) served as standard, Group III and IV received the test drug. Rats are injected with 0.1 ml of a formaldehyde solution in the sub planter surface of a left hind paw, on 1st and 3rd day of a test. Test and standard are administered orally once a day for 10 days. The rat paw thickness is measured daily for 10 days. The percent inhibition of mean increase in the paw edema of each group is calculated on 10th day and compared with the control. The paw edema is measured using digital vernier calipers or plethysmometer.^{25, 29, 34}

Phytoconstituents Act as Anti-Arthritic

Chemical constituent derived from plants that can modulate the expression of pro-inflammatory signals clearly have potential against arthritis. These include flavonoids, terpenes, quinones, catechins, alkaloids, anthocyanins and anthoxanthins, all of which are known to have anti-inflammatory effects. These phytoconstituents present in plant exert desired pharmacological effect on body and thus act as natural anti-arthritic agents given in table 1. Out of these, some polyphenols have been tested for the treatment of arthritis is discussed below in Figure 5.³⁸

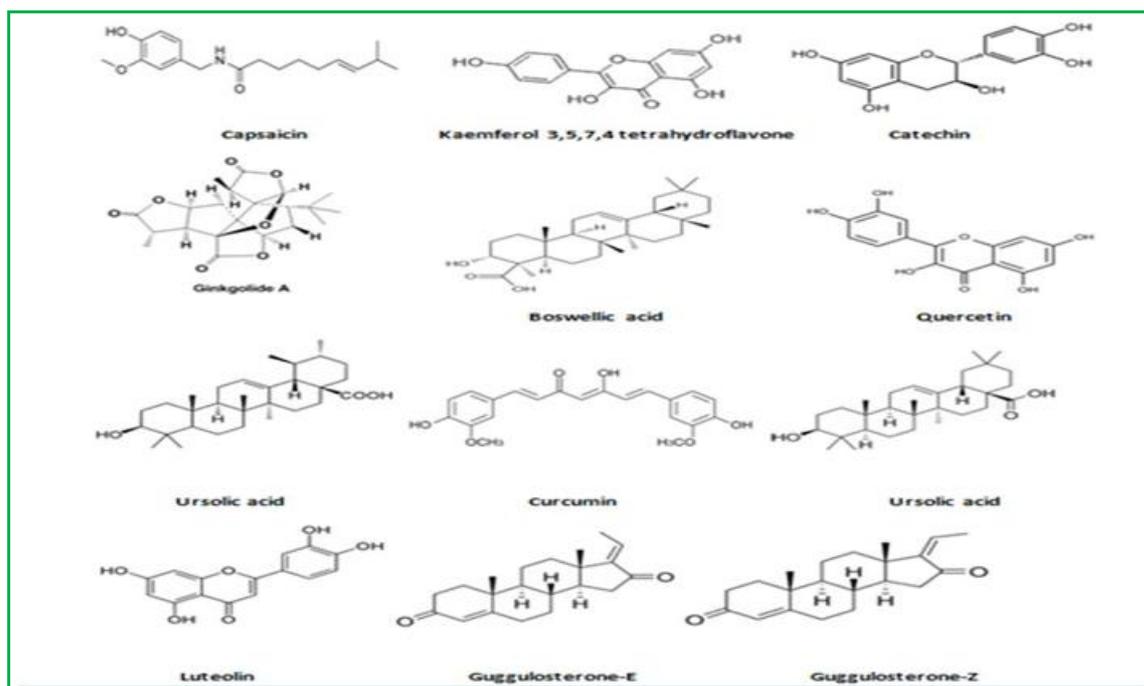


Figure 5: Various chemical constituents showing anti-arthritic activity

Table 1: Plants showing anti-arthritic activity

Botanical Name/Family	Common name	Part used	Chemical constituents	Biological activity towards arthritis
<i>Cissampelos pareira</i> , <i>Menispermaceae</i> ²²	Velvet-Leaf	Pareira roots	Alkaloid (beberine)	Anti-nociceptive, Anti-arthritic
<i>Barringtonia racemosa</i> , <i>Roxb.</i> , <i>Lecythidaceae</i> ²³	Mangrove	Fruits	Bartogenic acid	Anti-inflammatory, Anti-arthritic
<i>Curcuma longa</i> L., <i>Zingiberaceae</i> ²⁴	Turmeric	Rhizome	Curcumine, demethoxy curcumin, bisdemethoxy curcumin	Anti-inflammatory
<i>Cocculus hirsutus</i> , <i>Menispermaceae</i> ²⁵	Jal-jamni	Leaves	Cohirsinine, Jamtinine, d- Trilobine, dl-Coclaurine	Analgesic, Anti-inflammatory
<i>Aloe Vera</i> , <i>Liliaceae</i> ²⁶	Aloe	Gel from plant	Anthraquinone glycosides	Antioxidant, Anti-arthritic
<i>Camellia sinensis</i> , <i>Theaceae</i> ²⁷	Tea	Leaves	Kaempferol, Caffeine, quercetin, flavonoids,	Anti-inflammatory, Antioxidant
<i>Withania somnifera</i> , <i>Solanaceae</i> ²⁸	Winter Cherry	Roots	Alkaloids including Withanine, Withaninine, Withananinine, Pseudo- Withanine, Somnine, Somniferinine, Somniferine.	Anti-inflammatory, Antioxidant
<i>Lawsonia inermis</i> Linn, <i>Lythraceae</i> ²⁹	Henna/ Mehendi	Leaves	Flavonoids, Tannins, Phenolic compounds, Alkaloids, Terpenoids, Quinones, Coumarins	Immuno- stimulant, Anti- inflammatory, Antioxidant, Analgesic
<i>Boswellia carterii</i> , <i>Burseraceae</i> ³⁰	Frankincense	Gum-resin	Triterpenes of Oleanane, Ursane and Euphane series	Anti-inflammatory, Antioxidant
<i>Zingiber officinale</i> , <i>Zingiberaceae</i> ³¹	Ginger	Rhizome	Monoterpenes- Geranial and Neral Sesquiterpene	Anti-arthritic, Anti-inflammatory
<i>Buchanania lanzan</i> , <i>Anacardiaceae</i> ³²	Almondette tree	Kernel, Leaves, Flowers	Triterpenoids, Saponins, Tannins, Flavonoids	Anti-inflammatory, Antioxidant
<i>Coriandrum sativum</i> , <i>Apiaceae</i> ³³	Dhaniya	Seeds	alkaloids, flavanoids, tannins	Anti-arthritic
<i>Anisomeles malabarica</i> , <i>Labiatae</i> ³⁴	Malabar catmint	Leaves	Steroid, Flavonoids, Terpenoid	Anti-inflammatory, Anti-platelet, Anti-arthritic
<i>Vitex Negunda</i> , <i>Verbenaceae</i> ³⁵	Nirgundi	Leaves	Flavonoids	Anti-inflammatory, analgesic
<i>Commiphora mukul</i> , <i>Burseraceae</i> ³⁶	Guggul	Gum resin of bark	Z-guggulosteron, E- guggulosteron	Anti-inflammatory, Antioxidant
<i>Ficus bengalensis</i> Linn, <i>Moracea</i> ³⁷	Banyan tree or Barga	Bark	Flavonoids, tannins, steroids, saponin	Anti-arthritic, Anti-rheumatic, Immunomodulatory

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