Volume 3, Issue 10, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

THE POTENTIAL OF FENUGREEK SEEDS IN NATURAL ARTHRITIS AND INFLAMMATION CARE

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DOI: https://doi.org/10.5281/zenodo.17862438

Keywords

Fenugreek, Trigonella Foenum-Graecum, Arthritis, Rheumatoid Arthritis, Inflammation, COX/LOX, Anti-Oxidant

Article History

Received: 13 October 2025
Accepted: 24 November 2025
Published: 09 December 2025

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Abstract

Arthritis, especially rheumatoid arthritis (RA), is a long-term inflammatory disease that affects the whole body. It causes joint swelling, synovial hyperplasia, cartilage damage, and increasing disability. Current pharmacological treatments like NSAIDs, glucocorticoids and DMARDs help with symptoms but can have bad side effects and aren't always safe for a long time. This has led to more interest in plant-based medicines. Fenugreek (Trigonella foenum-graecum L.) is a leguminous herb that is grown every year and has been used in traditional medicine for a long time since it offers several health benefits. Fenugreek seeds are high in proteins, dietary fiber, saponins, flavonoids, alkaloids, polyphenols, and essential fatty acids. They also have strong antioxidant, antidiabetic, hypolipidemic, immunomodulatory, and anti-inflammatory effects. This review presents findings concerning the function of fenugreek seeds in the treatment of arthritis and inflammation. Experimental research investigating adjuvant-induced arthritis in rats indicate that fenugreek seed extracts and mucilage markedly decrease paw edema, ankle diameter, arthritic index, and inflammatory cells infiltration. Treatment also leads to enhanced body weight and significant decreases in cytokines that promote inflammation such as TNF-α and IL-6. Mechanistic studies suggest that fenugreek's therapeutic effects include an inhibition of activation of NF-B, suppression of COX/LOX pathways, decrease of oxidative stress, and modulation of leukotriene-mediated immunological responses. Antioxidant components also prevent tissue damage linked to chronic inflammation, maintain cell membranes, and reduce oxidative stress. Overall, the data indicate that fenugreek seeds have significant anti-arthritic properties and may be used as a supplemental or additional therapy method. Nonetheless, while preclinical data appear promising, additional clinical trials are required to validate efficacy, define optimal dosage, and assure long-term safety in populations of people.

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ISSN: (e) 3007-1607 (p) 3007-1593

INTRODUCTION

Many people know that eating medicinal herbs is important for staying well and avoiding diet-related diseases like diabetes, cancer, high blood pressure, inflammation, and heart problems (Thorat et al., 2019). Throughout history, diverse populations have employed botanicals globally for their medicinal properties and nutritional value. They do not work in the same manner as chemical drugs, nor are they a substitute for them (Horne et al., 1996, Vuorela et al., 2004). Over 80 percent of the global population, mainly in countries with lower incomes, uses medicinal plants to treat ailments and improve overall health. This is mostly due to the widespread perception that medications made from plants are inexpensive, easily accessible, and side effect-free (Gupta et al., 1998).

Due to their extensive nutraceutical qualities and safety features, the usage of herbal plants for the cure or prevention of numerous ailments is greatly practiced, despite the astounding advances in medicine and combinatorial drug creation. Many agricultural plants have beneficial, functional, therapeutic, and nutraceutical properties. One plant that possesses each of these qualities is fenugreek, which is also a highly valued spice crop in human diets. Methi, sometimes referred to as fenugreek (Trigonella foenum graecum), is an annual crop that is a member of the Leguminoseae (Fabaceae) family's subfamily Papilionacea (Ghosh et al., 2015). It is a flavorful leguminous plant that is used to season meals and enhance flavor (Mandal et al., 2016). "Greek hay" is what the Latin term foenum-graecum, which gives rise to the name fenugreek, means (Petropoulos et al., 2002). Originally, the plant was used to make fragrances (Wani et al., 2018). Because of the little, yellowish-white blooms' triangular form, Trigonella takes its title from an old Greek term that meaning "little triangle" (Mehrafarin et al., 2011). Around 1500 B.C., fenugreek was first recorded in writing on an Egyptian papyrus (Borchardt et al., 1999).

Although this is up for debate, fenugreek is believed to have originated in areas of Asia or the Mediterranean region of the "Old World" (Acharya et al., 2006). Trigonella foenum-graecum, T. balansae, T. corniculata, T. maritima, T. spicata, T. occulta, T. polycerata, T. calliceras, T. cretica, T. caerulea, T. lilacina, T. radiata, and T. spinos are among the species of the genus Trigonella that are used as medicinal agents (Aasim et al., 2018). *Trigonella foenum-graecum L* is the Latin name for fenugreek, and the seed is Foenugraeci semen (Petropoulos et al., 2002). There are several different names for fenugreek in different languages: Alholva, Fenogreco (Spanish), Koroha (Japanese), Hulba (Arabian), Halba (Malaya), K'u-Tou (China), Fenegriek (Dutch), Bockshorklee, Bockshornsamen-seed (German), Fieno greco (Italian), Pazhitnik, Pazhitnik grecheskiy (Russian) and Alforva, Feno-grego (Portuguese) (Srinivasan et al., 2006).

