



# The Potential Of Ginger's Bioactive Components In Managing Osteoarthritis - A Review

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## Abstract

The anti-inflammatory qualities of ginger and its active ingredients in osteoarthritis are gaining recognition despite the herb's long history of health benefits. Certain active ingredients in ginger have properties in common with synthetic medications such non-steroidal anti-inflammatory medicines. Ginger inhibits prostaglandin and leukotrienes by upregulating the expression of 5-lipoxygenase, cyclooxygenase 1, and cyclooxygenase 2. Inhibiting many genes associated in the initiation of the inflammatory response is another important function of ginger. Enzyme-encoding genes, chemokines, and cytokines are among them. Ginger has anti-inflammatory, antioxidant, and analgesic qualities without causing adverse effects on the kidneys or gastrointestinal tract. Up to 2–2.5 g of ginger per kg of body weight is considered a safe dosage without any negative effects. To validate ginger's potential as a treatment for osteoarthritis, more research on human subjects is required. This review established ginger's excellent bioactive profile and the therapeutic benefits of these active ingredients. The information in this review is current and covers the benefits of applying and consuming ginger for osteoarthritis pain reduction and enhanced knee function.

**Keywords :** *Chemokines; cyclooxygenase; inflammation; ginger; osteoarthritis; pain*

## Introduction

Osteoarthritis is a chronic disorder that impairs mobility in the elderly by steadily and gradually increasing the loss of articular cartilage. Around 250 million individuals globally are impacted by this degenerative and more prevalent joint condition[1]. Knee osteoarthritis affects twenty-one million people in the United States and 1-2 million elderly people in Indonesia[2]. It involves the deterioration of cartilage in joints, which triggers an inflammatory response and causes discomfort, stiffness, and reduced joint movement[3]. The American College of Rheumatology advises using pharmaceutical medication as a therapeutic strategy for managing inflammation and pain. This includes intra-articular and nonsteroidal anti-inflammatory medications[4].

Osteoarthritis acts on the underlying bone, articular cartilage, synovium, ligaments, and tendons, impairing the functionality of the entire synovial joint. The pathological hallmark of osteoarthritis is the ongoing deterioration of tissues, which leads to the eventual loss of articular cartilage. Protecting the ends of the bones and helping in the coupling of antagonist joint surfaces are two of cartilage's primary functions. The rubbing

of bones against one another damages the articular cartilage bones, causing stiffness, severe discomfort, and loss of movement in the joints[5]. Long-term use of these medications has been connected with a number of gastrointestinal problems, including gastritis and dyspepsia[6].

Ginger is a natural therapeutic agent that has been found to reduce the negative effects of pharmaceutical treatment. It gained attention due to several bioactive substances called gingerols, zingerone, shogaols, paradols, 6-dehydrogingerdione, and quercetin. Certain terpene chemicals, including  $\beta$ -bisabolene,  $\beta$ -sesquiphellandrene,  $\alpha$ -curcumene, and zingiberene, are also present in ginger. Ginger's abundance of polysaccharides, organic acids, lipids, and fibres gives it potent anti-inflammatory and antioxidant qualities[7]. Recent research has shown that an active ingredient in ginger lowers the risk of a number of diseases, including respiratory syncytial virus infection[8]. According to the World Health Organisation, ginger can help to improve one's health, because it contains bioactive elements that were given to us by God and can be used to treat nausea, the flu, gastrointestinal issues, and common colds[9].

According to these positive effects, several research on the effects of ginger on patients with osteoarthritis have concluded that ginger is a safe and useful therapeutic agent for the treatment of patients with joint impairment [10]. Ginger's active ingredients, primarily gingerol, have been shown in numerous studies to have anti-inflammatory and osteoarthritis-reducing effects. These effects are due to their inhibition of genes, transforming growth factor (TGF)- $\beta$ , interferon- $\gamma$ , cyclooxygenase (COX)-2, tumour necrosis factor (TNF)- $\alpha$ , and nuclear transcription factor (NF)-K $\beta$  in various cancer cell types [11-13]. Ginger is essential for managing weight because it has demonstrated significant effects on weight loss through lowering blood glucose levels[14]. Ginger has been utilised as a herbal remedy for a variety of diseases in recent research. However, China has utilised fresh ginger juice to boost the medicinal effect and change the bioactive ingredients targeted potential[15].

