Review Article

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A REVIEW ON RHEUMATOID ARTHRITIS-ITS COMPLICATIONS AND HERBAL TREATMENT

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ABSTRACT

Botanical and medicinal knowledge in India was documented and spread in magnificently illustrated herbals. But in most parts of the modern science, the source and knowledge of the old remedies have been neglected. Ancient science has presented mankind with the boon of natural remedies for various kinds of diseases. In present day, life of whole mankind has become mechanical, where people are supposed to afford many efforts both physically and psychologically. Our limbs and joints afford us much in our physical workouts and in return they are prime targets of our physical and mental stress. Irrespective of the age group, people are affected with various musculo-skeletal diseases. One among such diseases is Rheumatoid Arthritis(RA). According to survey of American College Of Rheumatology, more than 1 million Americans suffer from Rheumatoid Arthritis; about 75% of those affected are women. The present study is on reviewing complicated Rheumatic disorders and chronic degenerative diseases of musculo-skeletal system. Hence, an attempt has been made to discuss few old remedies for Rheumatoid Arthritis in modern science point of view.

Key words: Medicinal Plants, Rheumatoid Arthritis, musculo-skeletal system.

INTRODUCTION

Arthritis - It is a Greek word, Arthro – Joint; itis – Inflammation. Quite literally, Arthritis means joint inflammation. Rheumatoid arthritis is an auto immune disease. It is a chronic and also complicated systemic inflammatory disorder, affecting many tissues and organs. But flexible (synovial) joints are affected principally[1]. It is a painful condition which disables and further leads to substantial loss of proper functioning of limbs if left untreated adequately. Worldwide, there have been identified many chronic diseases which are making people disable and finally leading to tragic and sorrowful death. One among the life threatening diseases is Rheumatoid arthritis. Like other many diseases, RA is a chronic disease which if left untreated, gets aggravated. In early stages of RA, there may not be a complicated syndrome, but with its progress, the symptoms enhance and may even interfere our daily life. It is a term been using for pain in joint without any sign of associated inflammation. RA is systemic disease and the pattern of joint affected is usually symmetrical. Initially may begin in a couple of joints and attacks wrists, hands, elbows, shoulders, knees, ankles most frequently[2].

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Prevalence

It is reported that RA occurs in all the ethnic groups all over the world. About 1% of total world's population has RA, women are most often affected by RA than men. The prevalence of RA is lowest in Black Africans & Chinese where as it is found highest in Indians. It is around 1-1.5% with a female: male ratio 3:1 in Caucasians. Prevalence of RA increases with increase in age group with 5% of women & 2% of men over 55 years being affected. It is also reported that RA is uncommon in men under the age of 45 years while it is 6:1 female, excess which is shocking. Onset of RA is most frequent between ages of 40&50 but people of any age group can also be affected by RA.

Aetiology

The exact or particular cause of RA is still unknown. A combination of an abnormal auto immune system, genetic disorders, viral injection or hormonal changes triggers the raise of RA[3]. Agents such as mycoplasma,

clostrodium and also few viruses have been implicated in its aetiology. Also a genetic predisposition is strongly suspected because of certain histo compatibility markers associated with (HLA- DR4 & HLA DR-1) HLA-DR4 in the major halo type that is susceptible in most ethnic groups[4].

Genetically predisposed individual
↓
On exposure to the Infectious agent
↓
Auto immune disorder and formation of auto immune complexes with IgM anti-bodies in serum
↓
Deposition of Immune complexes in synovial membrane
↓
Initiation of self perpetuating chronic granulomatous inflammation of synovial membrane.

Ratio of Occurrence of RA in Males & Females

It is noted in many surveys that the women are more prone to RA when compared to men and ratio is as 3:1. The increased risk rate of RA in women (than in men) may be due to several factors like: Decreased levels of oestrogen in menopause nearing women, post partum conditions, low bone density, improper nutrition[5].

Risk Factors

Although, RA occurs at any age, mostly it begins between age 30 & 50. Gender: Although RA occurs at any age mostly between 30&50, female gender is risk factor of RA. Family history of RA, smoking, positive for rheumatoid factors in non-RA cases. A rheumatoid factor is an antibody directed against a specific region of the Fc fragment of the human IgG. It may be of any immunoglobulin class, though IgM anti-IgG is the rheumatoid factor most often measured in the first instance[6].

Latex Fixation Test

It is the traditional method of detecting IgM rheumatoid factor.