Figure 1: Fenugreek Seeds & Plant Structure

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ISSN: (e) 3007-1607 (p) 3007-1593

In autoimmune illnesses and other inflammatory disorders, tissue damage and destruction are caused by pathologic events that are facilitated by inflammatory processes. Rheumatoid arthritis (RA) is a multifactorial, chronic inflammatory illness that is characterized by joint deformity, vasculogenesis, cartilage and bone degeneration, and synovial hyperplasia (Tristano et al., 2009). Roughly 1% of people worldwide suffer with this illness, which is also linked to early death and long-term impairment. It is extremely important for researching the pathophysiology and pharmacological regulation of inflammatory processes and for assessing the anti-inflammatory properties of medications (Choudhury et al., 2013). The plant is 30 to 60 cm tall, with solid, rhomboidal seeds that are hard, pebble-like, and 3 to 5 cm long and 2 nm thick. The seed has a yellowish brown to light brown color and a somewhat spicy, bitter, and mucilaginous flavor. One of the earliest therapeutic herbs to be grown is fenugreek. Numerous investigations revealed that it develops antioxidant qualities in the leaves and seeds. Methi is another name for it. As an Ayurvedic medication, it is used to heal wounds, arthritis, bronchitis, abscesses, and digestive issues.

The Trigonella foenum-graecum, or fenugreek, plant is composed of several different substances, including volatile components, steroids, alkaloids, glycosides, and polyphenols. It has a wide range of medical uses, including as an anti-anorexic, antioxidant, antibacterial, hypoglycemic and hypocholesterolemic treatment, stomach stimulant, and anti-carcinogenic. The seeds are spicy and have a harsh, bitter flavor. They are also tonic, antipyretic, anthelmentic, stimulate the appetite, astringent to the intestines, heal leprosy, "vata," vomiting, pneumonia, piles, and help with heart problems (Aggarwal et al., 2006).

Fenugreek seeds have antibacterial, carminative, aromatic mildly bitter smell. Every 100 grams of fenugreek seeds has a fiber component that is made up of 20% soluble fraction (typically galactomannan) and 30% insoluble fraction. It also contains 20–30% proteins, 45–60% carbohydrates, and 5–10% lipids, the bulk of which are neutral lipids such phospholipids (450 mg/100 g) and triglycerides (6.3%) (Acharya et al., 2006). Moreover, it contains volatile oils (0.015%), sitosterol, cholesterol, amino acids, pyridine alkaloids, flavonoids, calcium, iron, and saponins (0.6–1.7%), in addition to vitamins A, B1, C, and nicotinic acid (Singh et al., 2013).

Table 1: Chemical Composition of Fenugreek Seeds

Component	Percentage / Amount	Notes / Source Information
Proteins	20–30%	High-quality plant protein
Carbohydrates	45–60%	Major nutritional fraction
Lipids (Total Fats)	5–10%	Mainly neutral lipids
Triglycerides	6.3%	Part of total lipid fraction
Phospholipids	450 mg / 100 g	Important structural lipids
Dietary Fiber (Total)	50%	Very high fiber content
Soluble Fiber (Galactomannan)	20%	Helps reduce glucose absorption
Insoluble Fiber	30%	Improves digestive health
Saponins	0.6–1.7%	Key anti-inflammatory & hypolipidemic compounds
Volatile Oils	0.015%	Contribute to aroma & bioactivity
Vitamins	A, B1, C, Nicotinic Acid	Present in small but important quantities
Minerals	Calcium, Iron	Support metabolic functions
Amino Acids	Phenylalanine, Leucine, Tyrosine, Aspartic acid, Glutamic acid	Essential & non-essential amino acids

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Phytochemicals	Alkaloids, Glycosides, Steroids	Flavonoids, Polyphenols,	Responsible for antioxidant & medicinal actions

Rich in nutrients, fenugreek seeds have the potential to improve overall health when used for human consumption as well as fodder (Olaiya et al., 2014). Fenugreek seeds have a high fiber content, which makes them useful as an emulsifier, adhesive, and food stabilizer to alter food texture for certain uses (Khorshidian et al., 2016). Fenugreek seeds are used as a preservative because they are rich in antioxidants like vitamin E, which protects biological tissue from harm affected by constituents known as free radicals that can destruction tissue, cells and organs (Aher et al., 2016).

It also contains a variety of essential amino acids, including as phenylalanine, leucine, tyrosine, aspartic acid, and glutamic acid (Ghosh et al. 2015). It possesses anti-diabetic, anti-carcinogenic, anti-hypoglycemic, anti-hypercholesterolemic, antioxidant, antibacterial, gastric stimulant, and anti-anorexic properties across a range of medical applications. The saponins and diosgenin in fenugreek seeds make them good for lowering cholesterol and blood sugar levels. Furthermore, fenugreek functions as a diaphoretic, promoting perspiration and supporting the body's detoxification processes. It also has a positive effect on blood purification. Additionally, fenugreek seeds aid in lowering the kidney's calcium oxalate content, which prevents kidney stones (Aher et al., 2016).

The anti-inflammatory, anti-arthritic, and antioxidant properties of fenugreek seeds have been discovered in their ethanol extract, mucilage, and flavonoids (Ahmad et al., 2016). Linolenic acid in fenugreek seeds petroleum ether extract showed strong anti-inflammatory efficacy in several serious models, including leukotrienes, carrageenan, prostaglandin E2, and arachidonic acid induced swelling, indicating that it can inhibit both the cyclooxygenase and lipoxygenase pathways. Most studies using polar fractions of fenugreek seeds show strong antioxidant-mediated anti-inflammatory and anti-arthritic effects.

