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Role of bioactive components of ginger in management of osteoarthritis: a review

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ABSTRACT
Ginger and its beneficial role have been known for centuries but the anti-inflammatory properties and its active constituents in osteoarthritis gain attention. Ginger and its certain active constituents possess similar properties with synthetic drugs such as non-steroidal-anti-inflammatory drugs. Ginger is involved in inhibition of prostaglandin and leukotrienes by suppressing the stimulation of cyclooxygenase 1, cyclooxygenase 2, and 5-lipoxygenase. Ginger also plays a vital role in inhibition of several genes involved in the initiation of inflammatory response. These include cytokines, chemokines, and enzyme-encoding genes. Ginger possesses anti-inflammatory, antioxidant, and analgesic properties with the lack of gastrointestinal and renal side effects. The safe dosage of ginger is up to 2–2.5 g per kg body weight without any toxicity. Further studies on human trials are needed to confirm the therapeutic role of ginger in osteoarthritis. This review cleared that ginger have great bioactive profile and these active compounds have health beneficial agents in clinical aspects. This review provides an up-to-date knowledge regarding the effectiveness of the intake and application of ginger in the pain relief of osteoarthritis and improved the knee function.

Introduction
Osteoarthritis is a chronic condition that gradually and constantly increases the loss of articular cartilage and causes the disability in elderly. Approximately 250 million people worldwide are affected by this degenerative and growing joint disease.¹ Twenty-one million people in the United States and 1–2 millions older persons in Indonesia are affected by knee osteoarthritis.² C-1: References should be number format

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It involves stimulating an inflammatory response by the decline of cartilage in joints leading to pain, stiffness, and decrease movement of joints. Pharmacological treatment is recommended by the American College of Rheumatology as a therapeutic management to reduce pain and inflammation. That involves nonsteroidal anti-inflammatory drugs and intra-articular drugs.

Osteoarthritis affects the functioning of entire synovial joint, and act on underlying bone, articular cartilage, synovium, ligaments, and tendons. Pathological symbol of osteoarthritis is continuous degradation of tissues and ultimate deprivation of articular cartilage. The major function of cartilage is protecting the ends of the bones, and involves in the coupling of antagonist joint surfaces. The bones stroking against each other leads to stiffness, severe pain, and deprivation of movement in the joints due to damage of articular cartilage bones. Due to continued use of these medicines certain gastrointestinal disorders that involves dyspepsia and gastritis are reported.

To reduce the side effects of pharmacological treatment a natural therapeutic agent, ginger has been identified and gained attention due to its certain bioactive compounds commonly known as gingerols, zingerone, shogaols, gingerenone A, paradols, 6-dehydrogingerdione, and quercetin. Ginger also consists of certain terpene compounds such as β-bisabolene, β-sesquiphellandrene, α-curcumene, and zingiberene. Ginger possesses effective anti-inflammatory and antioxidant properties due to the presence of polysaccharides, organic acids, lipids, and fibers. Recent studies reported that an active component present in ginger decreases the risk of various infections such as respiratory syncytial viral infection. The World Health Organization declares that ginger has a positive role in the improvement of health. Because it have God gifted bioactive ingredients that can be used in gastrointestinal problems, nausea, common cold, and flu.

Due to these beneficial effects, different studies on the effect of ginger on osteoarthritis patients reported that ginger is safe and effective therapeutic agent for treatment of patients with joints disability. Various studies reported that ginger consists of active components majorly gingerol, that have anti-inflammatory properties and also involve in reduction in osteoarthritis by inhibition of transforming growth factor (TGF)-β, interferon-γ, cyclooxygenase (COX)-2, tumor necrosis factor (TNF)-α, genes and suppression of nuclear transcription factor (NF)-Kβin different cancer cell types. Ginger had shown great impact on weigh lose by reducing the glucose level in blood, therefore it plays a vital role in weight management. In recent study, ginger has been used as herbal medicine for treating different diseases. However, fresh ginger juice has been used in China to enhance the therapeutic effect and alter the targeted potential of bioactive compounds.

This review cleared that ginger has a great bioactive profile and these active compounds have health beneficial agents in clinical trials. This review provides an up-to-date knowledge regarding the effectiveness of the intake and application of ginger in the pain relief of osteoarthritis and improved the knee function.

