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A REVIEW ON THE COMBINED EFFECT OF *Tinospora cordifolia* AND *Zingiber officinale* IN TREATMENT OF INFLAMMATION ASSOCIATED WITH RHEUMATOID ARTHRITIS

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Abstract:Rheumatoid arthritis is an inflammatory autoimmune disorder associated with the joints. It causes the eradication or destruction of the internal lining of the joints and thus reduces the synovial fluid between the joints. As a result, the individual suffers from inflammation and pain that could last long. RA is associated with inflammation and it serves as the root cause of the pain. Interplay between the genes and the environment could evoke inflammatory response. The presence of Rheumatoid Factors (RFs) in blood of an individual, act as an indicator to RA. Other factors that can be considered as the causative for the pain include lack of sleep, depression and stress. This inflammatory response prevailing in arthritic patients establishes the need for taking appropriate treatment measures. Analgesics, Non Steroidal Anti-Inflammatory Drugs (NSAID) and DMARD are in common use as medications for RA. The side effects and risk factors associated with such drugs paves a way to include plant based treatment procedures for RA. This review aims at bringing out the importance, need and potential combined effect of two medicinal plants namely, *Tinospora cordifolia* and *Zingiber officinale*, to act against the inflammation in RA patients.

Keywords:Rheumatoid Arthritis, inflammation, medicinal plants, rheumatoid factors

INTRODUCTION

Inflammation is the major visible symptom that Rheumatoid Arthritis patients face. The cause for the inflammatory response is not well known. Rheumatoid factors are those proteins that are associated with RA. Clinical tests for RA involve the detection of RFs in the blood. Higher the presence, higher is the susceptibility to RA (Vivekanand Tiwari *et al.* 2022). Rheumatoid Arthritis is the destruction of the inner lining of the joints thereby destroying and reduces the synovial fluid between the bones, causing it to rub against each other. It also involves the destruction of cartilages associated with the bones triggering the secretion of cytokines and degradable enzymes by the T cells as immune response. TNF-α, IL 1 and IL6 are the cytokines that are involved in secretion of metalloproteinase that leads to the destruction and dissolution of the joints and gradually loses its function and physical nature causing inflammation, stiffening and tenderness of joints and becomes arthritic. They act against self-cells and lead to arthritic response [36].

Rheumatoid Arthritis has become one of the most common autoimmune diseases affecting people of different age groups. This has made the daily life of individuals difficult. The occurrence of RA is deeply dependent on various factors like age, sex, environment and heredity. Smoking has also been one of the contributing factors to the increasing pace of the disease. The progressive pain associated with RA could be influenced by climatic and seasonal variations. This could lead to emotional and mental challenges in life. All together, the psychological self of being and the socio-economic aspects of life are affected. The World Health Organization (WHO) has stated that 1% of the total population of the world is affected with RA disease. Women are more susceptible to RA than men. In India, 20% of the population is arthritic. RA could also lead to other diseases like cancer, infections, diabetes, hypertension and hypothyroidism. Unemployment has also increased due to the prevalence of the disease[4].

POTENTIAL RISKS OF SYNTHETIC DRUGS

Treatment and the management of the disorder possess a challenging role since the cause of the disease is not well known and hence measures for cure are not precisely available. Various drugs prevailing in use as probable remedy for RA are having its own side effects and risk factors associated. The drugs in common use against RA include methotrexate, diclofenac sodium, leflunomide,

hydroxychloroquine sulphate and so on. These drugs are commonly recommended by doctors according to the symptoms told by the patient. They are said to cause long lasting side effects that are both known and unknown (Jim Morelli, 2022).