1.1. Overview and Definition of Arthritis

The term "arthritis" describes infections in and around the joints. The symptoms of this prevalent clinical chronic systemic inflammatory illness are pain, redness, swelling, and heat. In America, arthritis is a prevalent long-term debilitating illness.

1.2. Prevalence of Arthritis and Associated Disability

Based on information from the Nationwide Health Consultation Investigation, researchers obtained that around 22.7 percent of adult Americans had a medical diagnosis of arthritis, and 9.8 percent report restricted activities related to their condition, such as trouble dressing or using the restroom. Worldwide as well as in the United States, arthritis is a prevalent illness. Worldwide, 355 million individuals suffer with arthritis at the moment. By 2040, people with a diagnosis of arthritis are predicted to make up 25.9% of all adults in the United States (Hootman et al., 2016).

1.3. Impact on Function and Quality of Life

Severe joint pain and dysfunction brought on by arthritis can reduce mobility and lower quality of life. In clinical and public health systems, arthritis and associated restricted activities will continue to be major issues. Osteoarthritis is the most prevalent kind of arthritis, although other types of arthritis include gout, psoriatic arthritis, rheumatoid arthritis, and others. Osteoarthritis, sometimes referred to as worsening arthritis, is a worsening condition that primarily affects the elderly. It is characterized by reactive hyperplasia of the joint edge and subchondral bone as well as degenerative destruction of the articular cartilage. It is particularly prevalent in middle-aged and older adults. Although inflammatory arthritis such as RA, PsA, and other forms of arthritis are increasingly prevalent, their primary clinical symptoms are vasculitis and synovitis? Arthritis sufferers' mental health is greatly impacted by their acute joint pain and restricted exercise. Patients with knees osteoarthritis were shown to have a higher likelihood of depression, with 10.4% of these patients experiencing moderate to severe depression, according to

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ISSN: (e) 3007-1607 (p) 3007-1593

multicentred cross-sectional research (Akintayo et al., 2019, Baerwald et al., 2019).

It was shown that RA patients had a noticeably greater risk of depression than the overall population. Depression has a negative impact on RA therapy, increasing mortality and decreasing remission rate. Patients with PsA had a greater frequency of anxiety and depression overall, according to a meta-analysis (Zusman et al., 2020, Matcham et al., 2013). It was shown that 16.8% of PsA patients had serious depression (Matcham et al., 2013). It was shown that compared to other illnesses, degenerative arthritis and RA may have a higher influence on the chance of developing serious depression.

Survey data indicates that Major Depressive Disorder (MDD) is the second largest contributor to the burden of chronic illness, affecting around 6% of individuals globally each year. Furthermore, the risk of suicide is about 20 times higher among MDD patients than in the general population. According to clinical research, people with arthritis have a higher risk of developing severe depression. Lack of cross-sectional comparisons between major depression risks and various forms of arthritis has been seen, and few large sample studies have validated this link. This research used a nationwide demonstrative population based cohort design to investigate the association between major depression and arthritis, as well as the link between various forms of arthritis and major depression risk.

A prevalent, systemic, and chronic inflammatory illness, rheumatoid arthritis (RA) is defined by inflammation of the synovium in any joint, including the big joints of the knee and shoulder and the tiny joints of the hands and feet. Joint synovitis causes bone and cartilage degradation, which results in (radiographic) damage (Imboden et al., 2009). If treatment is not received, the erosion of the bone surface resulting from these damages can cause severe impairment or possibly irreversible loss of function (Silman et al., 2002, Majithia et al., 2007). The etiology of RA is complicated and has not yet been thoroughly investigated. It has a broad range of clinical symptoms, as well as variations in the severity, course, and responsiveness to treatment. These diverse RA symptoms might indicate that a range of variables, including genetic, hormonal, and environmental ones, may have a role in the development of this complicated characteristic.

1.4. Rheumatoid Arthritis Fatigue as an Outcome Measure

The inflammatory systemic disease known as rheumatoid arthritis (RA) is responsible for joint pain and swelling, disability, and psychological suffering [Conaghan et al., 1999]. A significant number of RA patients have reported experiencing tiredness, and its causation is probably complex (Tack et al., 1990, Belza et al., 1993). Nevertheless, it was absent from the seven globally recognized key outcome variables for RA clinical studies (Felson et al., 1993). In fact, despite the examination of many potential outcome measures, fatigue is not mentioned once in the series of international meetings that developed the core set. The OMERACT group, which stands for Outcome Measures in Rheumatology Clinical Trials, was instrumental in creating the core set in RA, working with other groups. The focus of the 2000 OMERACT 5 conference turned to the scores required in the core set measures for them to be considered to have changed significantly in response to therapy. The need to include the patient's perspective was one of the numerous technical debates, but it was also arguably the most significant advance (Wells et al., 2001).

