Med Discoveries
An open access journal of science and medicine

Article Type: Review Article
Volume 2, Issue 10
Received: Aug 15, 2023
Accepted: Sep 26, 2023
Published Online: Oct 03, 2023

Advances in the Application of 6-Gingerol in Diseases of the Central Nervous System

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Abstract

6-Gingerol is the main active component of ginger, which is widely used in traditional Chinese medicine. 6-Gingerol has a variety of pharmacological effects, including anti-apoptosis, antiviral, immune protection, antibacterial, anti-inflammatory, antioxidant and anti-tumor. Additionally, 6-Gingerol has shown therapeutic potential in various neurological diseases, including stroke, Alzheimer's Disease (AD), Parkinson's Disease (PD), Multiple Sclerosis (MS), and epilepsy. However, it's important to note that further research is needed to fully understand the mechanisms and clinical applications of 6-gingerol in these conditions. The article provides a systematic review of the therapeutic effect of 6-gingerol on central nervous system diseases. By examining existing research and evidence, this article aims to establish a foundation for further investigation into the pharmacological potential of 6-gingerol. Additionally, the article explores the possibility of utilizing 6-gingerol for the treatment of other central nervous system diseases. Overall, this article highlights the potential benefits of 6-gingerol in the field of neurology and suggests that further research is warranted to fully understand its therapeutic effects and expand its application in treating central nervous system diseases.

Keywords: 6-Gingerol; Pharmacological effect; Central nervous system diseases.

Introduction

Central nervous system diseases generally include neurodegenerative diseases, neurodevelopmental disorders, brain injuries and psychiatric diseases, which have the characteristics of diversity, complexity, and refractory treatment, which have brought great suffering to patients, families and even society [1]. Although more and more research on the central nervous system is being carried out, the pathogenesis of these diseases is complex and there is a lack of effective treatment. Traditional Chinese medicine monomer play a crucial role in traditional Chinese medicine, with a single composition, precise curative effect, few adverse reactions, and can play a targeted role. Therefore, in recent years, researchers have turned their attention to the field of traditional Chinese medicine to find solutions.

Ginger is a common and clinically widely used traditional Chinese herbal medicine that is listed as "Generally Recognized as Safe" by the U.S. Food and Drug Administration [2]. The health and therapeutic value of ginger can be attributed to its bioactive compounds such as gingerol, curcumin. 6-Gingerol is considered to be a functional polyphenol [3] and index component [4] of ginger, which can passively diffuse through the blood-brain barrier [5], and has been shown to have therapeutic properties for a variety of neurological diseases such as stroke, Alzheimer's disease, Parkinson's syndrome, Multiple sclerosis, and epilepsy in animal models.

However, the mechanism of 6-gingerol on central nervous system diseases has not been systematically reviewed. Therefore, the effects of 6-gingerol on central nervous system diseas-

Citation: Li W, Li M, Ma S, Tian Y. Advances in the Application of 6-Gingerol in Diseases of the Central Nervous System. Med Discoveries. 2023; 2(10): 1078.

es were elaborated in this paper, in order to provide ideas for further understanding of the therapeutic effects of 6-gingerol on central nervous system diseases, further promote the exploration of its medicinal value, expand the scope of clinical application, and provide evidence for clinical rational drug use.

6-Gingerol and central nervous system diseases

6-Gingerol and stroke

Stroke is the leading cause of disability and cognitive impairment and the second leading cause of death globally, accounting for 5.2% of all mortality globally, with a significant burden in low- and middle-income countries [6,7]. Strokes include cerebral ischemic stroke and hemorrhagic stroke [8]. Cerebral ischemic stroke, also known as cerebral infarction and cerebral infarction, refers to ischemic necrosis or softening of localized brain tissue caused by cerebral blood supply disorders, ischemia, and hypoxia [9]. Hemorrhagic stroke includes parenchymal hemorrhage, ventricular hemorrhage, and subarachnoid hemorrhage [10]. The pathophysiology of stroke, including cell excitatory toxicity, oxidative stress, cell death processes and neuroinflammation, and a large number of signaling pathways, whether harmful or neuroprotective, are also highly involved in the pathophysiology described above [11]. Diagnostic biomarkers for exosomes have potential applications in various stroke and processes [12]. Inhibition of microglia-mediated inflammatory response or inhibition of microglial activity in stroke can improve the inflammatory microenvironment, reduce brain damage, and promote brain tissue repair [13].

