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Review Article

Medicinal Plants with Potent Anti-inflammatory and Anti-arthritic Properties found in Eastern Parts of the Himalaya: An Ethnomedicinal Review

Bapan Banik[1,2], Sanjoy Das[2], Malay Kumar Das[2,*]

ABSTRACT

Since ancient times, medicinal plants performing a very essential role as a source of medicine and their medicinal properties have been well documented in the various traditional systems of medicine including Indian, Chinese and Korean medicines for the management of chronic inflammatory disorders. Arthritis is one of the harmful chronic inflammatory diseases and its pain vastly affects millions of people throughout the world. The inflammatory process of arthritis can stride very promptly causing swelling and destroying bone or cartilage cross the joints by various inflammatory mediators. Presently most commonly prescribed medication for the management of inflammation or arthritic pain is the NSAIDs, DMARDs and corticosteroids. Their prolonged use may cause a high spectrum of toxic effects. Hence, there is a demanding need to develop alternative therapeutic agents with minimum toxic effects. The Eastern Himalayan region is richly furnished with multifarious medicinal plants with potent anti-inflammatory and/or anti-arthritic properties that have been traditionally used by the local people. Few studies have been convened in Himalayan medicinal plants to validate their medicinal values. Thus, from the knowledge of traditional medicine and research on plant materials, one might be able to discover newer and cost-effective drugs for treating diverse forms of inflammation. This review highlights the medicinal plants from the Eastern Himalayan region which showed promising therapeutic activity against inflammatory diseases as well as novel formulation approaches of these medicinal plants.

Key words: Medicinal plants, Traditional medicine, Eastern Himalayan region, Inflammatory mediators, Anti-inflammatory, Anti-arthritic.

Bapan Banik[1,2], Sanjoy Das[2], Malay K Das[2,*]

[1]Department of Herbal Science and Technology, ADP College, Nagaon, Assam, INDIA.
[2]Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh, Assam, INDIA.

Correspondence

Dr. Malay K Das

Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh-786004, Assam, INDIA.

Phone no : +91-9954229317

E-mail: mkdps@dibru.ac.in

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INTRODUCTION

Inflammation is complex biological feedback of the immune system that can be initiated by several factors, such as damaged cells, pathogens (virus, bacterial or fungal infections) and hazardous chemical agents.[1] The process of inflammation is characterized by swelling, redness, heat, pain, loss of tissue function, which is resulting from local immune response, vascular dilation, leukocyte reinforcement and release of inflammatory mediators that are responsible for progression, persistence and eventual resolution of the acute state of inflammation.[2,3] Acute inflammation is an inborn, paramount and stereotyped response that is mainly occurring in the short duration of time via tissue injury.[4] If the inflammation may not appear in the acute phase or it is uncontrollable, there by inflammation may convert into a chronic phase. Chronic inflammation is long-term inflammation lasting for prolonged periods and plays a primary role in global burdening by contributing to a variety of chronic inflammatory diseases like cancer, diabetes, heart disease and arthritis.[5]

Apart from the various chronic inflammatory diseases, arthritis is a severe issue for both the medical and pharmaceutical communities because of its unknown pathophysiology. Arthritis is a chronic inflammatory condition and its pain affects millions of people worldwide. According to estimates, there is 1-2% of the world population is affected by arthritis and among them, women are three times more prone to the disease as compared to men.[6-8] There are different types of arthritis that have been described which are impacted public health. The most common types are osteoarthritis, which is known as non-inflammatory arthritis and rheumatoid arthritis which is known as inflammatory arthritis.[9,10] The main symptoms of arthritis include pain, stiffness, swelling, loss of joint function, or inflammation of the synovial membrane. If the arthritis is not treated timely, it may lead to a destruction of joints through the erosion of cartilage and bone resulting in permanent disability. Early treatment is important to eliminate symptoms, control disease activity, slow progression and counter joint destruction.[11-13] Presently, the most commonly prescribed classes of medication for the management of inflammation or pain is the non-steroidal

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anti-inflammatory drugs (NSAIDs), corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs). Their elongated use leads to a high spectrum of toxic or adverse reactions. Therefore, research is going on for relatively effective alternatives, non-toxic, less expensive therapies for treating inflammation or arthritis.[14-16]

Currently, medicinal plants are promising or vital resources for developing novel therapeutically active pharmaceutical products due to their less toxicity in comparison to synthetic drugs.[17] The exploitation of medicinal plants in the health care sector had been started long years ago for preventing and treating human diseases. The global market revenue of medicinal plant derivatives transcends $100 billion per year and its importance is growing rapidly.[18,19] As reported by WHO, from 119 plant-originated medicines, around 74% are utilized in the modern class of medicine in ways that are directly connected with their traditional practices as plant medicines by native cultures.[20] For that reason, modern medicine has also started accepting plant-based medicine or herbal medicine. Herbal medicine has a number of positive reputations in the treatment of chronic inflammatory disorders like arthritis.[21,22] A bunch of medicinal plants has been screened with various anti-inflammatory bioactive compounds like alkaloids, glycosides, flavonoids, coumarins, terpenoids, phytoestrogens, anthraquinones, thymoquinone, xanthones, tannins, saponins, lignans, essential oils and catechins. However, the research in natural products is greatly impacted by their geographical region, which has shouted the diversity and availability of medicinal plants.[23,24]

Himalaya is a treasure of various natural therapeutic plants due to the geographical diversity and variable climatic conditions, particularly the Eastern part where Nepal, Bhutan, Indian state Arunachal Pradesh, Sikkim, Darjeeling provinces are located. The eastern part of the Himalayas boasts a gold mine of medicinal plants given the region's climatic variation and diverse ecological habitats, such as mountains, hills, valleys, lakes and rain forests.[25-27] These medicinal plants have portrayed key aspects in the lives of indigenous peoples by delivering products for foods as well as medicines or traditional curative agents since ancient times.[28] But due to the scarcity of competent pharmacological exploration, Himalayan plant diversity is still restricted to their ethnomedicinal practices.[29] The traditional systems of medicine depend on the experience and practical knowledge of a distinctive local healer with respect to diagnosing and treating disorders utilizing natural materials.[30,31] Therefore, information reported by the traditional healers of the Eastern Himalayan region is invaluable for further research in the field of ethnopharmacology and the discovery of newer lead molecules. In this review, an attempt has been made to compile the medicinal plants from the Eastern Himalayan region, which have possessed potent therapeutic activity against chronic inflammatory and arthritic conditions along with novel formulation approaches of these medicinal plants.

The methodology of data extraction

As this study is an important research thus, thorough literature survey was conducted through online databases like PubMed, Science Direct, SpringerLink, Wiley Online Library, Google Scholar and ResearchGate. The manuscripts title and abstract of the articles were explored from earlier stated databases using the corresponding keywords such as medicinal plants, inflammation, arthritis, the biodiversity of the Eastern Himalayan region, ethnomedicine, traditional healers to validate the plants having good anti-inflammatory and anti-arthritic potential.

