IJBPAS, June, Special Issue, 2023, 12(6): 434-458

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

RE-IMAGINING THE ANTIARTHRITIC POTENTIAL OF GINGER (*ZINGIBER OFFICINALE*): A COMPREHENSIVE REVIEW

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Received 25th Jan. 2023; Revised 24th Feb. 2023; Accepted 15th April 2023; Available online 15th June 2023

https://doi.org/10.31032/IJBPAS/2023/12.6.1064

ABSTRACT

Inflammatory, persistent, and progressive joint degeneration caused by an autoimmune disease are the hallmarks of arthritis. It manifests itself in the various joints of the human body as swelling, discomfort, and inflammation in those joints. There are nearly as many individuals in the globe who suffer from arthritis as there are men, and among those people, women are more likely to be affected by arthritis than men. In the 21st century, researchers in the medical field are developing a variety of medications and treatments for arthritis prevention. Yet, as of now, there is no treatment or medication that is proven to be beneficial in curing arthritis. Hence, in this rapidly advancing age, scientists are studying the medicinal properties of various herbs with the hopes of finding a remedy for the condition. Ginger, which contains a large number of ingredients that have shown to be effective in treating arthritis, is the most well-known and widely used antiarthritic plant. Ginger has been reported to exhibit tremendous antiarthritic properties, and those activity will be addressed in this review.

Keywords: Arthritis, Inflammatory, Autoimmune Disease, Antiarthritic, Ginger

1. INTRODUCTION:

Arthritis or "disease of the joints" is characterised by acute or chronic joint inflammation, frequently accompanied by pain and structural damage **[1]**. Although there are over 100 different varieties of arthritis documented in the literature, the most frequent type of arthritis is osteoarthritis (OA), which is a non-inflammatory type of arthritis **[2]**. Inflammatory arthritis can develop as a result of an autoimmune reaction (rheumatoid arthritis (RA), crystal deposition-induced inflammation (gout), or infections (septic arthritis) **[3]**. Arthritis has a variety of etiologies depending on the type of arthritis. Age, female sex, joint trauma, and obesity are the contributory factors in OA; however, in RA, the interaction of multiple genetic factors (HLA-DRB1 and others) and environmental factors (smoking) leads to immune system activation and malfunction, resulting in inflammation **[1]**. In case of gout, prolonged hyperuricemia causes uric acid deposition in the joints, which leads to joint inflammation. OA is the most common form of arthritis, with more than 40% of the population at risk of developing it during their lifetime, with the risk increasing to 60% if their BMI is greater than 30 **[4]**. Females are more likely than males to get RA, and illness onset usually occurs in early adulthood, with a disease prevalence of 5% in women over the age of 65 **[5]**. Gout is the most common inflammatory arthritis in the United States, affecting more than 8 million people and accounting for more than 9% of all people over the age of 60. Septic arthritis affects 0.01 percent of the general population and 0.7 percent of rheumatoid arthritis patients **[6]**. OA is characterized by a degenerative process that results in cartilage loss and bone deterioration. Symptoms of RA are typically more severe than those of OA and is a systemic and chronic inflammatory state caused by an autoimmune response to an environmental trigger. In gout, needle-shaped monosodium urate salt crystals trigger an IL-1-mediated inflammatory response, resulting in the classic acute gouty arthritis flare **[7]**. The treatment and management of OA is usually a combination of non-pharmacological (or conservative) and pharmacological treatments aimed at limiting pain and improving function **[8]**. Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are the most common medications used to treat OA. Similarly, in case of RA, the treatment goals include to limit pain and inflammation and prevent joint and organ damage and is composed of NSAIDs and disease-modifying anti-rheumatic drugs (DMARDs) **[9]**. However, in recent years biological agents such as TNF monoclonal antibodies are used in the treatment of RA **[10]**.

Immunosuppressive and cytotoxic drugs such as cyclosporine, azathioprine, and cyclophosphamide are also used in the treatment of chronic patients of RA **[11, 12, 13]**. Although, most of these drugs has the ability to reduce pain and inflammation in RA patients, they lack in offering permanent curing capacity and are frequently accompanied with various side effects such as gastrointestinal irritation, allergy, headache etc. In addition, many selective cyclooxygenase COX-2 inhibitors have been linked to increase risk of cardiovascular events in multiple trials **[14]**. Also, several NSAIDs such as naproxen, indomethacin and ibuprofen were found to inhibit cartilage matrix synthesis *in-vitro* **[15]**, which is expected to hasten articular cartilage deterioration in OA patients.

It is worth to mention that plant extracts, fractions, and plant-derived molecules all have the potential to provide relief from a variety of diseases, including arthritis. Plants have long been a part of our civilization and have been utilised to treat a variety of ailments. A substantial number of modern medicines have plant origins and are drawn from therapeutic knowledge of hundreds of years of ancient medicine. Across the world, a large number of traditional plants have also been used for the treatment of arthritis. Among the various plants reported to have antiarthritic activity, ginger (*Zingiber officinale*) is one of the important plants which has the potential to use as both prophylactic and therapeutic purposes. By taking this view in consideration, the current study was conducted to review the antiarthritic activity of ginger and its reported phytoconstituents.

2. Arthritis - Pathogenesis, Present treatment available, Pathophysiology, Therapeutic targets:

Rheumatoid arthritis is an inflammatory illness marked by chronic inflammation caused by synovial hyperplasia, which leads to irreparable bone damage **[16]**. According to a recent epidemiological study, roughly 1% of individuals around the world today have rheumatoid arthritis, which has a substantial influence on quality of life **[17, 18]**. It is more common in women than in males across all populations. RA typically develops (in about 80% of cases) between the middle of the fourth and the last decade of life **[19, 20]**.

