ISSN PRINT 2319 1775 Online 2320 7876

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Autoimmune Arthritis: Prevalence, Pathology And Its Clinical Management

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ABSTRACT

Rheumatoid arthritis is a systemic autoimmune inflammatory disease having variable effects. Though RA occurs at any age, the most common age of onset of disease is 35 years and above, therefore predominantly affecting people of working age. Its prevalence is about 0.5% - 1% and steadily increases to 5% in women over the age of 70. RA is 2-3 times more common in females than males. About 350 million people are affected with RA worldwide. In U.S. nearly 40 million persons suffers are affiliated with RA, of these 60% are women.

Traditionally, RA treatment was mostly symptomatic with main purpose to decrease the inflammation, pain and slow the progression of the disease. Allopathic drugs which are used normally for the treatment of RA are NSAIDs (Paracetamol, aspirin) and DMARDs (methotrexate, penicillamine, gold and azathioprine) and biologics. Though effective for acute treatment, the long term use of these drugs is self-limiting due to their serious adverse effects and they are relatively non-specific in their actions.

Thus, plant-based therapeutic agents that not only slow down the disease progression with less/ no side effects but are also cost effective, continue to have scientific, social and commercial significance and appear to be gathering a momentum in health relevant areas.

Key words: Arthritis, Traditional Medicine, Toxicity, Autoimmun

1. INTRODUCTION

Rheumatoid arthritis (RA), first documented explanation was way back to 1800 and was made by Augustin Jacob Landré-Beauvais in his thesis for his medical doctorate (Landré-Beauvais,2001). RA is a long term autoimmune disease which means that the body's own immune cells like antibodies or lymphocytes attacks against own healthy substances or tissues normally present in the joints, causing pain and inflammation (Kaur et al, 2012). It is a very common disease of unknown etiology that has plagued people for centuries (Rothschild et al.,1998). Women are often affected more predominately by RA than men, the reason is still not clear but it is believed that this may be due to the effects of estrogen on the immune system. RA

ISSN PRINT 2319 1775 Online 2320 7876

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is a complex multifactorial polygenic disease and a number of risk factors like genetic and environmental factors (Alamanos.,2005) are responsible for the development of disease, which mainly affects diarthrodial joints in a symmetrical fashion. Multiple joints and other tissues in the body are affected causing inflammation and pain and subsequent cartilage and bone erosion, this will not only result in significant disability but is also associated with a reduced quality of life. Small joints are involved earlier than large joints (axial joints). In addition to this there are multiple prognostic indicators for progressive joint destruction such as rheumatoid factor (RF), anti cycliccitrullinated protein (a-CCP) antibodies, increased level of erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) which are present in early radiographic erosions, and swollen joints (Combe et al.,2007). The more numerous the unfavorable prognostic factors presented by the patient, the worse the prognosis.

Recent data shows that genetics is estimated to be involved in over 60% of total reported RA (MacGregor et al.,2000). The most significant hereditary risk factors includes class II human leukocyte antigen (HLA), which is responsible for about 30% to 50% of overall genetic propensity to RA (Imboden.,2009).

2.Prevalence

Arthritis prevalence increases with age and about 1-1.5% of the total population is affected with RA. In India the prevalence has been estimated to be 0.7%. RA is about two to three times more common in women compared to men. The high prevalence of RA in women, steadily increases with age to 5% in women over the age of 70 (Spector., 1990).

3. Symptoms of Rheumatoid Arthritis

Epidemiological data indicates that advancing age is a major risk factor for ocurance of RA, however it can occur at any age. Most of the sufferers are between 35 and 50 years of age and females are more prone than males, reason unknown (Woolf et al., 2003). RA develops slowly and gradually, symptoms are different for different patients. Moreover Joints pain, stiffness, swelling, limited mobility and occasionally warmth is the most frequently observed symptoms. All these symptoms lead to the progressive joint destruction of articular cartilage (Buckwalter et al.,2005).

ISSN PRINT 2319 1775 Online 2320 7876

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Fig 1. Synovitis of index and long finger proximal interphalangeal (PIP) joints. Swan neck and Boutonniere deformities of fingers (fromWikipedia)

4. Diagnosis of rheumatoid arthritis

The diagnosis of RA is primarily by clinical judgement and this can be supported by laboratory adjuncts.

