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REVIEW ARTICLE

Passiflora incarnata: Herbal Interventions in Arthritis

Suraj Shrishail Allishe*, Ashish Vilas Kulkarni, Gayatri Patil, Nisha Patil and Pooja Deshmukh
Department of Pharmacology, Dr.D.Y Patil College of pharmacy, Akurdi, Pune, Maharashtra, India.
***Corresponding Author:** Suraj Shrishail Allishe
Email: surajallishe144@gmail.com

ABSTRACT
Rheumatoid arthritis RA is an autoimmune condition with a suspected etiology, prevalence of 0.5% or more in the population and can cause disability through joint degeneration through synovitis inflammation and progressive cartilage and bone degeneration leading to slow steady rigidity or immobility. The biggest problem in the fact that presently available potent synthetic drugs are toxic and cause relapse upon cessation. Because of reduced size of existing drug molecules herbal drugs have acquired interest among RA patients. Herbal products are natural products that have in-borne medication that can heal a certain disease or ailments of arthritis symptoms. In this review the author concerns himself with updating the information about RA regarding its etiology, prevalence, and diagnosis, classification, pharmacotherapy and toxicity of orthodox anti-rheumatic drugs and the role of herbal medicines in the management of RA. Also the role, uses and toxicological profile of Passiflora incarnate linn. The present review is also interested in the medicinal. Plants which release the mediators of inflammation and for treating RA.
Keywords: *Rheumatoid arthritis, Pathogenesis, Prevalence, Classification of medicinal plants, toxicological profile.*

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INTRODUCTION

Inflammation of the joints, which can result in pain, stiffness, and swelling, is referred to as arthritis. It comes in different forms, such as gout, rheumatoid arthritis, and osteoarthritis, and it affects people of all ages and backgrounds. Rheumatoid arthritis is an autoimmune disease in which the body's immune system targets the joints, whereas osteoarthritis, the most prevalent type, usually arises from gradual wear and tear on the joints.[1] Although the symptoms might vary greatly, joint discomfort, decreased range of motion, and occasionally systemic symptoms like exhaustion are common. Depending on the kind, arthritis can have a variety of causes, but genetic, environmental, and lifestyle factors are frequently involved. Medication, physical therapy, lifestyle modifications, and occasionally surgery are all options for managing arthritis. A customised treatment plan and early diagnosis can help people effectively manage their symptoms and preserve their quality of life. As a chronic joint disease, RA typically affects the elderly and may be a leading cause of disability worldwide. 40 out of 100,000 RA cases are reported each year, representing a prevalence of about 1% of the global population. Because women are more susceptible to the disease than men, the gender ratio affected by RA is 2:1–3:1 (female: male) [2]. Inflammatory destruction of the spine and related joints, chronic synovitis, tissue damage, and inflammation are the disease's end results, which eventually cause significant functional decline, an increased risk of accidents, and early death. Furthermore, the cause of the elevated death rate also includes extra-articular symptoms such as infections, vasculitis, lymphoproliferative diseases, and involvement of the lungs, heart, and kidneys [3]. According to the primary cytology of comprehensive frailty, this illness ranks 42nd. These days, patients with RA have a higher chance of developing cancer. Although the precise pathophysiology of RA is yet understood, environmental, genetic, and immunological variables have all contributed to an increase in the development of RA that is clinically significant.[4] The two main environmental risk factors for RA are alcohol consumption and smoking, which can raise a person's risk of developing RA by 40 times compared to those who are not exposed.

Both innate and adaptive immunity contribute to immunological factors and have a significant role in the development of RA. Additional risk factors for RA include high intakes of sugar, sodium, red meats, proteins, and iron; low intakes of vitamin D and antioxidants; birth weight; breastfeeding; and place of birth.[5]

PATHOGENESIS OF ARTHRITIS

As a matter of fact, despite the fact that RA is considered to be one of the most prevalent IAs and has been widely used as an animal model for ADs for decades, an unequivocal explanation of the pathogenesis of this disease is still lacking. There is sufficient evidence to point to a biological link between the genetic and environmental contributions towards the development of RA. Immunological derangements, inflammatory processes, genetic and epigenetic changes, and metabolic contributes to the pathogenesis of RA, which can be discussed here. [6]

