



Review

Understanding the Molecular Mechanisms Underlying the Analgesic Effect of Ginger

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Abstract: Chronic pain has a high prevalence and a profound impact on patients and society, and its treatment is a real challenge in clinical practice. Ginger is emerging as a promising analgesic—effective against various types of pain and well-tolerated by patients. However, we are just beginning to understand its complex mechanism of action. A good understanding of its mechanism would allow us to fully utilize the therapeutical potential of this herbal medicine as well as to identify a better strategy for treating chronic pain. To provide this information, we searched PubMed, SCOPUS, and Web of Science for in vitro studies or animal experiments investigating the analgesic effect of ginger extract or its components. The analysis of data was carried out in the form of a narrative review. Our research indicates that ginger extract, through its various active ingredients, suppresses the transmission of nociceptive signals while activating the descendent inhibitory pathways of pain.

Keywords: ginger; shogaols; gingerols; TRPV1 receptor; NMDA receptor; chronic pain; reactive oxygen species



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1. Introduction

Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) is a herbaceous perennial plant belonging to the family Zingiberaceae [1]. It originates from South East Asia and has been naturalized in many other countries. Currently, it is widely distributed throughout tropical and subtropical parts of the world. The rhizome is frequently used in the food industry as a spice/flavoring agent as well as in traditional medicine owing to its multiple therapeutic actions [2]. It is used either fresh, dried, or as an extract. The global production of ginger reached 3.3 million tons in 2016 [3].

The therapeutic effects of the rhizome result from the extraordinary variety of active substances it contains, their proportion depending on several factors such as climate, soil properties, and processing conditions [4]. The fresh ginger rhizome contains up to 6% non-volatile oil and 3% volatile oil. The non-volatile oil is rich in phenolic compounds known as gingerols (derivatives of 5-hydroxy-1-(4-hydroxy-3-methoxy phenyl) decan-3-one), with 6-, 8-, and 10-gingerol being the most abundant. Other phenolic compounds include quercetin, zingerone, 6-dehydrogingerdione, and gingerenone-A [4]. The volatile oil contains sesquiterpenes (66.66%, with zingiberene being the most predominant, followed by beta-sesquiphellandrene and betabisabolene), monoterpenes (17.28%, with citronellyl n-butyrate being the most predominant, followed by zingiberenol, cineole, geranylacetate, terpineol, terpenes, borneol, geraniol, limonene, and linalool) and aliphatic compounds (13.58%) [5–7]. In dried ginger powder, gingerol is dehydrated to shogaol, which, after hydrogenation, can be further transformed into paradols. Other principal pungent compounds of the rhizomes are gingerdiols, gingerdiacetates, gingerdiones, 6-gingersulfonic acid, gingerenones, etc. The rhizome also contains diterpenes, gingerglycolipids, diarylheptanonesgingerenones, isogingerenone B, gingediol, galanolactone, gingesulfonic acid, galactosylglycerols, monoacyldi-vitamins, capsaicin, and phytosterols [5–8]. Other constituents of ginger include raw fibers, polysaccharides, lipids, and organic acids [7].

Z. officinale has been long used in Ayurvedic and traditional Chinese medicine for treating various diseases such as the common cold, pain, rheumatoid arthritis, bronchitis, anorexia, gastrointestinal disorders, motion sickness, pregnancy-induced nausea and vomiting, and colics [9]. The British Herbal Compendium reported its action as a carminative, antiemetic, spasmolytic, peripheral circulatory stimulant with anti-inflammatory properties [10]. These effects are supported by the results of various experimental studies [11–15].

Furthermore, in the last decade, the effects of the major constituents (Figure 1) were investigated.

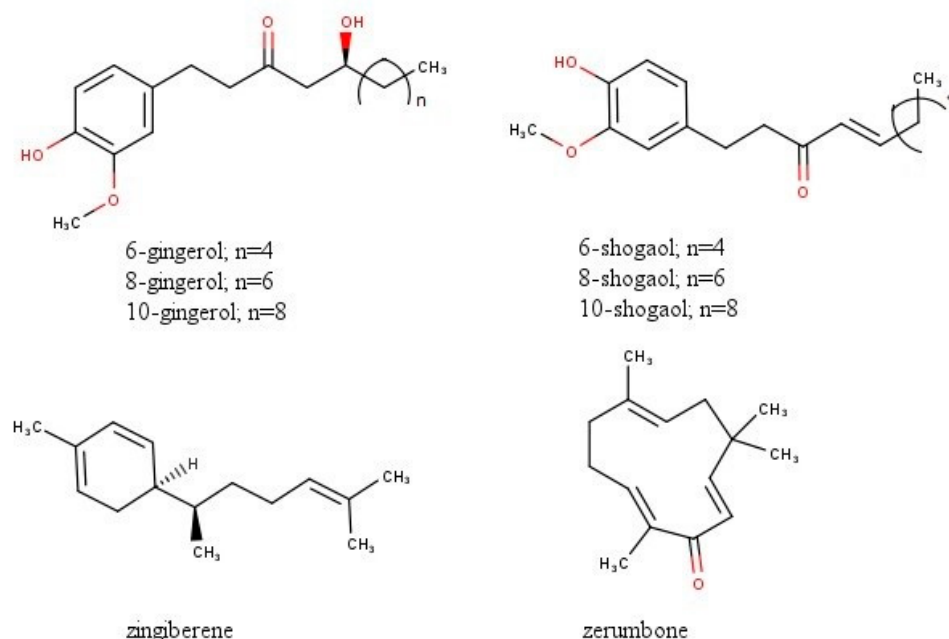


Figure 1. Chemical structures of the main components of Ginger.

Gingerols and 6-shogaol possess anti-inflammatory and antioxidant activities, which contribute to renal [16,17], hepatoprotective [18,19], and neuroprotective [20] effects, as well as improvement in the symptomatology of ulcerative colitis [21]. Shogaol but not gingerol possesses neuroprotective activities against hemorrhagic brain injury [22] and multiple sclerosis [23]. Additionally, it diminished the formation of amyloid beta in animal brains and prevented memory impairment by reducing microgliosis and astrogliosis and enhancing the levels of nerve growth factor and synaptogenesis in the brain [24].

Gingerols and shogaols also act as antitumor agents in various types of cancer [25–29] and enhance the activity of various antineoplastics [30,31]. Zerumbone and zingiberene, the major sesquiterpenoid compounds found in *Z. officinale*, also have anti-inflammatory, antioxidant, and anticarcinogenic properties [32–35].

