International Journal of Current Research and Review
DOI: https://doi.org/10.31782/IJCRR.2022.142005

Review Article

IJCRR
Section: Healthcare

Recent Findings on *Alpinia Galanga* (L.) Wild for the Treatment of Arthritis Part-1

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ABSTRACT

Arthritic inflammation of joints affects people of all age groups. The treatment is a challenge as arthritis is a complex disease and evolves over years. Patients often have to take medicines for the rest of their life. Commonly prescribed medicines like analgesic, glucocorticoids and non-steroidal anti-inflammatory drugs have side effects. The new disease modifying medicines are costly. People in the healthcare system are assessing the dynamics of complementary and alternative medicines. One such remedy is *Alpinia galanga* (AG) of Zingiberaceae family. It is characterized by the presence of rhizome, wide leaves and terminal inflorescence. The references for its medicinal uses are found in traditional medicines. It is cultivated in tropical regions of south east Asia. Its rhizome is highly aromatic and most frequently used as a food and medicine. The various extracts of AG are prepared by the researchers and studied for its phytoconstituents and pharmacological activities. Clinical, *in vitro*, *in vivo* and *in silico* experimentation techniques are used to validate the claims for various therapeutic activities. This article focuses on reviewing literature to ascertain anti-arthritic potential of AG. The article has been divided in 2 parts and includes analgesic, anti-arthritic, anti-inflammatory, antioxidant, other therapeutic effects as well as safety and toxicity of AG.

Key Words: Greater galangal, Ginger, Antioxidant, Anti-inflammatory, Analgesic, Rheumatic, Rhizome.

INTRODUCTION

The suffix "itis" is used to indicate inflammation and thus "arthritis" means inflammation of joints. Since the trigger for inflammation can vary, the group of medical conditions are collectively termed as arthritis e.g., rheumatoid arthritis (RA), osteoarthritis (OA), psoriatic arthritis, gout, ankylosing spondylitis, etc. The frequently observed conditions are RA and OA. Progressive degenerative changes which happen in the articular cartilages are hallmark of osteoarthritis. Rheumatoid arthritis is characterized by chronic systemic autoimmunity. Depending on aetiology and disease progression, patients frequently experience pain, swelling, redness and limited movements. Examination of the joints reveals a cascade of events. Comorbidities are often observed in patients suffering from rheumatoid arthritis.[1] Generally prescribed medications are analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, disease-modifying antirheumatic drugs (DMARDs)and biological agents. Treatment of arthritis usually requires long term therapy, which poses risk of complications associated with medication. The medication needs to be chosen such that benefits outweigh the risk. Here herbal remedies are of great benefit.

Pathophysiology of joints in arthritis

In joints, the surface of bone is coated with periosteum which has pain receptors.[2] At the tip of the bone is articular cartilage, which helps in gliding and shock absorption. Surrounding the joint is the synovial membrane, made up of cells known as fibroblast-like synoviocytes (FLS), produces synovial fluid. Due to inflammation, cells secrete excess fluid which results in joint swelling and pain. Macrophages, T cells, B cells, dendritic cells (DC), fibroblasts, mast cells and neutrophils infiltrate the inflamed synovium. T cells stimulate monocytes, macrophages, and synovial fibroblasts to produce cytokines and to secrete matrix metalloproteinases (MMP) through the release of mediators such as interferon-ɣ and interleukin-17. Interleukin-1, interleukin-6, and Tumour Necrosis Factor- α are the cytokines that play a major role in inflammation.[3,4]

FLS stimulate receptor activator of the nuclear factor kappa B ligand (RANKL) expression which together with cytokines stimulate osteoclast activity. This leads to bone erosion.[5] Neutrophils accumulate in inflamed joints in high numbers. Life of these neutrophils is increased due to delayed apoptosis. In the synovial fluid these produce proteases and reactive oxygen Species (ROS).[6] B-cells secrete proteins such

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ISSN: 2231-2196 (Print) **ISSN:** 0975-5241 (Online)

Received: 27.07.2022 **Revised:** 21.08.2022 **Accepted:** 18.09.2022 **Published:** 17.10.2022

as rheumatoid factors (RFs) and anti-citrullinated protein antibodies (ACPA). These two autoantibodies are key diagnostic markers in clinical management of RA.[7] With proliferation of cells and increased metabolic activities, there is an increased demand for nutrients which signals angiogenesis. Increased VEGF expression is detected in the articular cartilage of OA and RA.[8]

During inflammation phospholipase enzyme is secreted. Arachidonic acid, which is otherwise esterified to phospholipids, is set free by the action of phospholipase enzymes. This arachidonic acid through cyclooxygenase and lipoxygenase pathways produces prostaglandins and leukotrienes respectively. Prostaglandin specially prostaglandin E2 (PGE2) promotes local vasodilatation and attraction and activation of macrophages, neutrophils and mast cells.[9] Prostaglandins induce hyperalgesia, so a non-painful stimulus turns painful. During arthritis, there is an increased population of cells in the joints and available oxygen is insufficient to these cells. In hypoxic condition, mitochondrial respiration produces nitric oxide (NO) and reactive nitrogen species (RNS). Through chain of events, other free radicals such as hydroxyl free radical, superoxide free radical anion, lipid peroxide reactive oxygen species (ROS) such as singlet oxygen and hydrogen peroxide are accumulated in the joint. These reactive substances further triggers release of inflammatory substances and worsen the damaged joint.

