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Review article

A narrative review of therapeutic potential of cedrol and its intracellular signaling

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Abstract

Objective: Natural compounds are used as a therapeutic strategy for diseases. Cedrol possesses anti-inflammatory, antioxidant, antimicrobial, and anticancer activities. This paper summarizes the protective properties of cedrol on various body systems including the nervous, cardiovascular, respiratory, renal, gastrointestinal, and musculoskeletal systems as well as its anti-tumor impacts.

Materials and methods: Information retrieval was done by tracking the electronic databases including Google Scholar, Scopus, PubMed and Web of Science from the beginning of 2010 until the end of May 2026.

Results: Findings suggest that cedrol mainly exerts its protective impacts on body systems through inhibition of NF-κB signaling pathway, reduction of inflammatory cytokines production and alleviation of oxidative stress. Evidence demonstrates that a part of neuroprotective effect of cedrol is mediated by enhancement of brain-derived neurotrophic factor **(**BDNF) and estrogen receptor β (Erβ) activity. Upregulation of protective factors including nuclear factor erythroid 2-related factor 2 (Nrf2), and silent information regulator sirtuin 1 (SIRT 1) by cedrol can lead to ameliorate the inflammatory bowel disease (IBD) symptoms. Decreased expression of myostatin, MuRF1, and FoxO3a and increase of intracellular calcium by cedrol also can prevent muscle atrophy. The antitumor mechanisms of cedrol include induction of apoptosis, stimulation of autophagy, suppression of cell cycle, prevention of angiogenesis, and inhibition of phosphoinositide 3-kinases (PI3K)/AKT/mTOR/ERK1/2 pathway.

Conclusion: Taken together, cedrol protects organs by modulation of immune system responses and prevention of overproduction of reactive oxygen species (ROS), as well as induction of anticancer effects through inhibiting cell proliferation and triggering apoptosis.

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Introduction

Natural compounds are isolated from medicinal plants extract and are used as a therapeutic strategy for a large number of ailments (Nittayananta 2025; Nosratabadi et al. 2024). Among natural substances, terpenes are a group of plant aromatic compounds characterized by volatile nature and the number of isoprene units (Chen et al. 2024). Based on the number of isoprene units, terpenes include monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), and triterpenes (C30) (Degenhardt et al. 2009). Cedrol as a sesquiterpene (Figure 1) is extracted from essential oil of *Juniperus virginiana* L. It possesses many therapeutic properties such as anti-inflammatory, antioxidant, antimicrobial, and antitumor activities (Özek et al. 2021). Based on *in vivo* and *in vitro* studies, modulation of inflammation by cedrol leads to attenuation of brain damages caused by cerebral ischemia infarction in rats (Hu et al. 2024). Scientific reports also reveal that cedrol prevented apoptosis of chondrocytes exposed by interleukin (IL-1β) via inducing miR-542-5p expression (Dong et al. 2021). This aromatic compound also alleviated osteoporosis through reducing reactive oxygen species (ROS) and suppressing the nuclear factor kappa B (NF-κB) - related inflammatory responses (Xu et al. 2023). Cedrol also could apply the positive treatment effects against high-fat diet-caused obesity in mice (Zhao et al. 2023). Additionally, researchers suggested that cedrol promoted the generation of type 1 collagen in dermal fibroblasts through affecting the mitogen-activated protein kinase (MAPK)-related signaling pathway (Jin et al. 2012). According to the scientific reports, cedrol can be considered an effective natural compound for improving various types of cancers (Pourbagher Shahri et al. 2025). For example, in epidermoid carcinoma cells, cedrol exerted anticancer effect through upregulation of pro-apoptotic protein Bax and death receptors expression and downregulation of anti-apoptotic factor Bcl-2 (Oh et al. 2026). In a study designed by Hsiao et al., the antifungal impact of cedrol against *Phellinus noxius* has been documented (Hsiao et al. 2024). It also should be kept in mind that there are no human studies about therapeutic of cedrol.

