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RHEUMATOID ARTHRITIS: A REVIEW

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ABSTRACT

Herbal medicine also known as phytotherapy or herbalism, involves the use of plants or plant extracts to treat various health conditions,prevent disease and maintain overall wellness. Analgesics or anti-inflammatory are used in the treatment of pain or inflammation. Rheumatoid Arthritis is an immune mediated inflammatory disease (IMID) where the immune system attacks the tissues surrounding the joints driven the release of specific chemicals & enzymes that gradually damage cartilage and bone. This condition impacts all the joint in the body and in some cases, can also affect internal organs. Common symptoms of Rheumatoid Arthritis include joint inflammation, pain, swelling, which can lead to joint deformity and disability in severe substances. Herbal plants including Ashwagandha, Turmeric, Rosemary, Guduchi, Black pepper, Ginger. This review provides information on different analgesics sourced from nature. Medicinal plants play a significant role in treating rheumatism, with approximately 80% of the global population relying on traditional medicine. Rheumatism is a chronic autoimmune disorder that impacts the immune system and healthy tissue, leading to inflammation. Factors contributing to the risk of rheumatism include hormonal, genetic, environmental, nutritional, socio-economic influences, ethnicity, infections, and smoking. This review explores the use of various traditional medicinal plants, such as Aerva lanata, Mahuca longifolia, Acetaea spicata, Aesculus indica, and Hemidesmus indicus, in combating rheumatism. It also examines the mechanisms behind rheumatism, highlighting the inhibition of cartilage degradation. Notably, medicinal plants contain various active compounds, including lignans, flavonols, terpenes, and sterols, which have shown therapeutic benefits for rheumatism.

KEYWORDS: Rheumatoid Arthritis, herbal plants, anti- rheumatic activity,Analgesics, Inflammation, Treatment.

1. INTRODUCTION

1.1 HERBAL MEDICINE

Herbal medicine is one of the medicine, with roots in every culture around the world. Herbal medicines are made from leaves, stems, flowers, roots or seeds of plants.

Medicinal herbs are commonly utilized for addressing rheumatism and various other illnesses.[1-7] The majority of people rely on plants and trees for their survival and well-being. Those living in forested areas often trust traditional medicine for their primary health needs.[8-9] The treatment of various inflammatory diseases can be effectively managed with certain medicinal herbs. The World Health Organization (WHO) reports that 80% of the global population relies on traditional medicines for common health issues. The reliance on traditional remedies is growing steadily, as they can also help mitigate the side effects associated with modern pharmaceuticals. Rheumatism, a prevalent autoimmune disease, arises when the body's immune system mistakenly attacks healthy tissues, resulting in inflammation. This chronic condition leads to symptoms such as joint pain, swelling, stiffness, redness, and tenderness. In India alone, it is estimated that approximately 180 million people suffer from rheumatic pain.[9-10] Traditional medical expertise is being passed down through the generations in India. The Gonds, Koyas, and Naikpods are among the indigenous peoples who employ many known botanicals to treat rheumatic pain. Rheumatoid arthritis's main symptoms are pain and a developing incapacity to move, usually in the morning. Once the illness has been identified, a doctor or consultant will suggest a course of treatment. Rheumatism has no known cure, however certain treatments can help reduce or even reverse the disease's course. Rheumatism impairs a person's capacity to work and take care of oneself.[11] Rheumatism encompasses approximately 100 different illnesses but is not classified as any particular disorder. Rheumatism is sometimes referred to as "soft tissue rheumatism" or "regional pain syndrome." Our bones, muscles, ligaments, tendons, and joints are all impacted by rheumatic disorders. It is also occasionally referred to as musculoskeletal disorders. Joint discomfort, loss of joint motion, and inflammation (swelling, redness, and warmth in a joint or afflicted

area) are the most typical symptoms.[12–15]

1.2 EPIDEMIOLOGY

Among studies reporting the prevalence of rheumatoid arthritis (RA) in different populations, the rates ranged from 0.28% to 0.7%. Chopra et al. used the WHO-ILAR Community Oriented Program for Control of Rheumatic Diseases (COPCORD) census to perform a study in Bhigwan village, Pune, Maharashtra, in 1996. The study found that among approximately 6,000 people (2,998 men and 3,000 women) who were 16 years of age or older, the prevalence of RA was 0.6% for clinically diagnosed RA and 0.51% (95% CI: 0.3, 0.7) based on ACR diagnostic criteria. According to a COPCORD survey, the frequency was 0.7% in both urban and rural areas of Jammu. In the metropolitan Pune region, another COPCORD study with over 8,000 persons aged 16 and over (4,010 men and 4,135 women) revealed a raw.