A special arrangement was created for attendees who were patients at the subsequent meeting, OMERACT 6, in 2002. Eleven patients from seven different nations, five members of the organizing committee, and forty-one additional attendees of the OMERACT 6 meeting participated in the Patient Perspective Workshop. Three two-hour formal sessions, performing group conferences before and later the official conferences, in addition to an unplanned gathering of the longsuffering applicants made up the workshop (Kirwan et al., 2003). One thing that became evident from the workshop was that exhaustion, restless nights, and a general sense of well-being are among the additional outcomes that matter to some patients, if not all of them. This led to more research on the occurrence, perception, and assessment of tiredness in RA.

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Inflammation associated with arthritis

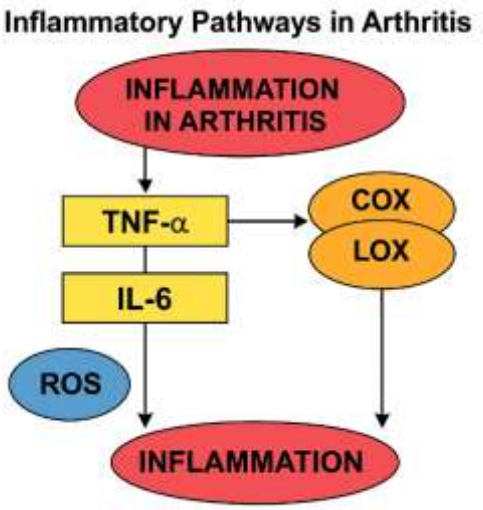

Figure 2: Mechanism of Arthritis Inflammation

Molecular complexes called inflammasomes are created in the cytoplasm of innate immune cells (Martinon et al., 2002). These signaling pathways get activated and develop a proteolytic activity that triggers inflammatory processes, including the generation of pro-inflammatory cytokine interleukin 1β (IL-1β) (Dinarello et al., 2019). Tissue injury and the presence of infections are among the insults that inflammatory enzymes may identify (Broz et al., 2016). Although inflammasomes' primary physiological roles are to trigger an immune response and aid in tissue homeostasis and repair, aberrant activation of inflammasomes can have negative effects. Hereditary and acquired autoinflammatory disorders are directly associated with many inflammasomes (Harapas et al., 2018). It has also been demonstrated that inflammasomes are essential for treating diseases with more complex etiologies that result in inflammation and tissue damage. Overactivation of inflammasomes has been linked to neurological illnesses, cancer, metabolic disorders (type 1 and type 2 diabetes), and autoimmune (systemic lupus erythematosus, or SLE). Another theory about the characteristics of aging is an increased inflammasome response (Latz et al., 2018). Aberrant involvement of inflammasomes is associated with several joint diseases. Rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), and gout patients were studied for this (Shin et al., 2019).

It will be easier to diagnose and treat aberrant inflammation, including arthritic disorders, if the processes behind the activation of inflammasomes in physiological and pathological situations are understood. Over the past 20 years, a lot of work has been done to understand how the various inflammasomes are controlled or triggered. A number of significant findings have significantly enhanced our comprehension of these pathways and prompted the creation of fresh treatment approaches focused on addressing downstream mediators. It is being discovered that drugs that directly target the assembly of inflammasomes might be useful in reducing inflammation in conditions where there is abnormal activation of the inflammasome. We go over significant developments that have enhanced our knowledge of the biology of inflammasomes in this review. We will also draw attention to a number of important, unanswered questions. Specifically, we will concentrate on the roles that various inflammasomes play in various forms of arthritis (Spel et al., 2020).

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Fenugreek seeds activity against inflammation

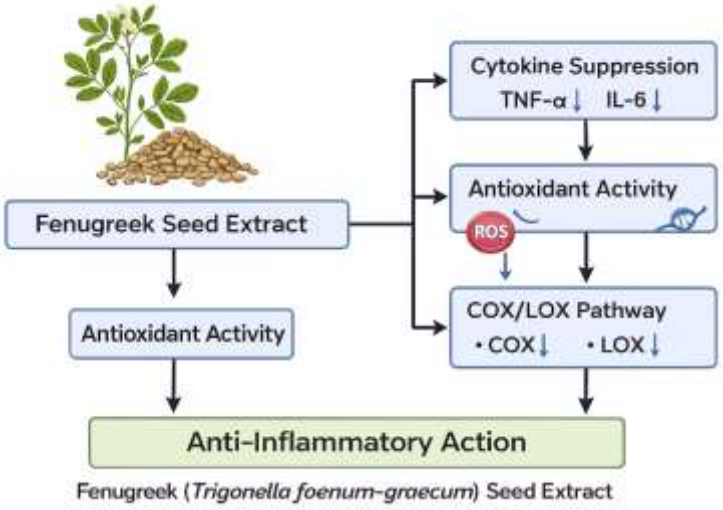

Figure 3: Anti-Inflammatory Action of Fenugreek

In general, "inflammation" refers to the complex biological reaction of vascular tissues to damaging stimuli. In addition, redness, heat, swelling, discomfort, and loss of function are associated with inflammation. Among other things, it involves membrane alteration, a rise in vascular permeability, and an increase in protein denaturation. It is well recognized that leukocyte migration from venous networks to the site of injury and the release of cytokines play a major part in the inflammatory response. Polymorphonuclear leukocytes are inflammatory cells that are particularly skilled in producing and releasing reactive oxygen species (ROS) and reactive nitrogen species (RNS), including hydroxyl radicals (•OH), superoxide anion (•O2-), hydrogen peroxide (H2O2), nitric oxide (NO), and 1O2 (singlet oxygen). Overproduction of reactive oxygen species (ROS) can harm cellular lipids and carbohydrates, causing damage to cells and tissues that exacerbates the inflammatory state (Pan et al., 2009).