Medicinal plant diversity of Eastern Himalayan region

The Himalayas are one of the richest ecosystems on earth and blessed with a huge quantity of precious medicinal plants because of their unique topographical, ecological, geographical, climatic and physiographical conditions.[32-34] Medicinal plants originated from the Himalayan region have an enormous historical background, written records of Himalayan plants being used as medicine found in old texts of Rig-Veda (4500 BC and 1600 BC), which describes 67 plants. Afterward, Ayurveda also describes the medicinal importance of 1200 plants.[35] In terms of recorded historical accounts, the use of Himalayan medicinal plants has increased in different other traditional health care systems, including Indian Homeopathic, Chinese, Tibetan, Korean and Folklore.[36] However, the exact depiction of the Himalayan medicinal plants is being utilized for initial health care and subsistence is still unpredictable. The local healers have formidable knowledge and experience in preparing traditional medicines for treating various kinds of diseases.[37,38]

The Eastern region of the Himalayas located at the junction of the Indo-Malayan, Palearctic and Sino-Japanese realms, stands out as being one of the richest reservoirs of the valuable medicinal plant species.[39] This region lies between the longitudes 88°5′-97°5′ East and altitudes 26°40′-29°30′ North, covers a total area of 93988 km^2, comprising the Eastern part of Nepal, Bhutan, Darjeeling Hills, Sikkim and Arunachal Pradesh in India (Figure 1).[40] The biodiversity of the Eastern region is exceptionally unique, rich with endemic biological taxa most of them being significant medicinal plants. It has been estimated that approximately 800 species of medicinal plants are reported from Nepal, 600 species from Bhutan, 140 species from Darjeeling, 36 species from Sikkim and 500 species from Arunachal Pradesh.[41-45] Interesting fact is that almost all medicinal plant species of the Eastern region are used in traditional medicinal practices by indigenous or ethnic people or local healers.[46] The local traditional healers have high knowledge and understanding of a wide range of medicinal plants that are useful to cure common ailments, in particular, skin diseases, stomach disorders, respiratory infections, inflammation-related diseases. Healers consider that medicinal plants are more efficient with very less adverse effects as contrast to new allopathic drugs; as a result, medicinal plants have regained a wide recognition among the scientific community in the field of herbal medicine.[47-50] However, many medicinal plant species seem to drastically decline due to over exploitation, unsustainable harvesting and lack of appropriate strategies for screening. And traditional knowledge of the use of various medicinal plant species is still intact with the indigenous people who are scientifically unexplored and is being eroded through modernization, loss of plant biodiversity, or lack of written documents.[51-53] Therefore, the assessment and documentation of ancestral knowledge of indigenous people on traditional plant medicines have become a recognized tool for

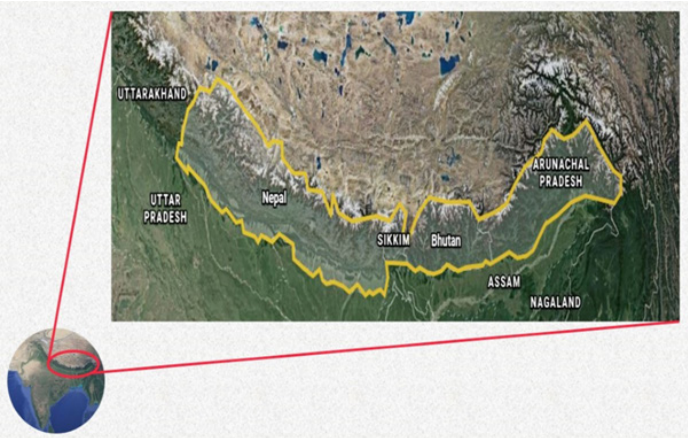

Figure 1: Google Earth© Map View of Eastern Himalayan Region. Eastern Region comprising countries Nepal, Bhutan, Indian States Sikkim and Arunachal Pradesh are highlighted in yellow color.

the development of new drugs and pharmaceuticals in modern medicine to treat various diseases like inflammation or arthritis.

Principal mediators of inflammation in arthritis

Inflammation has been found to play a very critical character in the pathogenesis of arthritis by initiating with developing the pain. During an inflammatory response, the molecular templates are perceived by receptors from innate immunity resulting in the production of diverse inflammatory mediators.[54,55] These mediators serve as important regulatory factors that control the generation and resolution of inflammation by altering the intracellular signaling pathways, gene expression and nature of joint tissues.[56,57] The changes in cellular signal transduction lead to elevated activation of the inflammatory pathways, the release of more inflammatory agents and enzymes. As a result, the anatomical and physiological mechanisms of the joint are changed.[58] The various inflammatory mediators involved in the progression of arthritis are discussed in Table 1.

Anti-inflammatory and Anti-arthritic potential of Eastern Himalayan medicinal plants

Nature has sanctified us with a tremendous wealth of medicinal plants. The medicinal plants are extensively allocated throughout the world as a feasible source of therapeutic agents for the cure and prevention of various inflammation-related disorders, namely arthritis, which is still one of the major health problems.[75] The scientific investigation explored the favorable property of medicinal plants in the management of arthritis because of the presence of various active phytoconstituents i.e., glycosides, alkaloids, phenolic compounds, terpenoids and flavonoids. These phytoconstituents produce desired pharmacological action in

Table 1: Inflammatory mediators and their desired functions in arthritis.

Sl. no.	Inflammatory mediator	Desired function	Ref (s)
01.	Inflammatory and anti-inflammatory cytokines	Inflammatory cytokines are produced by immune system cells that mediate innate immune response or inflammation. The Inflammatory and anti-inflammatory cytokines include TNF-α, IL-1, IL-1β, IL-4, IL-6, IL-9, IL-10, IL-13, IL-15, IL-17, IL-18 and IFNγ which are responsible for depriving metabolic homeostasis of tissues making joints by stimulating catabolic and destructive processes and play a key role in the arthritis pathogenesis.	[59,60]
02.	Inflammatory chemokines and chemokine receptors	Inflammatory chemokines are chemotactic cytokines that control the migration of the immune cells to the synovial tissue. Chemokines are categorized into CXCL (CXCL4, CXCL5, CXCL8/IL-8, CXCL10 and CXCL13), CCL (CCL2, CCL3 and CCL4), XCL (XCL1) and CX_3CL (CX_3CL1) supergene family and receptors for these chemokines are CXCR, CCR, XCR and CX_3CR. These chemokines recruit more immune cells leading to joint demolition and contributing pathogenesis of arthritis.	[61,62]
03.	Reactive Oxygen Species (ROS)	ROS are free radicals comprising oxygen molecules include OH^-, H_2O_2, O_2^- and OCl^- which modulate the intracellular signaling processes, apoptosis, synthesis and degradation of the extracellular matrix, synovial inflammation, mitochondrial and subchondral bone dysfunction. ROS can contribute to arthritis pathogenesis by the accession of membrane oxidation, bone resorption and irrevocable damage to the proteins/DNA in synovial tissues.	[63,64]
04.	Reactive Nitrogen Species (RNS)	RNS is the type of molecules derived from the rapid reaction of NO, $ONOO^-$ and other free radicals such as O_2^- via the enzymatic activity of inducible nitric oxide synthase 2 (NOS2). The increased production of RNS in synovial tissues has been linked to both protective and proinflammatory mechanisms associated with tissue damage in inflammatory disease. RNS can increase the proliferative synovitis and articular cartilage loss leading to arthritis progression.	[65,66]
05.	Cyclooxygenase metabolites	Cyclooxygenase (COX) is a key enzyme playing a crucial role in the biosynthesis of prostaglandins (PGs). COX catalyzes the two sequential reactions, firstly conversion of arachidonic acid (AA) to PGG_2 and latterly PGH_2/PGE_2. There are two isomeric forms of COX subsist, i.e., COX-1 and COX-2. COX-2 is associated with the inflammatory responses by inducing pro-inflammatory cytokines mainly, IL-1/TNF-α and enhanced synthesis of PGs in synovial tissues. Thus, the formation of arthritis and consecutive abrasion of articular cartilage or bone.	[67,68]
06.	Growth factors and transcription factors	Growth factors and transcription factors have crucial roles in the inflammatory response, neovascularization in painful joints and maintenance of immune effector cells. The growth factors involved in the pathogenesis of arthritis include fibroblast growth factors (FGF), vascular endothelial growth factor (VEGF), transforming growth factor (TGF-β) and transcription factors include NFκB, activator protein 1 (AP-1), STAT which regulate the expression of inflammatory target genes and modulate apoptosis synovial tissues.	[69,70]
07.	Intracellular signaling pathways	Abnormal intracellular signaling pathways playing a crucial role in arthritis. The involvement of deregulated Janus kinase (JAK)/signal transducers and activators of transcription (STAT), RANKL, mitogen-activated protein kinase (MAPK), phosphatidylinositide-3-Kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR), pathways and crosstalk endorse aggressive immune cell and synoviocyte proliferation, altered innate immunity, as a result, progression of arthritis.	[71,72]
08.	Major immune cells	Immune cells primarily, macrophage, B-cells, T-cells, dendritic cells (DCs) play an imperative function in arthritis pathogenesis. These cells can either circulate in peripheral blood or exist in synovium and secrete physiologically valuable proteins like rheumatoid factors (RFs), anti-citrullinated protein antibodies (ACPA). DCs along with macrophages and B-cell growth factors (toll-like receptor/TLR) have the potentiality to accede antigen to T-cells, leading to the evolution of adaptive immune responses and the formation of tissue destructive cells.	[73,74]