Prevalence of RA diagnosed utilizing a raw frequency of clinically diagnosed RA of 0.45% (95% CI: 0.32, 0.63) and ACR criteria of 0.28% (95% CI: 0.18, 0.42). Finally, a fourth study conducted in Ballabgarh Township, Haryana, discovered that 0.75% of the 40,000 people who were 15 years of age or older had the condition.[16,17,18,19]

The following is a list of herbal plants that are used to cure rheumatoid arthritis. These plants have anti-inflammatory or analgesic qualities; utilizing a raw frequency of clinically diagnosed RA of 0.45% (95% CI: 0.32, 0.63) and ACR criteria of 0.28% (95% CI: 0.18, 0.42). Finally, a fourth study conducted in Ballabgarh Township, Haryana, discovered that 0.75% of the 40,000 people who were 15 years of age or older had the condition.[20]

1.3 ANALGESICS

Analgesics are the substances used to relieve pain without causing a loss of conciousness. These drugs work in various ways on both the central and peripheral nervous systems. Analgesics can be classified into synthetic& natural categories, with natural analgesic including opioid analgesics.[21] The international association for the study of pain (IASP) defines pain as an unpleasant sensory and emotional experience connected to exsisting or potential tissue damage, or described in relation to such damage. Pain is classified into two categories based on duration; Acute or Chronic.[22]

__ACUTE PAIN:__ Acute pain results from tissue damage and is typically short-lived, making it easier to identify its causes. It often arises due to inflammation, which occurs when tissues or nerves are harmed. This damage can stem from various sources, including surgery, cancer, infections, fractures, diabetes, and chemotherapy.[23]

__CHRONIC PAIN__:* It can be intermittent and is generally more challenging to treat than acute pain.[24]

__Nociceptors:__ These are pain receptors located outside of the spinal column in the dorsal root ganglion. The sensory nerve endings resemble small bushy branches (Theken KN, 2018).[25]

Prostaglandins are produced by cyclooxygenase 2 (COX-2) enzymes, which are released from damaged cells and contribute to pain sensations through receptors linked to G-proteins, increasing cAMP levels in the cells. Currently, non-steroidal anti-inflammatory drugs (NSAIDs) are used to manage pain. These drugs act quickly; however, they have notable side effects, including stomach issues, itching, blurred vision, dizziness, skin rashes, and potential liver damage. Additionally, NSAIDs can be costly. To reduce side effects and expenses, researchers are exploring natural medicines derived from herbs.[26] Natural ingredients found in herbs that alleviate pain include volatile oils (such as monoterpenes and sesquiterpenes), coumarin, alkaloids, organic acids, glycoside steroids, limonenes, cineols, saponins, and phenolic compounds like thymol and carvacrol, as well as flavonoids like quercetin (Theken, 2018).[27]

Herbs containing flavonoids have demonstrated various effects by inhibiting cyclooxygenase enzymes and tannins. The chemical compounds iridoid and flavonoid found in herbal extracts contribute to their analgesic properties.[28]