6-Gingerol can significantly reduce cerebral infarct volume, improved brain edema and neurological scores, reduce the size of infarction, improve neurological functions and reversed brain histomorphology damage after I/R injury [14,15]. Its pathway mainly includes the following aspects: (1) 6-Gingerol can positively regulate the expression of transient receptor potential vanilloid subfamily 1(TRPV1) in the brains of cerebral ischemia/reperfusion (I/R) injury rats by inhibiting the expression of Fas-associated factor 1(FAF1), thereby reducing NLRP3 inflammation and apoptosis in 14 cerebral I/R injury [15]. (2) 6-Gingerol protected against ischemia cerebral injury in middle cerebral artery occlusion (MCAO) through suppressed phosphorylation of serine-threonine Protein Kinase (Akt) - 16mammalian Target of Rapamycin (mTOR) - signal transducer and activator of transcription 3(STAT3) signaling pathway in Lipopolysaccharide (LPS)-stimulated microglia [17]. (3) 6-Gingerol in cerebral ischemia-induced neuronal damage and to elucidate whether miR-210 mediated gingerol-induced neuroprotection by targeting Brain-Derived Neurotrophic Factor (BDNF) [16]. (4) 6-Gingerol suppressed the expression of Guanylate-Binding Protein 2 (GBP2) to activate the PI3K/AKT pathway, improve neurologic outcomes, reduce brain edema and neuronal apoptosis on Early Brain Injury (EBI) after Subarachnoid Hemorrhage (SAH) rats [17] (Figure 1). These findings highlight the therapeutic potential of 6-gingerol for stroke. However, the duration and dose of 6-gingerol therapy in stroke, phenotypic analysis, and signal integration need to be further explored in clinical trials to improve our understanding of the modulating role and therapeutic application of 6-gingerol in stroke.

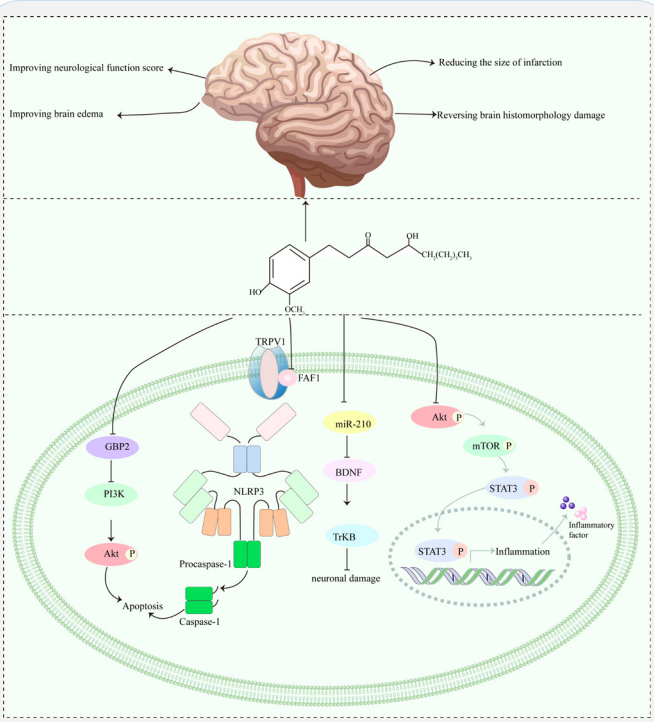

Figure 1: Representative scheme illustrating the potential mechanisms behind the regulatory role of the effect of 6-gingerol on stroke.
TRPV1: transient receptor potential vanilloid subfamily 1; FAF1: Fas-associated factor 1; GBP2: guanylate-binding protein 2; BDNF: brain-derived neurotrophic factor; TrkB: tropomyosin-related kinase receptor type B; mTOR: mammalian target of rapamycin; STAT3: signal transducer and activator of transcription.