In a sound individual, the resistant framework battles trespassers, like microbes and infections. With an immune system illness like RA, the resistant framework confuses the body's cells with unfamiliar intruders and deliveries fiery synthetics that assault those cells. In RA, it goes after the synovium, the tissue lining around a joint that delivers a liquid to easily help the joint move. The aroused synovium gets thicker and causes the joint region to feel excruciating and delicate and look red and

enlarged, and moving the joint might be troublesome **[21]**.

Rheumatoid joint pain influences everybody in an unexpected way. In certain individuals, joint side effects foster north of quite a while. In others, rheumatoid joint pain side effects progress quickly. Many have the opportunity with side effects (flares) and afterward time without any side effects (reduction). Symptoms of rheumatoid arthritis include **[22]**:

- ✓ Pain, swelling and tenderness in more than one joint.
- ✓ Stiffness, especially in morning or sitting for long time and lasts for 30 mins.
- ✓ Little joints (wrists, several joints in the hands and feet) are commonly impacted first
- ✓ Fatigue
- ✓ Weakness.
- ✓ Fever.

Though a lot of study has been done to figure out the specific process of arthritis-induced inflammation and tissue degradation, the actual mechanism(s) is yet to be discovered. Based on significant study into the pathophysiology of RA, it appears that the disease develops in a complex chain of events. The pathophysiology of arthritis is represented in figure 1. Alpha 4 beta1integrin is produced by activated T cells and binds to vascular cellular adhesion molecule (VCAM) on the surface of venules in inflamed tissues. As a result, activated T lymphocytes can pass past the endothelium wall and enter the extracellular fluid **[23]**. T cells are activated after encountering antigen via the class II major histocompatibility complex (MHC) on an antigen presenting cell and getting a second signal *via* the CD28 molecule on the T cell surface. T cells are produced through the action of cytokines such as IL-1, IL-6, IL-12, IL-15, IL-23, TCR, tumour necrosis factor (TNF), and transforming growth factor (TGF), which differentiate T cells into T helper 1 (TH1) and T helper 17 (TH17) **[24]**. The cytokine IL-17, which is secreted by TH17 cells, stimulates macrophages and IL-21, as well as IL-23, which is released by macrophages. The effects of tumour necrosis factor synergize to increase the potency of IL-17 **[24, 25, 26]**. Furthermore, through secreting IL-1, IL-6, TNF, and matrix metalloproteinase (MMPs), macrophage infiltration into the synovium worsens the severity and development of RA **[25]**. Recent evidence suggests that the new cytokines IL-18 and receptor activator of nuclear factor B (RANKL) are also involved in RA development **[27]**. The TNF superfamily includes RANKL. It is produced by activated T cells and found in abundance in synovial fibroblasts. Synovial fibroblasts and chondrocytes in the surrounding articular cartilage are stimulated to release enzymes by these cytokines. Additionally, these enzymes

breakdown peptidoglycan and cartilage, resulting in bone disintegration **[28]**. Osteoclasts, on the other hand, are activated by IL-17 and produce intrinsic nitric oxide synthase (iNOS), which contributes to bone deterioration. Following fibroblast activation, inflammation develops. TNF- and IL-18 produced by macrophages, as well as IL-17 from TH17 cells, activate fibroblasts. These fibroblasts subsequently create prostaglandin E2 by releasing IL-6, IL-8, LIF, and GM-CSF, which cause inflammation. In addition, macrophage-produced cytokines such as IL-1, IL-6, and TNF can directly contribute to inflammation.

Treatment for RA includes medications and lifestyle adjustments. Nonsteroidal anti-inflammatory medications (NSAIDs), such as salicylic acid, and steroids (usually cortisone injection) are being used in treatment **[29]**. Although these medications reduce pain, they do not restore injured tissues. Although a variety of medicines are administered to manage pain and delay the progression of RA, no therapy has been shown to entirely cure the condition **[30, 31]**. Furthermore, stomach ulcers have been seen in RA patients who are consistently taking NSAIDS and who have had their adrenals suppressed by steroids **[30]**. Patients frequently seek complementary and alternative medicine (CAM) to alleviate these unpleasant side effects **[29]**. According to a recent survey, those with RA who have chronic pain and are dissatisfied with allopathic treatment are more likely to seek alternative medicine, with 60-90 percent of arthritic patients using complementary and alternative medicine **[31]**.