Role of autoantibodies in Immunological basis of RA

The autoantibodies may be detected in a RA patient several years before the clinical sign of the illness, but the most common used in clinical practice is known as ACPA. The broken immune tolerance in RA patients is attributed to the fact that PADI is implicated in the posttranslational modification of arginine or glycine residues of normal proteins to citrulline.[7] Notably, citrullinated proteins have a higher affinity to HLA-DR and are more immunogenic than the non-methylated proteins. Citrullinated proteins have been also found to run abundant in neutrophil extra-cellular traps (NETs).[8] Our data suggest increased levels of circulation and synovial fluid NETs in RA patients as compared to healthy controls. NETs formation leads to the chronic inflammatory environment in joints. In the present investigation, exposure of FLS to citrullinated proteins derived from NETs can internalise through RAGE TLR9 which in turn leads to an inflammatory change in FLS with up regulation of membrane MHC II molecules. ACPAs serve not only as some special biomarkers reflecting the immune alterations of RA but also as the key regulatory factors of joint inflammation.[9] Moreover, in a predictive manner, ACPAs are connected with bone erosion and CVD. Beyond ACPAs and RFs, anti-carbamoyl peptide autoantibody, autoantibodies to cartilage specific antigens, such as type II collagen or gp39, and autoantibodies to extracellular antigens, GL-6-PI or GNRP-A2, are also significantly implicated in the development of new-onset and progression of RA. [10]

Prevalence of arthritis

Arthritis is also a major health challenge in India since it has become prevalent among a large number of citizens. Key findings include:

- It is estimated that there are about 180 million arthritis sufferers in India and out of these, OA affects about 60% of the patients. [11]
- India has 5-10 million RA sufferers, which is between 0.34% and 0.75% of the population. And notably, unlike many other causes of end-stage renal disease, it is more frequent in women rather than men. [12]

I] Regional Variations:

Surveys have indicated that there is regional variation in the incidence of arthritis; these have pointed out that rural areas present some remarkable cases of arthritis[13]

II] Economic and Social Impact:

Arthritis leads to poor quality of life, disability and substantial health and economic burden in terms of both, expenditure for health care and lost production. [14]

III] Age and Risk Factors:

OA is widely known to predominate in persons over 50 years of age, whereas RA and other inflammatory types of arthritis might develop at an earlier age. [The Indian Rheumatology Association] Some measures applicable to arthritis in India are population based epidemiological studies known as COPCORD, risk factors awareness and better access to rheumatology service. If you want more details about particular types and how to manage them, you can look up to the Indian Rheumatology Association or Map My Genome[15]

Advances in the treatment:

I] a historical overview

It was not long ago, until the 90s, when a diagnosis of rheumatoid arthritis indicated deteriorating functional status and joint destruction. There were few treatment choices, and many patients were treated with chronic glucocorticoids or NSAIDs, or both, with their side effects. Anti-rheumatic drugs, or DMARDs as they came to be termed in recognition of their capacity to slow down the progress of joint damage, became available from the 1970s and 80s. Possessing low efficacy and high toxicity, some of the first examples of DMARDs, gold salts and penicillamine,[16] have rather broad and partially understood

modes of action, and they are used only rarely nowadays. Other drugs like csDMARDs remained a role for patient with rheumatoid arthritis once joint damage was recognized and thus the perceived risks associated with disease modification were justified. Disease remission was rare. [17]

II] Early Disease Treatment

Efforts to quantify the inflammatory burden in RA (rheumatoid arthritis) finally culminated into the formation of the DAS (disease activity score) at the start of the subsequent year, the nineties. This composite clinical index covers 44 tender and swollen peripheral joint counts, ESR [Erythrocyte Sedimentation Rate] and a patient's overall assessment of the disease activity using VAS.[18] The foundation for this idea was set up in this work wherein it was determined a window period of early rheumatoid arthritis might exist and csDMARD induced suppression of the DAS is proportional to lesser joint damage as evidenced by clinical radiographs. Whilst this strategy gained support over the next decade following during subsequent clinical trials such as the tight control for rheumatoid arthritis (TICORA) trial in the year 2004.With treatment initiated following accomplishing the AIS, indicating moderate disease activity or worse at any of the monthly assessments leading to an incremental step up csDMARD approach, the subjects in the TICORA trial provided a much superior profile over the next 18 months to standard care.[19] These studies, using the DAS or a working version, such as the DAS28-ESR (disease activity score 28 for RA with erythrocyte sedimentation rate) corroborated the aims of treat-to-target strategies in never-treated RA patients. who are managed with current treatment directives. Currently, recommendations for consensus for treat to target have become part of clinical practice and model early arthritis clinic, which is becoming popular modern treatment services. However, as will be discussed further, while debate about treat-to-target is minimal, concerns emerge regarding the DMARDs and adjunctive glucocorticoids used to achieve target and what constitutes adequate clinical remission, as well as in what order DMARDs should be initiated.[20]