The body doesn't always benefit from inflammations. Certain illnesses result in the immune system unintentionally attacking the body's own cells, which can be detrimental. Excessive or chronic inflammation has been linked to a number of human illnesses and maladies, including obesity, neurological diseases, aging, and cancer. Growing evidence also suggests that many autoimmune disorders, including rheumatoid arthritis, diabetes (type 1&2), skin conditions like psoriasis, and inflammatory bowel infections, such as Crohn's infection, are closely associated with an abnormal inflammatory response (Pan et al., 2009). Therefore, the anti-inflammatory medications that target inflammation must be effective in removing both the inflammatory enzymes and the high quantities of reactive oxygen species.

One of the most popular anti-inflammatory pharmaceuticals used worldwide is NSAIDS (nonsteroidal anti-inflammatory drug). Ibuprofen and naproxen are used for orthopedic conditions that include fractures, soft-tissue injuries, and osteoarthritis, among others. Another family of drugs are glucocorticoids, which include cortisone and prednisone. They are linked to serious side effects and toxicity, which includes a higher risk of infection in some patient subgroups. Current medications lead to hypertension, hyperglycemia, renal damage, and G.I. ulceration and bleeding. The primary drawback of the powerful synthetic drugs of today is their toxicity and relapse of symptoms upon discontinuation. Because of this, it's crucial to test and develop drugs for their ability to reduce inflammation, and several efforts are being done to identify anti-inflammatory drugs derived from locally grown medicinal plants (Joshi et al., 2022).

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Because of their affordability, availability, and low toxicity, natural plant products are fast becoming a major alternative therapeutic option for developing anti-inflammatory drugs. Numerous epidemiological studies provide strong evidence for the diverse biological actions of naturally occurring dietary components that humans consume, such as flavonoids and polyphenols (Srinivasan et al., 2022).

Table 2. Reported Pharmacological Activities of Fenugreek (*Trigonella foenum-graecum*) Seeds

Pharmacological Activity	Description / Mechanism	Supporting Literature Evidence
Anti-inflammatory	Inhibits NF-κB activation; reduces TNF-α and IL-6; blocks COX/LOX pathways; decreases ROS production	Ahmad et al., 2016; Singh et al., 1997; Pan et al., 2009
Anti-arthritic	Reduces paw edema, arthritic index, cytokines; improves body weight in CFA-induced arthritis	Joshi et al., 2022; Suresh et al., 2012
Antioxidant	Rich in polyphenols, flavonoids, vitamin E; neutralizes free radicals and reduces oxidative stress	Ghosh et al., 2015; Aher et al., 2016
Antidiabetic	Improves glucose metabolism; slows carbohydrate absorption due to soluble fiber (galactomannan)	Acharya et al., 2006
Hypoglycemic	Stimulates insulin secretion and lowers blood glucose	Srinivasan et al., 2022
Hypolipidemic	Reduces cholesterol and triglycerides due to saponins and diosgenin	Aher et al., 2016
Anticancer / Chemopreventive	Antiproliferative effects via polyphenols and saponins	Pundarikakshudu et al., 2016
Antibacterial	Contains bioactive compounds (alkaloids, polyphenols) that inhibit bacterial growth	Singh et al., 2013
Gastroprotective	Reduces gastric ulceration; mucilage protects GI lining	Pundarikakshudu et al., 2016
Immunomodulatory	Regulates immune responses; reduces autoimmune activation	Raju et al., 2006
Wound healing	Stimulates fibroblast activity and tissue regeneration	Traditional Ayurvedic use; supported by bioactive compounds
Hypocholesterolemic	Lowers LDL and improves lipid profile	Aggarwal et al., 2006
Antipyretic	Reduces fever due to anti-inflammatory action	Singh et al., 2013
Digestive stimulant	Bitter principles stimulate gastric activity	Traditional use; phytochemical evidence

Herbal remedies function in a synchronous manner, in contrast to contemporary allopathic medications, which have a single active component and target a single route. Various chemicals found in plants collaborate to target distinct components of intricate biological pathways. For thousands of years, therapeutic plants have been a rich supply of compounds that are physiologically active. These compounds are employed as pure substances or as raw materials to treat a wide range of medical conditions. The use of herbal therapies is expanding due to the toxicity and adverse effects of allopathic treatments. The creation of potent medical medications depends heavily on medicinal plants. India may continue to be a major producer of raw materials, either directly for crude drugs or as bioactive compounds in the manufacture of pharmaceuticals and cosmetics, among other things, given that it has the greatest

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collection of medicinal plants in the world (Srinivasan et al., 2022).

India is a major producer of fenugreek, with more than 80% of the nation's production coming from Rajasthan. It was discovered that fenugreek seeds' mucilage, flavonoids, and ethanol extract have anti-inflammatory and anti-arthritic, plus antioxidant properties (Ahmad et al., 2016). Linolenic acid in fenugreek seed petroleum ether extract showed strong anti-inflammatory efficacy in a variety of serious models, including leukotrienes, carrageenan, prostaglandin E2, and arachidonic acid-induced swelling, indicating its ability to block both cyclooxygenase and lipoxygenase passageways. Most studies using polar fractions of fenugreek seeds show strong antioxidant-mediated anti-inflammatory and anti-arthritic effects. Numerous investigations have examined Trigonella foenum-graecum, revealing its potential benefits as an antidiabetic, antioxidant, anti-inflammatory, antipyretic, antiulcer, hypocholesterolaemia, immunomodulatory, wound-healing, CNS-stimulant, anticancer, gastroprotective, and chemo preventive agent (Pundarikakshudu et al., 2016).