Ginger has a remarkable bioactive profile, and this review demonstrated that these active chemicals have been shown in clinical trials to have positive health effects. Current research on the benefits of applying and consuming ginger for osteoarthritis pain reduction and increased knee function is presented in this review.

### **The bioactive components of ginger**

More than 400 chemical components can be found in ginger rhizome extracts[16]. The therapeutic effects of only a few components of ginger have been recognised. According to recent research, gingerols, shogaols, and paradols are primarily responsible for the anti-inflammatory properties of ginger[6]. Ginger's delightful fragrance stems from volatile oils such sesquiterpenoids and monoterpenes, of which  $\alpha$ -zingiberene (30–70%) is the primary constituent. Minor levels of  $\beta$ -sesquiphellandrene (15–20%),  $\beta$ -bisabolene (10–15%),  $\beta$ -phellandrene, and geraniol are also present. Analogues of gingerol, including zingerone, paradols, shogaols, and gingerols, cause a burning and heated sensation in the mouth. Recent studies have shown increased interest in phenylalkanoids, dialylheptanoids, and sulfonates components. Fresh ginger has components that include steroids and monoterpene glycosides. Alkaloids, xanthenes, and lactones are other significant components of ginger[15]. The bioactive ingredients of ginger are listed in Table 1 along with some of its potential uses.

Bioactive Components	Therapeutic Potential	References
Gingerol	Anti-Inflammatory Anti-Oxidant	[17]
Zingerone	Anti-Oxidant Anti-Bacterial	[18]
Ginger Flavonoids	Anti-Oxidant	[19]
Shagoal	Anti-Cancer Anti-Proliferation	[20]
1-Dehydro(10)gingerdiones Terpenoids	Activate p53 Induce Apoptosis Anti-Inflammation	[21]
1,7-Diarylheptane	Anti-Inflammatory Anti-Oxidant Anti-Tumor Anti Hepatotoxic Chemopreventive	[15]

Table 1 : Ginger's Bioactive components and its Therapeutic Potential

The phenolic hydroxy group that ginger contains next to the methoxy group is what inhibits the formation of progesterone[22]. the amount of gingerols, shogaols, and paradols in ginger extracts. Gingerols are dehydrated to form shogaols, are a major constituents of dried ginger powder. Gingerols can easily dehydrated to form the corresponding shogaols because of the presence of a -hydroxy keto group. Shogaols and zingerone are found in small amounts in fresh ginger but are substantially present in stored ginger. Ginger's bioavailability and pharmacological qualities are dependent on the degree of conversion[6]. Figure 1 displays the molecular structures of a few bioactive components that are present in ginger.