**Bioactive components of ginger**

Extracts of ginger rhizomes consist of more than 400 chemical compounds. Only few components of ginger have been identified for their medicinal properties. Recent studies suggested that major portion of ginger’s anti-inflammatory properties are due to a gingerols, shogaols, and paradols.

The pleasant aroma of ginger is derived from volatile oil such as sesquiterpenoids and monoterpenes, with α-zingiberene (30–70%) as the main component, and smaller amounts of β-sesquiphellandrene (15–20%), β-bisabolene (10–15%), β-phellandrene, and geraniol. Pungent and warm sensation in the mouth is due to Gingerol analogues such as gingerols, shogaols, paradols, and zingerene. Diarylethanoïds, phenylalkanoids, and sulfonates components have gained interest in recent research. Steroids and monoterpenoid glycosides components are present in fresh ginger. Moreover, alkaloids, xanthones, and lactones are important also constitutes of ginger. Table 1 shows the bioactive components of ginger and their possible therapeutic potentials below.

Role of ginger in inhibition of Progesterone synthesis is due to presence of the phenolic hydroxy group adjacent to the methoxy group. The geographic origin and extraction techniques determine
the amount of gingerols, shogaols, and paradols in ginger extracts. Gingerols are dehydrated to form shagoals, 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. In fresh ginger, shogaols and zingerone are present only in less amount but present in large amount in stored ginger. The extent of conversion is important for ginger bioavailability and pharmacological properties. Molecular structures of few bioactive components found in ginger shown in figure 1.

**Pharmacological activities of ginger**

Since ancient times, due to its therapeutic properties, ginger has been used as a source of medicine. Pharmacological activities of ginger involve as an antioxidant, anti-cancer, anti-inflammatory, and analgesic agent. Numerous studies reported the efficiency and beneficial role of ginger for
osteoarthritis treatment. Ginger has a positive role in reducing joint swelling and pain. One experimental trial study that involves 57 osteoarthritic cases have been reported that the ginger extract was better than conventional treatment before cross-over with non-steroidal anti-inflammatory drugs. In a randomized controlled trial, 122 female students aged as 21 years were given 250 mg capsules of ginger powder, the intervention showed minor impacts on arthritis. In comparison to Naproxen, a study examined the effects of co-supplementing ginger with turmeric extract and black pepper on prostaglandin in individuals with chronic knee osteoarthritis. The study included 60 participants with two varying degrees of knee osteoarthritis. The chosen intervention, when taken twice daily for 4 weeks, was shown to have a similar effect on prostaglandin levels in individuals with chronic knee osteoarthritis as the medicine naproxen. According to a randomized controlled clinical research, the G-Rup® syrup, which contains a combination of honey and ginger, may work better than standard therapy regimens for improving the symptomatic treatment of osteoarthritis.

Altman and Marcussenin one study that involves 247 patients with osteoarthritis were treated with ginger extract conducted for 6 weeks, reported a statistically significant reduction in knee pain. A positive response in patients treated with ginger extract compared with the control group was reported. The various experimental and clinical studies declare the therapeutic effects of ginger extracts in reducing inflammation and the improvement of osteoarthritis disorder. Active components of ginger that are involve in modulation and inhibition of certain biological activities are described in Table 2.

**Antioxidant activity**

Components that are involved in the neutralization of free radicals in an order to reduce oxidative stress are known as antioxidants. Antioxidants play a vital role in prevention and treatment of various diseases. Due to important properties of ginger in reduction of the lipid oxidation and inhibition of the progression of diseases, ginger is considered as an antioxidant agent. Numerous studies reported that ginger extract acts as an antioxidant and involve in scavenge superoxide anion and hydroxyl radicals and gingerol is involve in inhibition of lipid peroxidation in rat liver microsomes.

A study investigated the antioxidant activity and total phenolic content of ginger, freeze-dried, oven-dried, and air-dried methods were used. However, oven-dried ginger showed higher values for all individual phenolic compounds detected in this study as compared to those dried using other methods. A study looked at how ginger extracts protect against free radicals in cases of acute renal damage. Ginger, Zingiber officinale, is herb that has anti-inflammatory and anti-oxidant properties. The meta-analysis's findings corroborate the strong evidence for ginger extracts' preventive antioxidant activity in animals suffering from acute renal damage.