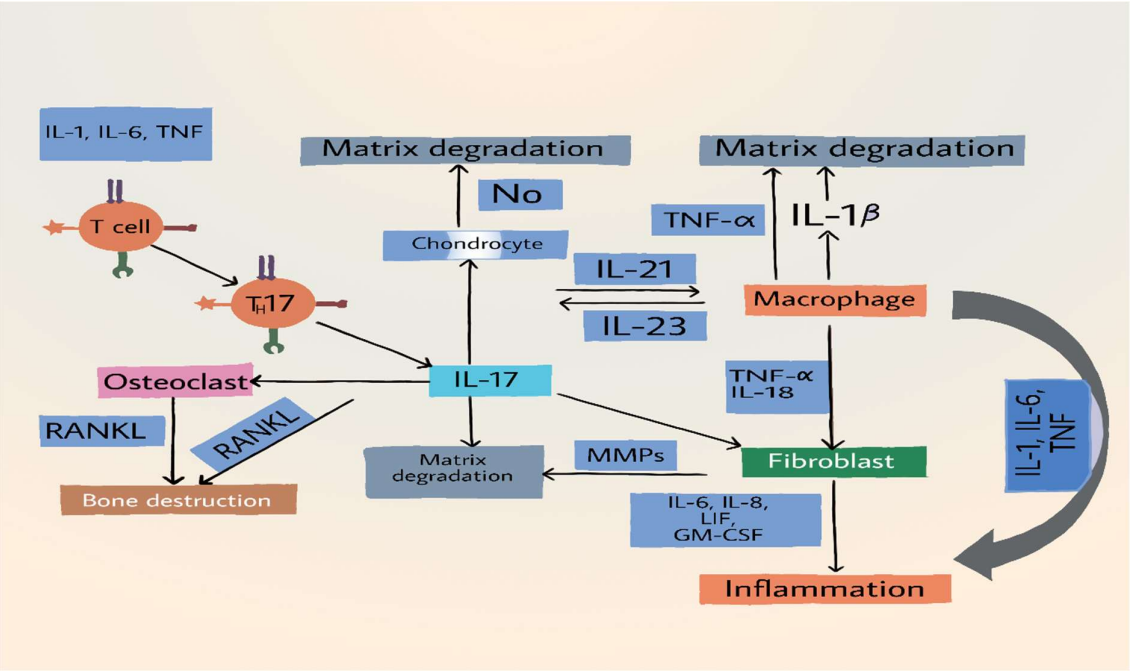

Figure 1: Pathophysiology of Arthritis

3. Ginger:

Ginger (*Z. officinale*) or ginger root is the rhizome of the plant *Z. officinale*, ate up as delicacy, remedy, or spice. It gets its name from the genus and family (Zingiberaceae) **[32]**. Rhizome of *Z. officinale* is widely used in both medicinal and culinary purposes globally due to its ethno-medicinal and nutritious value. Most of traditional and complementary systems of medicine such as Ayurveda, Siddha, Unani, Homeopathy, Tibetan, Chinese etc., prescribe *Z. officinale* individually or as a combination in both of infective and non-communicable diseases **[33]**. In RA and OR, ginger is used as an fherbal pain reliever and an anti-inflammatory agent **[32]**. The main phytochemical constituents of ginger are categorized into volatile and non-volatile constituents.

3.1. Vernacular names [34]:

In India	Outside India
Hindi : Adrak (Fresh), Sonth (Dried) Assamese: Ada Bengali : Ada Sanskrit : Adraka (Fresh), Shunthi (Dried), Shringaveran, Sringaaran Oriya : Ada, Adraka Tamil : Ingee Gujrati : Adhu(Fresh), Sunth, Shuntya (Dried) Malayalam: Inchi Marathi : Sunth, Shuntya (Dried), Alha (Fresh) Urdu : Adraka Telugu : Allam English : Ginger	Japanese : Shoga, Myoga Spanish : Jengibre Russian : Imbir German : Ingwer Swedish : Ingefara Farsi : Amveel, Zanjabil Dutch : Gember French : Gingembre Chinese : Jeung, Sang Keong, San Geung, Chiang, Jiang, Keong

3.2. Morphological features of ginger rhizome [35]:

General appearance: Sympodial branching, horizontal rhizome.

Colour: Buff.

Odour: Aromatic.

Taste: Pungent.

Surface: Longitudinally striated with occasional projecting fibers.

Shape: Laterally straightened on the upper side with short smoothed angled, obovate branches or fingers. Each branch is 1 to 3 cm

long and at its zenith shows a discouraged scar of the stem.

Size: Length 5 to 15 cm, width 3 to 6 cm; thickness 0.5 to 1.5 cm.

Fracture: Short, starchy, fibrous.

Fractured surface: Shows a tight bark, a very much stamped endodermis and a wide stele, showing various dispersed grayish focuses (fibro-vascular bundles) and more modest yellowish focuses (secretion cells)

3.3. Microscopic properties of Ginger Rhizome [35]:

Cork: Outer zone consists of irregularly arranged cells and inner zone consists of cells arranged in radial rows. Cork is absent in Jamaica Ginger.

Cortex: Cortex consists of thin walled, cellulosic rounded parenchyma with intercellular spaces. These cells contain simple, ovate or sac-shaped starch grains with hilum at the pointed end. Cortex contains closed collateral fibro-vascular bundles. Some cells contain yellow brown oleo resin.

Phellogen: It is indistinct

Endodermis: It is distinct and consists of tangentially elongated cells containing suberin in radial walls. Starch is absent.

Stele: Below the endodermis is a ring of vascular bundles without fibres. The remaining tissue contains fibro- vascular bundles, starch and oleo resin cells similar to cortex.

3.4. Classification of ginger:

Kingdom - Plantae

Order - Zingiberales

Family - Zingiberaceae

Genus - *Zingiber*

Species - *officinale*

The fresh and dried *Z. officinale* extracts were said to contain gingerols, 1,7-bis (40-Hydroxy-30-methoxyphenyl)-3,five-heptadione, adenine, 1- Dehydro-three-dihydro-gingerdione, Acetoxy-6-dihydroparadol, Isogingerol, five-Methoxy-gingerol, Methyl diacetoxy-gingerdiol, Methyl diacetoxy-gingerdiol, 1-Dehydro-gingerdione, Acetoxy-gingerol, Shogaol, Paradol, 1-(forty Hydroxy-30-methoxyphenyl)- 7-octen-three-one, 1-(40-Hydroxy-30-methoxyphenyl)-7-decen-three-one,1-(forty-Hydroxy-30-methoxyphenyl)-7-dodecen-three-one, beta-sitosterol palmitate, isovanillin, glycol mono palmitate, hexacosanoic acid 2,3-dihydroxypropyl ester, maleimide-5-oxime, p-hydroxybenzaldehyde and 1-(omega-ferulyloxyceratyl) glycerols **[36, 37, 38]**, these are the chemical constituents of ginger. The pungency of ginger is due to the gingerols and shogaols **[39]**. Ginger oil contains monoterpene, hydrocarbons, sesquiterpene hydrocarbons, oxygenated mono- and sesquiterpene **[40]**. The groups of phytochemicals present in the ginger rhizome is provided in **Table 1**.