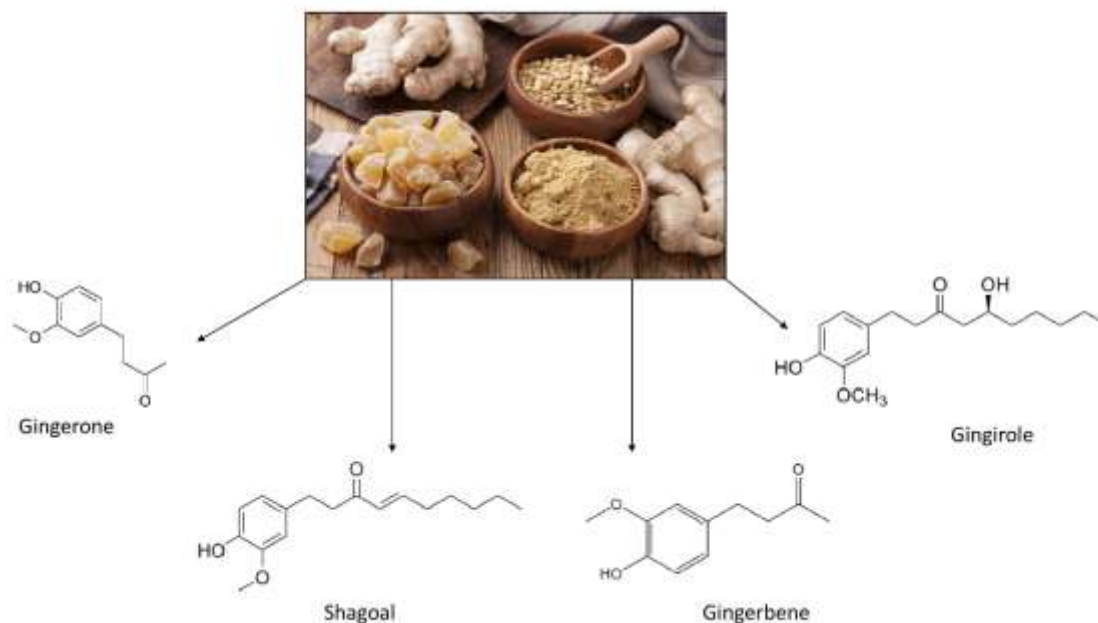


Figure 1 : Molecular Sturcture of Few bioactive component's found in Ginger.

### Ginger's pharmacological properties

Ginger has been utilised as a medicinal ingredient since ancient times because of its healing qualities. Ginger has pharmacological properties that include anti-inflammatory, anti-cancer, antioxidant, and analgesic effects. Numerous research have documented ginger's effectiveness and positive effects in the treatment of osteoarthritis. Ginger is helpful in lowering discomfort and swelling in the joints[23]. Ginger extract was found to be superior to conventional treatment before switching to non-steroidal anti-inflammatory drug therapy in an experimental trial research involving 57 instances of osteoarthritis[24]. In a randomised controlled study, 250 mg capsules of ginger powder were administered to 122 female students as young as 21. The intervention had negligible effects on arthritis[25]. A study investigated at the prostaglandin levels

in those with chronic knee osteoarthritis who co-supplement ginger with black pepper and turmeric extract compared to Naproxen. The research comprised of sixty individuals with two different levels of osteoarthritis in the knee. It was demonstrated that the selected intervention, when administered twice daily for four weeks, had an equivalent impact on prostaglandin levels in patients with osteoarthritis in their knees as the medication i.e Naproxen[26]. A randomised controlled clinical study suggests that G-Rup® syrup, which combines ginger and honey, may be more effective than conventional therapeutic regimens in reducing osteoarthritis symptoms[27]. In one trial, Altman and Marcussen treated 247 osteoarthritis patients with ginger extract for six weeks. The results showed a statistically significant decrease in knee pain. When compared to the control group, patients receiving ginger extract treatment showed improved results. Numerous clinical and experimental research attest to the beneficial effects of ginger extracts in lowering inflammation and improving osteoarthritis[28]. Table 2 lists the active components of ginger that are involved in the inhibition and regulation of specific biological functions.

Patients	Form of Drug	Route of Administration	Duration of administration	Visual analogue scale (VAS) & WOMAC score	References
Osteoarthritis	Capsule	250 mg	6 weeks	↓5.7 mm during walking ↓5.3 mm during standing	[4]
Knee Osteoarthritis	Capsule	255 mg	6 weeks	↓6.4 mm during walking ↓8.1 mm during walking	[24]
Knee Osteoarthritis	Capsule	500 mg	2 months	↓VAS score	[29]
Knee Osteoarthritis	Pill	50 mg diclofenac +750 mg gingerol	5 weeks	↓WOMAC score ↓VAS score	[30]
Knee Osteoarthritis	For massage use	Gingerol oil +meloxicam 15 mg	2 times for 5 weeks	↓VAS score ↓WOMAC score	[31]
Knee Osteoarthritis	Capsule	Ginger + glucosamine	1 month	↓VAS score	[3]

Table 2 : An overview of ginger's effects on osteoarthritis.