the human body by various basic mechanisms like downregulation of inflammatory signaling pathways, such as nuclear factor-kappa B (NF-κB) pathways mediates the release of proinflammatory cytokines (tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-8, IL-10, IL-1β) and inhibition of prostaglandin synthesis, suppression of oxidative stress, inhibition of cartilage degradation, abnormal intracellular signaling pathways as well as the increase of antioxidant potential.[76-80] The several modern drugs are used for controlling and suppressing the inflammatory response of arthritis-like NSAIDs, DMARDs, corticosteroids and monoclonal antibodies (mAbs). The long term usage of these drugs has resulted in toxic adverse effects, which include renal impairment, dyspepsia, peptic-ulcer, cardiovascular complications, gastrointestinal bleeding, liver cirrhosis, respiratory tract infection, bone marrow suppression, osteoporosis, diarrhea, skin rashes, itching, or severe uncontrolled infections.[81-84] For these consequences, newer and safer drugs are continuously being searched (Figure 2). Various scientific and research organizations currently conducting extensive research on plants or plant materials converged from the rain forests and hilly places for their potential medicinal values.[85] The tropical rainforest plants are biologically and chemically diverse resources as they synthesize a wide spectrum of bioactive compounds, which are acting as defense agents against inflammation or arthritis while minimizing the adverse effects towards host cells.[86-88] In the foothill zone of Eastern Himalayas, very minor documentation are attainable on species fullness of the ethnomedicinal plants and only a few species are listed to have medicinal properties, which are reserved in the traditional knowledge of the local people.[89] Thus, from the knowledge of traditional or indigenous medicine and research on plant materials, one might be able to discover newer and cost-effective drugs for treating inflammation or arthritis. The anti-inflammatory and antiarthritic potential of various medicinal plants found in the Eastern Himalayan region are discussed below.

Plant *Adhatoda vasica*

Adhatoda vasica (Family-Acanthaceae), commonly referred to as "Adosa or Malabar" nut tree or Vasaka is a well-accepted plant in traditional Ayurveda and Unani systems of medicine. The plant has been used in the indigenous system of medicine in India for over 2000 years.[90] It is widely spread all over India, Sri Lanka, Pakistan, Afghanistan, the lower Himalayan regionand is progressively introduced to other countries like China, Taiwan, Hong Kong, Ethiopia, Germany and also Southeast Asia.[91,92] *A. vasica* is acustomarily evergreen shrub, perennial, grows at a height of about 1 to 2.5 m with dark green color leaves and white or purple flowers embedded plant.[93] The phytochemical studies of the various parts of *A. vasica* revealed the presence of numerous bioactive compounds, namely alkaloids, glycosides, sterols, polyphenolics tannins, saponins, flavonoids and leaves and roots are rich in essential oils, Vitamin C and carotene.[94,95] The principal constituents of the plant are vasicine and vasicinone (quinazoline alkaloids) is biologically active and exert effective pharmacological actions against inflammation and arthritis.[96-98] Apart from the anti-inflammatory and anti-arthritic efficacy, the leaves, flower, fruits, barks, roots of *A. vasica* are commonly used in the treatment of bronchitis, cough, asthma, colds, fever, wound healing, tuberculosis, diarrhea, diabetes, jaundice and also skin disease from ancient times.[99-102] However, the scientific rationale and mechanisms by which it functions in these diseases are yet to be discovered. In a study, the anti-inflammatory properties of pyrroloquinazoline alkaloids from *A. vasica* roots was evaluated using carrageenan and Freund's Complete Adjuvant (FCA)-induced paw edema in rats. The results suggested that vasicine exhibited the most potent anti-inflammatory effects (59.51%) after carrageenan injection and vasicinone showed the maximum rate of inhibition (63.94%) after FCA injection by hindering the prostaglandin synthesis, which is involved in the process of inflammation and pain perception.[103] In another study, the anti-arthritic potential of methanolic extract of *A. vasica* leaf was evaluated against autoimmune arthritis in male Swiss albino mice using the Collagen-induced arthritis (CIA) model. The effect of *A. vasica* in the inflammatory response during CIA was investigated by measuring C-reactive protein, diverse cytokines in serum, spleen and synovial tissue. The observed results revealed that *A. vasica* is capable of regulating oxidative stress during CIA and thus, downregulating systemic release of pro-inflammatory cytokines, neutrophil accumulation and Toll-like receptors-2 (TLR-2) expression in serum, spleen and synovial tissues, which dictated its protective effect against rheumatoid arthritis.[104]

Plant *Alstonia scholaris*

Alstonia scholaris (Family-Apocynaceae), habitually known as "Devils Tree or Dita Bark Tree" is a traditionally valuable medicinal plant that has long been used in Ayurveda, Homoeopathy, Unani and Siddha or Tamil class of alternative medicinal systems to cure various human and livestock diseases.[105] The plant is grown in India, China, Africa, Southeast Asia, Sri Lanka, Malaysia, Latin America, Australia and Solomon Islands. It is widely cultivated throughout the Indian subcontinent to the sub-Himalayan region.[106-108] *A. scholaris* is an evergreen tropical tree up to 17 to 20 m in height having grayish rough bark, white milky latex, elliptic-oblong leaves, greenish-white flowers, long slender to cylindrical fruits follicles containing long surface covered seeds with brown ciliate hairs on the ends.[109] The various parts of the plant *A. scholaris* have generally been a huge source of alkaloids, steroids, terpenoids, iridoids, coumarins, phenols, flavonoids, tannins, carbohydrates, amino acids, vitamins, glycosides, volatile oils and diverse pigments. Alkaloids stand as major constituents in this plant amid the compounds present in the plant. To date, nearly 169 alkaloids have been identified from the leaves, roots, stems, bark, fruits and flowers of *A. scholaris*.[110-112] This chemical exploitation of *A. scholaris* is, therefore, likely to offer several pharmacological properties like antioxidant, anti-inflammatory, analgesic, anticancer, antimicrobial, antiplasmodial, antiulcer, antidiarrheal, antimutagenic, antimalarial, antifertility, antileprosy, wound healing, radioprotective, hepatoprotective, cardioprotective and broncho-vasodilatory activities.[113-118] Various study revealed that alkaloids and flavonoids are the chief constituents of this plant that exhibits anti-inflammatory and anti-arthritic bioactivity.[119,120] In a study, the anti-inflammatory and analgesic activities of the alkaloids fraction of ethanolic leaf extract of *A. scholaris* was evaluated against xylene-induced ear edema and carrageenan-induced air pouch formation in mice. The study results revealed that alkaloids fraction of ethanolic leaf

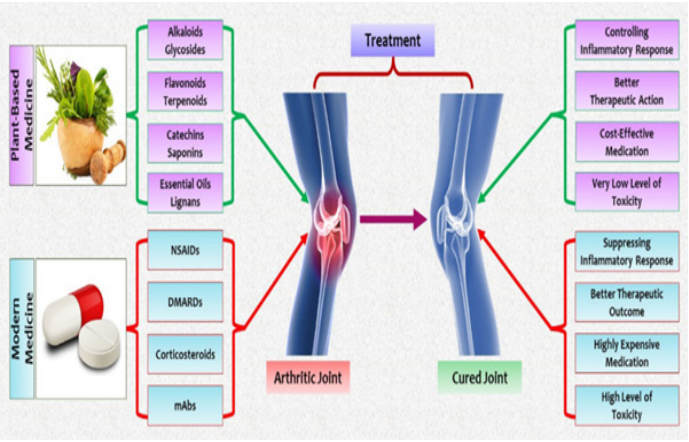

Figure 2: Plants-based medicine vs modern medicine for the management of inflammation and arthritic pain.