Fresh ginger is known to contain protein, fats, minerals, fibres, carbohydrates, lipids

(including glycerides, phosphatidic acid, lecithins, and fatty acids), protease, iron, calcium, magnesium, potassium, and phosphorous **[32]**. It also includes nutrients consisting of thiamine, riboflavin, niacin etc **[41,42]**. Some important structures of ginger constituents which carry the antiarthritic activities are as below-

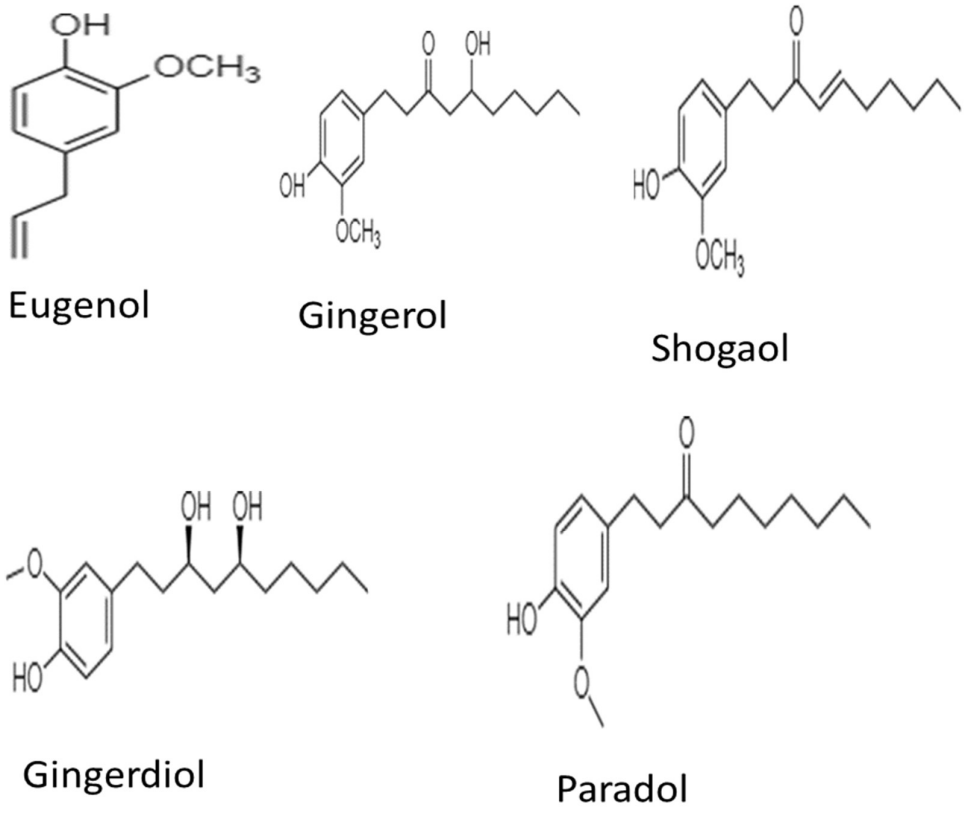

Figure 2. Structures of ginger constituents

Table 1: Phytochemicals present in Ginger rhizome [32, 33, 36, 37, 38, 39, 40, 41, 42]

Sl. No.	Phytochemical Group	Phytochemical Name
1	Terpene	α-Terpinene, α-Terpineol,4-Terpineol,Terpinolene, and c- Terpinolene
2	Alcohol	Cineole, β-Eudesmol, Nerol, trans-Nerolidol, 4-Isopropylbenzyl alcohol, 3,7-Dimethylocta-1,6-dien-3-ol, 3,7-Dimethyloct-6-en-1-yn- 3-ol, 3-Methylhexan-2-ol, cis-Piperitol, Borneol, Elemol, tau- Muurolol, 2-Methoxy-1,7,7-trimethylbicyclo[2.2.1]heptane, 1- Isopropyl-4-methylcyclohex-3-enol, 2-Tetradecanol, Myrtenol, Citronellol, Geraniol, cis-Linalool oxide, 4-Ethoxybutan-1-ol, α- Eudesmol, Nerolidol, Farnesol, trans-4-Isopropyl-1-methyl-2- cyclohexen-1-ol, cis-4-Isopropyl-1-methyl-2-cyclohexen-1-ol, 2- Heptanol, 1-Methoxy-2-methyl, cis-Sesquisabinene hydrate, cis-2-p- Menthen-1-ol, endo-Borneol, trans-Sabinene hydrate, 2-Nonanol, Propanol, cis-β-Sesquiphellandrol, trans-β-Sesquiphellandrol, β- Santalol, Zingiberol, tau-Cadinol, Zingiberenol, 2-Pinen-5-ol, Bornyl methyl ether, Isoborneol, 2-Decanol, Fenchol, Linalool, Plinol, Camphenol, trans-2-Decen-1-ol 10-O-β-D-Glucopyranosyl-hydroxyl cineole and Hentriacontanol.
3	Aldoketone	Butanal, Germacrone, 2,6-Dimethylhept-5-enal, 2Heptanone, (E)- Citral, (Z)-Citral, 2-nanone, 3-(3E,5E)-Deca-3,5- dienyl)cyclopentanone, β-Cyclocitral, 2-Undecanone, 1,7,7- Trimethylbicyclo[2.2.1]heptan-2-one,(1R)-(–)-Myrtenal,β- Citronellal, Crypton, 4-Isopropylcyclohex-2enone,Camphor, 6- Methyl-5-hepten-2-one,trans,trans Farnesal, Hexanal,Neral, Geranial,Octanal, Methyl heptanone, Nonyl aldehyde, Acetaldehyde, Propionaldehyde, Valeraldehyde, Perillal, (E)-Dodec-2-enal, (Z)-3,7- Dimethylocta-3,6-dienal, (E)-3,7-Dimethylocta-3,6-dienal, (E)-Dec-2-enal, Decanal, Citronella, 2-Octenal, Octanal, and Acetone.
4	Acid	L-Bornyl acetate, Geranic acid, Undecanoic acid,