The goal of medications against RA is to reduce the symptoms such as inflammation, stiffening, tenderness, irritation and disability. A complete cure is unknown and thus progressive approaches on treatment methodologies have to be taken. The commonly used drugs for RA include DMARDs, NSAIDs, analgesics and glucocorticoids. Disease modifying anti-rheumatic drugs (DMARDs) is those drugs that are recommended by doctors to treat RA patients. They act on the immune system and are involved in reducing the symptoms of the disease and thereby improving lifestyles of RA patients. But, they could lead to weakening of the immune system and may also cause long term side effects that may remain unknown. Non-steroidal anti inflammatory medications (NSAIMs) help in relieving pain associated with the joints by acting against the enzyme responsible for eliciting inflammatory response. They could only function along with other drugs like steroids or analgesics. The probable side effects known after using such synthetic drugs include low blood counts, blurry vision, headache, heartburn, lung and kidney related issues, high blood pressure, diarrhoea, nausea, infections, light sensitivity, malignancy, rashes, abdominal pain and the list goes on (Annie Stuart, 2020).

Another of the drawback of the drugs available in the market is its high cost. Hence, to prevent such risks, alternative measures have to be taken for the management of the disease (Dale Kiefer, 2019**).**

MEDICINAL HERBS FOR CURE

Traditional methods and practices for disease control have been in use since time immemorial. Medicinal plants were one of the major sources of such treatments. Since synthetic and chemical drugs posses its own risk factors on individuals, the need and the demand for natural measures for cure is hence established. Plants of medicinal value are natural healers of the wide variety of diseases and disorders under prevailing existence in the society. Many of its curing efficiency have been proved by the scientific community. One of the major advantage of the usage of such plants as medicines is its free availability and low cost. They are also rich in potential phytochemicals like tannins, alkaloids, lignin, coumarins and flavanoids that are involved in treating diseases. Local communities of the community suffer from such ailments and are facing challenges from the rising costs of such commercially available synthetic drugs. Hence, formulation of medications using herbs would act as an essential means of cure for such communities [16].

PROPERTIES OF *Tinospora cordifolia* AND*Zingiber officinale*

Medicinal plants have chemicals called phytochemicals that are responsible for treatment and cure of diseases. The presence or absence of tannins, lignins, terepenoids, steroids, proteins, flavanoids, alkaloids and other such phytochemicals determine the plant's curative significance. *Tinospora cordifolia* and *Zingiber officinale* are medicinal plants having anti-inflammatory, anti-microbial, anti-stress, anti-arthritic abilities. *Tinospora cordifolia* and *Zingiber officinale* are medicinal plant in use as ayurvedic and folk medicines due to its healing properties [20].

Tinospora cordifolia commonly known as "Guduchi" or"Giloy" in Ayurveda due to its widerange ofapplications as a medicinal plant. It is a deciduous andherbaceous vine belonging to the familyMenispermaceae native to tropical regions of India. Ithas got reddish fruits and heart shaped leaves and hencethe name "heart leaved moonseed". Chemical compounds like alkaloids, terpenoids, sreroids, lignins states the phytochemical and pharmacological activity of *Tinospora cordifolia*[23].The stem extract of *T. cordifolia* is known to have anti-inflammatory effects on arthritis patients and the whole plant helps in stimulating immune system [25]. It is of wide importance in Ayurveda as a medicinal plant having anti-inflammatory, anti-diabetic, anti-toxic, anti-stress, anti-osteoporotic and wound healing effects. The whole plant can be used to stimulate immune system in elucidating immune response [27].

Zingiber officinale, commonly known as "Ginger", belongs to the family Zingiberaceae and is used both as a spice and traditional herbal medicine. It is also used for the treatment of gastrointestinal problems. Sesquiterpenes and phenolic compounds present in ginger makes it a medicinal plant against arthritis. It also contains volatile and non-volatile compounds in them. It has anti-inflammatory, anti-nauseant, anti-ulcerogenic, anti-viral and chemo-protective properties (Shyama S. Kumar *et al*, 2015).