One study revealed that 6-gingerol protects against cardiac remodeling by inhibiting the p38 mitogen-activated protein kinase pathway [36]. Zingiberene also has protective and antiapoptotic effects on isoproterenol-induced myocardial infarction [37].

Gingerols and shogaols reduce serum lipid and suppress vascular smooth muscle cell proliferation [38–40], while the latter and zerumbone inhibit platelet aggregation.

These antioxidant constituents were shown to improve experimental osteoarthritis by modulating multiple pathways that interfere with the immune innate signaling responses in chondrocytes [41] as well as by reducing the production of free radicals, which contribute to articular joint deterioration [42].

Additionally, both preclinical and clinical studies demonstrate that ginger and its multiple individual constituents have analgesic properties and effectively ameliorate chronic pain in arthritic conditions, irritable bowel syndrome, primary dysmenorrhea, recovery from surgery, and migraine. The data on preclinical and clinical studies on this effect of

ginger as well as on its other effects are summarized in several excellent reviews [43–46]. Despite the existing evidence on the role of ginger as a broad-spectrum analgesic, a full picture of its mechanism of action has not yet been provided. The data on the analgesic effects of single ingredients, the specific types of pain they ameliorate, and the molecular mechanisms underlying these effects are rather dispersed.

This study aims to clarify this issue by analyzing 11 *in vitro* and 16 *in vivo* studies that assess the underlying mechanisms of the analgesic effect of ginger extract or its ingredients. A good understanding of these mechanisms would not only allow us to fully utilize the therapeutical potential of this herbal medicine but may also offer a better strategy for treating chronic pain by clarifying which key molecules should be simultaneously targeted to provide relief from this pathology.

2. Materials and Methods

This narrative review was written after extensive research of PubMed, SCOPUS, and Web of Science. We used the following keywords: “ginger” OR “shogaol” or “gingerol” OR “zingiberene” OR “zerumbone” AND “pain” OR “antinocicept*” OR “analges*”. The research followed Egger’s criteria [47], was time-limited (from 2010 to 2022), and restricted to English and *in vitro* studies or animal experiments investigating the analgesic effect of the ginger extract or its components. The analysis was carried out in the form of a narrative review (Figure 2). The following data were extracted: (a) for *in vitro* studies: utilized cell line, challenge, form and dosage of ginger, and study findings; (b) for *in vivo* studies: utilized animals, experimental model, form and dosage of ginger, and the results and associated molecular mechanisms. The animal studies not reporting any data on molecular mechanisms were excluded.

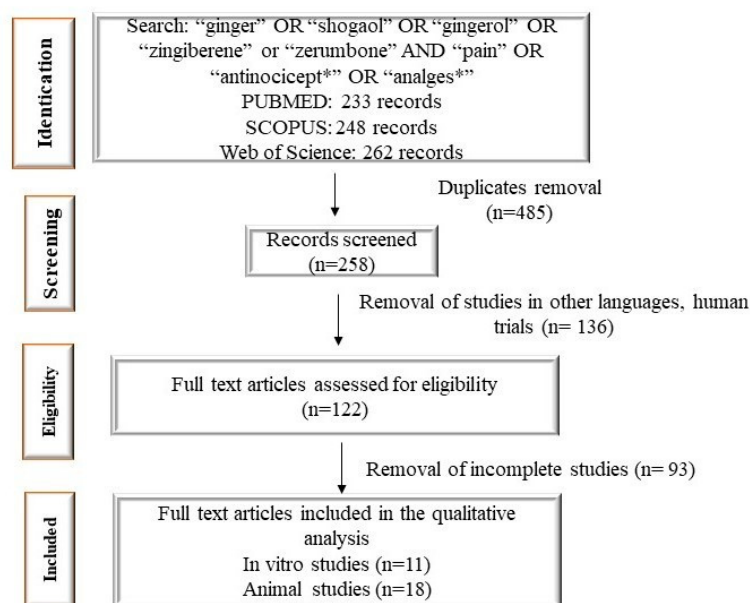


Figure 2. Studies included in the narrative review.

3. Molecular Mechanisms Underlying the Analgesic Effect of Ginger

3.1. *In Vitro* Studies

In vitro studies indicate a wide array of effects that could explain the antinociceptive effects observed for ginger extract and its related derivatives (Table 1). Thus, they elicit anti-inflammatory effects in LPS-challenged microglial cells [48–52]. LPS, a cell wall constituent of *E. coli*, activates the transcription factor nuclear factor-kappa B (NF-κB) signaling via the TLR4 pathway. The activation of TLR4 results in the release of more TLR4 endogenous ligands, leading to a persistent cycle of inflammation [53]. Ginger extract and its components inhibit NF-κBp65 signaling activation, resulting in a decrease in tumor

necrosis factor (TNF)- α , interleukin (IL)-1 β , and IL-6 levels [48,51,52]. A reduction in the levels of cyclooxygenase-2 (COX2) and nitric-oxide synthase (NOS) expression was also reported [52]. Furthermore, ginger possesses antioxidant properties, increasing the expression of antioxidant enzymes and decreasing the levels of reactive oxygen radicals [54,55]. Among all the gingerols, 6-gingerol is the compound with the highest antioxidant effect, and it yields the greatest anti-inflammatory effects [55]. Ginger extract and its components regulate enzymes, such as extracellular signal-regulated kinases (ERK) and histone deacetylases (HDAC)-1, as well as receptors, such as transient receptor potential vanilloid subtype (TRPV)1 and N-methyl-d-aspartate (NMDA) receptor 2B [48], and therefore are critical in nociception and nociceptive sensitization and in neuropathic and other forms of chronic pain.

Table 1. In vitro studies on the effect of ginger extract and its components.

