



Therapeutic potential of [6]-gingerol in musculoskeletal diseases through modulation of inflammation and oxidative stress: A mini-review

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ABSTRACT

Musculoskeletal diseases (MSDs), including osteoarthritis, rheumatoid arthritis, and osteoporosis, represent major contributors to chronic pain, functional impairment, and disability worldwide. Chronic inflammatory activity and disrupted redox balance are increasingly recognized as important drivers of disease development and worsening in these conditions, and may therefore offer relevant avenues for therapeutic intervention. Natural bioactive agents have drawn considerable interest in recent research, particularly [6]-gingerol ([6]-G), the principal pungent phenolic compound found in fresh ginger (*Zingiber officinale* Roscoe). Its well-documented antioxidant and anti-inflammatory activities have made [6]-G a compound of growing interest in the context of MSDs. This review summarizes the chemistry, pharmacological activities, pharmacokinetic characteristics, and delivery strategies of [6]-G, with particular emphasis on its potential applications in MSDs. Experimental studies suggest that [6]-G modulates interconnected processes involved in inflammatory signaling, oxidative stress regulation, extracellular matrix preservation, and bone remodeling, contributing to its protective effects in joint and bone disorders. However, most available data come from preclinical studies, with limited clinical validation of purified [6]-G. Overall, [6]-G shows promise as a multitarget natural compound for MSDs, although further research is needed to confirm its efficacy, tolerability, and clinical applicability.

Implication for health policy/practice/research/medical education:

[6]-Gingerol ([6]-G), a major bioactive constituent of ginger, represents a promising therapeutic candidate for musculoskeletal diseases, particularly through its ability to modulate inflammation and oxidative stress, which are key and interconnected contributors to disease onset and progression. This evidence provides a rationale for advancing [6]-G research toward therapeutic development and exploring its potential role as a complementary strategy for the prevention and management of musculoskeletal diseases.

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Introduction

Musculoskeletal diseases (MSDs) encompass a broad spectrum of conditions involving the bones, joints, muscles, and associated connective tissues. Common forms of MSDs include osteoarthritis (OA), rheumatoid arthritis (RA), and osteoporosis (OP) (1). According to the 2019 Global Burden of Disease assessment, MSDs affect an estimated 1.71 billion individuals globally, with an age-standardized prevalence of 210 cases per 1,000 people, marking a 62% rise from 1990 (2). The global

aging trend is likely to further increase the prevalence and overall burden of these diseases in the coming years. Owing to their high prevalence, chronic course, and disability, MSDs impose substantial socioeconomic and healthcare burdens worldwide (3).

Current management strategies for MSDs primarily focus on alleviating pain, suppressing inflammation, delaying disease progression, preserving musculoskeletal function, and improving patients' quality of life (4). Although pharmacological options are widely available,

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their prolonged administration can be constrained by safety issues and unwanted effects (4,5). Consequently, natural compounds sourced from therapeutic herbs are receiving growing interest as potential alternatives to conventional drugs, owing to their diverse bioactive constituents, multitarget actions, and generally favorable safety profiles (6). Among therapeutic herbs, *Zingiber officinale* Roscoe (ginger), a member of the Zingiberaceae family, has long been recognized for its use as a flavoring ingredient and natural remedy in the prevention and management of a range of disorders (7). Evidence from experimental research indicates that ginger and its principal constituents exhibit both antioxidant and anti-inflammatory activities (8,9). The biological activities attributed to ginger are largely linked to its rich content of phenolic constituents, particularly gingerols and shogaols (10). Among the phenolic constituents identified in ginger, [6]-gingerol ([6]-G; $C_{17}H_{26}O_4$; molecular weight 294.39 g/mol) is the predominant pungent compound in fresh ginger and has consequently received the greatest research attention among ginger-derived phytochemicals. Growing evidence suggests that [6]-G may influence both inflammatory and oxidative processes, which are closely interconnected and implicated in the development and worsening of OA, RA, OP, and other MSDs (11,12). This growing body of evidence has positioned [6]-G as a promising candidate for therapeutic applications in MSDs. Taken together, this review examines the available evidence regarding the anti-inflammatory and antioxidant properties of [6]-G, focusing on its underlying biological actions and its possible use in managing MSDs.

Materials and Methods

Literature search strategy

A structured search of the published literature was undertaken to locate reports examining the therapeutic actions and underlying molecular pathways associated with 6-gingerol in MSDs. Studies published up to March 2026 were retrieved from PubMed, Web of Science, ScienceDirect, Scopus, and Google Scholar. The literature search was performed using the keywords “ginger”, “extract ginger”, “6-gingerol”, “gingerol”, “musculoskeletal diseases”, “osteoarthritis”, “osteoporosis”, “rheumatoid arthritis”, “anti-inflammatory”, “antioxidant”, “oxidative stress”, and “inflammation”. Studies were included if the specified terms appeared in the title, abstract, or keywords of the retrieved publications.

Study selection

Eligible publications consisted of peer-reviewed experimental and clinical research conducted in cell-based or animal models, as well as studies involving human participants, that examined the effects of 6-gingerol on MSDs. Studies were selected based on their relevance to the topic and the availability of information regarding the disease model, treatment conditions, pharmacological

activities, and underlying molecular mechanisms. Review articles were included to provide supporting background information.