1.4 INFLAMMATION

The body uses inflammation as a defense mechanism against damaging stimuli including allergens and tissue damage. On the other hand, an unchecked inflammatory response can result in a variety of conditions that have a substantial financial impact on people and society, including cancer, metabolic syndrome, allergies, cardiovascular problems, and autoimmune diseases.[29] There are several medications available to manage and suppress inflammation, including steroids, nonsteroidal anti-inflammatory drugs, and immunosuppressants. These treatments often come with side effects, thus the objective is to use the minimum effective dose that provides maximum efficacy with minimal adverse effects. To enhance therapeutic outcomes and reduce unwanted side effects, the incorporation of natural anti-inflammatory agents into treatment regimens is essential.[30] Herbal medicines have gained attention in healthcare, highlighting the need for increased understanding of their properties. While complementary, alternative, and traditional medicines can offer valuable insights into herbal treatments, it is critical for modern medicine to validate these practices through scientific research before implementation. The purpose of this study is to assess the clinical evidence for the plants that are known to have anti-inflammatory properties.[31]

Vascular tissues' intricate biochemical reaction to

dangerous stimuli like infections, irritants, or damaged cells is inflammation. It acts as the organism's defense mechanism, working to get rid of dangerous stimuli and start the healing process of damaged tissue (Denko, 1992). The healing of wounds depends on this inflammatory process. But if inflammation is not controlled, it can lead to conditions like atherosclerosis, rheumatoid arthritis, and vasomotor rhinitis (Henson and Murphy, 1989).[32]

Classic symptoms of acute inflammation include pain, heat, redness, swelling, and most importantly, loss of function. These symptoms arise from the infiltration of serum and leukocytes into the affected tissues. In contrast, chronic inflammation is characterized by a gradual change in the types of cells present at the inflammation site, leading to concurrent destruction and repair of the tissue involved.[33]

According to Evans (1992), the cellular processes involved in inflammation can be categorized into four main types: a) alterations in blood flow driven by changes in smooth muscle cell activity leading to vasodilatation; b) changes in vascular permeability caused by cytoskeletal contractions in endothelial cells; c) the movement of phagocytic leukocytes to the inflammation site; and d) the process of phagocytosis.[34]

Early inflammatory responses in damaged tissues involve the release of various biologically active substances from polymorphonuclear leukocytes and lysosomal enzymes. Vascular effects are mainly regulated by kinins, prostaglandins, and vasoactive amines (such as histamine) released by mast cells, which increase vascular permeability and promote plasma exudation. Overall, the inflammatory response results from a complex interaction among blood cells, blood vessels, and the relevant tissue cells, functioning as a coordinated reaction involving numerous cells in response to an initial trigger(Henson and Murphy).[35]

1.5 RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a systemic condition characterized by symptoms such as rheumatoid nodules, vasculitis, inflammation of the eyes, and cardiovascular issues.[36] It is not inherited, although researchers suggest that certain genes may increase an individual's susceptibility to the disease. However, having these genes does not guarantee the onset of rheumatoid arthritis; typically, a "trigger," such as an infection or environmental factor, activates these genes. When triggered, the immune system reacts inappropriately by attacking the joints rather than protecting them, which can lead to the development of rheumatoid arthritis. As an autoimmune disorder, rheumatoid arthritis causes the body's immune system to mistakenly target healthy tissues. In a healthy joint, the lining is thin with few blood vessels, but in rheumatoid arthritis, the lining becomes thick and filled with white blood cells. These white blood cells release chemical substances like interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-alpha), resulting in pain, swelling, and joint damage. Recent findings have identified new cytokines, such as IL-17 and IL-18, that encourage synovial fibroblasts and chondrocytes in surrounding cartilage to produce enzymes that break down proteoglycans and collagen, contributing to tissue damage and the role of RANK ligand (RANKL) in chronic arthritis.[37,38] Through the release of various cytokines and inflammatory mediators, the synovium begins to proliferate and invade, a process known as pannus formation. The next stage, fibrosis, leads to decreased joint mobility, referred to as ankylosis. In cases of rheumatoid arthritis, the synovial membrane thickens, and cartilage is eroded, leading to its encroachment into the space between joints.