extract inhibits the ear edema and air pouch formation in animals by lowering the levels of nitric oxide (NO), Prostaglandin E_2 (PGE_2) and Malondialdehyde (MDA). It also showed COX-1, COX-2 and 5-LOX inhibition in *in vitro* assay, which supports the therapeutic effect of *A. scholaris*.[121] In another study, the anti-arthritic activity and antioxidant role of ethanolic extract *A. scholaris* (EEAS) leaves were investigated against FCA-induced arthritis in rats. The observed results suggested that EEAS effectively reduced the FCA induced inflammation by a significant reduction of inflammatory cells concentration (leukocyte, lymphocytes, monocytes migration) and increase the glutathione concentration from the blood into the synovial cavity, which is the main rationale behind the anti-arthritic activity of the plant.[122]

Plant *Asparagus racemosus*

Asparagus racemosus (Family-Liliaceae), readily recognized as "Shatavari or Satavar" means "who possesses a hundred spouses" is an important medicinal plant that have been reported in British and Indian Pharmacopoeias and Ayurveda, Siddha and Unani system of medicine.[123,124] This plant is extensively grow in tropical and subtropical parts of India, Sri Lanka, Indonesia, Australia, tropical Africa, Southern parts of China and in the Himalayan range. However, it is mainly cultivated in India.[125-127] *A. racemosus* is a much-branched spiny undershrub with tuberous short rootstock bearing numerous tuberous roots (30-100 cm long and 1-2 cm thick) that are white internally and silvery-white or ash-colored externally. These roots find use in various medicinal preparations due to the presence of various phytoconstituents.[128] The foremost secondary metabolites of *A. racemosus* roots are a group of steroidal saponins called Shatavarin (Shatavarin I-X). *A. racemosus* moreover contains alkaloids, flavonoids (quercetin and rutin), tannins, phytosterols, glycosides, carbohydrates and vitamins (A, B1, B2, C, E, Mg, P, Ca, Fe and folic acid). Other active constituents of *A. racemosus* are essential oils, proteins, fats, asparagine, arginine, resins and diosgenin.[129-132] These bioactive constituents impart a variety of pharmacological properties such as anti-inflammatory, antimicrobial, antioxidant, antiulcer, antidepressant, antidiarrheal, adaptogenic, immunostimulant, hepatoprotective, cardioprotective, neuroprotective, galactagogue effects.[133-139] Several studies show that the root and leave extracts of *A. racemosus* possesses anti-inflammatory and anti-arthritic potential by reducing the myeloperoxidase and inflammatory cytokine production. In a study, the anti-inflammatory effect of the ethanolic leaf extract obtained from *A. racemosus* was investigated using carrageenan-induced paw edema in Sprague Dawley rats. The observed result revealed that ethanolic leaf extract exhibited a marked anti-inflammatory effect at a dose of 600 mg/kg and causing a maximum inhibition of about 46% in paw edema by hindering the prostaglandin release.[140] In another study, the *in vivo* anti-arthritic activity of hydroalcoholic roots extract of *A. racemosus* was evaluated by using FCA-induced arthritis in Wistar albino rats. The explored results suggested that animals treated with hydroalcoholic extract of *A. racemosus* at a dose of 200 mg/kg and 400 mg/kg body weight displayed a maximum reduction in paw volume of both hind legs and total arthritic score as compared to control and standard group. These results support the *A. racemosus* roots extract to provide the desired pharmacological rationale against inflammatory ailments i.e., rheumatoid arthritis by downregulating the TNF-α and IL-6 cytokines level.[141]

Plant *Camelia sinensis*

Camelia sinensis (Family-Theaceae), commonly known as 'Tea', is a widely used medicinal plant by the tribal peoples of Asian countries and is also popular in various indigenous system of medicine like Ayurveda, Unani and Homeopathy. The medicinal effects of tea have been reported to date back nearly 5000 years ago.[142,143] Geographically, *C. sinensis*is found in the Southern and Eastern parts of Asian countries especially China, India, Thailand, Eastern Himalayas, Africa, Indonesia, Kenya. It is mainly native to China and arriving in the New World in the late century.[144-146] *C. sinensis* is a heavily branched evergreen shrub with dark-green, hairy, oblong, ovate leaves and entirely picked as young shoots, which can grow up to 25-30 feet, but in plantation, they are clipped at a height of 2-3 feet.[147] Based on the processing and degree of fermentation of the leaves, tea is available in three variants viz. Green tea (unfermented), Black tea (fermented) and Oolong tea (semi-fermented).[148] The plant is rich sources of various bioactive compounds include polyphenols (catechins and flavonoids), alkaloids, volatile oils, polysaccharides, amino acids, lipids, vitamins (A, B, C, E, K) and inorganic elements. However, the composition of tea varies based on the types. Green tea contains catechin, gallocatechin (GC), epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG), in contrast to Black and Oolong tea contains gallocatechin gallate (GCG) and all the above-mentioned compounds.[149-153] These compounds are found to have various pharmacological effects i.e., antioxidant, anticancer, anti-aging, antimicrobial, antidiabetic, hepatoprotective, neuroprotective, cardioprotective and anti-inflammatory actions.[154-157] The study revealed that tea flavonoids and polyphenolic catechins reduced the inflammation or pain in arthritis by downregulating the signaling pathways (MAPK, NF-κB, STAT, TNF-α, IL-6) and COX-2 enzyme activities.[158-160] In a study, the anti-inflammatory activity of green tea aqueous extract (GTE) and black tea aqueous extract (BTE) was evaluated in a rat adjuvant-induced arthritis (AIA) model. The observed results showed that 1 gm/kg body weight dose of GTE and BTE is significantly decreased the systemic production of pro-inflammatory cytokines and expression of chemokine receptor-5 in synovial tissues, which proved the effect of GTE and BTE in the AIA rat model.[161] In another study, the anti-arthritic activity of black tea aqueous extract (BTE) was evaluated against the FCA-induced arthritis rat model and patients with rheumatoid arthritis. BTE showed good anti-arthritic activity in both experimental rats and rheumatoid arthritis patients by decreasing the serum level of inflammatory cytokines TNFα, IL-1β, IL-6, cytokine-induced neutrophil chemoattractant (CINC) and PGE_2.[162]

Plant *Cedrus deodara*

Cedrus deodara (Family-Pinaceae), widely known as "Himalayan Cedar or Deodar", is a precious medicinal herb that has been broadly used in Indian systems of medicine and traditional Chinese medicine due to its pharmaceutical and nutritional effects.[163,164] The plant is abundantly found in the Himalayan region starting from Western Himalayas in Northern Pakistan, Northern Khyber Pakhtunkhwa, Eastern Afghanistan, South-Western Tibet, Eastern Himalayan parts of India and Nepal and also in the Mediterranean region. It is the national tree of Pakistan and is cultivated in areas with mild winters.[165,166] *C. deodara* is a large evergreen coniferous tree, reaching 85 m tall under a favorable condition with rough black bark and spreading branches, long elongated shots with dark or bluish-green needle-like leaves, monoecious flowers, branchlets are strongly scanted and durable.[167] The major bioactive compounds reported from the various parts of *C. deodara* namely essential oils (α-terpineol, linalool, anethole, eugenol, himachalol, allohimachalol, himadarol, limonene and caryophyllene), sesquiterpenes (himachalenes, atlantonesand humulene), flavonoids (myricetin, quercetin, kaempferoland isorhamnetin), lignans (wikstromal, matairesinol and benzylbutyrolactol), alkaloids, tannins, saponins, protein, vitamins and minerals.[168-172] As in the case of *C. deodara,* these bioactive compounds displayed notable therapeutic activities like anti-inflammatory, anti-arthritic, analgesics, antiulcer, antioxidant, antidiabetic, antihyperglycemic, anticancer, antibacterial, insecticidal, larvicidal, antispasmodic, antitubercular, antiapoptotic,

antihyperlipidemic, antiviral, anthelmintic, anticonvulsant, antigiardial and anxiolytic properties.[173-177] However, the anti-inflammatory and antiarthritic effects are displayed by *C. deodara* due to the presence of essential oils that inhibit the COX-2/TNF-α/NF-κB activation.[178,179] In a study, the anti-inflammatory and analgesic potential of *C. deodara* wood oil was screened against carrageenan-induced paw edema and FCA-induced arthritis in rats. The observed results suggested that *C. deodara* wood oil produced significant inhibition against exudative proliferative and chronic phases of inflammation by hindering the COX action and prostaglandin synthesis as well as delayed the Mycobacterium immune response.[180] In another study, the aqueous stem bark extract of *C. deodara* was investigated for its anti-inflammatory and anti-arthritic properties against carrageenin-induced edema, croton oil-induced granuloma pouch, formaldehyde and adjuvant-induced arthritis in rats. The study revealed that aqueous stem bark extract of *C. deodara* suppressed the primary and secondary phases of swelling and also secondary lesions in adjuvant arthritis, which support the therapeutic effect of *C. deodara*.[181]