The significant antioxidant and antimicrobial activities are showed by ginger oil and oleoresin while inhibitors of nitric oxide are 6-shogaol, 6 Dehydroshogaol, and 1-dehydro-6-gingerdione. One study reported that active component 6-shogaol in ginger has potent anti-oxidant properties due

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**Table 2. Summary of the effects of Ginger on Osteoarthritis.**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Form of drug</th>
<th>Route of administration</th>
<th>Duration of administration</th>
<th>Visual analogue scale (VAS) &amp; WOMAC score</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis</td>
<td>Capsule</td>
<td>250 mg</td>
<td>6 weeks</td>
<td>↓5.7 mm during walking</td>
<td>[4]</td>
</tr>
<tr>
<td>Knee Osteoarthritis</td>
<td>Capsule</td>
<td>255 mg</td>
<td>6 weeks</td>
<td>↓5.3 mm during Standing</td>
<td>[24]</td>
</tr>
<tr>
<td>Knee Osteoarthritis</td>
<td>Capsule</td>
<td>500 mg</td>
<td>2 months</td>
<td>↓VAS score</td>
<td>[29]</td>
</tr>
<tr>
<td>Knee Osteoarthritis</td>
<td>Pill</td>
<td>50 mg diclofenac +750 mg gingerol</td>
<td>5 weeks</td>
<td>↓WOMAC Score</td>
<td>[30]</td>
</tr>
<tr>
<td>Knee Osteoarthritis</td>
<td>For message use</td>
<td>Ginger oil + meloxicam 15 mg</td>
<td>2 times for 5 weeks</td>
<td>↓VAS</td>
<td>[31]</td>
</tr>
<tr>
<td>Knee Osteoarthritis</td>
<td>Capsule</td>
<td>Ginger + glucosamine</td>
<td>1 month</td>
<td>↓VAS</td>
<td>[3]</td>
</tr>
</tbody>
</table>
to presence of unsaturated ketone moiety. Another study reported that active phenolic substances in ginger exhibit effective anti-inflammatory, anti-oxidative, and anti-carcinogenic properties.

**Anti-inflammatory activity**

A complex immune process that involves stimulation of certain inflammatory mediators such as interleukin-1, tumor necrosis factor, and cytokines are referred as inflammation. Currently, pharmacological treatment that involve non-steroidal anti-inflammatory drugs is used to treat inflammatory disorders. Numerous rhizomes of plants plays an important role in suppression of inflammation. One study reported administration of ginger oil (33 mg/kg), resulted in significant repression of swelling in chronic osteoarthritis. Ginger is involved in suppression of stimulation of pro-inflammatory cytokines that involves interleukin-1, tumor necrosis factor, and interleukin-8. One study reported that ginger extract (100 mg/kg body weight) reduces the expression of TNF-α in liver cancer rats. Another study suggests that ginger plays a significant role in inhibition of Cyclooxygenase and 5-lipoxygenase and reduce stimulation of inflammatory genes. Ginger shows an important therapeutic effect by the inhibition of necrosis factor Kb, 5-lipoxygenase, Cyclooxygenase-2, and induction of apoptosis.

One study reported significantly different VAS pain ratings after 3 weeks of ibuprofen use than ginger extract and the placebo group. A highly significant difference between the ibuprofen condition and the ginger or placebo condition were reported by Friedman tests for multiple comparisons proven by statistical analysis were $P < .0001$. The study also reported a significantly better effect in both ibuprofen and gingerol groups compared with the placebo group proven by statistical analysis were $P < .05$.

One study compared Zintona EC 1 g/day with placebo before crossover. As a result, pain decreased significantly in both groups at week 12. While the pain in the Zintona – placebo group had increased, than placebo followed by ginger group, pain had reduced remarkably further 12 weeks after crossover. The study reported a highly significant differences between placebo – ginger group and ginger – placebo group were $P < .01$. Pain reduction is by a mean of 67.57 points on a 100-point VAS. Four tablets of acetaminophen were considered as a rescue medication throughout the study. Figure 2 unveils the anti-inflammatory role of ginger in health maladies.

**Figure 2.** Anti-inflammatory role of ginger in health maladies.
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).