Alpinia galanga

Alpinia galanga(AG) (*syn. Languas galanga*) also known as Thai ginger is used as a spice. It is known by different names in different parts of the world. e.g., English- Greater galangal, China-*Gao liang jiang*, India- *Kulinjan* (Hindi)-*Rasna* (Sanskrit), Indonesia- *Halawas*, Thailand- *Kha*.AG is grown/consumed in many countries like China, Thailand, Malaysia, India, Iraq, Turkey etc. AG has been traditionally used for various therapeutic activities suchas antibacterial, antifungal, antiallergic, antidiabetic, anti-arthritic activity etc.[10] Many traditional formulations from siddha medicine[11], unani medicines[12] and ayurvedic medicines[13] containing AG are popular. *Alpinia* species are listed in various pharmacopoeias like The Chinese Pharmacopoeia, The Ayurvedic Pharmacopoeia of India, The Herbal Medicines Formulary of the Brazilian Pharmacopoeia and The Japanese Pharmacopoeia.

Taxonomy Hierarchy

Kingdom: Plantae

Division:*Magnoliophyta*

Class:*Liliopsida*

Order:*Zingiberales*

Family:*Zingiberaceae*

Genus:*Alpinia*

Species:*A. galanga*

AG is anaromatic perennial largeherb. It can grow erect up to 3 m in height. It is a rhizomatous herb with rhizomes whitish externally and pale yellow internally. The rhizomes are highly branched, 2-4 cm wide and strongly aromatic. These are used as a spice in the food. The leaves are nearly hairless, green above and paler beneath. They are oblong-anceolate acute, glabrous, with slightly callus white margins, 20–35 cm long, 5–10 cm wide, and ligules are short and rounded. Terminal Inflorescence is 10-30 cm long, 5-7 cm wide and is densely flowered. Flowers are greenish white, fragrant and eaten as a vegetable. The fruit is a round or ellipsoidorange-red capsule 1-1.5 cm wide, which darkens on maturity. It contains 2-3 black seeds. AG grows best outdoors in moist, but well-drained, fertile soil.

Many articles have been published which summarizes constituents of AG.[14,15,16]A detailed overview of chemical constituents of AG in last 6 decades is given by Ma et al.[17] Few of the constituents are as follows-flavonoids, phenylpropanoids, lignans, terpenes etc. Most frequently detected compounds are galangin, kaempferol, 1′-acetoxychavicol acetate (ACA), galanganols 1,8-cineole, eucalyptol. Although rhizomes are the most frequently studied, other parts of the plants like leaf[18], stem[19], flower[20], fruit[21] and seeds[22] are also rich in bioactive phytoconstituents.

Several reviews on AG are published which describe different aspects of AG e.g., pharmacognostic, pharmacological etc. but non focuses on antiarthritic activity.[23,24] In this review, the findings on AG and its phytoconstituent's as a potential antiarthritic are presented (Figure 1).

Figure 1: Effects of *Alpinia galanga*.

Analgesic effect

Analgesic actions of 90% ethanolic extracts of AG rhizome were studied in albino mice of both sexes weighing 25 to

30 g. For the peripheral analgesic activity mice were placed on the hot plate and the time taken to show first sign of paw licking or jumping was recorded. AG treatment at 200, 400 and 800 mg/kg significantly increased withdrawal time in the hot-plate test. For central analgesic activity 0.1 mL of 0.6% acetic acid was injected intraperitoneally. The extracts of AG inhibited acetic acid-induced writhes. To ascertain the mechanism of action, along with a control group, additional groups were administered naloxone with morphine (2 mg/kg) and naloxone with AG extract at various concentrations. The results indicated that a central mechanism of analgesic action was exhibited at 400 mg/kg and a peripheral mechanism of analgesic action was exhibited at 800 mg/kg.[25]

In Swiss albino mice, Subhash et al.[26] observed similar results. They further performed *in silico* studies using Schrodinger software. The compounds studied were Galanal B, Galanal A, β-caryophyllene, α-humulene, β-phyllandrene, pomalidomide, linalool, limonene, 1, 8- cineole, borneol, α-pinene, α-terpineol, camphene, β-pinene, 4-terpineol, P-cymene and amrinone. Galanal B showed lowest binding free energy, lower than control (2AZ5) against human TNF alpha. QikProp version 3.6 software predicted Galanal A to have drug like properties and good oral absorption.