Data extraction

For each eligible publication, data were recorded on the first author, year of publication, research design, disease model, 6-gingerol dose or concentration, administration route where relevant, identified molecular targets and signaling pathways, and key therapeutic outcomes.

Overview of [6]-gingerol

[6]-Gingerol: chemistry, pharmacological activities and pharmacokinetic characteristics

Ginger is extensively consumed worldwide as a dietary spice and has also been traditionally recognized as a medicinal plant (13,14). Historically, ginger has been applied in traditional Chinese medicine, Ayurveda, and Western herbal practices to treat arthritis, rheumatic disorders, and musculoskeletal discomfort (11,15-17).

Phytochemical investigations of ginger rhizomes have revealed two principal groups of bioactive constituents: phenolic compounds, including gingerols, shogaols, and paradols, and volatile terpenes such as zingiberene, α -farnesene, α -curcumene, β -sesquiphellandrene, and β -bisabolene (18). In fresh ginger, phenolic constituents are largely represented by gingerols, with [6]-G occurring as the predominant homolog and contributing substantially to the characteristic pungency of the fresh rhizome. The abundance and stability of these bioactive constituents are not constant, as they can be influenced by handling practices after harvest as well as by the conditions under which the rhizomes are stored. Ghasemzadeh et al (19) reported that extended storage and elevated temperatures decreased the levels of [6]-G, [6]-shogaol, phenolic acids, and flavonoids in ginger rhizomes, accompanied by reduced antioxidant capacity as assessed using the ferric reducing antioxidant potential and 1,1-diphenyl-2-picrylhydrazyl assays.

From a chemical perspective, [6]-G (1-[4'-hydroxy-3'-methoxyphenyl]-5-hydroxy-3-decanone) is considered a key bioactive compound that contributes to the pharmacological properties of fresh ginger (20,21). Its structure consists of a substituted vanillyl group linked to an aliphatic side chain containing a hydroxyl group, a structural feature considered to contribute to its biological activity (22). Experimental evidence indicates that [6]-G exhibits a broad range of biological effects, including anti-inflammatory, antioxidant, antidiabetic, anti-obesity, and anticancer activities (23-28). Among these biological effects, particular attention has been given to the anti-inflammatory and antioxidant activities of [6]-G, as both are closely linked to major pathological mechanisms underlying the development and progression of chronic diseases, including MSDs.

Despite its diverse pharmacological activities, the clinical translation of [6]-G is constrained by unfavorable pharmacokinetic properties. Owing to its relatively high lipophilicity ($\log P_{ow}=3.13$), [6]-G has limited water solubility, resulting in inadequate dissolution in gastrointestinal fluids and subsequently restricting its oral bioavailability (29). Furthermore, [6]-G undergoes extensive presystemic biotransformation in both the intestinal tract and liver, where it is predominantly converted into glucuronide and sulfate conjugates. This rapid metabolism contributes to its short systemic persistence and results in relatively low circulating plasma concentrations after oral administration (29,30). In rats, orally administered [6]-G was absorbed rapidly, reaching peak plasma exposure at approximately 10 minutes. Thereafter, its plasma concentration declined in two phases, with an estimated terminal elimination half-life of about 1.8 hours. Despite its rapid systemic clearance, it exhibits extensive tissue distribution, with particularly high concentrations detected in the gastrointestinal tract (31). Collectively, these pharmacokinetic characteristics are considered major barriers limiting the therapeutic application of [6]-G. Several approaches have been investigated to enhance the bioavailability of [6]-G and support its further clinical development (32). A range of advanced formulation approaches, including self-microemulsifying systems, liposomes, nanostructured lipid carriers, cyclodextrin complexes, polymeric micelles, and solid dispersions, has been explored to enhance the solubility, stability, and oral absorption of [6]-G in preclinical research (29,32-40).

Beyond conventional formulation approaches, emerging biomimetic delivery platforms have recently attracted attention as potential strategies to modulate the biological performance of phytochemicals. Kaneta et al (41) reported that [6]-G encapsulated in ginger-derived extracellular vesicles (GDEVs) produced stronger anti-inflammatory effects than unencapsulated [6]-G in a mouse model of collagen antibody-induced arthritis. These findings

suggest that GDEVs may serve as a promising biomimetic platform for enhancing the therapeutic efficacy of [6]-G. Further development of such biomimetic delivery platforms may provide new opportunities to optimize the therapeutic potential of [6]-G. Nevertheless, evidence supporting most [6]-G delivery platforms remains largely limited to preclinical research. Additional investigations are required to establish their long-term safety, pharmacokinetic profiles, and therapeutic efficacy, while also overcoming formulation and manufacturing challenges that may hinder their transition into clinical use.

Biological activity of [6]-gingerol

[6]-G is a naturally occurring phenolic compound of plant origin that has been associated with diverse biological effects and potential health benefits. In this review, however, particular emphasis is placed on its antioxidant and anti-inflammatory activities.