This review collects and narrates the protective effects of cedrol on the nervous system, cardiovascular system, respiratory system, renal system, gastrointestinal system, and musculoskeletal system, as well as its anticancer effects in experimental studies. Thus, scientific evidence mentioned in this article helps researchers for future researches especially human studies.

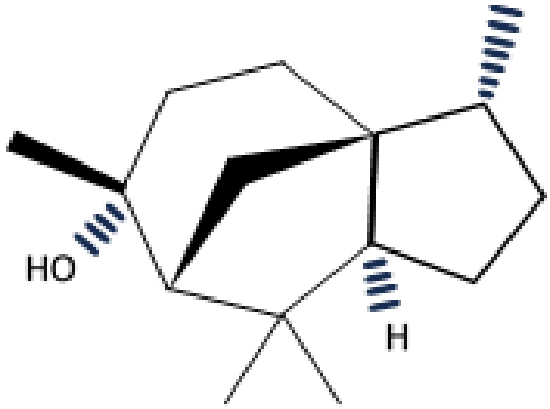

Figure 1. Molecular structure of cedrol

Materials and Methods

Information of this study was obtained from reputable scientific databases including Google Scholar, Scopus, PubMed and Web of Science from the beginning 2010 until the end of May 2026. Key words included “cedrol” and “nervous system” or “cardiovascular system” or “respiratory system” or “gastrointestinal tract” or “urinary system” or “musculoskeletal system” or ‘cancer”. Figure 2 illustrates flowchart of literature screening.