2. Literature Review:

Since ancient times, many of the plants we regularly eat have been valued for their therapeutic properties. Now, research is resuming in an effort to validate such theories using a more scientific approach by carefully examining and verifying the phytochemicals found in plants. The plant fenugreek (*Trigonella foenum-graecum L.*) is one such interesting plant. This study involves the extraction of crude extracts from fenugreek leaves and seeds using Soxhlet, the identification of phytochemicals, and the initial screening of metabolites, including flavonoids, alkaloids, phenolics, steroids, terpenoids, and saponins. It also describes the anti-inflammatory and antioxidant characteristics of the plant and discusses its potential application in the formulation of a medicinal cream. Future possibilities include the ability to conduct several studies that adhere to all quality criteria and the potential to demonstrate the product's anti-inflammatory qualities, making it a strong competitor against rheumatoid arthritis (Joshi et al., 2022).

In this work, we looked at the potential anti-arthritic benefits of the popular herb fenugreek seeds (Trigonella foenumgraecum) on experimental Wistar rats with CFA-induced arthritis. The test medications were contrasted with the reference medications, cyclophosphamide for secondary lesions and indomethacin for initial lesions. The findings of this investigation demonstrate the possible anti-arthritic properties of fenugreek seed extract. The administration of fenugreek seed extract, either alone or in combination, led to a noteworthy reduction in paw volume, ankle diameter, serum TNF-α, arthritic index, and an elevation in body weight. There was no statistically significant difference seen between any of the treatment groups when compared to the usual medication, cyclophosphamide, or indomethacin. Thus, we may conclude that the test medications, both by themselves and in combination, are equivalent to prescription medications. This observation is consistent with earlier research (Wilken et al., 2011, Fahey et al., 2007, Zahidah et al., 2012, Ahn et al., 2015, Zheng et al., 2015, Ravindran et al., 2010). The fenugreek seed extract-treated rats showed statistically significant reductions in serum TNF-α. According to a prior study, this observation is valid. This suggests that fenugreek seed extract lowers serum TNF-α levels. Group II rats' serum TNF-α may be explained by this (Suresh et al., 2012, Raju et al., 2006, and Kandhare et al., 2015). This result agrees with previous research by Suresh P, Kavitha CN, et al. The following factors might contribute to these effects: anti-inflammatory properties, the capacity toward lower TNF-α levels since high TNF-α stimulates leukocyte inflow at the place of swelling, stimulation of synovial fibroblasts, and angiogenesis.

DMARDs (disease-modifying antirheumatic medications), biologics, and nonsteroidal anti-inflammatory medicines (NSAIDs) are often used in modern therapy regimens. These drugs may, however, have drawbacks such as expensive side effects and insufficient effectiveness. Fenugreek (Trigonella foenum-graecum) seeds are one potential for alternative and complementary medicines, which are gaining attention as a result.

Rheumatoid arthritis (RA) is a chronic autoimmune illness characterized by

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ISSN: (e) 3007-1607 (p) 3007-1593

inflammation of the synovial joints, resulting in pain, swelling, and eventually joint destruction. In most modern treatment plans, nonsteroidal anti-inflammatory medications (NSAIDs) and disease-modifying anti-rheumatic medicines (DMARDs) are utilized. For certain people, these drugs may have limited effectiveness and be linked to adverse consequences. Fenugreek (Trigonella foenum-graecum) seeds are one natural remedy that has garnered attention due to this increased interest in studying alternative therapies.

A popular spice and therapeutic plant, fenugreek has a long history of usage in traditional medicine to treat a wide range of illnesses. Fenugreek seeds may have anti-inflammatory qualities; recent research has examined this, especially in relation to rheumatoid arthritis.

In a swine model of rheumatoid inflammation, fenugreek seed extract was investigated for its anti-inflammatory properties. When fenugreek seed extract was given to arthritic rats, the researchers saw a noteworthy decrease in joint inflammation and paw edema in comparison to the control group. Furthermore, the fenugreek-treated group exhibited a significant drop in the levels of inflammatory markers, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These results imply that fenugreek may reduce inflammation by altering important cytokines that are part of the inflammatory cascade.

Furthermore, molecular investigations have been conducted to investigate the possible processes behind fenugreek's anti-inflammatory action. According to a research, nuclear factor-kappa B (NF-κB), a transcription factor essential for controlling inflammatory responses, is inhibited by fenugreek seed extract. By reducing the expression of pro-inflammatory genes, inhibition of NF-κB activation might lessen the inflammatory process associated with rheumatoid arthritis.

It has been shown that fenugreek seeds exhibit antioxidant activity in addition to their anti-inflammatory characteristics. Rheumatoid arthritis is thought to be caused by oxidative stress, which also contributes to inflammation and tissue damage. Free radicals may be neutralized and oxidative stress in arthritic joints may be reduced by the antioxidant components found in fenugreek, such as flavonoids and polyphenols.