Inhibition of progesterone biosynthesis

Initially, one study reported the therapeutic role of plant from Zingiberaceae family in inhibition of progesterone synthesis.\[^{43}\] The study declares extracts of fresh ginger by chromatographic purification and analyses have a significant effect on progesterone synthesis. By detailed study of characteristics of ginger, study concluded that \[^{6}\]-gingerol and four structurally related compounds are involved in the inhibition of progesterone synthesis in rabbit renal medulla. Various studies reported ginger has anti-inflammatory and analgesic activities comparable in efficiency to non-steroidal anti-inflammatory drugs. Inhibition of arachidonic acid metabolism by cyclooxygenase stimulates the suppression of progesterone synthesis by non-steroidal anti-inflammatory drugs and ginger. This enzyme consists of two isoforms, commonly referred as cyclooxygenase-1 and cyclooxygenase-2 is commonly present in cells. While cyclooxygenase-2 is almost negligible in most tissues, but is present in remarkable amount at sites of inflammation.\[^{44}\] Certain studies reported that non-steroidal anti-inflammatory drugs negative effects are due to inhibition of cyclooxygenase-1 while positive effect reside in suppression of cyclooxygenase-2. One study reported the therapeutic effect of gingerols on cyclooxygenase enzyme in intact cells. A study reported that gingerols isolated from ginger are more powerful inhibitors of cyclooxygenase-2.\[^{22}\] The pharmacological medicines are commonly known for their side effects.\[^{45}\] Figure 3 shows the 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).

Inhibition of cytokine and chemokine

In chronic inflammatory conditions, synthesis of gene encoding pro-inflammatory cytokines are increased. Lymphocytes, macrophages, and fibroblasts secrete small proteins at sites of inflammation are referred to as cytokines. Cytokines act as a messenger between immune system cells and stimulation of inflammatory responses. A subset of cytokine that are major chemo attractants and involved in recruitment of effector cells to sites of tissue damage is referred to as chemokines. A positive approach to reduce inflammatory disorders and arthritis involves suppression of synthesis and metabolism of pro-inflammatory cytokines.\[^{46}\] Osteoarthritis involves stimulation of inflammatory response and leads to severe inflammation and pain. Tumor Necrotic factor and interleukin-1 is secreted by stimulation of synovial cells in joints. Various studies are conducted on human synoviocytes and chondrocytes to investigate the role of ginger extract in inhibition of pro-inflammatory cytokines. One study on synoviocytes obtained from osteoarthritic patients were stimulated with the cytokines involved in the inflammation, either tumor necrotic factor or interleukin-1. The study reported positive effect of ginger extract in inhibition of the expression of tumor necrosis factor in synoviocytes
activated by either interleukin-1 or tumor necrosis factor at the transcript. In activated chondrocytes, ginger extract is also involved in inhibition of tumor necrosis factor expression. Induction of genes encoding chemokines: interferon inducible protein-10 and monocyte chemotactic protein-1 are also inhibited by the ginger extract. Due to cyclooxygenase-2 gene induction cyclooxygenase-2, protein levels are also significantly increased in inflamed joint tissue. Up-regulation of cyclooxygenase-2 is a prominent feature of osteoarthritis that leads to inflammatory bowel disease, athero-sclerosis, tumors, and other pathological condition. Certain studies reported that [6]-gingerol isolated from ginger is a weak inhibitor of LPS-induced cytokine induction in monocylic THP-1 cells. A significant difference has been reported in the concentrations of sodium salicylate and aspirin needed for inhibition of Cyclooxygenase-2 induction by LPS.

Inhibition of nuclear factor-B

A major regulator of pro-inflammatory gene expression is nuclear factor-B. These involve pro-inflammatory gene encoding enzyme cyclooxygenase-2, cytokines, and chemokines. Recent studies reported presence of nuclear factor-B at sites of inflammation. A significant role of nuclear factor-B in synthesis of cytokine that leads to severe inflammation has been observed. In osteoarthritis, irregular nuclear factor-B stimulation has been reported in synovial tissues and various other chronic inflammatory disorders. Some studies reported in several animal model of inflammatory diseases nuclear factor-B therapies is beneficial. Several natural plant-based products exhibit anti-inflammatory properties by nuclear factor-B pathway inhibition.