### Activity of antioxidants

Antioxidants are substances that aid in the elimination of free radicals and reduce oxidative stress. Antioxidants are essential for both disease prevention and treatment. Ginger is regarded as an antioxidant agent because of its significant effects on lowering lipid oxidation and reducing the advancement of illness. Gingerol is involved in the suppression of lipid peroxidation in rat liver microsomes, whereas ginger extract functions as an antioxidant and scavenges superoxide anion and hydroxyl radicals, according to a variety of studies[32].

Ginger's total phenolic content and antioxidant activity were examined in a study that employed air, oven, and freeze-drying techniques. However, when compared to ginger dried by other techniques, oven-dried ginger displayed greater values for each distinct phenolic component found in this investigation[33]. In cases of acute renal injury, a study investigated the antioxidant properties of ginger extracts against free radicals. Zingiber officinale or ginger, is a herb with antioxidant and anti-inflammatory characteristics. The results of the meta-analysis support the compelling evidence for the preventative antioxidant effect of ginger extracts in animals with acute renal injury[34].

Ginger oil and oleoresin exhibit strong antibacterial and antioxidant properties, whereas 6-shogaol, 6-dehydroshogaol, and 1-dehydro-6-gingerdione are nitric oxide inhibitors[35]. Because ginger contains an unsaturated ketone moiety, one study found that the active ingredient 6-shogaol possesses strong antioxidant qualities[36]. A different study found that the active phenolic compounds in ginger have strong anti-oxidant, anti-inflammatory, and anti-carcinogenic effects[37].

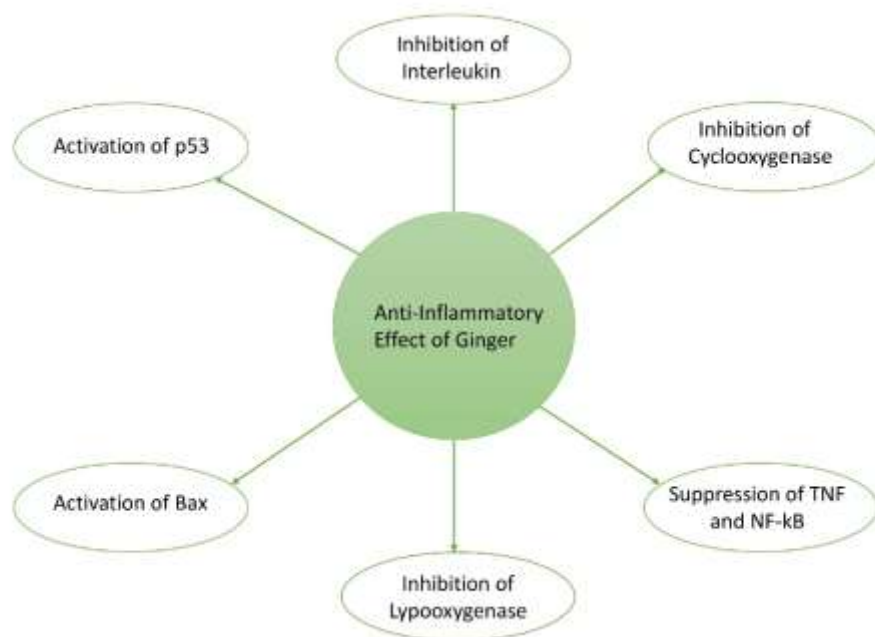


Figure 2: Ginger's anti-inflammatory properties in medical conditions.