Fenugreek's potential as a supplemental therapy is further supported by comparative research between it and standard medications used for rheumatoid arthritis. A study contrasted methotrexate, a DMARD that is often administered, with fenugreek seed extract's anti-arthritic properties. The outcomes showed that both the fenugreek and methotrexate-treated groups saw similar decreases in paw edema and joint inflammation. Furthermore, when compared to methotrexate a medication with a history of adverse effects fenugreek showed a safer profile.

It is important to recognize the shortcomings and gaps in the existing research on fenugreek and rheumatoid arthritis, although the encouraging results. The results of several investigations carried out in animal models must be transferred to human clinical trials in order to prove the safety and effectiveness of fenugreek as a supplemental treatment for RA. Based on existing research, fenugreek seeds may have anti-inflammatory properties when used to treat rheumatoid arthritis. Potential methods via which fenugreek may exert its therapeutic benefits include the regulation of inflammatory indicators and the suppression of NF-κB activation. It is necessary to do more study, especially in human clinical trials, to confirm these results and determine whether fenugreek may be used as an adjuvant treatment for rheumatoid arthritis.

Both unsaturated and saturated fatty acids were present in FSPEE. The amounts of linolenic and linolenic acids obtained from our investigation are almost equivalent to those reported by Skakovskii et al (Skakovskii et al., 2013).

Linolenic acid was found to have a strong anti-inflammatory impact in a number of acute models, including carrageenan, prostaglandin E2, leukotrienes, and arachidonic acid-induced inflammation (Singh et al., 1997). Indicating that it has the capacity to block the lipoxygenase and cyclooxygenase pathways. Carrageenan and formaldehyde-induced inflammation may be treated similarly by FSPEE, which is high in linolenic acid. The animals treated with FSPEE exhibited protection against the generation, migration, and cellular infiltration of chemoattractant factors, as evidenced by the

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decrease in cotton pellet weights. This might be as a result of FSPEE's antioxidant properties, which support the stability and integrity of cell membranes. The SGPT and ALP activity were significantly reduced, indicating a high antioxidant function for FSPEE. Hepatocyte enlargement has been linked to chronic inflammation and hepatomegaly (Bendele et al., 2001).

Lysosomal enzymes are released as a result of inflammatory disorders, and this in turn promotes prostaglandin production (Gupta et al., 1992). Under inflammatory circumstances, the liver's marker enzymes are elevated, which reflects general alterations in metabolism (Rainsford et al., 1982). Undoubtedly, omega fatty acids impact overall lipid metabolism. Recent research suggests that poor lipid metabolism contributes to increased generation of proinflammatory mediators (Gonzalez-Gay et al., 2005). CFA-induced arthritis shares many similarities with human arthritis in terms of clinical manifestations and immune responses. Most studies employing polar fractions of fenugreek seeds demonstrate potent anti-inflammatory and anti-arthritic effects mediated by antioxidant mechanisms (Suresh et al., 2012, Sindhu et al., 2012, and Liu et al., 2012).

Rats with adjuvant-induced arthritis have a well-established model for studying the inflammatory process; it has also been widely utilized to research the pathophysiology of RA and to discover possible targets for treatment (Andersen et al., 2004, Colpaert et al., 1982). In populations from several affluent nations, the prevalence of RA estimations was between 0.5% and 1% of the adult population (Amresh et al., 2007). In this model, the antiarthritic effect of different medications is indicated by measuring the swelling of the paws. The production of many mediators, including cytokines, is the cause of this persistent inflammation (Tatro et al., 1996). Paw volume was significantly reduced in this study when 75 mg/kg of fenugreek mucilage was administered as opposed to the arthritic control group. Paw edema may have decreased during the second week because of the mucilage's immune-boosting effects.

A local inflammatory response is triggered by pro-inflammatory cytokines produced by inflammatory foci, such as TNF-α and IL-6. The underlying pathophysiology of joint illnesses, including the degree of severity and present activity as well as inter-individual variability in disease, may be inferred from the levels of these inflammatory mediators (Barton et al., 2007). In CFA-treated rats, these cytokines are also implicated in the development of clinical signs such as weight loss, joint swelling, and blood neutrocytosis (Szekanecz et al., 2000). In this investigation, fenugreek mucilage therapy dramatically reduced elevated levels of IL-6 and TNF-α in the arthritic control. This decreased level of cytokines suggests that the severity of the arthritis has been lowered, which will slow the course of RA. The cytological analysis corroborated the preceding results by showing that treatment with fenugreek mucilage reduced severe inflammation with reactive mesothelial cells in the CFA group.

3. Discussion:

According to Jensen et al. (1992), *Trigonella foenum-graecum L.*, also known as fenugreek, is a spice bean crop that has been used historically as a medicinal herb. Evidence suggests that the seeds and leaves of the plant have antioxidant potential, and it was used by Hippocrates and the ancient Egyptians. The Mediterranean area is where fenugreek originated. Presently, India stands as the world's leading producer of fenugreek, turning out between 45,000 and 55,000 tons annually. Due to its medicinal qualities, fenugreek has long been used in traditional medicine and as a food ingredient (Smith et al., 2003).