Anti-inflammatory effects

Ginger has a long history of use in traditional medicine for managing and relieving a range of inflammation-related conditions (42). Ginger exerts anti-inflammatory activity through multiple molecular mechanisms, involving reduced activity of cyclooxygenase-1, cyclooxygenase-2, and 5-lipoxygenase (5-LO), modulation of nuclear factor kappa B (NF- κ B) signaling, and decreased production of inflammatory mediators, including prostaglandins, leukotrienes, pro-inflammatory cytokines, and nitric oxide (NO) (43,44). Within the bioactive compounds found in ginger, [6]-G stands out as the predominant pungent phenolic constituent of the fresh rhizome and is considered an important mediator of its anti-inflammatory activity (45-47). Consequently, numerous studies conducted using both cell-based and animal models have investigated the anti-inflammatory activity of [6]-G and provided insights into the signaling mechanisms that may account for these effects (Table 1).

Table 1. Anti-inflammatory effects of [6]-gingerol reported in preclinical studies

Method of study	Mechanism of action [6]-gingerol	Reference
In vivo— Male ICR mice and female Wistar rats were examined in experimental models involving acetic acid-evoked writhing, formalin-related nociceptive responses, and carrageenan-associated paw swelling.	The anti-inflammatory effect may involve inhibition of prostaglandin release and regulation of inflammatory mediators associated with inflammatory pain	(48)
In vitro— Murine peritoneal macrophages subjected to LPS stimulation	Reduced the release of pro-inflammatory cytokines, including TNF- α , IL-1 β , and IL-12, while preserving antigen-presenting and immune cell functions	(49)
In vitro— LPS exposure in murine macrophage cultures	Suppressed I- κ B α phosphorylation, NF- κ B nuclear activation, PKC- α translocation, and intracellular Ca ²⁺ mobilization; prevented mitochondrial membrane potential disruption; reduced TNF- α and iNOS expression	(50)
In vitro— Hepatocyte hypoxia/reoxygenation models In vivo— Mouse hepatic ischemia/reperfusion	Anti-inflammatory effects were associated with increased MKP5 expression and attenuation of p38 MAPK/JNK signaling, resulting in lower cytokine release	(51)

LPS: lipopolysaccharide; TNF- α : tumor necrosis factor- α ; IL-1 β : interleukin-1 β ; IL-12: interleukin-12; I- κ B α : inhibitor of nuclear factor kappa B alpha; NF- κ B: nuclear factor kappa B; PKC- α : protein kinase C- α ; iNOS: inducible nitric oxide synthase; MKP5: mitogen-activated protein kinase phosphatase 5; p38 MAPK/JNK: p38 mitogen-activated protein kinase/c-Jun N-terminal kinase.

In an animal study, Young et al (48) examined the analgesic and anti-inflammatory activity of [6]-G using several experimental models, namely acetic acid- and formalin-evoked nociception in mice and rats, together with the carrageenan-induced paw edema model. After intraperitoneal administration, [6]-G reduced the frequency of acetic acid-evoked writhing, lessened nociception during the later phase of the formalin assay, and decreased carrageenan-associated paw swelling in a dose-dependent fashion. At a dose of 100 mg/kg, [6]-G produced a reduction in carrageenan-associated paw swelling that was comparable to the effect achieved with 10 mg/kg indomethacin. At 25 mg/kg, [6]-G elicited an analgesic effect comparable to that of indomethacin in the acid-evoked writhing model. Collectively, these findings imply that the anti-inflammatory action of [6]-G may be linked to reduced prostaglandin biosynthesis together with the regulation of inflammatory mediators involved in pain-related inflammatory processes. A separate study by Tripathi et al (49) explored the immunoregulatory potential of [6]-G using mouse peritoneal macrophages challenged with lipopolysaccharide (LPS). Treatment with [6]-G substantially reduced the levels of tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , and IL-12, indicating a dampening effect on macrophage-associated inflammatory mediator release. By comparison, [6]-G did not alter the expression levels of major histocompatibility complex class II (MHC II) or the co-stimulatory markers B7.1 and B7.2. Notably, macrophage antigen-presenting cell (APC) function was preserved, indicating that [6]-G may selectively regulate inflammatory activation of macrophages without causing broad impairment of immune responses. Additionally, Lee et al (50) investigated how [6]-G mediates its anti-inflammatory effects in LPS-activated mouse macrophages. They reported that [6]-G suppressed inhibitor of nuclear factor kappa B alpha (I- κ B α) phosphorylation, thereby limiting NF- κ B activity in the nucleus and reducing the expression of TNF- α and nitric oxide synthase (iNOS). In addition, [6]-G reduced protein kinase C (PKC)- α translocation and intracellular Ca²⁺ accumulation while mitigating the disruption of mitochondrial membrane potential. These observations indicate that [6]-G may exert its anti-inflammatory effects by modulating signaling cascades involving NF- κ B and PKC. More recently, Yu et al (51) found that [6]-G enhanced the expression of mitogen-activated protein kinase phosphatase 5 (MKP5) while concurrently suppressing the p38 mitogen-activated protein kinase (p38 MAPK)/c-Jun N-terminal kinase (JNK) signaling cascade in mice subjected to liver injury caused by ischemia followed by reperfusion and in hepatocytes exposed to hypoxia followed by reoxygenation. The enhanced MKP5 expression, along with reduced activation of inflammation-related signaling pathways, was associated with decreased levels of inflammatory mediators. These findings indicate that modulation of the MKP5–mitogen-activated protein

kinase (MAPK) signaling axis may contribute to the anti-inflammatory activity of [6]-G.