6-Gingerol and alzheimer's disease

Alzheimer's disease is an age-related neurodegenerative disorder of the brain and the commonest cause of dementia. Extracellular neuritic plaques composed of amyloid-β (Aβ) protein and intracellular neurofibrillary tangles containing phosphorylated tau protein are the two hallmark proteins of AD [2]. Neuroinflammation, innate immune responses, inflammatory cell death pathways, and cytokine secretion are related to AD [3].

6-Gingerol may have therapeutic or/or preventive effects on AD [4]. 6-Gingerol can improve Aβ1-42 to induce cell viability of rat Pheochromocytoma Cells (PC12 cells) and reduce apoptosis. First, the decreased levels of 5 Nitric Oxide (NO) showed its anti-inflammatory role. Second, 6-Gingerol pretreatment markedly reduced the level of intracellular Reactive Oxygen Species (ROS) and Malondialdehyde (MDA), and the leakage of Lactate Dehydrogenase (LDH) and increased Superoxide Dismutase (SOD) activity compared with the Aβ1-42 treatment group reflected the anti-oxidative effects of 6-gingerol. Last, 6-Gingerol suppressing the activation of Glycogen Synthase Kinase 3β (GSK-3β) and enhancing the activation of Akt, thereby exerting neuroprotective effects [21]. In addition, 6-Gingerol can prevent Aβ-induced cytotoxicity and apoptosis by activating mRNA and protein levels of nuclear factor erythroid 2-related factor 2 (Nrf2) mediated antioxidant enzymes such as γ-Glutamyl Cysteine Ligase (GCL) and Heme Oxygenase-1 (HO-1), inhibiting intracellular accumulation of ROS and/or Reactive Nitrogen Species (RNS) and subsequent oxidation and/or nitroso damage [22] (Figure 2). However, these studies are preliminary and further research is needed to fully understand the effects of 6-gingerol on Alzheimer's disease in humans. However, it may be possible to incorporate new supplements into daily life under the guidance of a healthcare professional.

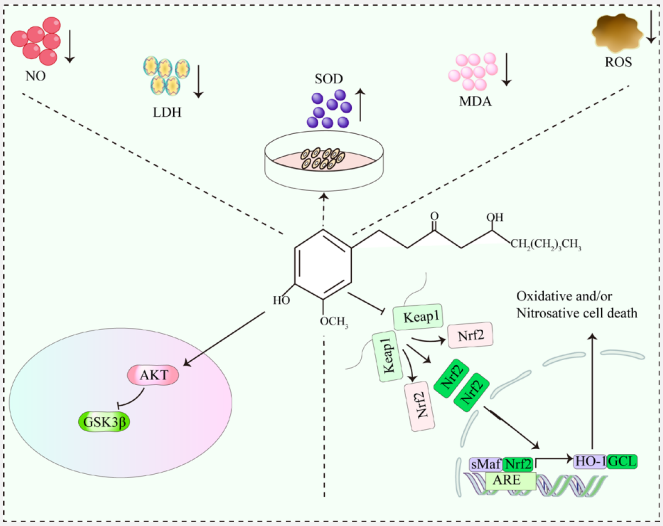

Figure 2: Representative scheme illustrating the potential mechanisms behind the regulatory role of the effect of 6-gingerol on Alzheimer's disease.
NO: nitric oxide; LDH: lactate dehydrogenase; SOD: superoxide dismutase; MDA: malondialdehyde; ROS: reactive oxygen species; GSK-3β: Glycogen synthase kinase 3β; GCL: γ-glutamyl cysteine ligase; HO-1: heme oxygenase-1; Nrf2: nuclear factor erythroid 2-related factor 2; ARE: Antioxidant Response Element; Keap1: Kelch-like ECH-associated protein 1; sMaf: small musculoaponeurotic fibrosarcoma.