III] Current Treatments

Glucocorticoids

The overall impact of glucocorticoids is therefore mainly at the genomic level since the molecules readily permeate the cell membranes, and combine with the cytoplasmic glucocorticoid receptors present in most tissues, translocating to the nucleus. These genomic pathways lead transactivation of genes encoding immune-modulatory molecules or trans-repression at nuclear factor-kappa B (NFκB) binding sites to down modulate inflammatory genes.by effectively having an impact on about 1% of the human genome, glucocorticoids exhibit extremely fast and non-selective immunosuppressive actions.[21] The high pharmacological activity of glucocorticoids has ensured sustained use in short term supplemental mode either orally or by intramuscular injections together with DMARDs in the management of early RA in attaining symptom reduction and prevention of joint destruction as recommended by many practice guidelines for the management of rheumatoid arthritis. More recently the glucocorticoid low dose in rheumatoid arthritis (GLORIA) trial comparing a low dose, 5mg/day prednisolone over two years with placebo in patients aged >65years demonstrated that glucocorticoids were beneficial for disease control However there was a higher infection rate but most were mild The potential side effects of glucocorticoids include infections, osteoporosis, cataracts, diabetes and many more pointed.[22]

CsDMARDs [conventional synthetic disease modifying rheumatic drugs]

However, csDMARDs are still the preferred first line therapy for RA, even in the light of technologic improvements and the increase in the number of therapeutic options. A number of clinical trial and observational studies directly compared the efficacy of methotrexate, the first-line csDMARD in early RA, to other csDMARD monotherapy and suggested that methotrexate has at least similar and possibly superior effectiveness, faster time to drug response, and higher treatment adherence.[23] Methotrexate monotherapy, with a short course of prednisolone, induced early sustained remission in about 40% of newly diagnosed patients., Methotrexate, therefore, serve as first-line csDMARD, apparently because other csDMARDs, which mainly include sulfasalazine, leflunomide, and hydroxychloroquine apart for methotrexate, were being used if methotrexate Hydroxychloroquinone alone should be used for patients with mild or Palindromic COVID-19 disease.[24]

Classification of Drugs used in arthritis

Table.1-Classification Of Drugs.

Disease Modifying Anti-rheumatic drugs	Adjuvant drugs	Biological Agents	TNF blocker	JAK inhibitor	Reference
Immunosuprresants:, Azathioprine, Cyclosporine, Methotrexate, Sulfasalazine, Leflunomide	Corticosteroids: Prednisolone and others	TNF inhibitors: Etanercept, Infliximab, Adalimumab. IL-1 Antagonist: Anakinra	Golimumab.	Baricitinib, Tofacitinib.	[25]

Herbal Plants Used in Arthritis.

Since ancient times, herbal remedies have been utilised to treat and manage arthritis, providing all-natural ways to lessen stiffness, discomfort, and inflammation. These are a few popular natural remedies for arthritis.

Table .2 Medicinal Plant with Their pharmacological action

Sr No	Plant Name	Biological Name	Part	Action	Reference
1	Curcumin	*Curcuma longa*	Whole part	anti-inflammatory and antioxidant	[26]
2	Gingerol	*Zingiber officinale*	Whole part	anti-inflammatory	[27]
3	Aloevera Linn Dose-	*Aloe barbadensis*	Plant	uterine tonic anti-inflammatory, diuretic, spermatogenic, laxative, purgative and fever reliever	[28]
4	Akkirakkaram	*Anacyclus pyrethrum*	Roots	Anti-arthritic, Anti-rheumatic. It gives relief in rheumatic arthritis by increasing circulation	[29]
5	cannabis	*Cannabis sativa linn*	Flower, Fruit	Anti-rheumatic, Anti-inflammatory, Anti-manic	.[30]
6	purple passionflower	*Passiflora incarnata L*	Leaves, flower	Anti-asthmatic, Anti-inflammatory	[31]
7	Alfalfa	*Medicago sativa*	Leaves	Used in treatment of osteoarthritis and rheumatoid arthritis	[32]
8	cat's claw	*Uncaria tomentosa*	**Bark**	anti-inflammatory	[33]
9	Eucalyptus	*Eucalyptus globulus*	**Leaves**	anti-inflammatory, anti-oxidant, and antitumor	[34]

Overview of *Passiflora Incarnata*

Fig .1 *Passiflora incarnata* L, Plant source – *Passiflora incarnata* L,Genus-Passiflora L. Genus-Specific Passiflora incarnate L Family - Passifloraceae

Morphological Features

A herbaceous perennial vine with eye-catching flowers and unusual three-lobed leaves that may attain a length of 6 1/2 feet or more. Though it is mostly found on the fringes of field and woods, passion flowers are increasingly showing up in many of Virginia's agronomic crops, particularly in areas that use conservation tillage.[35]

Active Substances:

Flavonoids (like Vitexin and chrysin) Alkaloids, including harmine and harmaline Glycosides Acid, caffeine.