Both *Tinospora* and *Zingiber* have anti-inflammatory properties against RA [30]. It has been found that they have been in use to reduce inflammatory pain and swelling by reducing the levels of inflammatory cytokines, COX, NO, MMPs, TNF-α and PGE2 [10, 35]. Macrophages, monocytes and neutrophils migrate and penetrate into the joints by increasing membrane permeability of joints and enter the synovial junction. These inflammatory products lead to bone damage and cause pain, swelling and stiffness of the joint. Thus, when in combination, *Tinospora cordifolia* and *Zingiber officinale* would act as satisfying and economic remedy against RA [11].

MECHANISM OF ACTION OF INFLAMMATORY RESPONSE ASSOCIATED WITH RHEUMATOID ARTHRITIS

The major effect of RA in patients is the progressive and painful inflammation. The known cause for the same is said to be related to prostaglandins. Prostaglandins (PGs) are lipids that are derived from Arachidonic Acid (AA). They are involved in pathogenic mechanisms to elicit inflammatory response. Anti-citrucillinated protein antibodies (ACPA) and Rheumatoid Factors (RFs) are the autoantibody systems that are associated with PGs for diagnosis of RA [14, 15]. Since Rheumatoid Arthritis is an autoimmune and genetic disease, the complete eradication is not yet known [13].

PGE2, PGI2, PGD2 and PGF2 are four biologically active prostaglandins. The production and the action of PGs depend upon the differential synthesis of different enzymes involved in inflammatory response. Acute inflammation involves four stages namely red flare, heat, swelling and pain. This is in response to the migration and inflation of leucocytes, vasodilatation, followed by edema formation

leading to pain. Prostanoids include both prostaglandins (PGs) and thromboxane A2 (TXA2). PG production and synthesis is mediated by COX enzymes. Cyclooxygenase enzyme (COX) exists in two isomeric forms, COX1 and COX2. During the biosynthesis, arachidonic acid (AA) is produced from the plasma membrane by phospholipases (PLAs) [17]. By the intervention of either COX1 or COX2, PGG2 and PGH2 are produced. PGH2 then leads to the synthesis of prostaglandins (PGI2, PGE2, PGF2) and thromboxane synthase (TXA2) [33, 34]. Drugs like NSAIDs and aspirin binds to the receptor sites of COX enzymes, preventing the production of prostaglandins (PGs) and thus act as anti-inflammatory drug [22, 26, 31].

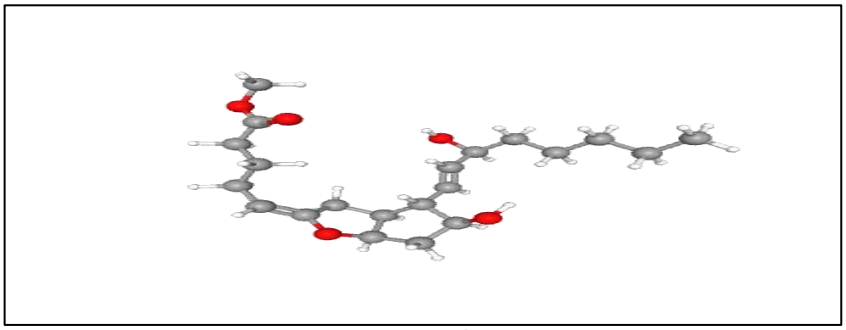

Diagram 1: 3D structure of prostaglandin (NCBI)