Table 1-American College of Rheumatology (ACR) diagnostic criterion for RA

1. Morning stiffness	Morning stiffness lasting greater than 1 hour before maximal improvement
2. Arthritis of three or more joint areas	Arthritic swelling or fluid (not bony overgrowth)present in more than 3 out of 14 joints and soft tissues or joint groups.
3. Arthritis of hand joints	At least one swollen area of wrist (metacarpophalangeal [MCP], proximal interphalangeal [PIP])
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2.) on both sides of the body (bilateral involvement of PIP, MCP or MTP joints is acceptable without absolute symmetry).
5. Rheumatoid nodules	Subcutaneous nodules present over specific places like-bony prominences, extensor surfaces, or in juxta-articular regions, observed by a physician.
6. Serum rheumatoid factor	Demonstration of abnormal level of serum RF detected by a method positive in less than 5% of normal controls.
7. Radiographic changes	Radiological changes typical of rheumatoid arthritis on posterioanterior hand and wrist radiograph, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints

***A patient is diagnosed with arthritis if he/she has 3 out of the above7 criterions**

5.Therapy

The main aim of RA treatment is to achieve maximum response to treatment and decrease pain, inflammation in the joints, reinstate physical function of joints, and averting joint damage i.e. provide symptomatic relief that help the patient live as active a life as possible. There is excellent evidence that early treatment and support can control formation of synovitis by decreasing multiplication of synovial fibroblast and may slow, or even stop radiographic progression of

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, S Iss 3,Dec 2022

disease and limit the impact of RA. However, despite all the current available therapies it may be very difficult to accomplish complete remission. Some drugs focus on to relieve symptoms and others attempt to maintain functional status by slowing down the progression of the condition (Holtzman et al, 2004).

(A) Allopathic therapies

There are five main conventional drugs that are used for treatment are, Analgesics, Non steroidal Anti-inflammatory Drugs (NSAIDS), Disease-Modifying Antirheumatic Drugs (DMARDS), Glucocorticoids, and Biologics. These drugs are frequently used in variety of mixtures to attain two major objectives: relief of pain and inflammation, and slowing down the disease progression. By achieving these goals, the patient's quality of life can be improved and they can regain their independence (Davis & Matteson, 2012).

Non steroidal Anti-inflammatory Drugs (NSAIDS) such as acetylsalicylate (Aspirin), naproxen (Naprosyn), ibuprofen (Advil) indomethacin and their selective COX-2 inhibitors, such as celecoxibetc are a class of drugs used in RA for both analgesic and anti inflammatory properties. Thus, they will help to relieve the pain and stiffness while also reducing inflammation associated with RA. However, they do not have major effect on disease progression or destruction of joints (Onysko& Burch, 2012). Due to partial efficiency and their incapability to modify the disease and associated gastrointestinal and cardiac toxicity, use of NSAIDs are limited (Schaffer et al.,2006).

Unlike NSAIDs which are used for symptomatisc relief, DMARDs improve the signs and symptoms of RA as well as slow down the disease progression due to their ability to inhibit the functioning of immune system by different pathways (Gibbon et al, 2008). It includes drugs such as methotrexate (MTX), sulfasalazine (SASP), and leflunomide (LEF), gold compounds, penicillamine, hydroxychloroquine, cyclophosphamide.

In addition, a few DMARDs such as the anti-rheumatic gold-compound, auranofin, as well as the antimalarial, quinacrine, have been shown to be potent inhibitors of the induction of IL-1 and TNF- (Bondeson&Sundler., 1998).

Biologics is a term that defines the new class of drugs that target specifically to cytokines. Biological agents are used for patients that do not respond to DMARDs and arthritis progression is uncontrolled. They consist of either soluble antagonist receptor or recombinant proteins that act by selectively blocking specific cytokines or immune system pathways in affected joints to cause a reduction in inflammation and joint destruction such as TNF-α inhibitors (etanercept, infliximab) and the IL-1 receptor antagonist, anakinra. They are usually taken in monotherapy or in combination with methotrexate or sometimes with other DMARDs, can enhance their efficiency and reduce the negative side effects they cause.