First Author	Cell lines	Treatment	Results
Chia et al., 2020 [56]	LPS-induced neuronal sensitization in SH-SY5Y neuroblastoma cells	ZER 8 μ g/mL for 24 h	increased the expression of α 2A-adrenergic receptors downregulated TRPV1 and NMDAR2B receptors
Borgonetti et al., 2020 [48]	LPS-induced inflammation in murine microglial cells	GE 10 μ g/mL 6-GEG 1 μ g/mL SEG 0.17 μ g/mL ZTE 3 μ g/mL for 4 h	GE: decreased expression of pERK1, pERK2, HDAC1, TNF- α , IL-1 β , IL-6, and NF- κ B p65 signaling activation GEG: decreased protein levels of pERK1 and pERK2 increased HDAC1 and IKB α SEG: decreased protein levels of pERK1, pERK2, IL-1 β , and IL-6 increased HDAC1 ZTE: decreased expression of HDAC1, IKB α , TNF- α , IL-1 β , and IL-6
Deng et al., 2019 [57]	HepG2 cell line	GE 1, 2.5, 5 mg/mL for 3 days	increased mitochondrial mass and mtDNA copy number (the effect was significant for 2.5, 5 mg/mL) determined the activities of mitochondrial respiratory chain complex I and IV increased levels of NDUFS1 (complex I), SDHA (complex II), UQCRC1 (complex III), COX4 (complex IV), ATP5A1 (complex V), p-AMPK α (Thr172), PGC1 α , NRF1, and TFAM
Mustafa et al., 2019 [49]	LPS-induced inflammation in murine macrophage cell line RAW 264.7	GE 25, 50, 100 μ g/mL	decreased NO production
Hosseinzadeh et al., 2017 [54]	IL-1 β -induced oxidative stress in C28I2 human chondrocytes	GE 5, 25 μ g/mL	increased the gene expression of catalase, superoxide dismutase-1, glutathione peroxidase-1, glutathione peroxidase-3, and glutathione peroxidase-4 reduced the IL-1 β -induced elevation of ROS, lipid peroxidation, the Bax/Bcl-2 ratio, and caspase-3 activity
Luettig et al., 2016 [58]	HT-29/B6 and Caco-2 human intestinal epithelial cells	6-SEG 100 μ M for 1 h	inhibited the NF- κ B and PI3K/Akt signaling activation
Hsiang et al., 2015 [50]	LPS-induced NF- κ B activation in HepG2/ NF- κ B cells	Ginger 0.5; 1; 2.5; 5; 10; 50; 100 μ g/mL Zingerone 0.5; 1; 2.5; 5; 10; 50; 100 μ g/mL	decreased NF- κ B activity

Table 1. Cont.

First Author	Cell lines	Treatment	Results
Villalvilla et al., 2014 [59]	LPS- or IL-1 β -challenged human chondrocytes/ ATDC5 murine chondrogenic cell lines	6-shogaol 5 μ M	completely inhibited the increase in NO production, IL-6, and MCP-1 expression, induced by LPS did not completely inhibit the increase in NO production, IL-6, and MCP-1 expression, induced by LPS
Ho et al., 2013 [51]	LPS-activated BV2 microglia cells	6-GEG, -SEG 5, 10, 20 μ M; 8-GEG, -SEG 5, 10, 20 μ M; 10-GEG, -SEG 5, 10, 20 μ M; Zingerone 5, 10, 20 μ M; GE 0.125–0.5 mg/mL for 20 h	8-GEG, 10-GEG, all SEG groups, and GE: decreased levels of TNF- α , IL-1 α , IL-6, iNOS protein, mRNA expression, NO production, and NF- κ B p65 activity
Ha et al., 2012 [52]	LPS-activated BV2 microglia cells	6-GEG 1, 5, 10 μ M; 6-SEG 1, 5, 10 μ M for 24 h	6-SEG 10 μ M: decreased expression of iNOS 6-SEG 5 and 10 μ M: decreased expression of iNOS and COX2
	LPS-activated primary microglia cells		All groups of 6-SEG: decreased NO production 6-SEG 10 μ M: decreased expression of COX2 6-SEG 5 and 10 μ M: decreased levels of IL-1 β and TNF- α
Villalvilla et al., 2012 [60]	LPS- or IL-1 β -challenged ATDC5 chondrocytes	6-shogaol 5 μ M 10-shogaol 5 μ M	inhibited cathepsin-K activity, Only 6-shogaol: inhibited the LPS-induced increase in nitrite, NOS2, and MyD88 expressions. Inhibited ERK pathway activation and the activities of MMP-2 and MMP-9 did not significantly reduce IL-1 β -induced nitrite accumulation
Dugasani et al., 2010 [55]	LPS-challenged RAW 264.7 cells	6-shogaol 6 μ M 8-shogaol 6 μ M 10-shogaol 6 μ M	reduced oxidative stress (direct scavenging effects against DPPH, superoxide, and hydroxyl radicals) inhibited the production of PGE2 and NO

Akt—protein kinase B, ATP5A1—the α subunit of mitochondrial ATP synthase, BAX/BCL2—apoptosis regular protein/antiapoptotic regular protein, BV2—microglial cell derived from C57/BL6 murine, COX2—cyclooxygenase 2, COX4—cyclooxygenase 4, DPPH—2,2-diphenyl-1-picrylhydrazyl, ERK—extracellular signal-regulated kinases, GE—ginger extract, GEG—gingerol-enriched ginger extract, GHE—ginger hexane fraction extract, HDAC1—histone deacetylase 1, HepG2—human liver cancer cell line, IKB α —nuclear factor of kappa-light polypeptide gene enhancer in B-cell inhibitor alpha, IL-1 α —interleukin-1 alpha, IL-1 β —interleukin-1 beta, IL-6—interleukin-6, iNOS—inducible nitric oxide synthase, LPS—lipopolysaccharide, MCP1—monocyte chemoattractant protein 1, MMP-2/8—matrix metalloproteinase-2/8, mRNA—messenger ribonucleic acid, mtDNA—mitochondrial DNA, MyD88—myeloid differentiation primary response 88, NF- κ B—nuclear factor kappa-light-chain enhancer of activated B cells, NDUFS1—NADH-ubiquinone oxidoreductase 75 kDa subunit, mitochondrial, NF- κ Bp65—nuclear factor kappa-light-chain enhancer of activated B-cell subunit p65, NMDAR2B—N-methyl-D-aspartate receptor subunit 2B, NO—nitric oxide, NOS2—nitric oxide synthase 2, p-AMPK α —phospho-adenosine 5' monophosphate-activated protein kinase, p-p38—phosphorylated p38 mitogen-activated protein kinases, NRF1—nuclear respiratory factor 1, pERK 1/2—phosphorylated extracellular signal-regulated kinase1/2, PGC1 α —peroxisome proliferator-activated receptor-gamma coactivator, PGE2—prostaglandin E2, PI3K—phosphatidylinositol-3-kinase, p-JNK—phosphorylated c-Jun N-terminal kinase, ROS—reactive oxygen species, SDHA—succinate dehydrogenase complex subunit A, SEG—shogaol-enriched ginger root extract, TRPV1—transient receptor potential vanilloid-1, TFAM—mitochondrial transcription factor A, TNF- α —tumor necrosis factor-alpha, UQCRC1—ubiquinol-cytochrome c reductase core protein 1, ZER—zerumbone, ZTE—*Zingiber officinale* terpenoid-enriched fraction.