Latex beads are coated to human IgG
↓
Addition of patient's serum to the test system and it allows
↓
Pentameric IgM antibody to bind with IgG
↓
Flocculation of latex particles
↓
+Ve latex fixation test

Although rheumatoid factor was named as it was first identified in patients with RA. although it occurs in other conditions and in few normal adults. Hence, identification of presence of rheumatoid factor is itself not the confirmation test for RA. Its principle use as a prognostic marker; IgG rheumatoid factor has greater specificity for major rheumatic disease.

Family History

Few people may inherit the genes that make them more susceptible to developing RA, but it does not seem to increase an individual risk

Smoking

Non-genetic risk, long term smoking is considered to be a very steady risk factor for RA, particularly in patients without a family history of RA[7].

PATHO PHYSIOLOGY

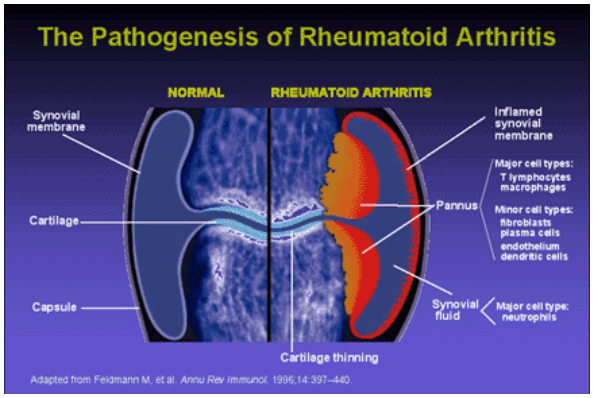

Fig 1: Pathophysiology of Rheumatoid arthritis

Initially the cellular infiltrates and fibrin exudates are accumulated in synovium leading to increase in the volume of synovial fluid. This leads to the development of inflammation which on prolongation leads to hypertrophy of synovial cells. Effusion of synovial fluid into

the joint space takes place during the active phase of the disease, there forms (pannus) fibrous tissue around the articular cartilage. Due to the adhesion of pannus, the articular cartilage is progressively eroded and destroyed loosing all its smooth texture with further progress of disease, the cartilage gets completely worn off and surface of the bone becomes raw (bony Ankylosis). In advanced cases of disease, the synovium gets distended and the ligaments those supports the joint are also stretched leading to the subluxation of the joint. The bones adjacent to the diseased joints may develop osteoporosis. Notably the tendons and muscles, the peri-articular cartilage tissues become oedematous by infiltration of cells and get ruptured spontaneously[8]. The persistence of the disease varies from patient to patient. In few, there may be only acute mild arthritic symptoms while in few others there might be chronic/severe complications due to the disease. Complete medical care is to be provided and also the precautions are to be taken to prevent the re-attack of the disease. Regular physical exercises are advised for the improvement of elasticity of tendons and ligaments which was lost because of arthritis. Also, few diet modifications are also advised to the patients

Stages of RA

RA can be divided into three different stages in the clinical point of view:

i. **Potentially reversible soft tissue proliferations:**
   In this stage, the disease is limited only to synovium. Hypertropy of synovium may be observed but no destructive changes can be observed on X-rays.
ii. **Controllable But irreversible soft tissue destructions:**
   A reduced joint space is observed on X-rays but the outline of articular surfaces is maintained normal.
iii. **Irreversible soft tissue and bony changes:**
   The articular cartilage is destroyed by the pannus and finally subchondral bone gets eroded.

Types of Arthritis

Arthritis can be divided in to two major types clinically. They are:

- Mono Arthritis
- Poly Arthritis

Mono Arthritis, is the condition in which only single joint is affected by RA, mostly knee is affected. Poly Arthritis, in this condition more than 2 or 3 joints are affected by RA. Chronic inflammatory mono arthritis persists for more than 6 weeks and 25% of untreated cases evolve to osteoarthritis.

Osteoarthritis

Osteoarthritis is also called as "wear and tear arthritis". Particular cause of it is not predicted but is suspected to be caused by the combination of several factors

- Osteoarthritis is mostly associated with ageing.
- Usually Osteoarthritis causes pain and limited motion. It is most common in knee and hip joints.

Pathologically, Osteoarthritis may be defined as a condition of synovial joints that are characterised by the focal loss of articular hyaline cartilage. As the cartilage is damaged, tendons and ligaments get stretched and this causes the pain initiation. Severe pain may be ccaused due to the eventual rubbing of bones against each other.