Overall, the available evidence suggests that [6]-G may exert its anti-inflammatory activity by limiting the production of cytokines and related mediators and by influencing several key signaling cascades, including NF- κ B, PKC, and MAPK. The broad regulatory effects of [6]-G on these molecular networks may underlie its potential therapeutic value in various inflammatory disorders.

Antioxidant effects

Oxidative stress arises when the generation of reactive oxygen species (ROS) exceeds the capacity of endogenous antioxidant defenses and has been implicated in aging-associated alterations and the development of chronic disorders, including MSDs (52,53). Excessive ROS accumulation can surpass the capacity of cellular antioxidant systems, thereby promoting membrane lipid oxidation, DNA injury, protein modification, and ultimately disrupting normal cellular function (54–56). Considering the substantial contribution of oxidative stress to pathological development, increasing attention has been directed toward compounds that may help restore cellular redox balance. Among these compounds, [6]-G has been extensively investigated due to its potent antioxidant properties.

Experimental evidence indicates that [6]-G may confer tissue protection under oxidative stress by curbing ROS buildup, reducing damage to cellular macromolecules, and strengthening intrinsic antioxidant defenses (Table 2). Kuhad et al (57) demonstrated that [6]-G exerted a renoprotective effect in rats exposed to cisplatin-induced oxidative stress and kidney damage. [6]-G treatment lowered lipid peroxidation and replenished reduced glutathione (GSH) levels, while also boosting antioxidant enzyme activity, ultimately contributing to better renal function. These observations indicate that [6]-G may help preserve renal integrity by attenuating oxidative injury and reinforcing the kidney's intrinsic antioxidant capacity. Similarly, Yang et al (58) assessed the antioxidant activity of purified [6]-G in HepG2 cells exposed to patulin-induced genotoxic stress. Pretreatment with [6]-G significantly reduced intracellular ROS generation, oxidative DNA damage, DNA strand breaks, and micronucleus formation, while restoring intracellular GSH levels. These findings indicate that [6]-G protects cells against oxidative stress-induced genotoxicity by enhancing cellular antioxidant defense. More recently, Ganjikutta et al (59) showed that purified [6]-G mitigated alcohol-related oxidative stress in cardiac tissue and reduced associated myocardial damage and apoptosis. In a rat model of alcohol-related cardiac injury, [6]-G lowered myocardial ROS accumulation and reduced DNA oxidation, as evidenced by decreased 8-hydroxydeoxyguanosine (8-OHdG) and protein carbonyl levels. It also helped restore antioxidant enzyme function, including that of superoxide dismutase

Table 2. Antioxidant effects of [6]-gingerol reported in preclinical studies

Method of study	Mechanism of action [6]-gingerol	Reference
In vivo—Rat model of cisplatin-associated renal dysfunction and oxidative stress	Alleviates oxidative damage in renal tissue by lowering oxidative stress and strengthening intrinsic antioxidant defenses	(57)
In vitro—HepG2 cells in a patulin-induced genotoxicity model	Mitigates genotoxic effects associated with oxidative stress through reinforcement of cellular antioxidant defenses	(58)
In vivo—Alcohol-induced cardiac injury model in rats	Mitigated ROS accumulation, DNA oxidation, and protein carbonylation, with reduced 8-OHdG levels and restoration of SOD and CAT activities	(59)
In vitro—Primary chicken embryo hepatocytes in H ₂ O ₂ -induced oxidative stress model	Exerts antioxidant activity through Nrf2 activation, enhancing antioxidant gene expression and reducing ROS accumulation	(62)

ROS: reactive oxygen species; 8-OHdG: 8-hydroxydeoxyguanosine; SOD: superoxide dismutase; CAT: catalase; Nrf2: nuclear factor erythroid 2-related factor 2.

(SOD) and catalase (CAT). Taken together, the available evidence supports the antioxidant potential of [6]-G across diverse experimental settings, primarily through limiting oxidative injury and reinforcing endogenous cellular defense mechanisms.

More recent evidence indicates that [6]-G can strengthen intrinsic antioxidant defenses by engaging redox-responsive signaling mechanisms. Among these pathways, nuclear factor erythroid 2-related factor 2 (Nrf2) serves as a major transcription factor that helps preserve intracellular redox balance. Under normal physiological conditions, Nrf2 activates the transcription of antioxidant and phase II detoxification genes, such as heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), and glutamate-cysteine ligase (GCL), thereby strengthening cellular defenses against oxidative stress (60,61). Yang et al (62) assessed the antioxidant activity of [6]-G in a cellular model of H₂O₂-triggered oxidative stress using cultured chicken embryonic liver cells. Their findings showed that [6]-G promoted Nrf2 nuclear translocation, leading to increased levels of downstream antioxidant genes, particularly HO-1 and NQO1. Importantly, pharmacological blockade of Nrf2 with ML385 substantially weakened the cytoprotective effect of [6]-G, supporting a role for Nrf2 activation in mediating its antioxidant properties. In addition, [6]-G treatment reduced intracellular ROS accumulation and enhanced antioxidant enzyme activities.