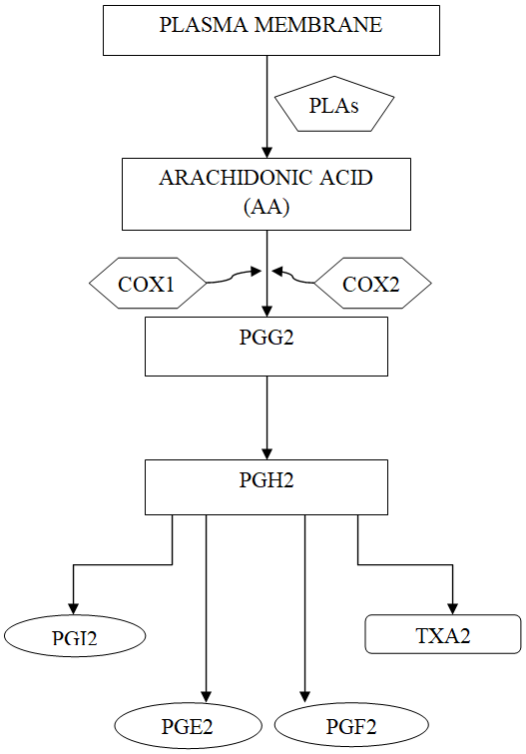

Diagram 2: Flowchart representing the biosynthesis of Prostaglandins

EFFECT OF HERBAL TREATMENT FOR RA

Rheumatoid Arthritis is caused due to the migration and inflation of neutrophils, macrophages and monocytes. Pro-inflammatory cytokines (IL-17, 1L-6, IL-1β, TNF-α), chemokines (MCP-1, RANTES), biochemical and osteoclastic mediators play a vital role in inflammatory pathogenesis related to RA. Th17 cells produce IL-17 cytokines that acts as one of the major contributing factor for inflammation [1]. They then release and secrete other pro-inflammatory cytokines, chemokines and mediators. A study on the effect of *Tinospora cordifolia* extract (TCE) on arthritic rats showed that they helped in downregulation of IL-17, RANTES and other associated inflammatory factors [3, 12]. TCE thus was found to reduce inflammatory response and bone damage associated with RA [24, 28, 29].

Zingiber officinale (Ginger) is a potential anti arthritic medicinal plant due to its therapeutic and pharmacological properties known. It has been widely used to treat liver and kidney associated diseases, reduced heat production, improves blood circulation and has analgesic and anti-inflammatory properties [6, 9]. It has been studied and proved that ginger extracts has helped in reducing inflammatory response in arthritic mice. It has showed significant reduction in the production of inflammatory cytokine IFN-γ and Th17 cytokine, IL-17. It has been previously proven that ginger extract has reduced levels of cytokines, NO and PGE2. Thus, *Zingiber officinale* extract also has the potential for anti-inflammatory activity [2, 32].

RECENT ADVANCEMENTS

Drugs available for treatment of diseases pose threats and risks to the community. They could even lead to long lasting side effects that could remain unknown for years. High costs of such drugs add to its insignificance. Hence, more people have turned to herbal drugs and medications that are plant based [7]. They are freely available in the market and overcome the disadvantages posed by drugs available in the market. There are various plant based medications and treatments that had been in use over decades. Natural products that have been found effective for treatment of RA include Tripterygium wilfordii Hoof F (TwHF) , Green Tea, Curcumin and Resveratrol [5]. These have been found to be having anti-inflammatory properties. Studies have proven that they had significantly reduced the action and levels of pro-inflammatory cytokines, NO, MMPs, PGE2, COX2, Th17, IFN-γ and TNFα [21]. Poor bio-availability of such drugs and unknown mechanism of action of herbal drugs makes its use challenging [18]. One of the solutions to this is the nanoparticle based delivery of plant related drugs. Nanoparticles help in the regulated delivery of drugs without causing any damage and require only small amounts of the drug. Hence it could act as a best suitable and dependable system for drug delivery [8, 19].

CONCLUSION

Progressive inflammatory response associated with RA patients implicate the essentiality of novel medications and treatments that are plant based in origin due to the risks involved in the usage of existing drugs against RA. In spite of the pain, RA possesses both psychological and socio-economic problems that make the daily lives of people difficult. *Tinospora* and *Zingiber* act as anti-inflammatory herbs that can be used in combination to treat arthritis. They have been proven to be in use in reducing the pro-inflammatory cytokines, bioactive mediators and other arthritic factors that cause damage of bones and joints causing pain and swelling. Hence, novel discoveries based on herbs could open wide opportunities for local communities of the society who suffer from diseases like arthritis that hasn't found a complete cure.

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