3.2. In Vivo Studies

Preclinical studies confirmed the findings of the in vitro studies. Ginger administration, in the form of ginger extract, ginger essential oil, gingerols, and shogaols, ameliorates pain in various animal models: spinal nerve ligation-induced neuropathic pain [48,56,61–68], inflammatory pain [64], diabetic neuropathy [69,70], oxaliplatin-induced neuropathy [71], and fibromyalgia [72]. Ginger extract and its active ingredients alleviated

all pain-related parameters including mechanical allodynia, and mechanical, thermal, and cold hyperalgesia (Table 2).

The results of the *in vivo* studies were consistent with the *in vitro* findings, indicating that the analgesic effect results from profound effects on nociceptive pathways. Thus, ginger decreases the mRNA expressions of TRPV1 and NMDAR2B in the spinal cord [69]. When activated, these receptors are critical for the transmission of the action potential throughout the afferent pathways of pain. The activity of the highest dose of ginger extract (400 mg/kg) in reducing the mRNA expression of TRPV1 and NMDAR2B was higher than that of the highest dose of 6-shogaol (15 mg/kg), thus indicating that other active ingredients in ginger extract interfere with their expression [69].

Additionally, it activates serotonin (5-HT) receptors 1A, 1B, 2A, 3, 6, and 7 and increases the expression of 5-HT1-A, α 1, α 2, β 1, and β 2 adrenoceptors [56] activating the descending pain modulatory circuits. The activation of heteroreceptor 5HT1-A inhibits the Ca^{2+} channel and thus reduces the firing of sensory neurons and the subsequent release of substances P and glutamate [73]. Furthermore, the activation of the 5-HT1A receptor, which is coupled with Gi/o protein, also inhibits adenylate cyclase activity, cAMP formation, and protein-kinase-mediated protein phosphorylation [73]. The activation of G-protein-coupled- α 2 adrenoceptors was shown to abolish spontaneous Ca^{2+} spikes [74].

The activation of the voltage-dependent K^{+} channel, the ATP-sensitive K^{+} channel blocker, the small-conductance Ca^{2+} -activated K^{+} channel, or the large-conductance Ca^{2+} -activated K^{+} channel results in decreased neuronal excitability [65]. Furthermore, 8-Gingerol is the most potent hERG K^{+} channel inhibitor among gingerol components [75].

Ginger demonstrated neuroprotective effects on neurons in the dorsal root ganglia of diabetic mice, which can further contribute to its beneficial effect on neuropathic pain [70].

Other involved mechanisms include the activation of cannabinoid (CB) 1 and of peroxisome proliferator-activated receptors [63]. It also inhibits glial cells and reduces neutrophil activation and the inflammatory response primarily by inhibiting NF- κ B signaling and decreasing COX expression and the levels of proinflammatory cytokines IL-1 β , TNF- α , and IL-6 [76]. The antioxidant effect was demonstrated by the reduction in free mitochondrial DNA levels (ccf-mtDNA) [62]. Each mitochondrion possesses its own genome (mtDNA), which replicates independently of nuclear DNA. mtDNA is released in the extracellular space and persists in extracellular fluids and, therefore, is a potential biomarker in several pathologies [77]. The decrease in the plasma ccf-mtDNA levels induced by ginger extract clearly demonstrates a reduction in mitochondrial oxidative stress [62].

Table 2. *In vivo* studies on the effect of ginger extract and its components. Associated molecular mechanisms.

Study	Animals	Model	Intervention	Results	Associated Molecular Mechanism
Kim et al., 2022 [78]	C57BL/6 mice	Oxaliplatin-induced neuropathic pain	[6]-shogaol 10 mg/kg, i.p., 1 dose	Significantly reduced cold and mechanical allodynia	activation of receptors 5-HT1A and 5-HT3 increase in GABA synthesis (increase in the levels of glutamic acid decarboxylase)

Table 2. Cont.

Study	Animals	Model	Intervention	Results	Associated Molecular Mechanism
Shen et al., 2022 [61]	Sprague Dawley rats	Spinal nerve ligation-induced neuropathic pain	GEG 0.375% (<i>w/w</i> in diet) 0.75% (<i>w/w</i> in diet) 30 days	Significantly reduced mechanical hypersensitivity	reduction in the levels of gene expression of zonulin and claudin-1 in the amygdala and colon of animals with nerve ligation as well as NF- κ B in the amygdala, colon, and ileum of animals with nerve ligation
Shen et al., 2022 [62]	Sprague Dawley rats	Spinal nerve ligation-induced neuropathic pain	GEG 0.75% (<i>w/w</i> in diet) 30 days	Reduced pain sensitivity after 10 days following operation. The effect persisted for up to 30 days.	reduction in mitochondrial oxidative stress, as reflected in the decreased plasma ccf-mtDNA levels the microbiome profile was strongly altered after SEG treatment
Chia et al., 2021 [63]	ICR mice	Spinal nerve ligation-induced neuropathic pain	ZER 10 mg/kg, i.p. Acute administration on day 14 postinjury	Reduced mechanical allodynia and thermal hyperalgesia	activation of CB1R and PPAR α
Fajrin et al., 2021 [64]	Male BALB/c mice	(1) complete Freund's adjuvant-induced inflammatory pain(2) partial sciatic nerve ligation-induced neuropathic pain	GE 100, 200, 400, or 600 mg/kg 14 days	Reduced thermal hyperalgesia	GE 600 mg/kg: reduction in COX-2 expression in the spinal cord and brain, and reduced NMDAR2B in the spinal cord increase in NMDAR2A expression in the spinal cord
Lee et al., 2021 [71]	C57BL/6 mice	Oxaliplatin-induced neuropathic pain	GE (100, 300, and 500 mg/kg) Acute administration	Significantly attenuated both cold and mechanical allodynia induced by oxaliplatin.	activation of 5-HT1A, but not 5-HT2A. The antiallodynic effect of GE against cold allodynia is also mediated by 5-HT3 activation. increase in mRNA expression of the spinal 5-HT1A receptor
Öz et al., 2021 [76]	Wistar rats	Complete Freund's adjuvant-induced inflammatory pain	GE 50 mg/kg/daily 32 days	Reduction in arthritis symptoms	decrease in serum levels of TNF- α , IL-6, IL-17, and DKK-1 increased sclerostin serum level decreases in the tissue levels of IL-17, TNF- α , COX-2, and NF- κ B

Table 2. Cont.