A number of studies confirmed the therapeutic role of ginger extract in inhibition of pro-inflammatory gene expression. One study conducted on the therapeutic effect of ginger extract reported a significant role of ginger extract on inhibition of nuclear factor-B expression in vitro. The study concluded inhibition of nuclear factor-B expression in activated synoviocytes at 100 g/mL is conducted by ginger extract. These mechanisms confirmed anti-inflammatory role of ginger extract on several cell types and tissues.

Vanilloid receptor agonists

The pro-inflammatory chemical mediators released at sites of inflammation lead to severe pain. An excessive response to noxious stimuli known as hyperalgesia is stimulated due to joint inflammation in osteoarthritis. Different inflammatory markers that involve progesteron, interleukin-6, tumor necrosis factor-alpha, interleukin-8, and interleukin-1 lead to inflammation and chronic pain. Inflammation-related pain in osteoarthritis and other inflammatory disorders are commonly treated with pharmaco-logical non-steroidal anti-inflammatory drugs. While plant-based ginger extract has similar role in reducing inflammation and joint pain through inhibition of progesterone synthesis and other pro-inflammatory agents. Recent studies reported a ginger constituent was identified, that has a significant role in reduction of inflammation and pain. Dedov et al. reported that gingerol act as agonists at vanilloid receptors. These receptors are known as receptors stimulated by capsaicin and are involve in initiation of joint pain. Ginger extract consists of gingerols and zingerone that act as vanilloid receptor agonists and stimulate analgesic effect. In vivo studies revealed the pain relieving role of ginger by stimulation of analgesic effect and modification of inflammatory mediator.

Recommended dose

Certain plant constituents play a vital role in prevention of diseases and management of health. Measurement of safe dosage of ginger to avoid toxicity is important in disease management. Various studies in animal model reported different dosage of ginger for health management. One study reported dose of 0.5–1.0 g of ginger powder for 3 to 2.5 years were recommended as a safe dosage. Another study reported 2.5 g/kg body weight was recommended safe without
any adverse effects. While increasing the dose to 3–3.5 g/kg body weight increased the mortality.\textsuperscript{[56]} One study on animal model conducted on pregnant rats for 10 days reported that different dosage of ginger extract 100 mg/kg, 333 mg/kg, 1000 mg/kg did not cause any toxicity.\textsuperscript{[56]} One study conducted on rats reported the dosage of ginger extract 500, 1000, and 2000 mg/kg per body weight for 35 days did not cause any mortality and abnormality in behavior, food, and water.\textsuperscript{[57]}

**Conclusion**

Various studies concluded that ginger plays a vital anti-inflammatory role by inhibiting progesterone synthesis similar to non-steroidal anti-inflammatory drugs. There are certain components such as gingerol, shagoals, and paradols present in ginger that are involve in the inhibition of synthesis of progesterone and leukotrienes by the suppression of cyclooxygenase and lipooxygenase enzymes stimulation. Due to the therapeutic role of ginger, it can be used as an alternative to non-steroidal anti-inflammatory drugs without any critical gastrointestinal and renal complications. The conventional treatment for osteoarthritis, cancer, diabetes, and heart disease involves non-steroidal anti-inflammatory drugs, analgesic injections, and chemotherapy that are effective in reducing pain but stimulate certain gastrointestinal side effects and are costly too. To reduce the progression of disease, a safe, economical, and effective alternative is needed to avoid side effects and suppress the progression of diseases. Ginger and its constituents have an ability to suppress number of genes that are involved in different disease stimulation. In short, ginger and its anti-inflammatory and bioactive components have a beneficial effect on osteoarthritis, further studies on human trials are needed for confirmation.

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**Credit authorship contribution statement**

Hafsa Maryam, Sameen Azhar, Nadeem M. Akhtar and Muhammad Afzaal proposed this idea and drafted the initial manuscript. Aasma Asghar, Huda Ateeq, Noor Akram and Mohd Asif Shah helped in preparing figures and tables, Farhan Saeed’ Haroon Munir and Waqas Anjum helped in improving the overall quality of the manuscript.

**Consent to participate**

Corresponding and all the coauthors are willing to participate in this manuscript.
Informed Consent

For this type of study, formal consent is not required.

Data availability statement

Data will be provided on a request basis.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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