### Activity of Anti-Inflammation

Inflammation is a complicated immunological response that includes the activation of certain inflammatory mediators such as interleukin-1, tumour necrosis factor, and cytokines. Inflammatory illnesses are currently treated pharmacologically using non-steroidal anti-inflammatory medication therapy. Plants with many rhizomes have a significant impact on the reduction of inflammation. According to one study, giving ginger oil (33 mg/kg) to those with persistent osteoarthritis significantly reduced their swelling[38]. TNF, interleukin-1, and interleukin-8 are among the pro-inflammatory cytokines that ginger suppresses the activation of[39]. A study found that in rats with liver cancer, ginger extract (100 mg/kg body weight) decreased TNF- $\alpha$  expression[23]. According to another study, ginger inhibits cyclooxygenase and 5-lipoxygenase and reduces the activation of genes that cause inflammation[40]. Through the inhibition of 5-lipoxygenase, cyclooxygenase-2, necrosis factor K $\beta$ , and induction of apoptosis, ginger demonstrates a significant therapeutic impact[41].

In comparison to the ginger extract and placebo groups, one study found that after three weeks of ibuprofen treatment, VAS pain ratings were considerably different. According to Friedman tests for multiple comparisons, there was a statistically significant difference ( $P < .0001$ ) between the ibuprofen and ginger or placebo conditions. Additionally, compared to the placebo group, the ibuprofen and gingerol groups showed a considerably better effect in the trial, as demonstrated by statistical analysis with a  $P < .05$ [23].

Before crossover, one research contrasted Zintona EC 1 g/day with a placebo. As a result, by week 12, both groups' discomfort had considerably diminished[42]. Twelve weeks after the crossover, pain was

significantly decreased even though it had increased in the Zintona-placebo and ginger groups. According to the study, there were significant differences between the placebo-ginger and ginger-placebo groups, with  $P < .01$ . On a 100-point VAS, the mean reduction in pain is 67.57 points. Throughout the trial, four paracetamol tablets were thought of as a rescue drug. The anti-inflammatory properties of ginger in medical conditions are shown in Figure 2.

### Progesterone biosynthesis inhibition

The Zingiberaceae family of plants was first shown to have medicinal benefits in suppressing the synthesis of progesterone[43]. According to the study, progesterone production is significantly impacted by fresh ginger extracts by chromatographic purification and analysis. Based on an in-depth analysis of ginger's properties, researchers came to the conclusion that [6]-gingerol and four structurally related substances suppress the synthesis of progesterone in the renal medulla of rabbits. Ginger has been shown in several trials to possess analgesic and anti-inflammatory properties that are with non-steroidal anti-inflammatory medication efficacy. Ginger and non-steroidal anti-inflammatory medications reduce the synthesis of progesterone via stimulating the inhibition of arachidonic acid metabolism by cyclooxygenase. The two isoforms of this enzyme, known as cyclooxygenase-1 and cyclooxygenase-2, are frequently found in cells. While cyclooxygenase-2 is not noticeable in the majority of tissues, it is remarkably abundant in areas of inflammation[44]. A few studies have shown that the good effects of non-steroidal anti-inflammatory medicines come from suppressing cyclooxygenase-2, while the unfavourable effects are caused by inhibition of cyclooxygenase-1. A study documented the beneficial impact of gingerols on the cyclooxygenase enzyme within intact cells. According to a study, the cyclooxygenase enzyme is more effectively inhibited by gingerols that have been extracted from ginger[22]. Pharmacological medications are widely recognised for their adverse reactions[45].