5	Ester	Neryl acetate, Methyl 11-(cyclopent-2-enyl) undecanoate, Geranyl propionate, endo-Bornyl acetate, sec-Butyl acetat, 3,7-Dimethyl-2,6- octadienyl acetate, Neryl propionate, Geraniol formate, Myrtenyl acetate, Geranyl acetate, Formic acid ethyl ester, Ethyl butanoate, Citronellyl acetate, Heptyl acetate, Methyl acetate, Ethyl acetate, Butyl acetate and 2-Octyl acetate.
6	Fat hydrocarbon	allo-Aromadendrene, β-Sesquiphellandrene, α-Cedrene, β-Thujene, Cadina-5,8-diene, Bicyclo[2.2.1]heptane, (E)-2,7-Dimethyloct-3-en-5-yne, (Z)-2,6-Dimethylocta-2,6-diene, (E)-three,7-Dimethylocta-1,3,6- triene, β-Phellandrene, α-Bergamotene, α-Gurjunene, Sabinene, (+)- Cyclosativene, (Z)-β-Farnesene, (E)-β-Farnesene, (Z,Z)-α-Farnesene, Zingiberene, α-Farnesene, (E)-five-Methylocta-1,6-diene, 5-Methyloct- 3-yne, 7-Methylocta-3,4-diene, γ-Elemene, γ-Humulene, Thujopsene, β-Elemene, β-Bisabolene, α-Pinene, β-Pinene, Caryophyllene, β- Caryophyllene, Tricyclene, Moslene, Cedrene, (–)-allo- Aromadendrene, Neoclovene, 3-Octyne, 1-Octene, β-Myrcene, β- Eudesmene, Eudesma-3,7(eleven)-diene, Caryophyllene, Bicyclo[3.1.1]heptane, 1-Cyclopropylpentane, 3-Carene, 2-Carene, (+)-Aromadendrene, Fenchene, δ-Elemene, D-Limonene, β- Phellandrene, 10-Epizonarene, Octane, Nonane, α-Bergamotene, β- Bisabolene, τ-Epi-α-selinene, 4-Carene, Camphene, α-Phellandrene,(Z)-3,7-Dimethylocta-1,3,6-triene, Germacrene, δ-Cadinene, α-Cubebene and α-Copaene.
7	Arene	α-Curcumene,2-Isopropyltoluene,o-Cymene,Styrene, Methylbenzene, Cumene, p-Cymene,
8	Others	P-Cymen-8-ol, 2-Acetoxy-1, 8-cineole, Diethyl sulphide, Ethyl isopropyl sulphide, Methyl allyl sulphide, Dibutyl phthalate, 2-(3′- Methyl-2′-butenyl)-3-methylfuran, Isoeugenol and 2-(2′, 3′-Epoxy-3′-methylbutyl)-3-methylfuran.

3.5. Variety of ginger:

Several ginger cultivars are grown in India's various ginger growing regions, and they are often named after the regions where they are cultivated. Maran, Kuruppampadi, Ernad, Wayanad, Himachal, and Nadia are some of the most well-known indigenous cultivars. The exotic cultivar 'Rio-de -Janeiro' has also gained a lot of popularity among growers. Some of the varieties of ginger is shown in table 2. The enhanced ginger types and their distinguishing characteristics are listed below. IISR Varada is good for fresh ginger, dry ginger, and candy production, whereas IISR Rejatha has a lot of essential oil **[43]**.

Table 2: Variety of Ginger

Variety	Maturity (days)	Dry recovery (%)	Essential oil (%)
IISR Varada	200	20.7	1.8
IISR Rejatha	200	19.0	2.4
IISR Mahima	200	23.0	1.7
Suruchi	218	23.5	2.0
Subhada	210	22.4	2.0
Suprabha	229	20.5	1.9
Suravi	235	23.5	2.1
Himagiri	230	20.6	1.6
Karthika	220-240	21.6	3.2
Athira	220-240	22.6	3.1
Aswathy	220-240	19.7	3.3

3.6. Distribution of Ginger:

Since ancient times, ginger has been grown in tropical Asia. Ginger has not been found in wild forms, and its origin is unknown, however it is supposed to originate in India. Arab traders from India carried it to Europe and East Africa. Ginger, along with pepper, was one of the most widely sold spices in the 13th and 14th centuries. During the 16th century, the Portuguese transported ginger from East Africa to West Africa and other tropical locations. Around the same time, the Spanish introduced ginger to Jamaica, which continues to produce excellent ginger today. Ginger is currently grown in the tropical tropics **[44]**.