(B) Alternative therapies

Although highly effective, long term use of all the available allopathic drugs is associated with classical adverse effects, including gastric ulcer and cardiovascular complications, skin rashes

ISSN PRINT 2319 1775 Online 2320 7876

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etc. The growing interest in treatment of various diseases by use of herbal medicines over conventional therapy could be due to conventional therapies and medicines proving to be ineffective or inadequate and also reported to have severe side effects (Borashan et al. 2009). Consequently, there is evidence which shows that persons who are suffering with RA switch their treatment strategy from allopathic to herbal medicines. Over 60–90% of Americans used Complementary and Alternative Medicine (CAM) suffering from chronic pain, as in RA. However, despite the increasing popularity and usage of herb based products among the peoples worldwide, the major drawback of their use is the insufficient information regarding their mechanisms of action and objectivity in evaluating efficacy (Rao et al.,1999). Thus, there is a dire need to investigate the mechanistic aspects of action by which some plants afford their therapeutic potential, if any, for providing newer and safer treatment options with minimum side effects.

Medicinal plants are one of the valuable blessings of nature for the humans, especially for livelihood of poor communities and tribal races all over the world (Ambastaet al.,2016). Herbal medicines provide great prospect in health care and are basis for diverse traditional medicine systems worldwide. In the current scenario about 25% are herbs in currently used crude drugs and another 25% are chemically modified natural products (Ernst.,2000). According to report published by WHO the demand for medicinal plants based drugs is approximately US $14 billion per year, which is likely to increase at the rate 15% to 25% annually and expected to reach approximately 5 trillion US Dollars in 2050 (Kala et al., 2005). In India, medicinal plants related trade is estimated to be approximately 1 billion US Dollars per year. WHO has reported that about 80% of world population uses medicinal herbs for some aspect of primary health care, thus resulting in abrupt increase in demand of herbs (Kala.,2005). India has rich biodiversity of medicinal plants which are in use very commonly even today. Till date more than 2000 plants of medicinal value are cited in traditional systems of medicine (Calder.,1996). In Ayurveda it is classified as a rasayana (group of plant derived drugs) is a special type of treatment that improve overall physical and mental health and put off diseases by rejuvenating the body. In India people use herbal drugs regularly as home remedies, spices as well as health foods or also as drugs prescribed in traditional system of medicine. **Thus, being a rich source of compounds/molecules with therapeutic potential, development of plant-based therapeutics or their derivatives have clinical, social and commercial relevence and appears to be relevant in health areas.**

Herbal drugs in the treatment of RA

Due to unavailability of effective pharmacotherapy capable of bringing back the original form of the damaged cartilage/synovial tissue, and limitation of current conventional therapy, herbal remedies and dietary supplements provide an alternative approach for novel, safe and effective treatment for arthritis. Herbal medicines are used for the treatment of various inflammatory diseases since long to combat disease (Mobasheri 2012). Historically herbs have always been a

ISSN PRINT 2319 1775 Online 2320 7876

 UGC CARE Listed (Group -I) Journal Volume 11, S Iss 3,Dec 2022

rich source of a large variety of therapeuticaly active compounds, which led to the discovery of number plant-derived drugs. Hence, herbal medicines provide a substitute with good efficacy and professed less/nil toxicity in the treatment of disease, specifically for non responders to conventional therapy (long et al 2001). Herbal therapy occupies a large portion of alternative therapy. A number of herbs with naturally occurring immunomodulatory, anti-inflammatory and anti-arthritic efficacies have been studied world over and their usages have been validated. Some of them are listed below-

(I) Indian shallaki *(Boswelliaserrata*Linn)

Boswelliaserrata is actively grown in India, Middle East, and Northern Africa. In India it is specifically found in Madhya Pradesh, Bihar and Gujarat. Extract of *Bswelliaserrata* is shown to have anti-inflammatory and anti-arthritic properties in animal model of arthritis. In adition β – boswellic acid is most active component of *Boswelliaserrata*, which has reported to have anti-arthritic, anti-inflammatory and anti-atherosclerotic activities.

(II) Harshingar *(Nyctanthesarbortristis*Linn)

Since centuries it has been used widely as a decoction for the treatment of arthritis and sciatica in Indian traditional system of medicine. Hydro alcoholic leaves extract of *Nyctanthes* has been shown to possess antiinflammatoy activity by reducing production of inflammatory cytokines in experimental arthritis.