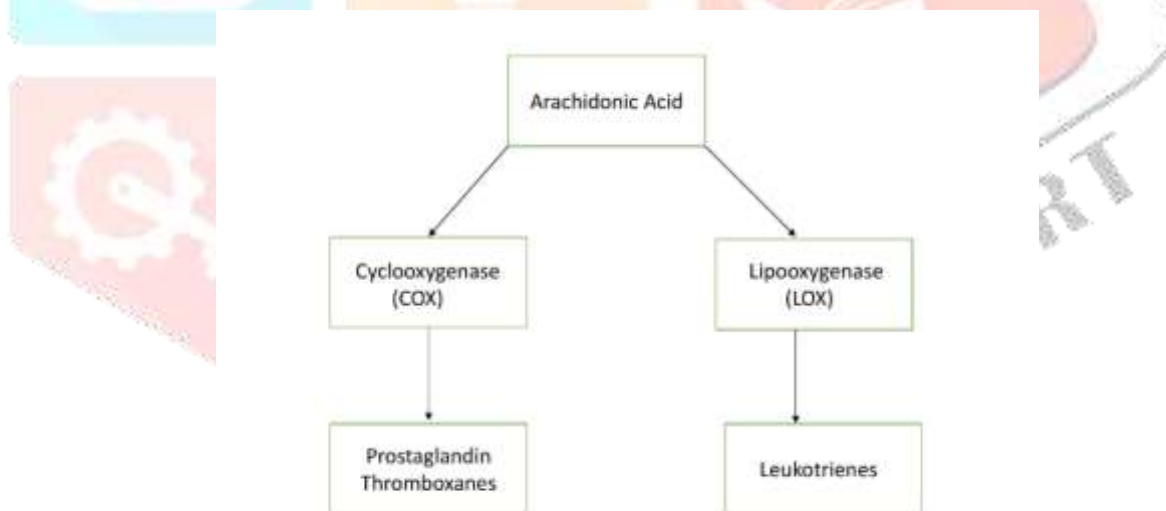


Figure 3: Metabolism of Arachidonic acid involve two pathways (Cyclooxygenase pathway metabolism results in the synthesis of progesteron and thromboxanes and lipoxygenase metabolism results in the synthesis of Leukotrienes).

Figure 3 illustrates the two routes involved in the metabolism of arachidonic acid: the lipoxygenase pathway produces leukotrienes, while the cyclooxygenase pathway produces progesterone and thromboxanes. The production of genes encoding pro-inflammatory cytokines is elevated in chronic inflammatory diseases. Small proteins known as cytokines are secreted at sites of inflammation by fibroblasts, macrophages, and lymphocytes. Cytokines serve as a mediator between immune system cells and the trigger for inflammatory reactions. Chemokines are a subclass of cytokines that play a crucial role in chemoattractant recruitment, meaning they help draw effector cells to areas of tissue injury. Suppression of the synthesis and metabolism of pro-inflammatory cytokines is a promising strategy to minimise inflammatory diseases including arthritis[46]. Osteoarthritis causes excruciating pain and inflammation by inducing an inflammatory reaction. Joint synovial cells are stimulated to release interleukin-1 and tumour

necrotic factor. Numerous investigations are carried out on human chondrocytes and synoviocytes to examine the function of ginger extract in suppressing pro-inflammatory cytokines. In one study, interleukin-1 or tumour necrotic factor, two cytokines implicated in inflammation, were used to stimulate synoviocytes taken from individuals with osteoarthritis. The study found that ginger extract had a beneficial effect on interleukin-1- or tumour necrosis factor-activated synoviocytes' ability to suppress TNF expression at the transcript level[47]. Additionally, ginger extract inhibits the expression of tumour necrosis factor in stimulated chondrocytes[48]. The ginger extract also prevents the induction of genes that code for chemokines, such as interferon inducible protein-10 and monocyte chemotactic protein-1[49]. Inflamed joint tissue also exhibits considerably higher protein levels as a result of cyclooxygenase-2 gene activation[50]. One of the main characteristics of osteoarthritis is the over-expression of cyclooxygenase-2, which can result in tumours, inflammatory bowel disease, and other pathological conditions[51]. Studies have shown that the ginger extract [6]-gingerol is a modest inhibitor of the generation of cytokines in monocytic THP-1 cells produced by LPS. It has been found that there is a considerable difference in the amounts of aspirin and sodium salicylate required to block the induction of Cyclooxygenase-2 by LPS[44].

### **Nuclear factor-B inhibition**

Nuclear factor-B is a key modulator of pro-inflammatory gene expression. These include cytokines, chemokines, and the pro-inflammatory gene that codes for the enzyme cyclooxygenase-2. According to recent research, nuclear factor-B is present in inflammatory areas. It has been shown that nuclear factor-B plays a major part in the synthesis of cytokines that cause severe inflammation. Non-consistent nuclear factor-B activation in osteoarthritis has been documented in synovial tissues and several other long-term inflammatory conditions[52]. According to several studies, nuclear factor-B treatments are helpful in a number of animal models of inflammatory disorders. Nuclear factor-B pathway inhibition confers anti-inflammatory properties to a number of naturally occurring plant-based compounds[53].