Oligo Arthritis

It is also caused as pauci-articular disease**.** In this type 2, 3 or 4 joints/joint groups, get affected. (Eg: Wrist, mid foot has many joints but is counted as a single site). In this type of arthritis, sequential involvement that ascends a limb i.e, initially a mid foot followed by ankle and later knee on same side. Mostly osteoarthritis is considered as the primary cause for Oligo Arthritis.

Poly Arthritis

This is the condition in which 5 or more than 5 joints are affected at once. It is symmetrical or asymmetrical poly arthritis persisting for more than 6 weeks is predicted to be viral.

Rheumatoid Arthritis

It is a chronic, systemic inflammatory disorder that affects many tissues and organs. Synovial joints are principally attacked in this type.

Juvenile Arthritis

Juvenile idiopathic arthritis is a type of persistent, inflammatory arthritis, known to begin mostly in people of age group <16 for which no particular cause is known.

Infectious Arthritis (Septic Arthritis)

It is known to be caused by bacteria, which are mostly spreading from either skin or upper respiratory tract. The synovial fluid and tissues of the joint are primarily affected. Despite many advances in areas of anti-microbial therapy, there has no improvement in cure of this type of arthritis.

Viral Arthritis

Mostly this type of arthritis is self-limiting and often presented with acute poly arthritis, fever and rashes. Poly arthritis may also occur due to Hepatitis B& C, Rubella infections.

Gouty Arthritis

It is a condition in which the excess accumulation of urate crystals in the joint and swelling of joint take place. Toe & Knee are the most common regions that present gouty arthritis**.**

Pseudo Gouty Arthritis

It is also a type of gouty arthritis but it is the condition where the inflammatory of the joint is caused due to the excess decomposition of the calcium crystals in the joints. Eg: Knee joints.

Lupus Arthritis

It is the most common manifestation of systemic lupus erythroamaticus.

Psoriatic Arthritis

It is usually presented as asymmetrical oligo arthritis.

Systemic Arthritis

This is least common type that is known to occur in any age group persons (even < 2years) are mostly affected[1]. Joints affected in Rheumatoid Arthritis

Symptoms

Morning Stiffness is the most common symptom faced by many patients even in their early stages of R.A or Osteoarthritis. The joint system that is caused in patients suffering from osteoarthritis may usually clear up within half an hour. Even the stiffening of joints after few motionless moments is also noticed[9].

Swelling & Pain

They are said to occur at least 6weeks before the actual/complete diagnosis of R.A. the joints get swollen and are felt rigid or tight while using the joint. The pain caused due to swelling of joints is most often symmetrical but may also be severe on one side of the body.

Specificity of Joints affected

RA is mostly developed in wrists, knuckles, knees and joints of the ball in the foot. Rarely RA is also shown to develop in cervical spine, shoulder, elbow, even in joints in between tiny bones in inner ear. Osteoarthritis mostly present in finger tips where RA is very rarely presented. Osteoarthritis occur maximum in hand and wrist joints, the pain in the box of thumb often radiates downwards of thumb and back over the radial wrist. The most common site for arthritis is the knee. It is also most common site for the trauma and peri-articular lesions. Pain tends to increase while going down and up the stairs. Also foot, ankle, hip joints are also most often regions those are affected by RA[10].

Rheumatoid Nodules

A small sized at about a pea sized or slightly larger nodules or lumps caused due to the inflammation of small blood vessels under the skin are noticed in 20% of people with RA. Mostly these nodules are located near the elbow, also shown up elsewhere. These nodules are said to occur throughout the course of the disease and they may turn to sore full and infected nodules rarely. Eg: If a rheumatoid nodule located in the ankle, it might experience more stress while using the ankle joint and then to a sore and infected nodule[11].

Excessive fluid in joint spaces

People with RA are reported with excess accumulation of the synovial fluid in the joint spaces. Most often the ankles accumulate more fluid and appear swollen than usual. A baker cyst felt like tumour that is caused due to the over accumulation of fluid in joint sac behind

the knee. Systemic vasculitis also seen and baker cyst is also developed in people without RA. In few people systems are also experienced in early stages of RA. Besides the pain and swelling in the joints, high fever and chills are the common signs/symptoms of juvenile arthritis in children. In this a small pink rash on skin may also be noticed[12].