Study	Animals	Model	Intervention	Results	Associated Molecular Mechanism
Gopalsamy et al., 2020 [65]	ICR mice	Spinal nerve ligation-induced neuropathic pain	ZER 10 mg/kg, i.p. Acute administration on day 14 postinjury	Reduced mechanical allodynia, and thermal hyperalgesia	activation of voltage-dependent K ⁺ channel, ATP-sensitive K ⁺ channel blocker, small-conductance Ca ²⁺ -activated K ⁺ channel, large-conductance Ca ²⁺ -activated K ⁺ channel activation of opioid receptors
Borgonetti et al., 2020 [48]	CD1 male mice/BV2 cells	Spinal nerve ligation-induced neuropathic pain/LPS challenge	GE 200 mg kg ⁻¹ 7 days	Reduced mechanical and thermal allodynia in the spared nerve injury mice model.	reduction in spinal neuroinflammation GE, 6-gingerol, and 6-shogaol reduced pERK levels GE and terpene fraction: reduced HDAC1 protein levels, inhibited NF-κB signaling activation, and decreased IL-1β, TNF-α, and IL-6 release
Chia et al., 2020 [56]	ICR mice	Spinal nerve ligation-induced neuropathic pain	ZER 10 mg/kg, i.p. Acute administration on day 14 postinjury	Decreased mechanical allodynia and thermal hyperalgesia	inhibition of TRPV1 increased the expression of α ₁ , α ₂ , β ₁ , and β ₂ adrenoceptors downregulation of NMDA NR2B receptors
Fajrin et al., 2020 [69]	Balb/C mice	Streptozotocin-induced diabetic neuropathy	SEG (5, 10, 15 mg/kg/day, orally) GE (100, 200, 400 mg/kg/day, orally), Between days 28–49 after streptozotocin administration	SEG 15 mg/kg: Reduced mechanical allodynia and thermal hyperalgesia GE 200 and 400 mg/kg: Reduced thermal hyperalgesia, not mechanical allodynia	SEG 15 mg/kg: decreased mRNA expressions of TRPV1 and NMDAR2B in the spinal cord GE 400 mg/kg: decreased mRNA expressions of TRPV1 and NMDAR2B in the spinal cord
Gopalsamy et al., 2020 [65]	ICR mice	Spinal nerve ligation-induced neuropathic pain	ZER 10 mg/kg; i.p. 14 days	Reduced mechanical allodynia and thermal hyperalgesia	activation of voltage-dependent K ⁺ , ATP-sensitive K ⁺ channel blocker, small-conductance Ca ²⁺ -activated K ⁺ channel, or large-conductance Ca ²⁺ -activated K ⁺ channel activation of opioid receptors

Table 2. Cont.

Study	Animals	Model	Intervention	Results	Associated Molecular Mechanism
Fajrin et al., 2019 [70]	Balb/C mice	Alloxan-induced diabetic neuropathy	GE 100, 200, 400, 600 mg/kg orally Acute administration on day 14 postinjury	Decrease in thermal hyperalgesia	reduction in ROS and protection of cells in the spinal cord inhibition of ROS accumulation with a subsequent decrease in TRPV1 activation and deactivation of NMDAR2B in the dorsal horn of the spinal cord
Montserrat-de la Paz et al., 2018 [72]	C57BL/6 J mice/macrophages	Intermittent cold stress-induced fibromyalgia/LPS challenge	GER 0.5%, 1% in diet 56 days	Reduced mechanical and thermal allodynia and mechanical hyperalgesia and improved behavioral changes related to cognitive disturbances, anxiety, and depression.	reduction in the inflammatory response of proinflammatory mediators such as NO, PGE ₂ , TXB ₂ , and IL-1 β in LPS-stimulated macrophages
Mata-Bermudez et al., 2018 [66]	Wistar rats	Spinal nerve ligation-induced neuropathic pain	GEG 10 μ g, intrathecal one dose, on day	Reduced mechanical allodynia	activation of spinal 5-HT _{1A} /1B/1D/5A receptors increase in nitric oxide-cyclic guanosine monophosphate and activated adenosine triphosphate-sensitive K ⁺ channel pathway Naloxone (non-selective opioid receptor antagonist) did not prevent the [6]-gingerol-induced antiallodynic effect.
Gopalsamy et al., 2017 [67]	ICR mice	Chronic constriction injury	ZER (5, 10, 50 mg/kg/d, i.p.) 14 days	Decreased mechanical allodynia, mechanical hyperalgesia, thermal hyperalgesia, and cold allodynia	ZER 10, 50 mg/kg: reduced IL-1 β , TNF- α , and IL-6 levels in the plasma/spinal cord no change in IL-10 levels in plasma and spinal cord

Table 2. Cont.

Study	Animals	Model	Intervention	Results	Associated Molecular Mechanism
Chia et al., 2016 [68]	ICR mice	Chronic constriction injury	ZER 10 mg/kg, i.p. Acute administration on day 14 postinjury.	Decreased mechanical allodynia and thermal hyperalgesia	activation of 5-HT receptors 1A, 1B, 2A, 3, 6, and 7 with subsequent enhancement of the descending serotonergic transmission

5-HT1A/2A/3/1B/1D/5A—serotonin receptor subtype 1A/2A/3/1B/1D/5A, ATP—adenosine triphosphate, CB1R—cannabinoid receptor type 1, ccf-mtDNA—circulating cell-free mitochondrial deoxyribonucleic acid, COX-2—cyclooxygenase 2, DKK-1—dickkopf-related protein 1, GE—ginger extract, GEG—gingerol-enriched ginger extract, HDAC1—histone deacetylase 1, IL-1 β —interleukin-1 beta, IL-6—interleukin-6, IL-10—interleukin-10, IL-17—interleukin-17, LPS—lipopolysaccharide, mRNA—messenger ribonucleic acid, NF- κ B—nuclear factor kappa-light-chain enhancer of activated B cells, NMDAR2B—N-methyl-D-aspartate receptor subunit 2B, NMDAR2A—N-methyl-D-aspartate receptor subunit 2A, NMDA NR2B—N-methyl-D-aspartate receptor subunit 2B, NO—nitric oxide, pERK—phosphorylated extracellular signal-regulated kinase, PGE2—prostaglandin E2, PPAR α —peroxisome proliferator-activated receptor alpha, ROS—reactive oxygen species, SEG—shogaol-enriched ginger root extract, TNF- α —tumor necrosis factor-alpha, TRPV1—transient receptor potential vanilloid-1, TXB2—thromboxane B2, ZER—zerumbone.