Plant *Curcuma longa*

Curcuma longa (Family-Zingiberaceae), commonly known as "Turmeric or Haldi", has a long history of traditional uses ranging from Indian systems of medicine like Ayurveda, Unani and Siddha to Chinese systems of medicine for the curing of a large variety of ailments.[182,183] The plant is believed to be originated in Southeast Asian countries like India, China, Nepal, Bangladesh, Sri Lanka, Pakistan, Myanmar, Indonesia, Laos, Vietnam, Madagascar, Cambodia, Thailand, Taiwan and the lower Himalayan region. Currently, it is cultivated throughout the tropical and subtropical countries of the world.[184-186] *C. longa* is a perennial herbaceous plant, which stature reaches upto 1 m and is highly branched, yellow to orange, cylindrical, aromatic rhizomes are tapered at the distal end and measure 2.5 to 7 cm in length and 2.5 cm in diameter. When the rhizome is dried, it can be ground to yellow color with a bitter, slightly acrid and sweet taste, which has medicinal values.[187-189] The main active constituents of *C. longa* rhizomes are polyphenolic curcuminoids (curcumin, dihydrocurcumin, demethoxycurcumin) and volatile oils (phellandrene, curcumenol, turmerone, arturmerone, cinol, borneol, zingiberene and sesquiterpenes). *C. longa* rhizomes are also reported to contain carbohydrates, proteins, fats, sugars, resins and minerals.[190-194] Curcuminoids mainly, curcumin are major isolated components of *C. long* being responsible for various biological actions such as anti-inflammatory, antioxidant, antimicrobial, anticancer, anti-HIV, anticoagulant, antifertility, antimalarial, antimutagenic, antiobesity, cardioprotective, hepatoprotective, gastroprotective, nephroprotective, neuroprotective and wound healing activities.[195-199] However, various preclinical and animal studies revealed that both curcumin and essential oils are responsible for showing protective action against inflammation and arthritis.[200,201] In a study, the comparative anti-inflammatory activity of curcuminoids and oil-free aqueous extract (COFAE) of *C. longa* was evaluated against curcuminoids and turmerones (volatile oil) in xylene induced ear edema and cotton pellet granuloma in mice and rat model. The results showed that COFAE of *C. longa* significantly inhibits the inflammation in both models by hindering the inflammatory cytokines TNF-α, IL and down-regulates the COX-2 and Janus kinase activity.[202] In another study, the anti-arthritic effect of *C. longa* polar extract (PCL) was investigated against Monosodium Iodoacetate induced osteoarthritis in rats. The results revealed that PCL exhibits significant anti-osteoarthritic action on arthritis induced joints via up-regulation of the type II collagen gene (COL2A1) and downregulation of Matrix metalloproteinases (MMP-3) and MMP-7 expression.[203]

Plant *Oroxylum indicum*

Orozylum indicum (Family-Bignoniaceae), popularly known as "Sonapatha or Shyonaka" is an indigenous medicinal plant widely used in the Indian Ayurvedic system of medicine for thousands of years.[204] The plant is spotted in the tropical region of Southeast Asian counties India, Sri Lanka, China, Japan, Malaysia, Bhutan, Nepal, Bangladesh and Thailand. However, it is native to the Indian sub-continent. In India, this plant is mainly found in North-East, Himalayan foothills as well as Western and Eastern Ghats.[205-208] *O. indicum* is a small or medium-sized transient tree up to 12 m in height with soft grayish or light brown bark, pinnate ovate or elliptic or acuminate leaves, reddish-purple to pinkish yellow flowers and flat or sword capsules shaped fruits full of papery and flat thin shaped seeds broad salivary wings.[209] Different parts of this plant are rich in flavonoids (baicalein and its glucosides, chrysin and its glycosides, oroxylin-A, scutellarein and its glucuronides), isoflavonoids (prunetin, biochanin-A), triterpenoids (ursolic acid, lupeol), steroids (β-Sitosterol, stigmasterol), naphthalenoids (lapachol, faramol) phenolic (ellagic acid), anthraquinones (Aloe-emodin), cyclohexylethanoids and fatty acids.[210-214] These bioactive compounds of *O. indicum* exhibits a wide spectrum of pharmacological activities involving anticancer, antioxidant, antimicrobial, anti-inflammatory, anti-arthritic, antimutagenic, antiulcer, antidiarrheal, antidiabetic, hepatoprotective, immunostimulant and antiproliferative actions.[215-219] However, *O. indicum* is mainly showing the inhibitory effect against inflammation or arthritis due to the presence of flavonoids and phenolic compounds that inhibits the release of prostaglandin and also suppress the nitric oxide and proinflammatory cytokines (IL-6 and TNF-α) secretion.[220-222] In a study, the anti-inflammatory and analgesic activities of ethanol extract of stem bark of sonapatha *O. indicum* was investigated against xylene-induced ear edema and formalin-induced paw edema in mice. The results revealed that *O. Indicum* ethanolic extract exhibits anti-inflammatory and analgesic activities, which may be due to the presence of flavonoids and other polyphenols that reduced the activation of cytokines like NF-κB, TNFα, IL-1β, Interferon gamma (IFNγ) and COX-2.[223] In another study, the anti-arthritic activity of petroleum ether root bark extract of *O. indicum* (L.) vent against adjuvant-induced arthritis in the rat model. The results suggested that root bark extract of *O. indicum* exhibits a potent anti-arthritic activity owing to the existence of phenolic constituents by increasing the total reduced glutathione and significant inhibition of lipid peroxide and Cathepsin-D content in cartilage. These results proved that the root bark of this plant has tonic and astringent properties and it is also used in rheumatism.[224]

Plant *Piper nigrum*

Piper nigrum (Family-Piperaceae), popularly known as "Piper", is one of the widely used medicinal plants in different folk and traditional systems of medicine including Ayurveda, Siddha and Unani for treating various diseases. The plant is also considered to be the "King of Spices" because of its pungent odor and massive trade share in the global market.[225,226] Geographically, *P. nigrum* is distributed in the tropical and subtropical regions of the world throughout the Indian subcontinent, Sri Lanka, China, Indonesia, Malaysia, Vietnam, Brazil, Southern America, Cambodia and North-Eastern Himalayan region.[227-229] *P. nigrum* is a flowering, woody perennial climbing vine with the grayish stem, dark or pale green leaves, broadly ovate, acuminate and glabrous, elongated, slender spikes or catkins bear minute, white flowers in slightly interrupted glabrous spikes with single-seeded dark red berries and many rootlets grow from swollen stem nodes.[230] The phytochemical screening of various parts of *P. nigrum* revealed the presence of a range of bioactive compounds like alkaloids (piperine, piperidine and piperettine, piperamine, piperolein B, piperamide), terpenoids