X-Ray changes

Erosions of the articular or peri-articular cartilage are observed on external examination, swollen boggy joints as a result of intra-articular effusion, synovial hypertrophy and oedema of per-articular cartilage. Severe muscle spasm may also be shown subluxation or dislocation of the joints is noticed in the later stages of RA[13].

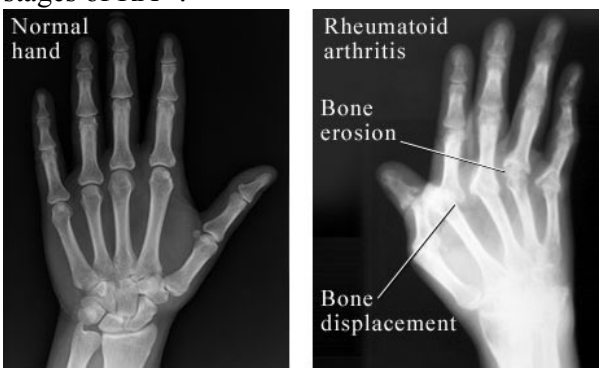

Fig 2: X-Ray changes seen in hand with RA.

Diagnosis of RA

All the above mentioned symptoms say morning stiffness, swelling of joints and pain in flexation of joints, rheumatoid nodule, any four or more of these symptoms may half reveal that R.A has been attacked. Still it is difficult to diagnose R.A as many other conditions resemble the symptoms of R.A. Blood tests and radiological examination may not reveal the changes occurred for months even after the onset of RA[14]. http://www.uptodate.com/contents/diagnosis-and-differential-diagnosis-of-rheumatoid-arthritis/abstract/7

Elevated ESR

Erythrocyte sedimentation rate, it measures the rate of sedimentation of red blood cells in a fine glass tube filled with patient's blood. Elevated ESR severely does not help in determining how active the condition within. Presence of rheumatoid factors along with the evidence of bone damage on x-rays suggests a change for progressive joint damage. Presence of R.F does not completely several RA attack but most often 80% of RA cases show positive test for rheumatoid factor[15].

C Reactive Protein

Increased CRP levels indicate the condition of active inflammation. But a medical practitioner should also consider a patient's body mass index (BMI) because obesity also leads to increased level of CRP[16].

Anti-CCP Antibody

In the combination of test for RF, CCP antibody test is known to be a best predictor for patients to develop severe RA. The presence of CCP, cyclic citrullinated peptides help in identifying RA even before its symptoms arises. Generally, x-rays are not much helpful in detecting the early stages of RA, as the soft tissue images cannot be seen on x-rays. Also, anaemia is associated with progressive RA[17].

Synovial Fluid

Colour of SF is changed to dark pink in RA cases. Volume of SF is also quietly inclined in RA cases. Also, the blood tests should be carried out to determine the levels of liver enzymes like-Serum Alanine Transaminase (SAT), Aspartame Amino Transaminase (AST), Alkaline posphatase (ALT), γ- glutanyl transpeptidase (GGT), Total Bilirubin, Albumin, Urea, Uric acid, Creatinine, Superoxide dismutase, Glutathione Peroxidase (GSH-PX), Malondialdehyde (MDA), Xantine Oxidase (XOD), Prostaglandin in serum are carried out as many of above liver enzymes tend to increase in RA cases[18]. Despite of many allopathic drugs, there have been discovered many herbal drugs and their active phytoconstituents in treating all pronouncing diseases would wide. Also there have been discovered many herbs in treating rheumatoid arthritis, a chronic joint disease. There are many plants that have been reported with their active chemical constituents potent in treating both acute and chronic RA. Few of anti-arthritic activity reported plants namely listed below: *Aloe vera* (Lilliaceae), *Boswellia carterii* (Burseraceae), *Kalopanax pictus* (Araliaceae),

Lucas aspera (Labiatae), *Ocimum sanctum* (Labiatae), *Vitis* vinifera (Vitaceae)

Anisomeles malabarica, a medicinal plant is also one of the reported plants that has been using as the folk medicine in treatment of RA and swelling. In the essential oil of Foenicum vulgare (Apiaceae) one of the components named Anethole was a potent inhibitor of NF-KB activation in various number of *in-vitro* studies[19]. In a Carragenan induced rat paw oedema test model, the ethanolic extract of roots of *Peucedanum ostruthium* (Apiaceae) and *Coumarin ostrutin* have shown good anti-phlagostic activity[20]. Roots of Asparagus recemosus are used in treating inflammation and rheumatism[21]. A sesquiterpene lactone, Helenalin found in species Arnica and Inula of family Ateraceae, has shown anti-inflammatory activity both *in-vitro& in-vivo*[22]. A medicinal herb named *Symphytum officinale*, containing allantoin & rosamarinic acid which have anti-phlagostic activity[23].