In osteoarthritis, animal models not only offer evidence that ginger alleviates associated pain, but that it also could provide a protective effect, as 6-shogaol inhibits the interaction between TLR4 ligands and the TLR4/MD-2 complex in chondrocytes and also reduces ERK phosphorylation, preventing cartilage loss [41].

4. Discussion

The in vitro and in vivo studies bring to light a complex effect of ginger extract and its ingredients on various elements of nociceptive pathways. In this section, we further discuss the specific contribution each element might have to the analgesic effect of ginger and how these elements are intertwined.

Modulation of pain-related neurotransmissions

Studies indicate that TRPV1 and NMDA receptors are the primary targets of the active ingredients in ginger extracts [56].

TRPV1 is a member of the TRPV channel family. It is a non-selective cationic ligand-gated channel located on the membranes of sensory neurons or non-neuronal cells [79]. Peripherally, TRPV1 is primarily expressed in the dorsal root ganglion and centrally, in the thalamus, striatum, amygdala, etc. [80]. It is critical for recognizing and integrating nociceptive chemical and thermal stimuli. TRPV1 activation increases intracellular Ca²⁺, resulting in the depolarization and propagation of action potentials in myelinated A- and unmyelinated C-fibers [81]. Thus, nociceptive signals are transmitted along the sensory nerve fibers to the central areas involved in pain processing [82]. Another interesting aspect is that TRPV1 channels are sensitized by phosphorylated prostaglandin (PG)E2 and ROS [83].

The members of the shogaol, gingerol, and zingerone families possess a vanillyl head group that interacts with the S4–S5 linker of the TRPV1 channel similar to capsaicin. Minor structural changes do not seem to substantially alter the interaction with the TRPV1 channel or its energetics. Zingerone, which lacks an aliphatic tail, possesses a much lower potency than shogaols and gingerols [84].

The prolonged firing of C-fiber nociceptors causes the release of glutamate, which in turn activates N-methyl-d-aspartate (NMDA) receptors in the spinal cord. More precisely, the phosphorylation of the NR2B subunit by CaMKII is responsible for TRPV-potentiated NMDAR response [85]. Peripheral inflammation activates NMDA receptors in the spinal cord, generating allodynia, hyperalgesia, and central sensitization. NMDAR activation

results in an increase in intracellular calcium and the phosphorylation of protein kinase C and ERK2 [86]. Nitric oxide synthase (NOS) is a downstream target of the NMDA receptor associated with hyperalgesia and allodynia [87]. Molecular docking studies confirm that 6-gingerol inhibits the human NR2B-containing NMDA receptor by interacting with the aminoterminal domain, the glutamate-binding site, as well as within the ion channel [88]. In vivo studies indicate that ginger extract and its major constituents decrease the activity and the expression of these receptors throughout the central nervous system [69].

In vivo and in vitro studies indicate that CB-1 receptors and opioid receptors might contribute to the analgesic effect of ginger [63]. CB-1 receptors are activated by endocannabinoids, while opioid receptors are activated by endogenous opioids and are substantially expressed in nociceptive primary sensory neurons as well as in central areas processing pain [99]. Furthermore, they are often co-localized with TRPV1 receptors. The activation of CB-1 receptors results in the desensitization of TRPA1 and TRPV1, thus inhibiting nociceptive transmission and suppressing hyperalgesia and allodynia [89]. However, the activation of opioid and CB-1 receptors is associated with effects such as euphoria and addiction [90,91], which were not reported following the administration of ginger extracts. Therefore, we posit that this is a minor mechanism of action.

Besides inhibiting the sensory fibers that carry pain sensation to the brain, ginger also activates the descendent inhibitory pathways of pain. The serotonergic receptors mostly expressed in peripheral sensory neurons are 5HT1A, 5HT1B, 5HT1D, 5HT2A, 5HT2C, and 5HT3 receptors. These receptors are all involved in peripheral pain processing [92,93]. The activation of 5HT1 receptors decreases cAMP signaling, further reducing nociceptive neurotransmission. The activation of 5-HT1A receptors also opens G protein-gated K^+ channels and inhibits voltage-gated calcium channels; thus, hyperpolarization occurs, and neuronal firing is reduced [73]. As autoreceptors, they are located presynaptically on the perikaryon and dendritic spines of serotonin-containing neurons. The activation of 5-HT1A autoreceptors decreases the release of 5-HT. As a heteroreceptor, they are located in many brain regions [73], on neurons receiving input from serotonergic neurons. The activation of 5-HT1A heteroreceptors expressed on the afferent nociceptive fibers in the dorsal horn of the spinal cord results in the diminished release of glutamate and substance P from the afferent fibers and thus exerts an analgesic effect [94]. The activation of the 5-HT(1B/1D) receptor in the ventrolateral periaqueductal gray activates the descending pain-modulating pathway [95]. Moreover, 5-HT1B receptor activation selectively induces ERK1/2 activation through both the $G_{\alpha i}$ subunit and β -arrestin proteins [96]. The increase in the expression of $\alpha 1$, $\alpha 2$, $\beta 1$, and $\beta 2$ adrenoceptors has a similar effect on the descending pain modulatory circuits [97].

Inhibition of NF- κ B signaling activation

NF- κ B is composed of homo- and heterodimers of different Rel family proteins (p65, RelB, c-Rel, p52, and p50) [98]. In most unstimulated cells, NF- κ B dimers are localized in the cytoplasm, bound to the inhibitory subunit I- κ B. Various stimuli, such as bacterial or viral products, cytokines, or UV-induced DNA damage, induce the activity of I- κ B kinases (IKKs) [99].

These enzymes catalyze the phosphorylation of I- κ B within the NF- κ B dimer/I- κ B complex. Phosphorylated I- κ B is ubiquitinated and then degraded by a proteasome complex. The free NF- κ B translocates into the nucleus, where it binds to the promoter region of various genes [100], activating their transcription. The activation of the NF- κ B pathway results in the release of inflammatory mediators such as NO, TNF- α , IL-1 β , and IL-6 [99].