2. SYMPTOMS OF RHEUMATOID ARTHRITIS

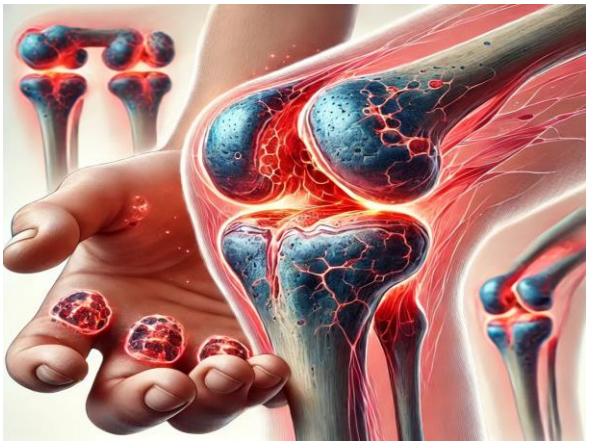
Symptoms of rheumatoid arthritis include joint swelling, pain, morning stiffness, disrupted sleep, fatigue, weight loss, and flu-like feelings. The condition is identified through the presence of rheumatoid factor, which consists of abnormal antibodies (IgG) found in the blood. These antibodies interact with antigens, forming complexes that result in pain and inflammation of the synovial membrane. The American College of Rheumatology stipulates that a diagnosis requires at least four of the following seven criteria:[39-40]

- Morning stiffness around joints lasting at least one hour
- Arthritis in three or more joints for a minimum of six weeks
- Arthritis affecting hand joints for at least six weeks
- Arthritis on both sides of the body for at least six weeks
- Presence of rheumatoid nodules under the skin
- Detection of rheumatoid factor in blood tests
- X-ray evidence of rheumatoid arthritis

Rheumatoid arthritis affects about 1-2% of the global population, with women being three times more likely than men to develop the condition. It accounts for billions of dollars spent annually on treatment and research.

Historically, before synthetic drugs were introduced, people relied on medicinal plants for disease treatment, as the healing properties of these plants were well-known. In the 19th century and earlier, natural extracts from plants were the primary source of folk medicine. The late 19th century saw the isolation of biologically active organic molecules for medicinal use, with salicylic acid, a precursor to aspirin, being isolated from willow bark in 1874. While several synthetic drugs are now standard treatments for rheumatoid arthritis, their adverse effects may hinder effective treatment, increasing the interest in herbal alternatives. This review focuses on the medicinal plants utilized in managing rheumatoid arthritis.[41,42,43]

2.1 COMMONLY AFFECTED JOINTS BY RHEUMATOID ARTHRITIS INCLUDE



Rheumatoid Arthritis (RA) primarily affects specific joints, including the small joints in the hands and feet, as well as the wrists, elbows, shoulders, knees, and ankles. Various factors can contribute to the onset of RA; for instance, a family history may increase risk, with genetics accounting for roughly 30% of the risk. RA is more prevalent in women, and hormonal variations can elevate the chances of developing the disease. While it typically appears between the ages of 40 and 60, anyone can be affected at any age, although older adults are more commonly diagnosed. It's crucial to note that RA is not contagious. Environmental influences, particularly smoking, have a strong association with RA.[44]

3. PATHOPHYSIOLOGY

1. Genetics*

Recent advancements in our understanding of the genetics of rheumatoid arthritis have arisen from extensive research utilizing advanced genetic techniques. Genome-wide association studies employing single nucleotide polymorphisms have identified numerous loci that increase susceptibility to the disease, many of which are linked to immune response mechanisms and some to other inflammatory conditions. The HLA system is particularly significant in relation to both the development and progression of rheumatoid arthritis; its strong correlation has prompted hypotheses regarding the role of peptide binding in the disease's pathogenesis. The HLA type not only helps predict the likelihood of developing the disease but also its severity, possible complications, and risk of mortality.[45]

While the HLA system is crucial, there are several other important loci associated with rheumatoid arthritis that influence mechanisms like cytokine signaling, altered co-stimulatory pathways, innate immune activation, and lymphocyte receptor activation thresholds, including CD28, CD40, and PTPN22.[46]

Patients commonly present with characteristic autoantibodies, such as rheumatoid factor, found in up to 70% of individuals. Another significant marker is the autoantibodies against citrullinated peptides (ACPAs), which exhibit greater specificity than rheumatoid factor.[47]