Overall, the available evidence supports the antioxidative capacity of [6]-G, characterized by reduced oxidative injury and strengthened cellular defense mechanisms, with Nrf2-associated signaling likely contributing to these effects.

Inflammation and oxidative stress in musculoskeletal diseases

Inflammation in musculoskeletal diseases

Inflammation has emerged as an important contributor to the pathogenesis and progression of several MSDs, including OA, RA, and OP. Nevertheless, the extent to which inflammation contributes to disease pathology, as well as the nature of its involvement, differs across individual disorders (63-65). Although inflammation plays a physiological role in tissue healing and host

immune protection, persistent or dysregulated inflammatory responses can disrupt tissue homeostasis and promote progressive structural damage (23,66). In addition, age-related, persistent low-level inflammation—often termed inflammaging—is increasingly recognized as an important contributor to both the development and progression of these diseases. Inflammaging is associated with disrupted mitochondrial function, defective autophagic processes, and metabolic imbalance, which may collectively exacerbate oxidative stress and accelerate tissue deterioration in age-related disorders, including sarcopenia, OA, and OP (66-68).

OA involves progressive cartilage deterioration accompanied by sustained low-grade inflammation, which is primarily triggered by factors such as mechanical overload, aging-related changes, and joint injury. Following activation or cellular injury, chondrocytes, synovial tissue-derived cells, and infiltrating immune populations can release various inflammatory mediators, with IL-1 β , TNF- α , and IL-6 serving as major drivers of the inflammatory response. These inflammatory signals can activate NF- κ B signaling, thereby increasing the expression of enzymes responsible for cartilage breakdown, particularly matrix metalloproteinases (MMPs) and members of the a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTSs) family, and consequently interfere with normal chondrocyte function. As a result, type II collagen and aggrecan are progressively degraded, leading to cartilage degeneration and OA progression (69,70).

In postmenopausal and age-related forms of OP, estrogen deficiency and aging can disturb immune homeostasis, thereby eliciting immune responses and increasing the local abundance of inflammatory cytokines within the bone microenvironment (71,72). This disruption of immune balance enhances the production of TNF- α , IL-6, and IL-1 β , subsequently disturbing the regulation of the receptor activator of nuclear factor kappa-B ligand (RANKL)/osteoprotegerin (OPG) system. An elevated RANKL/OPG ratio favors osteoclast formation and accelerates bone resorption, whereas inflammatory cytokines negatively affect osteoblast differentiation and reduce bone-forming capacity (73,74). This disruption of bone remodeling homeostasis ultimately results in

continuous bone loss, compromised bone mechanical strength, and a higher susceptibility to osteoporotic fractures (75).

In RA, an autoimmune-mediated dysregulation of immune responses primarily occurs within the synovial membrane, resulting in persistent synovial inflammation that drives disease initiation and progression. Activated immune cells, particularly macrophages, along with fibroblast-like synoviocytes, help sustain chronic inflammation through the release of key inflammatory mediators, notably TNF- α , IL-6, and IL-1 β . These mediators can drive synovial tissue expansion and pannus development, thereby contributing to ongoing joint damage. They may also increase RANKL expression in synovial cells and stimulate osteoclast activity, ultimately promoting bone erosion and further deterioration of the affected joints. Meanwhile, persistent NF- κ B activation in immune and synovial cells further amplifies inflammatory responses and maintains the pathogenic microenvironment of RA (63,76-80).

In summary, although the inflammatory mechanisms differ among MSDs, chronic inflammation is a common pathological process that contributes to tissue degeneration and disease progression, making inflammatory signaling pathways attractive therapeutic targets.

Oxidative stress in musculoskeletal diseases

Oxidative stress is widely regarded as a critical pathological factor involved in the initiation and advancement of a variety of chronic diseases (81). Under physiological conditions, ROS produced at relatively low levels during cellular metabolism serve as important signaling mediators and contribute to the regulation of cellular processes and the preservation of homeostasis. A moderate increase in ROS can activate the Kelch-like ECH-associated protein 1 (Keap1)–Nrf2 signaling axis, thereby inducing the transcription of genes involved in antioxidant defense and cellular protection. This adaptive response contributes to the restoration of redox balance and helps protect cells from oxidative injury (55,82,83). However, under chronic pathological or environmental conditions, a variety of pathological and environmental factors can promote persistent ROS production. Oxidative stress occurs when oxidant production surpasses the ability of intrinsic antioxidant defense systems to sustain cellular redox balance (84,85). This imbalance in cellular redox status can cause oxidative injury and engage redox-responsive pathways, notably NF- κ B and MAPK, which in turn exacerbate inflammation, impair cellular function, and contribute to progressive tissue deterioration (81,86,87).