Anti-arthritic effect

Randomized, double-blind clinical studies were carried out for 6 weeks in 261 patients with moderate-to-severe knee pain due to osteoarthritis. The patients were divided in 2 groups-placebo and treatment. Treatment group received 255 mg extract of dried ginger rhizomes and dried galanga rhizomes twice daily. Reduction in knee pain on standing was24.5 mm for treatment group and 16.4 mm for placebo group, reduction in pain after walking 50 feet was 15.1 mm and 8.7 mm for treatment and placebo groups.[27] In yet another 12-week study, carried out at two centres in a randomised, double –blind, placebo-controlled, parallel group manner, reduction in knee pain on standing was measured using a visual analog scale. The treatment group received 1 capsule twice daily containing 150 mg ginger rhizome (*Zingiberis officinale* rhizome) powdered extract with 125 mg galangae rhizome (*Alpinia officinarum* rhizome) dry extract. At the end of the study patients in the treatment group reported reduction in pain. More studies need to be carried out to confirm the preliminary data.[28]

Usha et al.[29] prepared 3 extracts of AG using solvents: petroleum ether, chloroform and alcohol. These extracts were formulated in 3% polyethylene glycol ointment base. Anti-arthritic study was carried out in male Wistar albino rats injected with Complete Freund's Adjuvant into the planter region of the left hind paw. Study was carried out for 28 days, and the percentage inhibition of various groups was 5.50, 66.96, 48.69, 44.63 and 54.78 in rats treated with placebo, piroxicam, ether extract, chloroform extract and alcohol extract respectively.

Porcine articular cartilage was dissected from a metacarpophalangeal joint. These cartilages were stimulated with recombinant human interleukin-1β at a concentration of 25 ng/ml to cause its degradation. Further they were exposed to hexane extract of AG. The AG extract at 25 to 100 µg/ml inhibited dose-dependent degradation of cartilage. The loss of Uronic acid from cartilage and the release of extracellular matrix (ECM) biomolecules s-GAG and HA to the medium was reduced. The results were comparable to the Diacerein ® (0.0625-1 µM). AG extract significantly reduced catabolic activity of MMP-2 and MMP-9 in the culture medium of chondrosarcomas. Similar effects were observed in case of synovial Fibroblasts. The AG extract not only reduced catabolic effect but enhanced anabolic effect. There was an increase in type II collagen, SOX9 and aggrecan gene expression.[30]

DISCUSSION

AG is consumed in many parts of the world as a food and medicine. Rhizome of AG has been most studied but it's been used in different forms in studies – from fractions obtained after physical treatments like fresh juice, oils to fractions obtained after chemical treatments like solvent extraction and even combinations like microwave assisted solvent extraction, lyophilization of solvent extract etc. This has caused variation in type and quantity of phytochemicals in the study, in addition to variation due to geographical location. A plethora of phytoconstituents have been isolated and studied systematically for various pharmacological effects through *in silico*, *in vitro*, preclinical and clinical studies. Many old articles disclose studies with details of extraction procedure and findings of pharmacological activity, current trend encompasses identification studies also. This has become possible due to availability of sophisticated analytical techniques.

Analgesia is the first sought effect by the patients. AG contains monoterpenes which are known to have antinociceptive effect.[31] Clinical trials in osteoarthritic patients have shown that polyherbal formulations containing AG are effective. Few of studies have been carried out, with only AG or plants of genus *Alpinia* using animal models. Complete Freund's Adjuvant induced adjuvant arthritis is considered to be the closest animal model to induce autoimmune disease. Oral as well as topical application has shown positive results compared to placebo formulation.

CONCLUSION

Treatment of arthritis usually requires long term therapy, which poses risk of complications associated with medication. Careful selection of therapeutic agents is the key. Here herbal remedies are of great benefit. AG has shown analgesic and

ant-arthritic effects. Anti-inflammatory, antioxidant and other therapeutic effects as well as safety and toxicity of AG are discussed in part -2 of the article.

ACKNOWLEDGEMENT

Authors are thankful to Prin. K.M. Kundnani College of Pharmacy, Mumbai, India for their support in this work.

SOURCE OF FUNDING

We did not receive any funding for this work.

CONFLICTS OF INTEREST

Authors declare no conflict of interest. The authors alone are responsible for the content and writing of this article.

AUTHORS' CONTRIBUTION

Roopam Raut collected and analyzed the data and drafted the manuscript. Jessy Shaji critically reviewed the manuscript. All authors have read and approved the final manuscript.

ETHICAL CLEARANCE

None.

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