4. Ginger and its role in preventing arthritis:

4.1. Ethno-pharmacological reports of ginger-

Since ancient times, India and China have used ginger as a spice and medicine. Its medical benefits were also known in Europe from the 9th century and in England from the 10th

century **[45]**. Wild ginger rhizome has reportedly been utilised by Native Americans to control menstruation and heartbeat. Ginger is supposed to decrease nausea by acting directly on the gastrointestinal system. It is thus used to treat nausea caused by chemotherapy, motion sickness, and surgery **[46]**. Ginger is widely used as a nausea treatment during pregnancy. Morning sickness, colic, upset of stomach, gas, bloating, heartburn, flatulence, diarrhoea, loss of appetite and dyspepsia are all conditions that ginger is used to treat for. Ginger is advised for improving food digestion in the Indian Ayurvedic medical system **[47]**.

Apart from these benefits, ginger has been used to treat arthritis, muscle aches, chest discomfort, low back pain, stomach pain, and menstruation pain. It can be used to treat infections of the upper respiratory tract, cough, and bronchitis. It is advised for joint disorders as an anti-inflammatory medication. Ginger juice has been demonstrated to help with skin burns. Ginger's active ingredient is used as a laxative and an antacid. It is also used to warm the body, which helps with circulation and blood pressure. Ginger functions as an antiviral in the treatment of colds and flu due to its warming impact. Ginger is often used to flavour foods and beverages, as well as to scent soaps and cosmetics **[47, 48]**.

4.2. Antiarthritic activity of ginger reported:

A study investigated the antiarthritic results of ginger and its bioactive ingredients, a properly characterised crude ginger extract changed into in comparison with a fraction containing 6-gingerol and their derivatives to inhibit joint swelling in an animal version of rheumatoid arthritis, streptococcal cellular wall-prompted arthritis **[32]**. Ginger's anti-inflammatory effects may be due in part to its inhibition of cyclooxygenase, inducible nitric oxide synthase, and lipoxygenase activities, as well as suppression of inflammatory prostaglandin synthesis and interference in cytokine signalling **[49, 50, 33, 28]**. A number of ginger constituents including gingerols, shogaols, and diarylheptanoids may contribute to these actions **[49, 33]**. Crude ginger extract, 6 - gingerol to reduce joint swelling in animals induced with rheumatoid arthritis and exhibited potent anti-inflammatory action **[51]**. Van Breemen *et al* reported the mechanism of anti-inflammatory effect of ginger parts. They discovered that 10-gingerol, eight-shogaol, and 10-shogaol strongly inhibited COX-2 and thereby appreciably reduced infection **[52]**. Although most papers show that ginger reveals its anti-inflammatory effect by way of blocking off COX-2 enzymes, Grzanna *et al* has mentioned blocking the sports of both COX-1 and COX-2 **[33]**. Eun *et al* (2009) evaluated pharmacological effects of 14 phytochemicals isolated from *Z. officinale* using the uncooked 264.7 cell line **[53]**. They located that 6-shogaol, 1-dehydro-10-gingerdione, and 10-gingerdione substantially

decreased LPS-brought on nitric oxide manufacturing even as the first two remarkably reduced iNOS expression, all through improvement of RA excessive degree of nitric oxide and iNOS play pivotal role in cartilage damage and infection. So, those compounds may also have beneficial effect to reduce the irritation in RA **[54]**. Lee *et al* demonstrated that 6-gingerol isolated from *Z. officinale* exhibited anti-inflammatory effect by using blocking NF-kB and protein kinase C (PKC) signalling pathways **[54]**. 6-Gingerol appreciably suppressed IκBα phosphorylation, NF-kB nuclear activation, and PKC-α translocation which in turn inhibited Ca2+ mobilization and disrupted mitochondrial membrane potential in LPS inspired macrophages, consequently inducible nitric oxide synthase and TNF-α expression have been notably inhibited and reduced inflammation **[53]**.

Consumption of ginger has been shown to help relieve joint pain linked with rheumatoid arthritis **[55]**. Kiuchi *et al* confirmed ginger's anti-inflammatory properties for the first time in 1982 **[56]**. They discovered four novel chemicals in ginger, all of which have the ability to suppress prostaglandin formation, which is the key to inflammation. In a 1992 study, researchers discovered that ginger has anti-inflammatory properties by blocking both prostaglandin and leukotriene production **[57]**. A catechol-containing diarylheptanoid showed action against 5-lipoxygenase, which prevented leukotriene production, resulting in an anti-inflammatory effect. Another component, yakuchinone A, suppressed prostaglandin production, resulting in an anti-inflammatory action once more.

Thomson and his colleagues evaluated the anti-inflammatory effect of *Z. officinale* in rats **[55]**. For four weeks, rats were given an aqueous extract of *Z. officinale* either orally or intraperitoneally. Although ginger did not diminish prostaglandin E2 levels at low dosages, it did so dramatically at large doses. As a result, ginger may help to lessen RA-related inflammation.

Ribel-Madsen *et al* recently investigated the anti-inflammatory effects of ginger *in-vitro*, isolating synovial cells from synovial membrane or synovial fluid **[58]**. TNF-was used to activate the cells. Ginger inhibited the production of cytokines IL-1 and IL-6 in the same way that betamethasone did, indicating an anti-inflammatory action.

5-lipoxygenase is one of the most important components of inflammation, and lowering this factor helps to reduce inflammation. According to Flynn *et al*, gingerol and gingerdione have strong analgesic and anti-inflammatory properties through blocking PGE2 production **[59]**.