While oxidative stress is widely observed across MSDs, the underlying sources and pathways driving excessive ROS accumulation vary according to the specific disease. In OA, several factors—including aging, excessive or abnormal mechanical stress, obesity, and persistent low-grade inflammation—may increase ROS accumulation

through mitochondrial impairment and NADPH oxidase-dependent mechanisms, ultimately contributing to chondrocyte dysfunction and extracellular matrix (ECM) degradation (88). Accumulating evidence indicates that impaired Nrf2 signaling contributes to OA progression by weakening the antioxidant defense of chondrocytes (89-91). To further support this finding, Li et al showed that modulation of the Nrf2/HMGB1/NF- κ B axis decreased chondrocyte apoptosis and suppressed the expression of cartilage-destructive mediators, including MMP-13 and ADAMTS-5, thereby attenuating cartilage deterioration (92,93). Consistent with these results, Zhang et al reported that Nrf2 stimulation by phillygenin reduced oxidative stress and NF- κ B activity, limited ECM breakdown, and attenuated OA progression in both IL-1 β -challenged chondrocytes and mice subjected to DMM-induced OA (93).

In RA, oxidative stress mainly results from persistent autoimmune inflammation. Activated macrophages, neutrophils, and synovial fibroblasts continuously produce large amounts of ROS in the inflamed synovium, creating a cycle in which oxidative stress further enhances inflammation and joint damage (94). Clinical studies consistently show that individuals with RA generally exhibit greater oxidative stress and a weaker antioxidant defense profile than healthy individuals, including reduced activities of SOD, CAT, and glutathione peroxidase (95,96). Experimental studies further demonstrate that loss of Nrf2 aggravates oxidative damage and inflammatory joint injury, whereas activation of Nrf2 reduces oxidative stress and improves arthritis severity (97,98).

In OP, excessive ROS are mainly produced as a result of aging, estrogen deficiency, glucocorticoid exposure, and mitochondrial dysfunction, leading to disruption of bone redox homeostasis (99-101). Sustained oxidative stress negatively affects osteoblast differentiation and viability, while simultaneously enhancing RANKL-mediated osteoclast formation, ultimately disturbing the dynamic equilibrium between bone generation and bone resorption (102). Nrf2 is a central regulator of cellular antioxidant defenses and contributes substantially to the maintenance of redox equilibrium in bone tissue (100,103). By preserving intracellular redox balance, Nrf2 also supports osteoblast differentiation and function (103-105). Studies in mice lacking Nrf2 have demonstrated that Nrf2 deficiency can exacerbate skeletal loss, an effect associated with increased expression of RANKL (106). Furthermore, findings from *in vitro* studies suggest that the absence of Nrf2 intensifies oxidative stress and promotes osteoclast differentiation driven by RANKL, accompanied by enhanced NF- κ B and MAPK signaling and increased expression of the transcription factors c-Fos and c-Jun (107).

In general, current evidence indicates that oxidative stress represents a shared pathogenic mechanism underlying multiple MSDs despite their distinct etiologies.

Although the sources of excessive ROS differ among OA, RA, and OP, persistent oxidative stress disrupts cellular homeostasis, activates inflammatory signaling pathways, and accelerates tissue degeneration. Accordingly, targeting the Nrf2-dependent antioxidant response may offer a potential therapeutic approach for re-establishing redox balance and slowing the progression of MSDs.

[6]-Gingerol in musculoskeletal diseases

[6]-Gingerol in arthritis

Arthritis comprises a range of disorders affecting the joints and represents a major contributor to musculoskeletal pain and impaired mobility. Arthritis encompasses a broad spectrum of inflammatory joint disorders, with OA and RA representing the two most prevalent forms (78,108). OA is among the most prevalent joint disorders associated with advancing age. The prevalence of OA is 16.05%, and the incidence is over 500 million people worldwide (109). OA pathogenesis involves the interplay of oxidative stress, inflammatory responses, and apoptosis, which collectively impair the balance between the synthesis and breakdown of the ECM. Meanwhile, RA is a long-standing autoimmune inflammatory disease characterized by abnormal proliferation within the synovium, accompanied by progressive damage to joint cartilage and the underlying bone. RA development is shaped by the combined influence of genetic predisposition and various environmental triggers. RA affects roughly 1% of the worldwide population, and its pain is strongly associated with inflammatory activity and oxidative imbalance (110). Untreated RA causes disability and early mortality (111). Although OA and RA arise through different disease processes, both can result in persistent pain, impaired joint function, and a diminished quality of life. Conventional pharmacological treatment for arthritis, encompassing anti-inflammatory medications, glucocorticoid therapy, and disease-modifying agents, has shown efficacy in alleviating clinical symptoms and limiting disease activity in affected patients (112,113). Nevertheless, prolonged pharmacological management may be constrained by treatment-related adverse effects, substantial financial burden, and variable therapeutic efficacy (114). These therapeutic limitations have encouraged increasing interest in naturally derived compounds as potential complementary options for arthritis management.

Among plant-derived constituents explored for arthritis, ginger phenolics, particularly [6]-G, have received substantial research interest because of their reported anti-inflammatory and antioxidant activities. [6]-G has been reported to regulate inflammatory mediator production through modulation of arachidonic acid metabolism, including inhibition of cyclooxygenase (COX), 5-LO, and prostaglandin E synthase activities (115). In addition, accumulating evidence suggests that [6]-G modulates inflammatory signaling pathways and oxidative stress responses, which are central mechanisms

involved in arthritis progression. The effects of [6]-G in experimental arthritis models are reviewed below, emphasizing its potential anti-inflammatory, antioxidant, and joint-preserving properties.