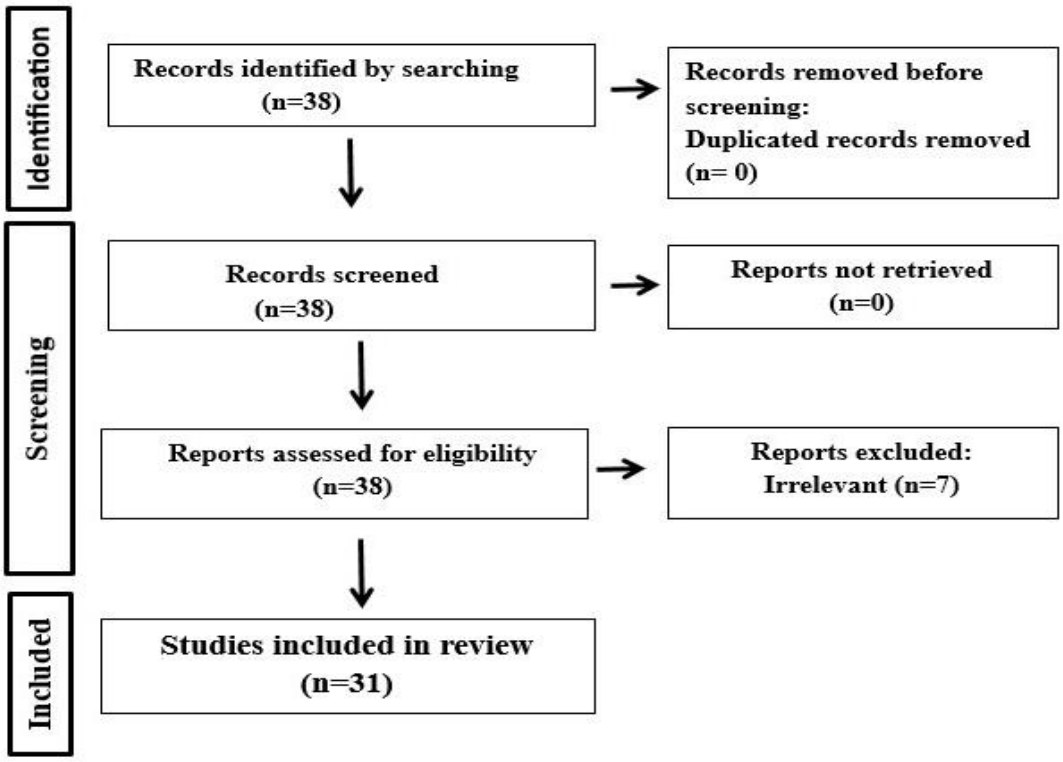

Figure2. Flowchart for literature screening

Results

Protective effects of cedrol on the nervous system

Brain ischemia is a disturbance that happens when there is not adequate blood supply to the brain (Liao et al. 2026). Cardiac arrest is one of main causes of brain ischemia. Interruption or reduction in blood flow of the brain resulting from cardiac arrest can lead to unconscious and if treatment is not done, irreversible brain injuries and death will happen (Perkins et al. 2021). Despite extensive studies, there is not a precise therapeutic procedure to relieve the harmful effects of brain ischemia. Medicinal plants and natural compounds have been suggested as effective strategy to alleviate the symptoms of brain ischemia (Jiang et al. 2025; Yoo et al. 2025). In a rat model of global ischemia/reperfusion (I/R) -induced brain injury, cedrol at 7.5, 15 and 30 mg/kg was used for one week. Then, memory retention by passive avoidance test and level of malondialdehyde (MDA), thiol, nitric oxide (NO) and brain-derived neurotrophic factor (BDNF) in hippocampal tissue of the animals were evaluated. The results indicated that improvement of the behavioral performance was accompanied by significant reduction in level of MDA and NO and increased content of thiol and BDNF in the hippocampus of groups treated by 15 and 30 mg/kg of cedrol compared to global I/R group (Asgharzade et al. 2025). Among all the factors involved in brain damage, the role of neuroinflammation has been highlighted (Lombardozzi et al. 2026). Neuroinflammation can be a consequence of acute cerebral ischemia (Zhang et al. 2025). Additionally, two types of microglia including M1 and M2 have been recognized in the brain tissue (Qin et al. 2019). Activation of M1 macroglia leads to excessive production of proinflammatory cytokines, whereas activation of M2 macroglia results in decrease of glutamate level and increase of neuroprotective factors including BDNF and glial cell line derived neurotrophic factor (GDNF) in the brain tissue (Domingues et al. 2020). Macroglia are susceptible to stimuli such as

stroke and usually change into M1 type when they are stimulated by this stimulus (Li et al. 2021). It has been also recognized that activation of estrogen receptor β (ERβ) applies protective effects against neuronal damages resulting from inflammation (Katola et al. 2024). Bi et al checked the effect of cedrol against neuroinflammation *in vitro* and *in vivo*. *In vitro*, microglia were treated by cedrol at 20 and 50 μM doses for 2 hr and then exposed by 100 ng/mL dose of lipopolysaccharide (LPS). The results of real-time polymerase chain reaction (real-time PCR) revealed that cedrol downregulated the expression of IL-1β, IL-6, tumor necrosis factor alpha (TNFα) and cyclooxygenase-2 (COX-2), and consequently attenuated LPS-evoked inflammatory reactions. Molecular assessment also displayed that cedrol binds to ERβ and exerts its anti-inflammatory effects. *In vivo*, the middle cerebral artery was occluded in mice. Then, cedrol 40 mg/kg dose was injected for 3 days, and behavioral responses, infract size and modified neurologic severity score (mNSS) were evaluated. Reduction in infarct size and mNSS, and improvement of behavioral responses by mice confirmed the positive therapeutic impacts of cedrol on acute cerebral ischemia. Altogether, the findings of this study suggest that neuroprotective effects of cedrol against acute cerebral ischemia can be mediated by suppressing the microglia-associated neuroinflammation and affecting ERβ-NF-κB signaling pathway (Bi et al. 2024).

Peripheral and central administration of LPS has been suggested to frustrate cognitive actions and learning process via inducing neuroinflammation and oxidative stress (Anaeigoudari 2025). In Wistar rats exposed to 1 mg/kg of LPS, administration of cedrol at 7.5, 15 and 30 mg/kg doses for 2 weeks was done. Then, behavioral indices by Morris water maze (MWM) and passive avoidance tests along with inflammatory and oxidative stress biomarkers were monitored. The data exhibited that cedrol effectively ameliorated memory deficits and mitigated the concentration of TNF-α, IL-1β and MDA and acetylcholinesterase (AChE) activity and elevated the level of thiol and superoxide dismutase (SOD), suggesting anti-inflammatory and antioxidant properties (Farimani et al. 2024).