The disease's pathogenesis is closely linked to epigenetic factors that integrate both genetic and environmental influences. A recent large study identified ten risk positions associated with increased susceptibility to the illness. Typically, the biology of leukocytes and fibroblasts is modulated through DNA methylation and histone acetylation, and disruptions to these processes have been connected to rheumatoid arthritis. Current research is focused on examining the effects of microRNA treatments on patients with the condition.[48]

Autoimmune Response

Patients with seropositive rheumatoid arthritis typically experience a more severe form of the disease, marked by extensive joint damage and increased mortality rates. This severity may stem from the formation of immune complexes that activate complement pathways. The discovery of antibodies against citrullinated self-proteins marked a significant milestone in diagnosing rheumatoid arthritis. ACPAs can often be detected in the serum up to ten years before a formal diagnosis is made, indicating a stage of pre-rheumatoid arthritis. As time progresses, concentrations of ACPAs and associated cytokines rise, leading to the development of clinical symptoms of the disease. The presence of ACPAs across various immunoglobulin isotypes suggests the involvement of T-cell assistance.[49]

Osteoclast activation, which contributes to bone loss, can happen through Fc-receptor involvement or immune complex formation. When treating diseases like rheumatoid arthritis, levels of specific antibodies such as ACPAs and RF (rheumatoid factor) usually decrease or even disappear. Other antibodies, like acetylated peptide autoantibodies and anti-citrullinated antibodies, have also been detected in patients.[50]

Inflammation

Joint swelling is a sign of inflammation in the synovial membranes, where the immune system is activated. This causes immune cells (leukocytes) to enter the synovial space, leading to joint damage. Both the adaptive and innate immune systems are involved in this process, which can result in joint destruction. Studies suggest there are different types of synovial involvement, including lymphocytic-dominant, fibroid-dominant, and myeloid-dominant, and identifying these types helps guide treatment.[51]

Inflammation is driven by cytokines (signaling molecules like TNF, IL-6) and chemokines, which stimulate the immune response. These molecules trigger the activation of endothelial cells and immune cells in the joints, further inflaming the area. As fibroblasts activate osteoclasts (bone-resorbing cells), cartilage is also damaged by enzymes, contributing to joint degradation.[52]

4. Clinical Evaluation

A detailed history and physical exam are essential for diagnosing rheumatoid arthritis (RA). The disease often begins with non-specific pain, joint tenderness, and swelling, which can be slow to progress. Symptoms like morning stiffness, polyarthralgia (pain in many joints), and involvement of small joints are common. RA typically affects joints symmetrically, especially in the hands, and the presence of these symptoms helps differentiate RA from other conditions.[53]

Extra-Articular Manifestations and Comorbidities

If untreated, RA can lead to complications outside of the joints, such as lung disease, vasculitis, heart problems, and even lymphoma. However, proper treatment significantly reduces these risks. Drugs like methotrexate and TNF inhibitors are effective but can sometimes cause nodules that may resemble those seen in RA itself.[54]

5. TREATMENT

In treating Rheumatoid arthritis, the main goals are to prevent lasting joint damage and manage inflammation, with pain relief also being essential. The cornerstone of rheumatoid arthritis treatment involves disease-modifying anti-rheumatic drugs and newer biologic medications. Corticosteroids, which are steroid hormones produced by the adrenal glands, play a significant anti-inflammatory role but can have long-term side effects; thus, they should be used sparingly and at the lowest effective dose to allow time for DMARDs to work. Non-steroidal anti-inflammatory drugs (NSAIDs) can alleviate pain and inflammation associated with arthritis but do not prevent disease progression or damage.[55]

The synovium, a delicate lining in the joints, has various important functions, including the production of joint lubricants like hyaluronic acid and structural collagen. Typically, the synovial lining is 1-3 cells thick, but in Rheumatoid arthritis, it can thicken to 8-10 cells. The subintimal region of the synovium, which usually has few cells, becomes heavily infiltrated with inflammatory cells such as T and B lymphocytes, macrophages, mast cells, and mononuclear cells in RA. Cartilage, mainly composed of type II collagen, is normally flexible and absorbs stress, while bone, primarily made of type I collagen, experiences destruction in RA, possibly due to substances released by activated synovial cells. The synovial cavity contains a small volume of viscous fluid, rich in hyaluronic acid and filled predominantly with neutrophils, indicating high levels of inflammation.[56]