Recently, Yao et al (116) examined the anti-inflammatory activity of [6]-G in synovial cells, GES-1 gastric epithelial cells, and an experimental rat model of arthritis. The authors found that treatment with [6]-G markedly lowered inflammatory mediator levels while enhancing the viability of both synovial and GES-1 cells. At the mechanistic level, [6]-G increased miR-30c-2-3p expression, which directly targeted transforming growth factor- β activated kinase 1-binding protein 1 (TAB1), thereby suppressing NF- κ B pathway activation and attenuating inflammatory responses. In arthritic rats, [6]-G alleviated pathological changes in the synovium and gastric mucosa; notably, blocking miR-30c-2-3p with an antagomir weakened these beneficial effects, supporting a role for the miR-30c-2-3p/TAB1/NF- κ B axis in mediating the anti-inflammatory action of [6]-G.

Abusarah et al (117) examined protandim and [6]-G in IL-1 β -challenged human OA chondrocyte cultures, and further evaluated protandim in mice with DMM-induced OA. Both treatments maintained chondrocyte viability, promoted Nrf2 expression and phosphorylation, restored glutathione S-transferase A4-4 (GSTA4-4) levels, and suppressed IL-1 β -triggered 4-hydroxynonenal accumulation, suggesting their ability to alleviate oxidative stress. Moreover, both agents dose-dependently reduced IL-1 β -stimulated release of inflammatory and ECM-degrading mediators, including NO, prostaglandin E2 (PGE2), and MMP-13. Notably, [6]-G exhibited greater inhibitory effects on NO, PGE2, and MMP-13 than protandim at the highest tested concentration. Interestingly, [6]-G did not affect IL-1 β -triggered MAPK or NF- κ B activation, suggesting that its protective activity may be mediated mainly through Nrf2/GSTA4-4-dependent antioxidant defense instead of direct regulation of these inflammatory signaling cascades.

[6]-Gingerol in osteoporosis

OP is a common metabolic disorder of the skeleton characterized by disruption of the normal balance between osteoblast-mediated bone formation and osteoclast-driven bone resorption. The disruption of this physiological balance gradually reduces bone mass and weakens the structural properties of bone, ultimately making the skeleton more vulnerable to fragility fractures (118). The prevalence of OP globally is 18.3% based on data from 2021, and is significantly higher in women (23.1%) than in men (11.7%) (119). Despite their established benefits in treating OP, medications that promote bone formation or suppress bone resorption may still cause unwanted effects, including digestive disturbances, elevated blood calcium levels, jawbone necrosis, and atypical fractures of the femur. For this reason, natural compounds have attracted

growing interest as adjunctive options for OP treatment, particularly because they can act on multiple biological targets while having favorable safety profiles (120,121).

Among these natural compounds, [6]-G has attracted particular interest for its potential role in maintaining bone homeostasis by modulating both osteoblast differentiation and inflammation-related osteoclastogenesis. Although evidence remains limited, current studies consistently support its osteoprotective potential. To explore the influence of [6]-G on osteoclastogenesis under inflammatory conditions, Hwang et al (122) employed IL-1-treated primary calvarial osteoblasts from mice co-cultured with bone marrow cells, along with RANKL-stimulated bone marrow-derived macrophages (BMMs) as an additional experimental model. The authors found that [6]-G attenuated osteoclast differentiation triggered by IL-1 in the osteoblast–osteoclast precursor co-culture model, but had no significant influence on osteoclast formation when BMMs were directly stimulated with RANKL. Mechanistically, [6]-G reduced PGE2 synthesis in IL-1-stimulated osteoblasts through the inhibition of COX and PGE synthase activity, which was subsequently accompanied by decreased RANKL expression. Notably, supplementation with exogenous RANKL or PGE2 abolished the suppressive effects of [6]-G, leading to the recovery of RANKL expression in osteoblasts and osteoclast differentiation. These findings indicate that [6]-G inhibits inflammation-induced osteoclastogenesis primarily by regulating the osteoblast-derived PGE2/RANKL pathway.

In a separate investigation, Fan et al (123) examined how [6]-G influences the growth and osteogenic differentiation of human MG-63 osteoblast-like cells under both normal and inflammatory conditions. They found that [6]-G was non-cytotoxic at concentrations of up to 50 μ M and promoted osteoblastic differentiation, as reflected by enhanced alkaline phosphatase (ALP) levels

and greater collagen synthesis after 48 h of treatment. Under TNF- α stimulation, MG-63 cells exhibited reduced viability, lower ALP levels, and diminished collagen synthesis; however, these detrimental changes were partially alleviated by [6]-G, indicating its potential to counteract inflammation-related impairment of osteoblast differentiation. In addition, [6]-G decreased IL-6 release and limited the nuclear translocation of NF- κ B in TNF- α -challenged cells, effects that may underlie its ability to alleviate inflammation-related dysfunction in osteoblast-like cells. Collectively, these findings suggest that [6]-G promotes osteoblast differentiation under both physiological and inflammatory conditions and may have potential relevance for OP.