An established model in rats for studying the inflammatory process, adjuvant-induced arthritis has been validated as a model to look into the pathophysiology of RA and to find possible targets for treatment (Andersen et al., 2004). (Colpaert et al., 1982). According to Amresh et al. (2007), the prevalence of RA estimations in adult populations from several industrialized nations ranged from 0.5 to 1%. In this model, the antiarthritic effect of different medications is indicated by measuring the swelling of the paws. Multifactorial mediator release, including cytokines, is the cause of this persistent inflammation (Tatro et al., 1996). When compared to the arthritic control group, the treatment of 75 mg/Kg of fenugreek mucilage in this research resulted in a significant reduction in paw volume. Paw edema may have

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decreased during the second week because of the mucilage's immune-boosting effects.

The term "arthritic index" refers to the average score assigned to the severity of the lesions, which takes into account the joint index of inflammation, the development of nodules, and the degree to which the illness has spread to other organs. The perivenular invading cells eventually develop into lymphoid follicles and produce cytokines, RF, and other immunoglobulins. Rats given mucilage showed a decrease in their arthritis index of CFA and a substantial rise above normal. Fenugreek mucilage's immunosuppressive properties may be distinguished from its anti-inflammatory properties by a specific decrease in the arthritis score (Yu et al., 2006).

Prominent immunological abnormalities, such as immune complexes in joint fluid cells and vasculities, may play a role in the pathophysiology of RA. These complexes are facilitated by the production of antibodies, such as RF, by plasma cells ACCEPTED MANUSCRIPT 8. The accurate indicator of RA's clinical manifestation is RF. B cell activation through TLRs and various genetic predispositions to arthritic disorders are involved in RF production in arthritis (Dörner et al., 2004). The administration of mucilage to the rats resulted in a considerable decrease in the levels of these indicators of inflammation and autoimmune activation. According to the current study's findings, fenugreek mucilage may have anti-inflammatory properties because it inhibits B cell activation.

The release of mediators is involved in chronic inflammation. These mediators may be responsible for the deterioration of bone and cartilage, as well as discomfort that can cause significant impairment from inflammation. Leukotriene synthesis from arachidonic acid is accomplished by LOX, which is recognized to be crucial to the LOX pathophysiology of RA. Leukocyte infiltration into the RA joint is mediated by the chemoattractant LT (Mathis et al., 2007). There, these cells multiply and create an invasive pannus that destroys bone and cartilage (Chen et al., 2006). The reduction in LOX activity observed after fenugreek mucilage treatment raises the possibility that LT synthesis inhibition is a further mechanism by which the mucilage exerts its anti-inflammatory effects.

COX-1 and COX-2, two different but related enzymes, interact to generate prostaglandins. The normal renal function, gastric mucosa integrity, and homeostasis are maintained by the constitutive enzyme COX-1 (Parente et al., 2003), while the increased production of prostaglandins in inflammatory tissue is believed to be caused by the inducible isoform COX-2 (Ruan et al., 2011). Prostaglandins are produced in response to elevated COX activity in paw tissue and PBMCs during arthritis, which reduces pain and the severity of the condition. However, the mucilage injection markedly decreased their activity, suggesting that prostaglandin synthesis was inhibited.

Two powerful inflammatory mediators that are involved in the pathophysiology of RA are PGE2 and TXA2. (Honda et al., 2006). In RA, PGE2 induces vasodilatation and draws neutrophils to the impacted joints. PGE2 also causes edema by plasma extravasation and sensitization to bradykinin and histamine-induced nociceptive stimuli, which all contribute to inflammatory pain. Following treatment with ACCEPTED MANUSCRIPT 9 mucilage, there was a decrease in PGE2, which was accompanied by a reduction in vasodilation, neutrophil migration to joints, and inhibition of COX activity.

A local inflammatory response is triggered by pro-inflammatory cytokines called TNF-α and IL-6 that are produced by inflammatory foci. Finding the levels of these inflammatory mediators can provide details on the underlying pathophysiology of joint illnesses, including the severity and activity level at the moment, as well as inter-individual differences in the condition (Barton et al., 2007). Additionally, these cytokines contribute to the development of clinical symptoms in CFA-treated rats, such as blood neutrocytosis, joint swelling, and body weight loss (Szekanecz et al., 2000). In this investigation, fenugreek mucilage therapy dramatically reduced elevated levels of IL-6 and TNF-α in the arthritic control. This lower cytokine level suggests that the severity of the arthritis is being inhibited, which will slow the advancement of RA. The cytological analysis corroborated the preceding results by showing that treatment with fenugreek mucilage reduced severe inflammation with reactive mesothelial cells in the CFA group.

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Conclusion:

This study demonstrates that first- and third-year medical students have strong baseline awareness of thalassemia and largely positive attitudes toward prevention, particularly regarding the importance of genetic counselling and support for discouraging consanguineous marriages due to associated genetic risks. Most participants also reported appropriate preventive intent, including recommending genetic screening in relevant clinical scenarios. However, notable gaps were identified in core genetic concepts especially the correct inheritance pattern of thalassemia and a substantial proportion of students reported no formal education on the relationship between consanguinity and thalassemia during their medical training. These findings indicate a need for strengthened and standardized undergraduate teaching on inheritance, carrier screening, and culturally sensitive counseling skills, alongside structured awareness initiatives to improve prevention-oriented practices and reduce the long-term burden of thalassemia in high-risk populations.

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