(III) Saffron *(Crocus sativus Linn)*

Commonly known as Saffron (Iridaceae), is used in folkflore system of medicine for various motives, found in Kashmir. It has anti-inflammatory action due to presence of active constituents such as crocetin and carotenoids in the stigma of saffron. Several line of experimental studies have shown that various extracts of saffron have ameliorating effect against chemically induced inflammation (Zamani et al.,2015).

(IV) Ginger rhizome (*Zingiberofficinale* Linn)

Ginger is the one of the most useful herbal supplement. It is native of warmer parts of Asia such as Mauritius, Taiwan and India. It is also grown in part of South America Caribbean island, Africa, Australia,.Gingerols, a non volatile chemical found in the rhizome of ginger was identified as the major active components. Ginger has various different medicinal properties like antioxidant, anti-inflammatory and anti-arthritic activity etc (Al-Nahain et al., 2014; Ramadanet al.,2013). Sesquiterpenoids, with (-) zingiberene is the major constituents, responsible for its anti-inflammatory activity.

(V) Giloy *(Tinosporacordifolia*Linn)

Tinosporacordifolia is distributed throughout the tropical Indian subcontinent such as India, Sri Lanka, Myanmar and China. The main active constituents are tinosporine, tinosporaside, tinosporide, cordifol, cordifolide and heptacosanol. It is reported to possess immunomodulatory, anti-inflammatory and antipyretic properties. It has antiarthriticpropert and shown to reduce paw volume in collagen induced arthritic rats (Sannegowda et al.,2015).

ISSN PRINT 2319 1775 Online 2320 7876

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(VI) Mulhathi*(Glycyrrhizaglabra*Linn*)*

*Glycyrrhizaglabra*is produced in countries like India, Iran, Afghanistan, China, Pakistan, Iraq, Azerbaijan and is reported to have anti-inflammatory, immunomodulatory, antitumour, antimicrobial, hepatoprotective effects etc (Chien et al.,2011). Glycyrrhizin is basically a saponin glycoside and is considered the primary active ingredient of *Glycyrrhizaglabra*. Oral treatment of methanolic extract of *Glycyrrhizaglabra* at a dose of 150mg/kg body weight for 21 days after the induction of arthritis in rats showed significant reduction in inflammation and ameliorates the arthritic related symptoms (Mishra et al.,2011).

(VII) Greentea *(Camellia sinensis*Linn*)*

Green tea is a type of tea derived from leaves of the plant Camellia sinensis. It is one of the most frequently consumed beverages in the world with no reported side effects. The phenolic compounds derived from green tea possess antiinflammatory properties. The possible disease-modifying effect of green tea on arthritis came to light when treatment of animal model of arthritis with EGCG caused significant suppression of the inflammatory mediators and cartilage destruction (Kim et al.,2008; Lee et al.,2016; Min et al.,2015). Additionally, immunoglobulins (IgG) specific to type II collagen and total IgG levels were also found to be decreased in serum and arthritic joints of green tea fed mice (Haqqi et al.,1999).

Table 2. Medicinal plants being effectively usedas a anti-arthritic and anti-inflammatory agents for thetreatment of RA

S.No	Common name	Botonical name	Part use	Refrence
1.	 Wild Celery	Kelussiaodoratissima	Whole plant	Zahra et al.,2014
2.	 Wujia	*Acanthopanaxchiisanensis*	root	Jung et al.,2005
3.	 Bel / Siriphal	*Aeglemarmelos*	Fruits	Desai et al.,2012
4.	 Pineapple	*Ananascomosus*	Fruits	Kargutkar and Brijesh,2016
5.	 Shallaki	*Boswelliaserrata*	gum oleoresin	Sengupta et al.,2011
6.	 Tea flower	*Camellia sinensis*	Used as tea	Ramadan et al.,2015
7.	 Gotu kola	*Centellaasiatica*		Sharma et al.,2014

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8.	 Camphor tree	*Cinnamomumcamphora*	Oil	Li et al.,2009
9.	 Saffron crocus	*Crocus sativus*	Flower	Ding et al.,2013
10	 Indian redwood	*Caesalpiniasappan*		Mueller et al.,2016

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