6. HERBAL FORMULATION DATA

Sr.No.	PLANT	PLANT SPECIES	FORMULATION	TABLET/ CAPSULE/ SYRUP	REFERENCES
1	Tulsi	Ocimum sanctum	Immunity booster	Syrup	K. N. Nair, "The Medicinal Plants of India", 2005
2	Ashwagandha	Withania somnifera	Stress reliever	Capsule	P. K. Warrier, "Indian Medicinal Plants", 1995
3	Neem	Azadirachta indica	Antibacterial formulation	Tablet	K. Biswas, "Biological Activities of Neem", 2002
4	Amla	Phyllanthus emblica	Vitamin c supplement	Syrup	A. Kapoor, "Ayurveda and Herbal Medicine", 2010
5	Giloy	Tinospora cordifolia	Immunity enhancer	Tablet	R. Sharma, "Herbal Drug Technology", 2012

7. List of Herbal plants which is used in the treatment of Rheumatoid Arthritis. These plants have analgesic or anti- inflammatory properties

- Ashwagandha
- Turmeric
- Ginger
- Black pepper
- Rosemary
- Giloy

- **ASHWAGANDHA (WITHANIA SOMNIFERA LINN)**

Common Name: Winter cherry, withania root.
Biological Name: Withania somnifera Linn.
Biological source; it is obtained from the roots & sometime the leaves.
Family: Solanaceae

CHEMICAL CONSTITUENTS: It contain alkaloids, steroids, flavonoids and phenols.
Ashwagandha is also known as Indian ginseng, It is an ancient plant used in traditional Indian medicine(Ayurveda and Unani). Its roots have medicinal properties due to the presence of alkaloids and steroid lactones.
It grows in dry, sub-tropical regions of India (Rajasthan, Punjab, Haryana, etc.)
Roots contain alkaloids like withanine, tropine, and somniferine.
Two acyl glucosides, sitoindoside-7 and sitoindoside-8, are also present in the roots.

Ashwagandha is used to treat various health issues, including: Anxiety and stress, Neurological disorders, Inflammation, Asthma, Ulcers. It provides various health benefits or long lasting result. It prevent or slow down

tumor growth. It improves aging, anemia, arthritis, and fatigue.[57,58]

- **TURMERIC (CURCUMA LONGA LINN)**

Common Name: Turmeric root, Indian saffron
Biological Name: Curcuma longa Linn.
Family: Zingiberaceae.
Chemical Constituents: It contain (Cucuminoids-curcumin, demethoxycurcumin), volatile oils-(turmerone, atlantone), Resins, Flavonoids, Alkaloids.

Turmeric is grown for its underground stem in countries such as India, China, Sri Lanka, Indonesia, Jamaica, and Peru. It contains essential oils, resins, starch granules, and yellow compounds referred to as curcuminoids. The primary compound among the curcuminoids is curcumin. Curcumin, a natural substance found in the rhizomes of the Curcuma longa plant, has shown anti-inflammatory properties [56]. It is utilized in the healing of wounds, protection of the liver, and safeguarding nerve health, among other uses. Additionally, it exhibits antimutagenic, antispasmodic, antimicrobial, and anticancer properties. Administering a low daily dose of purified curcuminoids (4 mg of total curcuminoids per kg of body weight) through injection reduced joint inflammation during both acute and chronic stages of arthritis.[59,60,61]

Originating from the Curcuma herb, turmeric is an essence. Turmeric's polyphenol extract, curcumin, has long been used in traditional Chinese medicine and Ayurvedic treatments due to its strong antioxidant properties.[62] Numerous related mechanisms are connected to curcuma's anti-inflammatory properties. It has been demonstrated that curcuma therapy significantly lowers the specific production of inflammatory mediators, such as interleukin (IL)-1, tumor necrosis factor-alpha (TNF-), IL-8, NO, and a variety of MMPs, by blocking the functions of the NF-B, protein kinase M (Akt), and MAPK signaling pathways [63,64]. It has been demonstrated that curcuma inhibits COX-2, which lowers prostaglandin synthesis.[65] The anti-osteoarthritic properties of curcumin and turmeric extract have recently studied.