(myrcene, limonene, α- and β-pinene, camphene, phellandrene, calamenene, eugenol, myristicin, cinnamic acid), lignans, steroids, phenolics, tannins, carbohydrates, proteins and saponins. However, piperine is reported to be the principal pungent alkaloid of this plant.[231-234] These bioactive compounds were found to possess important pharmacological properties namely, anti-inflammatory, anti-arthritic, antioxidant, analgesic, antibacterial, antitumor, antimutagenic, antihypertensive, antithyroid, antidiarrheal, anticonvulsant, antidiabetic, hepatoprotective, insecticidal and immunomodulatory activities.[235-239] However, the anti-inflammatory and antiarthritic action exhibited by *P. nigrum* was due to the presence of alkaloids, mainly piperine that inhibits the TNF-α, IL-6, IL-1β, IL-1, MMP-8, MMP-13 and PGE_2 production.[240] In a study, the anti-inflammatory properties of pure compound piperine and hexane/ethanolic fruit extracts of *P nigrum* L. were screened against carrageenan-induced paw inflammation in rats. The observed results indicated that piperine and hexane/ethanol extracts of *P nigrum* L hold significant inhibition of prostaglandin release mediated anti-inflammatory activities.[241] In another study, the anti-inflammatory and anti-arthritic effects of piperine obtained from black pepper extract were evaluated against carrageenan-induced acute paw pain and arthritis in rats. The results suggested that piperine hinders the expression of TNF-α, IL6, IL1β, MMP13 and production of PGE_2, which proved that piperine owns potential anti-inflammatory and anti-arthritic effects.[242]

Plant *Swertia chirayita*

Swertia chirayita (Family-Gentianaceae), customarily known as "Chiretta or Chiratitka", is a popular medicinal herb used in traditional Ayurveda, Unani and Siddha systems of medicine to treat an array of diseases. Its medicinal benefits are well cited in Indian Pharmaceutical Codex, British Pharmacopoeias and American Pharmacopoeias.[243] The plant is abundantly found in the temperate Himalaya region of India mainly Kashmir, Sikkim and Khasi hills, Nepal, Bhutan, tropical Asia, mountainous regions of Europe, Africa and North America.[244-246] Typically *S. chirayita* is an annual/biennial herb with vertically growing orange-brown or purple colored stems, leaves are soft, stalkless and oval, tetramerous and symmetric, axillary flowers in greenish-yellow color with a purple tinge, fruits are superior capsulated with brownish color small seeds, roots are a yellow color and fibrous in nature.[247,248] The whole plant contains various important secondary metabolites and phytoconstituents, which include xanthones (chiratanin, chiratol, decussatin mangiferin, mangostin, swertianin), alkaloids (gentiamine, gentiocrucine, enicoflavine), triterpenoids (episwertenol, episwertenol, oleanolic acid, swertanone, swertenol, ursoilic acid), seco-iridoid glycosides (amarogentin, amaroswerin, sweroside), lignans (syingaresinol), triterpene alcohol (lupeol, taraxerol), flavonoids, steroids, saponins and ascorbic acid.[249-252] The presence of these active principles traits the *S. chirayita* medicinal properties and made a leading therapyeutic impact on the human body due to anti-inflammatory, anti-arthritic, antioxidant, antimalarial, antifungal, anticancer, antiviral, antidiarrheal, antidiabetic, wound healing, hepatoprotective, neuroprotective and gastroprotective activities.[253-259] The various studies revealed that the anti-inflammatory and anti-arthritic potential of *S. chirayita* is due to the presence of xanthones, terpenoids, flavonoids, glycosides, which sufficiently suppress the pro-inflammatory cytokines TNF-α, IL-1α, IL-6, PGE_2, COX-2 and NF-κB/MAPKs/Akt, JAK2/STAT3 signaling.[260,261] In a study, the anti-inflammatory action of ethanolic extract of *S. chirata* root was studied using carrageenan-induced paw edema in the rat model. The obtained results illustrated that the root extract remarkably reduced the paw edema volume through inhibition of cell mediator's bradykinin and prostaglandin synthesis.[262] In another study, the anti-inflammatory and anti-arthritic activities of *S. chirayita* stem aqueous extract was assessed in adjuvant-induced arthritis in mice. The results revealed that aqueous stem extract of *S. chirayita* possesses potent anti-inflammatory and anti-arthritic effects by reduction of proinflammatory and anti-inflammatory cytokine balance of TNF-α, IL-1β, IL-6, IL-10 and IFNγ.[263]

Plant *Vitex negundo*

Vitex negundo (Family-Verbenaceae), habitually known as "Chaste Tree or Nirgundi", is an ethnobotanically important plant with immeasurable medicinal properties has been well documented in the Indian Ayurveda, Unani, Siddha systems of medicine and traditional Chinese medicine for treating a bunch of diseases.[264,265] The plant thrives in humid places and distributed extensively in India, China, Pakistan, Afghanistan, Sri Lanka, Malaysia, Nepal, Bhutan, Bangladesh, Philippines, Japan, Indonesia, Thailand, South America, Madagascar, Eastern Africa and the Himalayan region.[266,267] Naturally, *V. negundo* is a small slender tree with quadrangular branches covered by white small hairs, leaves are long-petioled with entire leaflets, flowers are bluish-purple with long panicles, fruits are oval or egg-shaped, black when ripened, consist of four seeded drupes.[268] Almost all parts of the *V. negundo* contains important bioactive phytoconstituents chiefly volatile oils (linolenic acid, palmitic acid, valencene), lignans (vitedoin A, vitexdoin A to vitexdoin H, vitelignin A, negundin B), flavonoids (luteolin, vitexin, vitexicarpin), steroids (β-sitosterone, β-sitosterol, stigmasterone), glycosidic iridoids (agnuside, negundoside), polyphenols (coumarins), terpenoids (di-, tri-, sesqui-terpenoids), alkaloids, Vitamin C and carotene.[269-272] Due to the presence of these bioactive compounds, *V. negundo* possesses versatile pharmacological effects like anti-inflammatory, anti-arthritic, antioxidant, anticancer, analgesic, antidiabetic, anti-allergic antihypertensive, antimicrobial, antibacterial, antitussive, anticonvulsant, anthelminthic, hepatoprotective and larvicidal activities.[273-277] However, the anti-inflammatory and antiarthritic potential of *V. negundo* are mainly because of lignans, flavonoid and essential oils, which down-regulates the pro-inflammatory mediators via inhibition of NO production, COX-2, p38, ERK1/2 and JNK pathways.[278-280] In a study, the anti-inflammatory properties of *V. negundo* aqueous leaves extract were evaluated by carrageenan-induced paw edema in rats. The observed results suggested that *V. negundo* leaves extract exhibits potential anti-inflammatory and pain suppressing activities probably mediated by inhibition of prostaglandin and histamine synthesis, prevention of oxidative stress and membrane-stabilizing effect in damaged tissues.[281] In another study, the anti-arthritic effects of total lignans from *V. negundo* seeds extract (TOV) were investigated against collagen-induced arthritis in rats. The results revealed that TOV significantly decreased the paw edema and arthritis index via reduction of COX-2, iNOS expression and levels of pro-inflammatory cytokines TNF-α, IL-1β, IL-6, IL-8, IL-17A, MMP-3, MMP-9. These results proved that TOV has potent anti-arthritic properties.[282]

Plant *Withania somnifera*

Withania somnifera (Family-Solanaceae), popularly known as "Ashwagandha or Indian Ginseng", is one of the prominent medicinal herb used in Indian Ayurveda, Siddha and Unani systems of medicine for more than 3000 years and has been categorized as Rasayana or Rejuvenator in Ayurveda for its multiple health benefits against diseases, adverse environmental conditions, aging and revitalize the body.[283,284] The plant is abundantly distributed throughout the sub-Himalayan tracts in India, Pakistan, Afghanistan, Nepal, Sri Lanka, Bangladesh, China, South Africa, Egypt, Jordan, Spain, Australia, Morocco and also Mediterranean regions.[285,286] Ordinarily, *W. somnifera* is a straight evergreen shrub with a short stem and long tuberous roots, branches