Shimoda *et al* assessed acetic acid-induced writhing and foot pad edema tests as acute and chronic inflammatory models in trials with ginger **[60]**. The anti-inflammatory activity of

Z. officinale was demonstrated by a significant reduction in the frequency of writhing and footpad edema. To figure out the process, they looked at the influence of prostaglandin and nitric oxide production in mouse leukemic monocytes (RAW 264 cells) induced by lipopolysaccharide. They found that ginger extract significantly reduced the generation of nitric oxide (NO) and prostaglandins. Bioassay guided separation was used to identify the active ingredients, and they discovered that 6-shogaol, gingerdiols, and proanthocyanidins were responsible for the unique effects.

Young *et al* discovered that 6-gingerol, one of the principal phytochemical elements of *Z. officinale* has analgesic and anti-inflammatory properties **[58]**. The anti-inflammatory effects of acetic acid writhing and formalin induced licking were assessed, whereas the analgesic effect of carrageenan caused paw edema was investigated in male ICR mice. Ojewole discovered that an ethanol extract of dried *Z. officinale* has analgesic and anti-inflammatory properties. Analgesic effects were assessed using hot plate and acetic acid tests in mice, whereas anti-inflammatory effects were investigated using egg albumin-induced pedal edema in rats. These experimental animal experiments revealed that ginger has potential analgesic and anti-inflammatory effects, which could be used to treat arthritic pain and inflammation **[61]**.

Funk's group studied the antiarthritic effect of crude extract ginger from *Z. officinale* in animal models of rheumatoid arthritis and *Streptococcal* cell wall induced arthritis **[62]**. The therapeutic potency of crude extract was compared to that of gingerol and its derivatives, a phytochemical ingredient. They discovered that specific phytochemicals had a significant impact. Surprisingly, the crude extract including essential oils and more polar chemicals had greater anti-inflammatory and anti-bone-degeneration properties. They concluded that *Z. officinale* non-gingerol substances, as well as gingerol, exhibited significant antiarthritic efficacy. Another study by Sharma's group found that ginger oil had powerful antiarthritic and anti-inflammatory properties **[63]**. In the study, arthritic rats were given ginger oil orally at a rate of 33 mg/kg for 26 days. Both paw and joint swelling were dramatically reduced by ginger oil. Srivastava *et al* discovered that ginger has antiarthritic efficacy in patients with rheumatoid arthritis, osteoarthritis, and muscle discomfort **[64]**. More than three-quarters of the RA patients in the research reported significant reductions in pain and swelling. Surprisingly, after ingesting ginger powder, all of the patients with muscular discomfort reported a reduction in pain. The favourable benefits of ginger in reducing RA pain were found to be attributable to suppression of prostaglandin and leukotriene production, according to this study **[64]**.

The mechanism of ginger components' anti-

inflammatory activity was reported by van Breemen *et al.* They discovered that 10-gingerol, 8-shogaol, and 10-shogaol all inhibited COX 2 and thereby reduced inflammation considerably **[65]**. Though most studies suggest that ginger reduces inflammation by inhibiting COX-2 enzymes, Grzanna *et al* has reported that ginger inhibits both COX-1 and COX-2 enzymes. This study also discovered that ginger inhibits 5-lipoxygenase, which inhibits leukotriene production **[66]**. Nurtjahja-Tjendraputra *et al* also discovered that ginger inhibits COX-1 activity. Their research demonstrated that ginger's 8-paradol is a powerful COX-1 inhibitor **[67]**.

As previously stated, macrophages play a critical part in the development of arthritis by producing various cytokines and chemokines. Inflammation can be minimised if the macrophage can be rendered inactive. Tripathi and her colleagues investigated the effects of ginger on this condition **[68]**. Interestingly, the components of *Z. officinale* were found to considerably block the release of proinflammatory cytokines (IL-12, TNF-, and IL-1), as well as proinflammatory chemokines, in LPS-induced macrophages **[69]**.

Phan *et al* studied the effects of ginger extract on inflammation associated with RA in human synoviocytes **[70]**. *Z. officinale* was found to decrease cytokine expression significantly in the study. Gingerols and shogaols were found to have strong anti-inflammatory effect by Lantz *et al* **[71]**. They discovered that gingerols, but not shogaol, could reduce LPS-induced COX-2 expression. Haghighi and his colleagues compared ginger's anti-inflammatory effect to that of ibuprofen (a commonly recommended anti-inflammatory medicine for arthritic patients) in an experiment **[72]**. Ginger and ibuprofen both have anti-inflammatory properties, indicating that ginger could be used as an anti-inflammatory medication.

Yoshikawa's group investigated the analgesic efficacy of ginger extract in 261 patients with osteoarthritis of the knee **[73]**. 247 (94.6%) of the patients reported a reduction in pain, indicating a possible analgesic effect from the administration of *Z. officinale* extract.

Tjendraputra and colleagues **[74]** looked into the mechanism of ginger extract inhibition of COX-2. The primary phytoconstituents of ginger, 8-paradol and 8-shogaol, dramatically lowered COX-2 enzyme activity. They discovered three possible ways for 8-paradol and 8-shogaol to exert their COX-2 inhibitory effects in the same study: (I) lipophilicity of the alkyl side chain, (II) substitution pattern of hydroxy and carbonyl groups on the side chain, and (III) substitution pattern of hydroxy and methoxy groups on the aromatic moiety.