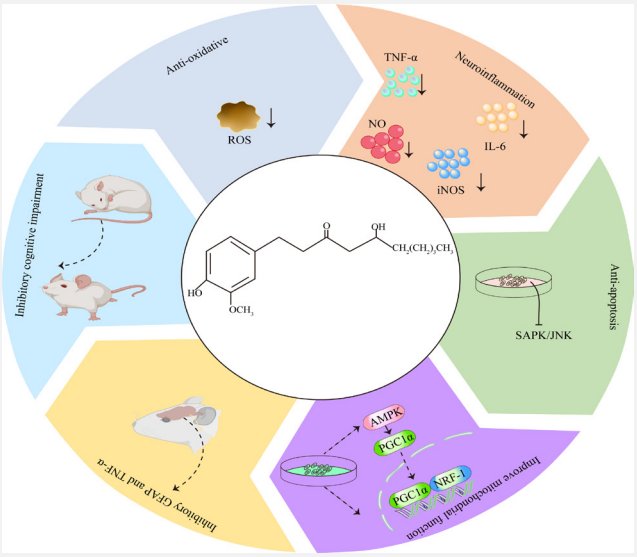

Figure 3: Representative scheme illustrating the potential mechanisms behind the regulatory role of the effect of 6-gingerol on Parkinson's disease.
ROS: reactive oxygen species; NO: nitric oxide; iNOS: inducible NO synthase; IL-6: Interleukin-6; TNF-α: tumor necrosis factor α; SAPK/JNK: stress-activated protein kinase/c-Jun N-terminal kinase; AMPK: AMP-activated protein kinase; PGC1α: proliferator-activated receptor gamma coactivator 1 alpha; NRF1: nuclear respiratory factor 1; GFAP: glial fibrillary acidic protein.

6-Gingerol and parkinson's disease

Parkinson's disease is the second most common neurodegenerative disease, which is specified by cardinal motor symptoms such as tremor, stiffness, bradykinesia, postural instability, and non-motor symptoms [2,3]. The key molecular pathogenic mechanisms of PD include α-synuclein misfolding and aggregation, mitochondrial dysfunction, impairment of protein clearance, neuroinflammation and oxidative stress [4].

6-Gingerol inhibits neuroinflammation in LPS-induced C6 astroglioma cells by reducing levels of ROS, TNF-α, IL-6, NO, and inducible NO Synthase (iNOS) [5]. 6-Gingerol can play a protective role in blocking 6-OHDA-induced cell damage through SAPK/JNK anti-apoptosis pathway [27]. 6-Gingerol can specifically improve mitochondrial function of PD by activating AMPK/PGC1α axis [26]. In addition, 6-Gingerol inhibits LPS-induced TNF-α and Glial Fibrillary Acid Protein (GFAP) elevation, and inhibits LPS-induced cognitive impairment [26] (Figure 3). However, it is important to note that most of the research on the potential benefits of 6-gingerol for Parkinson's disease has been conducted in animal models or in vitro studies. Human clinical trials are limited, and their results are not yet available. Therefore, while 6-gingerol shows promise as a potential therapeutic agent for Parkinson's disease, further research is needed to determine its efficacy, optimal dosage, and potential side effects in humans.

6-Gingerol and 2 multiple sclerosis

Multiple Sclerosis (MS) is a typical T cell-mediated inflammatory demyelinating autoimmune disease that affects the central nervous system with an increased incidence worldwide [3]. Dendritic cells with a crucial role in immune system activation, and autoimmune disorders [4]. BBB breakdown and immune cell infiltration into the central nervous system are early hallmarks of MS [5]. But, the exact cause of MS is unknown and no cure for MS currently.