are wrapped with minute star-shaped hairs, leaves are alternate, petiolate and ovate shaped, flowers are small and greenish or yellow in color, fruits are smooth and fleshy, orange-red when ripened having many discoid seeds.[287] The various parts of the *W. somnifera* contain a range of biologically active chemical constituents like alkaloids (ashwagandhine, anahygrine, tropine, somniferine, withanine, withasomine), steroidal lactones (withanolides A-Y, withaferin, withanone), saponin glycosides (sitoindosides), phenolic (gallic acid, rutin, quercetin), terpenoids and others miscellaneous compounds (amino acid, coumarins, tannins, sugar).[288-292] These bioactive compounds provide the various therapeutic potentiality of *W. somnifera* including analgesic, anti-inflammatory, antiulcer, anticancer, antioxidant, antimicrobial, antidiabetic, cardioprotective, hepatoprotective, neuroprotective, antimalarial, anti-stress, anxiolytic, wound healing and rejuvenating properties.[293-297] Various studies suggested that the anti-inflammatory and antiarthritic effects of *W. somnifera* may be due to the presence of steroidal withanolides, alkaloids and polyphenols, which reduce the levels of LPO and proinflammatory cytokines TNFα, IL-1, IL-6, IL-8, IL-12, NO, via modulation of NF-κB, AP-1, JAK/STAT, MAPK pathways.[298-300] In a study, the anti-inflammatory activity of methanolic leaves extract of *W. somnifera* was investigated on stainless steel-induced inflammation in adult zebra fish. *W. somnifera* leaf extract showed potent anti-inflammatory effects by blocking TNFα and NF-kB activation.[301] In another study, the anti-arthritic effect of *W. somnifera* aqueous roots extract (WSAq) was screened against collagen-induced arthritis in rats. The observed results suggested that oral administration of WSAq appreciably attenuated the production of inflammatory cytokines TNF-α, IL-1β, IL-6, MMP-8 via inhibition of the NF-κB pathway, which supports the potential anti-arthritic functionalities of *W. somnifera*.[302]

Plant *Zingiber officinale*

Zingiber officinale (Family-Zingiberaceae), commonly known as "Ginger", is a valuable medicinal plant that has been extensively used in traditional Ayurveda, Tibb-Unani herbal, Chinese and Iranian medicines all over the world since ancient times for a wide bundle of unrelated ailments.[303,304] The plant is basically originated in the Indo-Malayan region, but presently it is cultivated throughout tropical and sub-tropical regions including India, China, Sri Lanka, Nepal, Bangladesh, Brazil, Australia, Africa, New Zealand, Jamaica, Nigeria, Thailand, Taiwan, Philippines and sub-Himalayan regions.[305,306] Typically, *Z. officinale* is a straight perennial herb with a branched, horizontal, fleshy, aromatic, white or yellowish rhizome bearing narrow, pointed, lanceolate leaves, the stem is leafy consisting of three fold flowers subtending with bracts and bracteoles, three-lobed short calyx, pointed shorter corolla, dark-purple lip spotted and striped with yellow, the fruit is dehiscent comprising large seeds.[307] The rhizome parts of the *Z. officinale* are rich in various bioactive constituents like polyphenols (gingerol, paradol, shogaol, zingerone, quercetin), essential oils (zingiberene, zingiberol, linalool, geranial, limonene, cineole, neral, α-farnesene, α-curcumene, β-bisabolene, β-sesquiphellandrene), proteins (alanine, cysteine, arginine, glutamate, proline), sugars (polysaccharides, cellulose, soluble sugar), vitamins, minerals, resins, flavonoids, alkaloids, saponins, tannins and inorganic elements.[308-313] The presence of these bioactive compounds imparts a wide variety of pharmacological properties including anti-inflammatory, anti-arthritic, anticancer, antioxidant, antifungal, antibacterial, antiemetic, antidiabetic, antihypertensive, antiallergic, antitussive, antiulcer, neuroprotective, gastroprotective, hepatoprotective, cytotoxic and hypoglycemic activities.[314-317] The anti-inflammatory and antiarthritic efficacy of *Z. officinale* may be due to the presence of essential oil and polyphenolic compounds, which inhibits the pro-inflammatory cytokines, TNF-α, IL-1, IL-1β, IL-8, NO, MMP9, PGE_2 via suppression of ROS/NF-κB/COX-2 activation.[318-321] In a study, the anti-inflammatory activity of aqueous extract of *Z. officinale* rhizome was explored using carrageenan-induced paw edema in rats. The obtained results suggested that *Z. officinale* rhizome extract ameliorated rat paw edema by inhibiting the PGE_2, TNF-α, IL-6 and MCP-1 production.[322] In another study, the anti-arthritic effect of *Z. officinale* extract was investigated against collagen-induced arthritis in mice. The results revealed that *Z. officinale* extract prevents arthritis progression by hindering the secretion of Th1/Th2/Th17 cytokines and inflammatory mediators TNF-α, IL-1β, IL-6, NO, PGE_2, in macrophages and synovial tissues.[323]

The medicinal plants of the Eastern Himalayan region which possess impressive anti-inflammatory and anti-arthritic actions are depicted in Figure 3 and their potential therapeutic mechanisms are highlighted in Table 2.

Novel formulations of Eastern Himalayan medicinal plants

The plant-based traditional preparations or bioactive compounds isolated from the medicinal plants are in high demand for treating a bunch of diseases. But these traditional herbal remedies or phytomolecules have numerous drawbacks of poor aqueous solubility, slow absorption, less bioavailability, toxic effects in non-target organs and are often prone to deterioration during storage.[324,325] As a result, loss of active component, formation of metabolites with no efficacy and in extreme cases formation of toxic metabolites, which is a serious issue in the field of phytochemistry and natural medicines.[326] The use of novel formulation approaches, especially nanoparticles, microparticles, nanoemulsions and topical herbal gels can resolve the potential drawbacks associated with the plant-based products viz. improving solubility, storage stability, extending half-life, minimizing toxic effects and thereby specifically targeting disease cells with better therapeutic response.[327-330] Table 3

Figure 3: Anti-inflammatory and anti-arthritic medicinal plants of the Eastern Himalayas.

Table 2: Eastern Himalayan medicinal plants along with their probable anti-inflammatory and anti-arthritic mechanisms.

Sl. no.	Medicinal plant	Therapeutic activity	Form of extract	Inhibitory mechanism	Ref (s)
01.	*Adhatoda vasica* (Acanthaceae)	Anti-inflammatory	Ethanolic roots extract	Inhibition of prostaglandin synthesis	[103]
		Anti-arthritic	Methanolic leaf extract	Downregulation of TLR2 and pro-inflammatory mediators release	[104]
02.	*Alstonia scholaris* (Apocynaceae)	Anti-inflammatory	Ethanolic leaf extract	Inhibition of COX-1, COX-2, 5-LOX and lowering NO level	[121]
		Anti-arthritic	Ethanolic Leaves extract	Reduction of inflammatory cells concentrations	[122]
03.	*Asparagus racemosus* (Liliaceae)	Anti-inflammatory	Ethanolic leaf extract	Inhibition of prostaglandin release	[140]
		Anti-arthritic	Hydroalcoholic roots extract	Downregulation of the TNF-α and IL-6 cytokines level	[141]
04.	*Camelia sinensis* (Theaceae)	Anti-inflammatory	Aqueous green/black tea extract	Inhibition of pro-inflammatory cytokines/chemokine production	[161]
		Anti-arthritic	Aqueous black tea extract	Downregulation of TNFα, IL-1β, IL-6, CINC and PGE_2 serum level	[162]
05.	*Cedrus deodara* (Pinaceae)	Anti-inflammatory	Wood oil	Inhibition of COX action and prostaglandin synthesis	[180]
		Anti-arthritic	Aqueous stem bark extract	Suppression of diverse phases of swelling and secondary lesions	[181]
06.	*Curcuma longa* (Zingiberaceae)	Anti-inflammatory	Oil-free aqueous rhizome extract	Downregulation of TNF-α, IL, COX-2 and Janus kinase activity	[202]
		Anti-arthritic	Polar rhizome extract	Downregulation of MMP-3 and MMP-7 expression	[203]
07.	*Oroxylum indicum* (Bignoniaceae)	Anti-inflammatory	The ethanolic stem bark extract	Reduction of NF-κB, TNFα, IL-1β, IFNγ and COX-2 activity	[223]
		Anti-arthritic	Petroleum ether root bark extract	Inhibition of lipid peroxide and Cathepsin-D content in cartilage	[224]
08.	*Piper nigrum* (Piperaceae)	Anti-inflammatory	Hexane/ethanolic fruit extract	Inhibition of prostaglandin release	[241]
		Anti-arthritic	Black pepper extract	Downregulation of IL6, IL1β, TNF-α, MMP13, PGE_2 production	[242]
09.	*Swertia chirayita* (Gentianaceae)	Anti-inflammatory	Ethanolic root extract	Inhibition of bradykinin and prostaglandins synthesis	[262]
		Anti-arthritic	Aqueous stem extract	Reduction of TNF-α, IL-1β, IL-6, IL-10 and IFNγ	[263]
10.	*Vitex negundo* (Verbenaceae)	Anti-inflammatory	Aqueous leaves extract	Inhibition of prostaglandin and histamine synthesis	[281]
		Anti-arthritic	Ethanolic seeds extract	Reduction of IL-1β, IL-6, IL-8, COX-2, iNOS, TNF-α, MMP levels	[282]
11.	*Withania somnifera* (Solanaceae)	Anti-inflammatory	Methanolic leaves extract	Blockingof TNFα and NF-kB activation	[301]
		Anti-arthritic	Aqueous roots extract	Inhibition of TNF-α, IL-1β, IL-6, MMP-8 level and NF-κB pathway	[302]
12.	*Zingiber officinale* (Zingiberaceae)	Anti-inflammatory	Aqueous rhizome extract	Inhibition of PGE_2, TNF-α, IL-6 and MCP-1 synthesis	[322]
		Anti-arthritic	Aqueous rhizome extract	Hindering the TNF-α, IL-1β, IL-6, NO, PGE_2or Th1/Th2/ Th17 release	[323]