The dual activity, in murine macrophages, 6-shogaol suppressed LPS-induced upregulation of iNOS and COX-2 activity **[75]**. Western blotting and reverse transcription-PCR

investigations revealed that 6-Shogaol significantly inhibited iNOS and COX-2 protein and mRNA expression. Figure 3 highlights the effect of *Z. officinale* on the physiological mechanism of arthritis.

Using the RAW 264.7 cell line, Eun *et al* (2009) assessed the pharmacological effects of 14 phytochemicals derived from *Z. officinale* **[76]**. They discovered that 6-shogaol, 1-dehydro-10-gingerdione, and 10-gingerdione inhibited LPS-induced nitric oxide production considerably, while the first two dramatically reduced iNOS expression. High levels of nitric oxide and iNOS play a key role in cartilage degradation and inflammation during the progression of RA. As a result, these chemicals may help to decrease inflammation in RA patients.

Pragasam *et al* conducted both *in-vivo* and *in-vitro* tests to assess the effect of 6-gingerol as an inflammatory agent. Gouty arthritis was modelled in mice using monosodium urate crystal-induced inflammation **[77]**. They discovered that 6-gingerol lowered the levels of lysosomal enzymes and inhibited lactate dehydrogenase and acid phosphate. They concluded that these findings showed that ginger phytochemicals have anti-inflammatory properties.

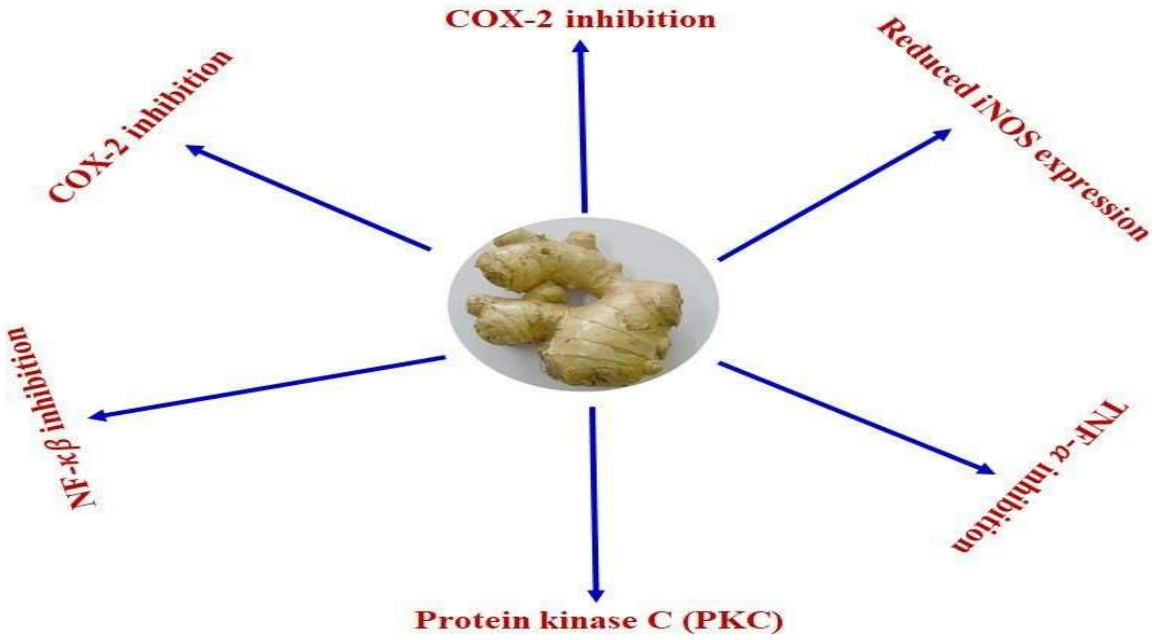

Figure 3: Effect of *Zingiber officinale* on physiological mechanism of Arthritis

5. Grading of ginger and quality characteristics:

Ginger is generally sold as raw ginger in local markets but there are several other products of ginger like dry ginger, ginger powder, ginger oil, and oleoresin. The oleoresin and oil are known as high value and low volume products, which have great demand in many countries. The varieties with less fibre, high dry matter recovery, and high oil and oleoresin contents are having great export potential in international markets. In International market several grades are available and on the basis of that ginger has been categorized in different grades **(Table 3)**. The assortments with less fibres, high dry matter recuperation, and high oil and oleoresin contents are having extraordinary product potential in global business sectors **[78]**.

Table 3: The quality characteristics of different grades in ginger [79]

Sl. No	Quality characters	Limits		
		Grade-I	Grade-II	Grade- III
1	Extraneous matter % by mass (max.)	2.0	3.0	5.0
2	Insect damaged matter, % by mass (max.)	1.0	3.0	5.0
3	Non-volatile ether extract content of the dry matter % bymass (min.)	5.0	3.0	2.0
4	Volatile oil as ml/100 gm (min.)	0.7	0.5	0.3
5	Dry matter, % by mass (min.)	22.0	20.0	18.0
6	Volatile oil as ml/100 gm (min.)	0.7	0.5	0.3
7	Crude fibre content of the dry matter % by mass (max.)	8.0	10.0	12.0

6. CONCLUSION:

Arthritis is a major disease world-wide. The present drugs available can only reduce the pain and inflammation however, are unable to provide cure for arthritis. Several phytochemicals have been screened for antiarthritic potential with the hope to provide suitable remedy for arthritis. Among different plant resources, it has been observed that ginger is comparatively effective and contains different constituents that possessed strong antiarthritic activity. In the present review it has been discussed about the action of ginger and its constituents towards fighting arthritis. Hence it can be highlighted that ginger is effective and good resource which has immense potential to treat arthritis effectively.

8. Conflict of Interest: Declared None

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