6-Gingerol as a novel anti-inflammatory agent can direct regulatory effect on dendritic cells activation via inhibition of NF-κB and MAPK signaling, and induced tolerogenic DCs (tolDCs), effectively improving the clinical disease severity of experimental autoimmune encephalomyelitis (EAE) (an animal model of MS [31] (Figure 4). These findings will provide the basis for new therapeutic effect against multiple sclerosis of 6-gingerol. Promoting myelin regeneration is a major treatment for MS. The blocking of Oligodendrocyte Progenitor (OPC) differentiation in MS lesions is the main reason for the failure of myelin regeneration. Compounds that promote OPC differentiation are used as drugs to promote myelin regeneration [32]. However, 6-Gingerol did not significantly affect OPC maturation or directly promote myelination. Therefore, further mechanism research is needed.

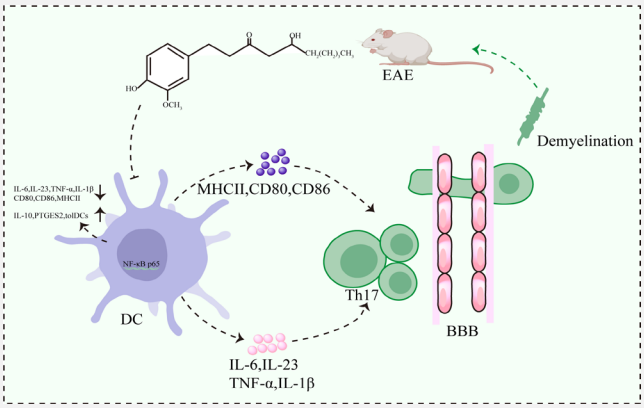

Figure 4: Representative scheme illustrating the potential mechanisms behind the regulatory role of the effect of 6-gingerol on multiple sclerosis.
DC: dendritic cell; EAE: experimental autoimmune encephalomyelitis; Th17: T-helper 17; BBB: Blood-Brain Barrier; IL-6: interleukin 6; IL-23: interleukin 23; TNF-α: tumor necrosis factor α; IL-1β: interleukin 1β; MHCII: major histocompatibility complex class II; IL-10: interleukin 10; PTGES2: prostaglandin E synthase 2; tolDCs: tolerogenic DCs.

6-Gingerol and epilepsy

Epilepsy is a neurological disorder causing by aberrant synchronized firing of populations of neurons primarily due to imbalance between excitatory and inhibitory neurotransmission [1]. 2 γ-aminobutyric acid (GABA) and glutamic acid (Glu) are two key neurotransmitters in the central nervous system underlying the expression of seizure discharges [3,4].

6-Gingerol may mediate anticonvulsant effects by restoring the balance between GABA and Glu in the epileptic brain in zebrafish model [36] (Figure 5). Although zebrafish have become a powerful animal model for studying the physiology and pathology of human diseases, there are still some limitations to consider. However, other models of 6-gingerol for the treatment of epilepsy are lacking.

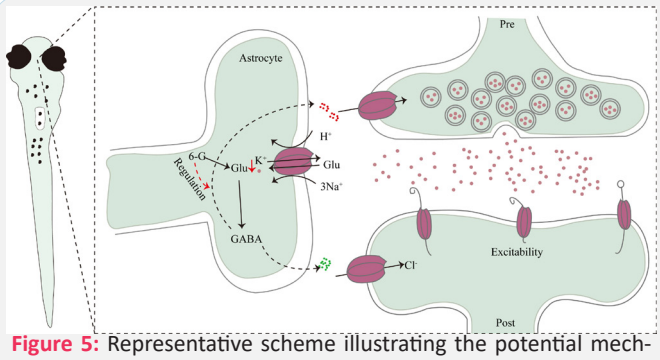

Figure 5: Representative scheme illustrating the potential mechanisms behind the regulatory role of the effect of 6-gingerol on epilepsy.
6-G: 6-gingerol; GABA: γ-aminobutyric acid; Glu: glutamic acid.