The anti-phlagostic action of 6 tri-terpene glycosides namely; Bryonicide B,C,E & G; Cabenoside D and Bryoamaride of Bryonia docia (Cucurbitaceae) was stronger in TPA-induced mouse ear oedema model than with Quercetin reference[24]. An extract of Citrullus colorynthis (Cucurbitacceae) showed anti-inflammatory activity in a carragenan induced rat paw oedema model[25]. The inflammation was inhibited by 19 to 42% when the aqueous extract of Centarum erythreae, was topically applied in an air pouch granuloma assay model[26].

Hypericum perforatum (Hypericaceae) is one of the old medicinal herbs that is said to process the properties of wound healing, anti-rheumatic, diuretic and anti-depressant activities. IL-12 production *in-vitro* was reduced possibly by the reduction of NF-KB activation by hypericum constituent of *Hypericum perforatum*[27].

The essential oil of Rosemary, *Rosemarinus officinalis* (Lamiaceae) was used externally to treat gout. For both of its analgesic and anti-phlogetic effects, Rosemary has much value in Europe[28]. The roots of *Arphodelus allous* (Lilliaceae) contains anthraquinones which are laxatives[29].

Viscum album (Loranthaceae) posses the properties of hypotension, vasodialation, sedation, anti-phlagostic activities[30]. Eugenol, chemical constituents of Myristica fragrans (Myristicaceae) is said to posses anti-oxidant and anti-inflammatory properties and also found to inhibit the various mediators[31].

Avena sativa (Poeceae) is used to treat gout, rheumatism, liver and skin diseases in Europe. Juice of *Rubia tinctorum* (Rubeaceae) is useful to soothe joint pains and streangthen the weak bones[32]. European Pharmacopoeia has approved the willow bark extracts (Saliaceae) rarely for treating fever, headaches and rheumatic disorders. Salicin and other related glycosides of salix species are responcible for these properties. Cox-2 induced PGE2 release and the release of TNF-α & IL-1β actions were inhibited by the extracts of willow bark significantly both *in-vitro & in-vivo*[33]. All around the world many of the *Physalis* species have been using as folk medicine for treating various diseases like Asthma, Malaria, Rheumatism, Hepatitis, Dermatitis etc.,

In various *in-vivo* inflammation models, anti-phlagostic activity of *Physalis ampulata* was studied and examined and was noted that the methanolic extract of the plant shown 68% of inhibition at 200mg/kg in carragenan induced rat paw model[34]. Many of the Daphne species have been traditionally using for inflammatory problems and Daphne tangutila is used to treat chronic Rheumatism and also gout[35]. A medicinal herb of family Verbanaceae by name Verbana officinalis has been used for treating Rheumatism. Iridoids are the chief chemical components that are present in Verbana officinalis. Other important components of Verbana officinalis are Verbanoside flavonosides and triterpene acids & sterols[36]. The CO_2 extract of the plant has shown strong inhibition in carragenan induced rat paw oedema model[37].

Also there are many potent natural agents for treating arthritis. It is strongly believed that the natural agents which are plant derived and enough capable to modulate the expression of pro inflammatory signals are said to be clearly potent anti-arthritic agents. Such few anti-arthritic phyto-constituents are flavonoids, quinines, catechins, anthocyanins and anthoxanthins and all of these are also known to possess anti-inflammatory properties for many natural and synthetic agents to be a potent anti-arthritic. The commonly used turmeric,

Curcuma longa contains a yellow colouring agent within it by name 'curcumin'. It is widely used as a spice severe in India for over many centuries. In ayurveda, the Indian synthesis of medicine curcumin is well documented as a potent anti-inflammatory agent and several studies show both *in-vitro & in-vivo* suggests curcumin is t,here by potent even against arthritis.

CONCLUSION

As rheumatoid arthritis is considered as one of the major and life threatening diseases, it should be treated adequately after its prediction. Inspite of allopathic remedies, there have been many efficient herbal remedies rheumatoid arthritis which have been proved scientifically also. These herbal remedies for rheumatoid arthritis showed no complications after their use. Hence herbal medicine is finding its vast use in present day to day life.

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