Numerous investigations have validated the beneficial function of ginger extract in suppressing the expression of pro-inflammatory genes. According to one study on the medicinal benefits of ginger extract, ginger extract significantly reduces nuclear factor-B expression in vitro. The study found that ginger extract inhibits nuclear factor-B expression in activated synoviocytes at a concentration of 100 g/mL[44]. These processes supported the ginger extract's anti-inflammatory effects on a variety of cell types and tissues.

### **Agonists for vanilloid receptors**

Severe pain is caused by pro-inflammatory chemical mediators that are released at the sites of inflammation[53]. In osteoarthritis, inflammation of the joints causes hyperalgesia, an exaggerated reaction to painful stimuli. Inflammation and chronic pain are caused by various inflammatory indicators, including progesterone, interleukin-6, interleukin-8, tumour necrosis factor-alpha, and interleukin-1. Pharmacological non-steroidal anti-inflammatory medications are frequently used to relieve pain associated with inflammation in osteoarthritis and other inflammatory illnesses. However, ginger extract derived from plants plays a similar impact in lowering joint pain and inflammation by blocking the creation of progesterone and other pro-inflammatory chemicals. According to recent research, a component of ginger has been found to play a major impact in reducing pain and inflammation. Gingerols have been shown by Dedov et al [54] to function as vanilloid receptor agonists. These receptors, often referred to as capsaicin-stimulated receptors, are involved in the start of joint discomfort [54] Zingerone and gingerols, which are vanilloid receptor agonists and enhance the analgesic action, are the components of ginger extract. Studies conducted in vivo shown the potential of ginger to reduce pain by altering inflammatory mediators and stimulating analgesic effects[1].

### **Recommended Dose**

A few plant components are essential for managing health and preventing disease. It's critical to measure the safe dosage of ginger in disease management to prevent toxicity. Different dosages of ginger for managing health were reported by several research using animal models. A safe dosage of 0.5–1.0 g of ginger powder for children aged 3 to 2.5 years was suggested by one study[55]. According to another study, a safe dosage of 2.5 g/kg body weight was suggested with no negative side effects. The death rate rose when the dosage

was raised to 3–3.5 g/kg of body weight[56]. According to one animal model study, which used pregnant rats for ten days, varying dosages of ginger extract—100 mg/kg, 333 mg/kg, and 1000 mg/kg—did not result in any harm[56]. In one study, rats given dosages of 500, 1000, and 2000 mg/kg per body weight of ginger extract for 35 days did not experience any mortality or abnormalities in behaviour, food, or water[57].

## Conclusion

Numerous investigations came to the conclusion that ginger, like non-steroidal anti-inflammatory medications, inhibits the manufacture of progesterone, which performs a crucial anti-inflammatory role. Certain components found in ginger, including gingerol, shagoals, and paradols, are involved in the regulation of cyclooxygenase and lipoxygenase enzyme activation, which in turn inhibits the manufacture of progesterone and leukotrienes. Ginger has medicinal properties that make it a viable substitute for non-steroidal anti-inflammatory medications without seriously harming the kidneys or gastrointestinal tract. Non-steroidal anti-inflammatory medicines, analgesic injections, and chemotherapy are the standard treatments for osteoarthritis, cancer, diabetes, and heart disease. While these treatments are efficient in relieving pain, they can also have unfavourable effects on the gastrointestinal tract and become expensive. A cost-effective, safe, and alternative is required to prevent side effects and slow the advancement of diseases in order to slow down the rate at which they progress. Many genes associated in various disease stimulation pathways can be suppressed by ginger and its components. Shortly put, ginger and its bioactive and anti-inflammatory ingredients help treat osteoarthritis; however, more research on human subjects is required to validate this.

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