In conclusion, the available evidence indicates that [6]-G exerts osteoprotective effects through complementary actions on both bone-forming and bone-resorbing processes (Table 3). By promoting osteoblast differentiation while suppressing inflammation-driven osteoclastogenesis, [6]-G may help sustain the balance of bone remodeling, highlighting its potential as a natural candidate for further research in OP and other disorders of bone metabolism. However, the available evidence remains largely confined to in vitro research. Further rigorously designed animal studies and clinical trials are therefore required to verify its therapeutic efficacy and provide deeper insight into how [6]-G exerts its effects in vivo.

Conclusion

Accumulating evidence suggests that [6]-G might be a promising natural bioactive compound for MSDs because it can modulate chronic inflammation and oxidative stress, two interconnected pathological processes that are commonly implicated in OA, RA, and OP. Through regulation of multiple signaling pathways involved in inflammatory responses, redox

Table 3. Effects of [6]-gingerol in musculoskeletal diseases reported in preclinical studies

Model	Disease/condition	Mechanism of action [6]-gingerol	References
In vitro—Synovial and GES-1 cells In vivo—Rat arthritis model	Arthritis	↓ Inflammatory factors; ↑ cell viability; ↑ miR-30c-2-3p expression; suppression of TAB1/NF- κ B signaling; protected synovial tissue and gastric mucosa	(116)
In vitro—IL-1 β -stimulated primary human OA chondrocytes In vivo—DMM-induced mouse OA model	Osteoarthritis	↑ Nrf2 expression and phosphorylation; ↑ GSTA4-4 expression; ↓ 4-hydroxynonenal production, NO, PGE2, and MMP-13 production; preserves chondrocyte viability and attenuates oxidative stress	(117)
In vitro—IL-1-stimulated POB/BMC co-culture and RANKL-induced BMM differentiation	Inflammation-associated osteoclastogenesis	↓ PGE2 generation in response to IL-1 through COX/PGES suppression → ↓ RANKL expression in IL-1-exposed osteoblasts → attenuation of inflammation-related osteoclastogenesis.	(122)
In vitro—Cultured human MG-63 osteoblast-like cells	TNF- α -induced suppression of osteoblast differentiation	↑ Osteoblast differentiation, ALP activity, and type I collagen synthesis → attenuation of TNF- α -induced inhibition of osteoblast differentiation → ↓ IL-6 production and NF- κ B p65 nuclear translocation	(123)

TAB1: transforming growth factor- β activated kinase 1-binding protein 1; NF- κ B: nuclear factor kappa B; IL-1 β : interleukin-1 β ; DMM: destabilization of the medial meniscus; OA: osteoarthritis; Nrf2: nuclear factor erythroid 2-related factor 2; GSTA4-4: glutathione S-transferase A4-4; NO: nitric oxide; PGE2: prostaglandin E2; MMP-13: matrix metalloproteinase-3; IL-1: interleukin-1; POB: primary mouse calvarial osteoblasts; BMC: bone marrow cells; RANKL: receptor activator of nuclear factor kappa-B ligand; BMM: bone marrow-derived macrophage; COX: cyclooxygenase; PGES: prostaglandin E synthase; TNF- α : tumor necrosis factor- α ; ALP: alkaline phosphatase; IL-6: interleukin-6.

homeostasis, ECM degradation, osteoblast differentiation, and osteoclastogenesis, [6]-G exerts a broad range of pharmacological effects that may collectively support the preservation of joint and skeletal homeostasis. Nevertheless, although a growing body of research has documented the biological activities of [6]-G, its value as a therapeutic agent remains to be conclusively established. To date, most findings have come from preclinical research, while direct clinical investigations evaluating purified [6]-G in MSDs remain scarce. Furthermore, many previous studies have evaluated ginger preparations or ginger extracts rather than isolated [6]-G, the extent to which [6]-G itself accounts for the reported therapeutic benefits remains difficult to establish. In addition, poor aqueous solubility, extensive metabolism, and limited oral bioavailability represent important pharmacokinetic challenges that may restrict systemic exposure and therapeutic efficacy. Therefore, future research should further characterize the pharmacological actions and pharmacokinetic profile of [6]-G while pursuing improved formulation and delivery approaches to enhance its solubility, stability, absorption, and overall bioavailability. Further rigorous preclinical investigations and well-conducted randomized studies in human populations are needed to establish the most appropriate formulation and dose of [6]-G, confirm its therapeutic efficacy and long-term safety, and support its development as an evidence-based treatment candidate for MSDs. Nevertheless, this review has several limitations. The current evidence specifically focusing on purified [6]-G in MSDs remains limited, with most studies based on preclinical models and with insufficient clinical validation. Furthermore, heterogeneity in experimental models, doses, formulations, and outcome assessments may limit direct comparison and comprehensive interpretation of the available findings.

Authors' contribution

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Conflict of interests

The authors reported no conflicts of interest related to the research, authorship, or publication of this article.

Declaration of AI-assisted tools in the writing procedure

To improve the readability and linguistic quality of this manuscript, ChatGPT (OpenAI, San Francisco, USA) and Grammarly were used by the author for grammar refinement and sentence-level language enhancement. These tools were used exclusively for language editing purposes.

Ethical considerations

This review article does not use human or animal-derived samples. The manuscript adheres to accepted ethical publication practices and contains no plagiarized material, as confirmed through thorough screening. The findings presented here are based on an impartial synthesis of existing literature and were prepared in accordance with principles of academic integrity.

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