Conclusions and future directions

The treatment of central nervous system diseases has always been a difficult problem, which seriously affects human health. Its pathogenesis is extremely complex, so it is an effective means to seek treatment from traditional Chinese medicine. Ginger, as a traditional Chinese medicine, has been widely used in clinical practice. Modern pharmacological studies have confirmed that 6-gingerol, an important component of ginger, has therapeutic effects on a variety of central nervous system diseases and can be used as a potential drug for research and development. This review summarizes current evidence on the role of 6-gingerol in regulating the various central nervous system diseases. We demonstrated that 6-gingerol in enhancing the potential in the treatment of central nervous system diseases and has promising prospects as an effective therapeutic drug for central nervous system diseases.

However, the potential mechanism of action of 6-gingerol in the treatment of central nervous system diseases is not fully explored. In future studies, transcriptomics, proteomics, metabolomics and other new technologies should be used to further explore the efficacy of 6-gingerol at different levels. For the exploration of molecular pathways, agonists, antagonists, gene knockout/overexpression can be used to clarify the regulatory signaling pathway of 6-gingerol and the expression of its upstream and downstream molecules, so as to find more new pathways and new targets. In addition, the research on the basis of traditional Chinese medicine efficacy substances around the efficacy of ginger traditional Chinese medicine, or the close integration with traditional Chinese medicine theory, is less and not in-depth, which needs to be further explored by researchers. It is hoped that more scholars at home and abroad will conduct relevant research on 6-gingerol in the future, contribute to the modern application of traditional Chinese medicine, and strive to show the charm of traditional Chinese medicine.

In addition, 6-Gingerol has a variety of pharmacological activities, including metabolic regulation, anti-apoptosis, antiviral, immune protection, antibacterial, anti-inflammatory, antioxidant and anti-tumor effects on a variety of stem cells, which may provide ideas for further research. 6-Gingerol has preventive and therapeutic effects on a variety of central nervous system diseases, but there is currently no treatment for neurodevelopmental disorders, so the great potential of 6-gingerol for the treatment of neurodevelopmental disorders can be further explored.

Declarations

Acknowledgments: Not applicable.

Funding: Not applicable.

Author contributions: Not applicable.

Availability of data and materials: Not applicable.

Ethics approval and consent to participate: This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication: All authors agree to the publishing of this article in Med Discoveries.

Competing interests: The authors declare no conflict of interest.

Abbreviations: AD: Alzheimer's disease; AMPK: AMP-activated protein kinase; ARE: Antioxidant Response Element; BBB: Blood-Brain Barrier; BDNF: brain-derived neurotrophic factor; DC: dendritic cell; EAE: experimental autoimmune encephalomyelitis; FAF1: Fas-associated factor 1; GABA: γ-aminobutyric acid; GBP2: guanylate-binding protein 2; GCL: γ-glutamyl cysteine ligase; GFAP: glial fibrillary acidic protein; Glu: glutamic acid; GSK-3β: Glycogen synthase kinase 3β; HO-1: heme oxygenase-1; iNOS: inducible NO synthase; IL-6: Interleukin-6; IL-10: interleukin 10; IL-23: interleukin 23; IL-1β: interleukin 1β; Keap1: Kelch-like ECH-associated protein 1; LDH: lactate dehydrogenase; MDA: malondialdehyde; MHCII: major histocompatibility complex class II; mTOR: mammalian target of rapamycin; MS: multiple sclerosis; NO: nitric oxide; NRF1: nuclear respiratory factor 1; Nrf2: nuclear factor erythroid 2-related factor 2; OPC: oligodendrocyte progenitor; PD: Parkinson's disease; PGC1α: proliferator-activatedreceptorgammacoactivator1alpha; PTGES2: prostaglandin E synthase 2; ROS: reactive oxygen species; SAPK/JNK: stress-activated protein kinase/c-Jun N-terminal kinase; sMaf: small musculoaponeurotic fibrosarcoma; SOD: superoxide dismutase; STAT3: signal transducer and activator of transcription; Th17: T-helper 17; TNF-α: tumor necrosis factor α; tolDCs: tolerogenic DCs; TRPV1: transient receptor potential vanilloid subfamily 1; TrkB: tropomyosin-related kinase receptor type B.

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