Phytochemical

The phytochemical characteristics of Passiflora incarnata's aerial portions include the presence of a pattern of many main ingredients, including flavonoids, Indole alkaloids, cyanogenic glycosides, and maltol.

Among them, flavonoids-taking compounds are 2.5% and found with vitexin, isovitexin, orientin, isoorientin, apigenin, kaempferol, vicenin, lucenin, saponarin and, quercetin.[36]

Health Advantages and Applications:

Stress and Anxiety Reduction: Passionflower's relaxing effects on the nervous system are well documented. It is frequently used to lessen stress and anxiety symptoms. According to research, it might raise the brain's concentration of gamma-aminobutyric acid (GABA), which lowers anxiety and calms nerve activity.

Sleep Aid: Passionflower is frequently used as a natural treatment for insomnia and sleep disorders because of its calming qualities. It might make it easier for folks to fall asleep and enhance the quality of their sleep.

Alcohol Withdrawal- It has been described recently that a BZF moiety is involved concerning the multiple CNS uses of P. incarnata Linn. In by recognizing the applicability, already evidenced, of the BZF moiety in reversing the effects of withdrawal of substances such as cannabinoid and nicotine by the authors and also, the bioactive BZF moiety has been examined in mice receiving an addictive solution containing ethyl alcohol, in order to determine results of its application. mitigating the effects for alcohol dependence. The chronic administration P. incarnata preventive effects were found to be better when used with alcohol in the treatment of P. incarnata. more than the single acute treatment with P. incarnata in alcohol dependent mice. These results indicated that the treatment of P. incarnata extract could be used as a safe line of treatment or as companion to the conventional cancer treatment. Substitute for alcohol selectively as an antidyskinasie drug and for alcohol withdrawal.[37]

Discomfort Relief: According to certain research, passionflower may be able to lessen inflammation and discomfort, especially in relation to ailments like arthritis and muscular spasms.[38]

Effects of Antioxidants: *Passiflora incarnata's* flavonoids and other components have antioxidant properties that may help shield the body from oxidative stress and lower the chance of developing chronic illnesses Muscle Relaxant: Due to its modest muscle-relaxant qualities, passionflower may help treat a variety of ailments that result in tight muscles, including restless legs syndrome and muscle spasms. Support for Heart Health: According to certain studies, passionflower may have a slight hypotensive impact, which lowers blood pressure by encouraging calmness and lowering stress levels. Anticonvulsant Effects: Passionflower's ability to reduce seizures has been investigated. It has been used traditionally to treat epilepsy and is believed to have a minor anticonvulsant effect.[39]

TOXICOLOGICAL PROFILE

Despite the fact that the consumption of herbal products is considered safe, however, there are still, history of the presence of cyanogenic compounds in Despite this, the dislike of many butterflies for the Passiflora species, their toxicity can't be ruled out at higher levels. P. incarnata is mentioned as "safe herbal sedative" in the FDA of America and also, there is no any available monograph whose matter is *P. incarnata* do not speak of the toxicity of this or any contra-indication plant [40]. Since the physiological actions and the mode of CNS injury are not well understood, the recommendations are based on succeeding or failing clinical trials of treatments for those with MTBI.[mild Traumatic brain injury] relating to depressant activity have not been reported frequently, it has have been told that the P. incarnata should be used carefully when taken with other Central Nervous System depressants or stimulants A few people have vomited with this plant even in the early stages of ingestion of this plant medicinal doses[41]. While moderate doses are used as an antispasmodic or somewhat narcotic. Otherwise, side effects begin with excessive doses and include spasm. and even paralyzing in animals. Thus, it has been warned not to take Of P. incarnata with anti-neoplastic drugs procarbazine, potentially

to minimize CNS depression. The other reason is that it has neuromuscular relaxing effects of P. incarnata, have been boosted by the application of the aminoglycoside antibiotic as clindamycin.[42]

CONCLUSION

The present text provided a small approach to the RA management as well as centralizing updated information on the topic. Controlling autoimmune disease has become topical in recent years, several studies examining different forms of interventions to patients with RA. Although AL-amyloidosis remains untreatable, the disease is considered progressive and patients' quality of life is significantly improved. Proposed disease prevention and early detection programs for individuals at risk over RA, as well as disease monograph information available to the population are crucial to reducing epidemiological data. The primary strategy in managing RA is to initiate early intense drug therapy with the aim of achieving complete disease remission, if not, at least considerable decrease in signs and symptoms of arthritis.

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