represents the novel formulation approaches of a few Eastern Himalayan medicinal plants along with their therapeutic actions.

CONCLUSION AND FUTURE PERSPECTIVES

There is a hopeful prospect of medicinal plants that are widely distributed all over the world and their unseen potency of medical activities could be fruitful in the treatment of chronic ailments. The eastern part of the Himalayas boasts a gold mine of medicinal plants due to the regional climatic variation and diverse ecological habitats. Medicinal plants of this part are used for the prevention and treatment of inflammation and arthritis in various conventional ways for generations to generation and are connected unswervingly with their traditional practices as plant medicines by local cultures, which are scientifically unexplored. Because of these reasons, few studies have been conducted on Himalayan medicinal plants to validate their medicinal properties. Scientific reports explored that the beneficial action of medicinal plants in the treatment of inflammation and arthritis is due to the presence of various bioactive compounds, which affect the various stages of the process engaged in inflammatory responses, inhibiting the inflammatory cytokine production, suppression of oxidative stress and also downregulating the various abnormal intracellular signaling pathways. The plant-derived bioactive compounds are always safe and produce very little toxicity as compared to synthetic drugs. However, the potential of herbal medicine

Table 3: Novel formulation approaches of Eastern Himalayan medicinal plants.

Sl. no.	Medicinal plant	Formulation type	Plant material	Therapeutic purpose	Anti-inflammatory / anti-arthritic activity	Ref (s)
01.	*Adhatoda vasica*	Silver nanoparticles, CuO/ carbon nanocomposites, polyherbal gel	Leaf extract	Anticancer Antibacterial Antimicrobial	Not reported	[331-334]
02.	*Alstonia scholaris*	Silver nanoparticles, zinc oxide nanoparticles, mPEG-PLA microspheres	Bark extract and leaf extract	Antimicrobial Antiepileptic	Anti-inflammatory activity was assessed by *in vivo*	[335-338]
03.	*Asparagus racemosus*	Silver nanoparticles, cobalt nanoparticles, copper nanoparticles, liposomes	Rhizome extract and root extract	Antimicrobial Antibacterial Anticancer	Anti-inflammatory activity was assessed by *in vitro*	[339-342]
04.	*Camelia sinensis*	Gold nanoparticles, silver nanoparticles, chitosan nanoparticle, topical gel	Leaf extract and catechin	Anticancer Antimicrobial Antioxidant	Not reported	[343-346]
05.	*Cedrus deodara*	Nanocapsules, solid lipid nanoparticles, microspheres, emulsion	Wood oil and AP9-cd lignan mixture	Antibacterial Anticancer Larvicidal	Not reported	[347-350]
06.	*Curcuma longa*	Polymeric nanoparticles, silver nanoparticles, microemulgel	Leaf extract, rhizome extract and curcumin	Anticancer, Antimicrobial, Wound healing	The anti-inflammatory and anti-arthritic activity was assessed by *in vivo*	[351-354]
07.	*Oroxylum indicum*	PLGA-PEG nanoparticles, topical herbal gel	Chrysin and leaf extract	Anticancer Antibacterial	Not reported	[355, 356]
08.	*Piper nigrum*	Silver nanoparticles, nanoemulsion, polyherbal gel	Fruit extract, leaf extract and essential oil	Anticancer Antimicrobial Antifungal	Anti-inflammatory activity was assessed by *in vitro*	[357-360]
09.	*Swertia chirayita*	Silver nanoparticles, ZnO nanoparticles, MgO nanoparticles	Leaf extract and whole plant	Antioxidant Antimicrobial Antibacterial	Not reported	[361-364]
10.	*Vitex negundo*	Silver nanoparticles, gold nanoparticles, nanoemulsion, herbal gel	Leaf extract and essential oil	Anticancer Antimicrobial Antioxidant	The anti-inflammatory and anti-arthritic activity was assessed by *in vivo*	[365-368]
11.	*Withania somnifera*	Silver nanoparticles, Se nanoparticles, transdermal gel herbo-mineral formulation	Root extract and leaf extract	Antimicrobial Anticancer Antioxidant	The anti-inflammatory and anti-arthritic activity was assessed by *in vivo*	[369-372]
12.	*Zingiber officinale*	Silver nanoparticles, Plygersic gel, emulgel, nanoemulsion	Rhizome extract and essential oil	Antioxidant Antimicrobial Antibacterial	The anti-inflammatory and anti-arthritic activity was assessed by *in vivo*	[373-377]

is substantially hindered by its poor solubility, bioavailability and stability problems. These drawbacks can be overcome by the novel formulation approaches and provides outstanding therapeutic benefits to plant bioactive compounds. Therefore, advanced research on medicinal plants with potential anti-inflammatory and antiarthritic activities and their specific mechanism of action in the human body is one of the developing fields in the modern era of biomedicine in the near future.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ABBREVIATIONS

NSAIDs: Non-steroidal anti-inflammatory drugs; **DMARDs:** Disease modifying anti-rheumatic drugs; **ROS:** Reactive oxygen species; **RNS:** Reactive nitrogen species; **COX:** Cyclooxygenase; **FGF:** Fibroblast growth factors; **VEGF:** Vascular endothelial growth factor; **TGF:** Transforming growth factor; **JAK:** Janus kinase; **STAT:** Signal transducers and activators of transcription; **MAPK:** Mitogen-activated protein kinase; **DCs:** Dendritic cells; **RFs:** Rheumatoid factors; **ACPA:** Anti-citrullinated protein antibodies; **NF-κB:** Nuclear factor-kappa B; **TNF-α:** Tumor necrosis factor-α; **IL:** Interleukin; **mAbs:** Monoclonal antibodies; **CIA:** Collagen-induced arthritis; **TLR-2:** Toll-like receptors-2; **NO:** Nitric oxide; **PGE_2:** Prostaglandin E_2; **MDA:** Malondialdehyde; **EEAS:**

Ethanolic extract *A. scholaris*; **GC:** Gallocatechin; **EC:** Epicatechin; **ECG:** Epicatechin gallate; **EGC:** Epigallocatechin; **EGCG:** Epigallocatechin gallate; **GCG:** Gallocatechin gallate; **GTE:** Green tea aqueous extract; **BTE:** Black tea aqueous extract; **COFAE:** Curcuminoids and oil-free aqueous extract; **PCL:** *C. longa* polar extract; **MMP:** Matrix metalloproteinases; **TOV:** *V. negundo* seeds extract; **WSAq:** *W. somnifera* aqueous roots extract.

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