NF- κ B transcription factors are ubiquitously expressed in the organism of mammals, including throughout the peripheral and central nervous system, as well as in neurons and glial cells. In the nervous system, specific factors such as amyloid [101], nerve growth factor [102], and excitatory neurotransmitters (e.g., glutamate) are able to activate the NF- κ B pathway [102]. Evidence indicates that NF- κ B might be activated in a Ca^{2+} -dependent manner in the synapses [103].

Dysregulations of the NF- κ B pathway are associated with chronic inflammation [104], neurodegenerative processes [105], and alteration in synaptic plasticity, and are involved in the pathogenesis of various types of pain [100]. NF- κ B p50 knockout mice presented a reduced nociceptive response to acute and inflammatory noxious stimulation, further supporting the role of this subunit in nociceptive transmission [106]. The reduced nociceptive response is correlated with a reduced COX-2 expression in the spinal cord [106]. In a rat model of neuropathic pain, a single injection of NF- κ B decoy at the site of nerve lesion significantly alleviates thermal hyperalgesia for up to 2 weeks and suppresses the expression of mRNA of the inflammatory cytokines, iNOS, and adhesion molecules at the site of nerve injury [107].

Thus, the NF- κ B-activation cascade is critical in the development and processing of pathological pain. The inhibition of this pathway is clearly associated with analgesic effects in various types of pain: inflammatory [108,109], neuropathic [107], osteoarthritic [110], postoperative [111], bone cancer pain [112], etc.

Ginger extract and all its constituents were shown to inhibit NF- κ B signaling. The inhibition of TRPV1 [65–67] and NMDA is known to reduce NF- κ B pathway signaling. Furthermore, zerumbone was associated with the activation of PPAR α , which is known to inhibit the downstream signaling cascade-mediated nuclear factor- κ B (NF- κ B) [113].

Inhibition of arachidonic acid metabolism

Ginger extract reduced the expression of COX2 in the spinal cord and brain [64,76]. The isoform COX2 is inducible in several cell types, particularly in inflammatory cells. It is a rate-limiting enzyme that converts arachidonic acid to prostaglandin (PG) E₂. The factors that induce COX2 in inflammatory cells include IL-1 β , TNF α , and ROS [114]. PGE₂ is a molecule abundantly produced in injured nerves. It activates four specific G-protein-coupled receptors expressed in inflammatory cells and DRG neurons, inducing inflammatory and nociceptive effects. PGE₂ is associated with the initiation of neuropathic pain, as its downstream signaling contributes to the hyperalgesia associated with chronic neuropathy. However, it may also induce chronic effects on local inflammatory cells in injured nerves via autocrine and paracrine pathways. Furthermore, IL-1 β -induced COX2 expression is mediated through NF- κ B activation [115].

Reduction in levels of proinflammatory cytokines

Cytokines are secreted by various types of cells, particularly by helper T cells and macrophages [116]. Following peripheral nerve injury, macrophages and Schwann cells accumulate locally and secrete cytokines and growth factors. Furthermore, proinflammatory cytokines TNF- α , IL-1 β , and IL-6 released in the periphery produce nociceptor sensitization and can further be transported in a retrograde manner to the dorsal root ganglia and the dorsal horn [117], interfering with neuronal activity and leading to central sensitization and/or hyperalgesia [118].

IL-1 β and TNF- α are associated with hyperalgesia observed in various pain models: autoimmune encephalomyelitis [119,120], inflammatory [121], and neuropathic pain [122–124]. Furthermore, they induce the production of substances P and PGE₂ in neurons and glial cells. IL-6 is associated with the activation of microglia and astrocytes, thus substantially contributing to neuroinflammation and the progression of the neuropathic state [125,126].

Persistent inflammation alters nociceptive processing and induces persistent pain even after the inflammation has resolved, resulting in a neuropathic state. Thus, a reduction in cytokine levels would result in the inhibition of pain processing at multiple levels (peripheral nociceptors, dorsal root ganglia, spinal cord, and supraspinal areas) [127].

As discussed above and demonstrated by experimental work, ginger decreases the serum levels and the tissular levels of the expression of proinflammatory cytokines.

Modulation of mitochondrial activity and reduction in oxidative stress

Mitochondria are the main intracellular source of ATP. They also regulate cellular functions such as Ca^{2+} signaling and apoptosis and are major sites for the production of reactive oxygen species (ROS) [128]. The increase in ROS was shown to be intimately associated with the pathogenesis of neuropathic pain [129–131]. ROS seem to modulate the functions of the redox-sensitive signaling enzymes involved in persistent pain [132], such as activating protein kinase A, protein kinase C and CaMKII and inactivating protein phosphatases [133,134].

These alterations induced by moderately elevated levels of ROS generate neuronal dysfunctionality and lead to central sensitization [132]. ROS activates the NF- κ B pathway mainly via inhibiting the phosphorylation of I κ B α , resulting in its ubiquitination and degradation and subsequent activation of the NF- κ B pathway [135].

Ginger extract directly scavenges ROS, increases the endogenous antioxidant defense, and also reduces mitochondrial oxidative stress as clearly indicated by the decrease in the plasma ccf-mtDNA levels [62]. Furthermore, this indicates that ginger extract modulates overall mitochondrial activity. The mitochondrial $\text{Na}^+/\text{Ca}^{2+}$ exchange is critical for presynaptic calcium control in sensory neurons and thus for glutamate release and postsynaptic activity [136].

In the spinal cord, the inhibition of mitochondrial Ca^{2+} uptake impairs the phosphorylation of several protein kinases associated with pain processing, such as protein kinase C, protein kinase A (PKA), and extracellular signal-related kinase (ERK). Ginger extract, shogaol, and gingerol, but not the terpenoid-enriched fraction, decreased the protein levels of pERK1 and pERK2 (19), which further supports the hypothesis that mitochondria are key targets for ginger. An in vitro study demonstrates that ginger extract, particularly 6-gingerol, promotes mitochondrial biogenesis and improves mitochondrial functions via the activation of the AMPK–PGC1 α signaling pathway [57].

Reactive oxygen species and nitric oxide activate mitochondria with the subsequent release of cytochrome C. This forms a complex with apoptotic protease activity factor-1 and caspases-9, which initiates the cleavage and activation of downstream/effector caspases, thus resulting in neuronal death [137]. Ginger was shown to decrease the Bax/Bcl-2 ratio and caspase-3 activity, thus preventing mitochondrial-induced apoptosis [54].