- **GINGER(ZINGIBER OFFICINALE)**

Common Name: Ginger root.
Biological Name: Zingiber officinale.
Family: Zingiberaceae.
Chemical constituents: It contain Alkaloids, Flavonoids, Phenolic acids, Zingiberene, 6-Gingerol, 8- Gingerol and Resins.

GINGER (ZINGIBER OFFICINALE)(Ahmad et al., 1993, Karthika et al., 2018): Joint swelling is treated with ginger rhizome extract. Ginger has been shown to help rheumatoid arthritis patients with their pain and swelling.

Osteoarthritis and people who have muscle soreness for three months to two and a half years without any negative side effects. The primary goal is to investigate ginger juice's potential as an analgesic.

The active ingredients in ginger inhibited the Cox (cyclooxygenase) and lox (lipoxygenase) pathways involved in the metabolism of arachidonic acid. Ginger is one of the best herbal supplements available. Although it is grown in Africa, the Caribbean, Australia, Mauritius, Taiwan, and India, its native region is South East Asia. over 30% of Indian manufacturing. Inorganic substance, fiber, fat, starch, volatile oil, and residual moisture make up ginger. oxygenated monoterpine, sesquiterpine hydrocarbons, and hydrocarbons are all present in ginger oil. Ginger is utilized as a flavoring ingredient, stimulant, carminative, aromatic, and stomachic. It is used to cure diarrhea, vomiting, and nausea. Antioxidant, anti-inflammatory, antiseptic, anticarcinogenic, antifungal, and antimicrobial properties are also employed. Physicians prescribe ginger extract as one of the most efficient treatments for arthritis joint discomfort. The primary components are sesquiterpenoids, including zingiberene. Its anti-inflammatory properties are attributed to natural substances called sesquiterpene lactones (SLs).[66,67,68,69]

- **BLACK PEPPER**

Common NAME: Pepper
Biological Name: Piper nigrum Linn.
Family: Piperaceae.
Chemical Constituents: it can Alkaloids (Piperine, piperanine, piperettine, pipercine) Terpenes (Myrcene, sabinene, 3-Carene), essential oils.

Native to South India, black pepper is grown there. Additionally, Indonesia, Brazil, Malaysia, and Sri Lanka cultivate it. India is the world leader in the production of this medication. The alkaloid piperine, volatile oil, strong resins, piperidine, and starch are all found in pepper. It has stimulating, stomachic, carminative, and fragrant properties. It makes the stomach juices more secreted. Additionally, it makes some medications more bioavailable. Black pepper is separated from piperine. In patients with carrageenan-induced acute paw arthritis 1, piperine given orally at doses of 20 and 100 mg/kg/day for eight days reduces arthritic symptoms.

In addition to being a common spice in human diets, black pepper (Piper nigrum) is also utilized in many Asian countries as a medication, preservative, and scent. It is generally recognized that an extract of piperine, the active phenolic component, has positive physiological effects. It increases the bioavailability of certain medicinal medications, lowers lipid peroxidation, protects against oxidative damage, and stimulates the pancreatic digesting enzymes. Furthermore, it has been shown to have anti-inflammatory properties in rat models of granuloma caused by cotton pellets, croton oil-induced granuloma pouch, and carrageenan-induced rat paw edema. The enzymes 5-lipoxygenase and COX-1,

which are in charge of leukotriene and prostaglandin production, respectively, have been demonstrated to be inhibited in vitro by components of the piper species.[70,71]

- **ROSEMARY**

Common Name: Saliva rosmarinus.
Botanical Name: Rosmarinus officinalis.
Family: Lamiaeceae.
It has both analgesic or anti- inflammatory actions, which contribute to its pain relieving & anti-inflammatory effects.