Increase in zonulin and claudin-1 expression

The blood–brain barrier (BBB) and blood–nerve barrier (BNB) present gap junctions through which selected molecules can enter from the blood into the central and peripheral nervous systems, respectively. Tight junction proteins seal the intercellular space through the formation of a paracellular barrier, thereby controlling the influx of molecules. Claudin-1 is a tight junction protein crucial in maintaining the integrity of BNB. Different neuropathies such as nerve crush, chronic constriction injury (CCI), and partial sciatic nerve ligation are associated with the leakage of the BNB owing to a reduction in TJP expression [138,139]. This enhances the invasion of immune cells and local production or influx of inflammatory mediators such as cytokines, which is followed by the onset of neuropathic symptoms [140].

Zonulin, a protein produced by small intestine epithelium, can rapidly increase small intestinal permeability, as well as BBB permeability, via the epidermal growth factor receptor (EGFR) and the proteinase-activated receptor 2, resulting in the reorganization of the F-actin belt and modification of the localization of ZO-1, claudin-5, and occludins [141].

Thus, a ginger-induced increase in the expression of claudin-1 and zonulin can restore the protective function of BNB, preventing neuroinflammation and its complications [141].

A summary of the main pathways associated with the antinociceptive effects of the ginger extract is given in Figure 3.

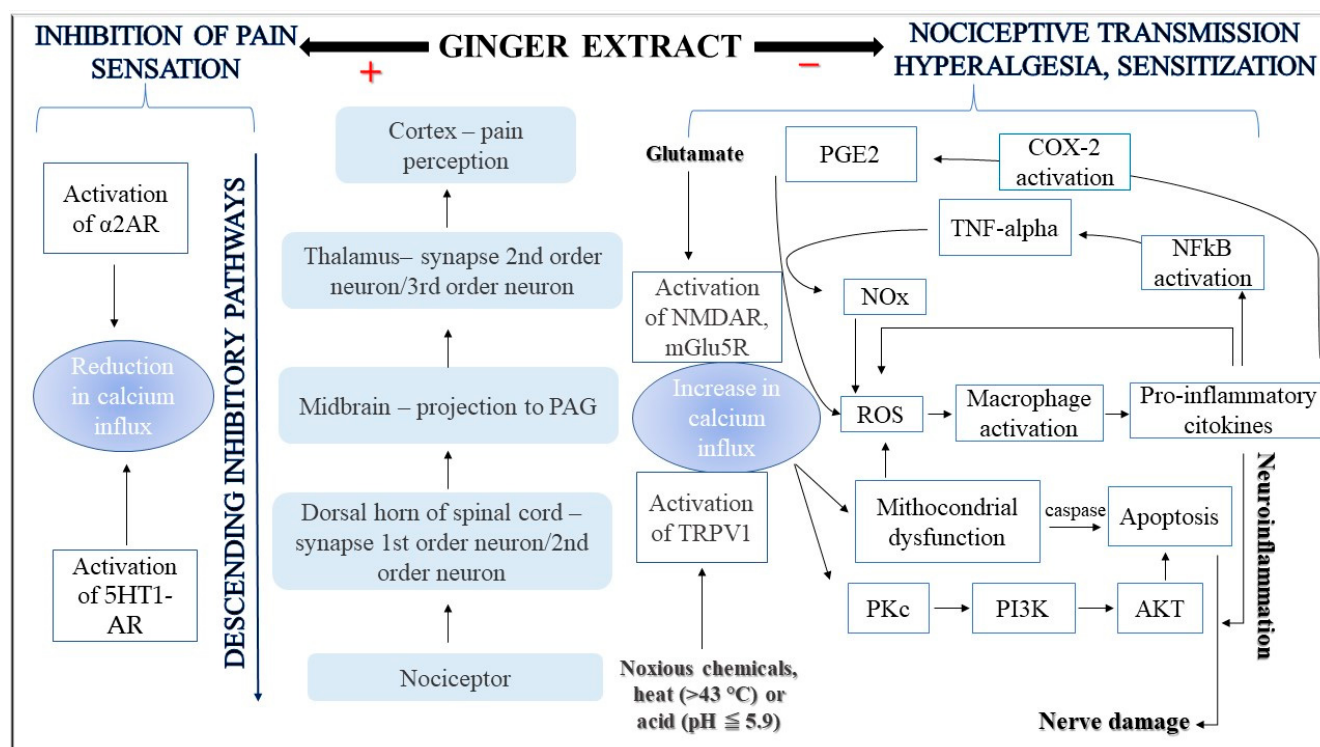


Figure 3. The main mechanisms mediating the antinociceptive effect of ginger extract. Legend: 5HT1-AR, serotonergic receptor subtype 5HT1-A; α 2AR, adrenergic receptors α 2A; AKT, protein kinase B; COX-2, cyclooxygenase 2; mGlu5R, metabotropic glutamate receptors 5; NF- κ B, nuclear factor-kappa B; NMDAR, glutamatergic receptor subtype NMDA; NOx, NADPH oxidase enzymes; PAG, periaqueductal gray; PGE2, prostaglandin E2; PI3K, phosphoinositide 3-kinases; PKC, protein kinase C; ROS, reactive oxygen species; TRPV1, transient receptor potential cation channel subfamily V member 1.

5. Conclusions

Ginger extract, through its various active ingredients, behaves like a single multitarget antinociceptive agent. Its broad-spectrum analgesic efficacy results from the inhibition of the activity of NMDA and TRPV1 receptors, which in turn inhibit NF- κ B signaling, cytokine release, and ROS production and prevent the mitochondrial-activated apoptosis of the cells in the central nervous system. Thus, it suppresses the transmission of nociceptive signals along the sensory fibers to the brain and has neuroprotective effects. Ginger also activates the descendent inhibitory pathways of pain via 5HT1A and noradrenergic presynaptic receptors.

These results highlight an extremely complex mechanism underlying the analgesic effect of ginger—several of its ingredients modulate various components of nociceptive signaling pathways. Owing to this mechanism, ginger is a promising wide-spectrum analgesic, effective in various types of pain, including neuropathic and inflammatory pain, which are currently unmet medical needs. The data provided herein demonstrate that the key to an effective analgesic strategy is targeting multiple key elements regulating the nociceptive process.

However, future systematically designed research, including sufficient sample size, should assess the extent of ginger's usefulness in specific types of pain in humans and the type of extract with the best analgesic effect. Furthermore, its comparative efficacy reported in other alternative interventions should be also investigated.

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