Analgesic action:
Carnosic acid: it inhibits pain signaling pathway
Rosmarinol: it activates pain- relieving receptors.

Anti-inflammatory action:
Ursolic acid: it inhibits inflammatory enzymes.
Carnosic acid: it suppresses inflammatory cytokines.

In an open-label study, the effects of rosemary extract were evaluated in patients with fibromyalgia, rheumatoid arthritis, and osteoarthritis (OA) over a 4-week period. Patients who showed an increase in hs-CRP, an indicator of the presence of inflammation, showed a significant decrease in inflammation related to pain scores during treatment, but fibromyalgia scores did not remit.[70] According to research supporting R. officinalis's anti-inflammatory potential at the molecular level, rosmarinic acid can readily disrupt complement system activation by blocking C3b attachment; a very low dose of 34 µM is needed to achieve this effect.[72]

- **GILOY (TINOSPORA CORDIFOLIA)**

Common Name: Guduchi.
Biological Name: Tinospora Cordifolia.
Family: Menispermaceae.

Tinospora cordifolia, commonly referred to as Giloy, is an Ayurvedic climbing shrub belonging to the Menispermaceae family. It is also known by various names including Guduchi, Heart-leaved moonseeds, Amrita, Gurach, and Tinospora.[73] Renowned for its remarkable medicinal properties, it has received FDA approval for its benefits. Native to India, Giloy thrives in tropical and subtropical regions at altitudes above 600 meters, with its distribution extending up to 1200 meters from Kumaon to Assam and further into West Bengal, Bihar, the Deccan region, Karnataka, and Kerala. Additionally, Giloy is found in countries like Myanmar, Malaysia, Vietnam, Bangladesh, and parts of North and South Africa.[74]

This vigorous climber can grow over the tallest trees in forests, featuring several long, twisting branches. Its aerial roots are squarish in shape and develop from mature branches, appearing in colors that range from light grey-brown to creamy white, with a bitter taste and no odor. The plant's stem is succulent, long, and cylindrical with a slight twist. The starch derived from the stem, known as "Guduchi Sava," is highly nutritious and beneficial for digestion. The leaves measure about 10-15 cm in length and are green, transitioning to yellowish-green in mature specimens; these leaves are rich in protein, calcium, and phosphorus.[75]

Giloy sticks are frequently recommended by various Ayurvedic institutions as a means to enhance immunity against COVID-19. Patanjali Ayurveda, an organization in India focused on Ayurvedic practices, has developed a medicinal kit called "coronil," with Giloy, along with ashwagandha and tulsi, being key ingredients.[76]

8. Risk Factors

In addition to genetic predispositions, several environmental factors have been linked to the onset of rheumatoid arthritis. These include lower educational achievement, poor socioeconomic conditions, and smoking. While periodontal disease has been cited as a risk factor, its link is not firmly established. Certain microorganisms, such as Escherichia coli, Proteus mirabilis, and Epstein-Barr virus, have also been associated with the disease, potentially due to molecular mimicry.[77]

Animal studies have highlighted a connection between the gut microbiome and the emergence of rheumatoid arthritis, which may also extend to other chronic inflammatory diseases. Research is ongoing to validate this connection in humans, with findings indicating microbial changes between affected and unaffected individuals, particularly in salivary, oral, and gastrointestinal areas. These alterations have been correlated with varying treatment responses, although the underlying mechanisms remain unclear.[78]

9. CONCLUSION

Research on medicinal plants reveals their potential not only for treating rheumatism but also for various other ailments. The effectiveness of these plants is linked to their bioactive compounds, which target specific diseases. Historically, these plants have been recognized for their pharmaceutical benefits in the treatment of rheumatism. Unlike synthetic drugs, medicinal plants are considered safe and carry no side effects. Rheumatism is associated with inflammation and pain, and the studied plants exhibit a range of anti-inflammatory properties. Additionally, these anti-inflammatory plants can be beneficial for other inflammation-related conditions. As a result, effective natural compounds have been identified for treating rheumatism, confirming their value in therapy.

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