Parkinson's disease (PD) is an ailment of nervous system which is characterized by resting tremor in one hand or one food (khazdair et al. 2021). Reduction of dopamine (DA) resulting from destruction of dopaminergic neurons in nigrostriatal pathway has been recognized to be the cause of PD (Knani et al. 2025). There is a pile of reports that emphasizes on the role of neuroinflammation and brain oxidative stress in pathogenesis of PD (Chen et al. 2025; Cai et al. 2025). Plant remedies have been also shown to have positive therapeutic effect on neurodegenerative disorders such as PD (Haxhiu et al. 2025). Forouzanfar et al. tested the ability of cedrol at 10 and 20 mg/kg doses to relieve the cognitive dysfunctions and motor disorders in a rat model of PD induced by 6-hydroxydopamine (6-OHDA). In this study, positive alterations in cognitive and motor functions in rats treated by cedrol were associated with meaningful decline in MDA level and increment of thiol concentration and SOD activity in the striatum tissue of the brain (Forouzanfar et al. 2025).

Anxiety disorders include a group of mental disturbances in which individuals feel anxiety and fear (Ayomen et al. 2025; Bakhshi Aliabad et al. 2016). These psychiatric disorders may be accompanied by physical and cognitive impairments (Abareshi et al. 2019). Researchers believe that plant extracts and phytochemicals can modulate the symptoms of anxiety (Shahanewz et al. 2025). Evidence also exhibits that neurotransmitters such as DA and 5-hydroxytryptamine (5-HT) affect anxiety diseases (Zarrindast and Khakpai 2015). Although reports approve the anxiolytic effects of cedrol, its underlying mechanism still has been not cleared

(Dayawansa et al. 2003). Zhang et al designed a study to clarify the possible mechanism of anxiolytic effect of cedrol in male mice. They used WAY100635 (2 mg/kg) as 5-HT1A receptor antagonist, SCH23390 (0.125 mg/kg) as dopamine D1 receptor antagonist, sulpiride (40 mg/kg) as dopamine D2/D3 receptor antagonist, and flumazenil (2 mg/kg) as benzodiazepine receptor antagonist. Cedrol was employed at 1200 mg/kg dose. Then, behavioral responses were followed using light-dark box (LDB) and elevated plus maze (EPM) tests. Evaluations illustrated that SCH23390 was only compound that antagonized the anxiolytic effect of cedrol. Cedrol decreased the concentration of DA and norepinephrine in stratum, hippocampus and hypothalamus. These evidences prove that anxiolytic effect of cedrol probably is mediated by affecting the dopamine D1 receptor-linked intracellular pathway (Zhang et al. 2020). Evaluation of anxiolytic impacts of cedrol at 200, 400, 800, 1200 and 1600 mg/kg doses in female rats also was programed. In this work, in addition to examining the behavioral functions by EPM and LDB, level of monoamines including DA and 5-HT and their metabolites in brain tissue were measured and compared with diazepam as a positive control drug. The findings indicated that cedrol at 200, 400 and 800 mg/kg did not exert significant changes in behavioral parameters or level of monoamines and their metabolites in comparison with control group. Use of 1200 and 1600 mg/kg doses of cedrol effectively increased the percentage of entries and stay time in open arms in the EPM, and enhanced time spent in light room in LDB reflecting the anxiolytic effect of cedrol. Biochemical tests also displayed that the level of 5-hydroxyindoleacetic acid (5-HIAA), 5HIAA/5-HT ratio, and DA were lower and level of 5-HT and 3,4-dihydroxyphenyl acetic acid (DOPAC)/DA ratio were higher in groups treated by 1200 and 1600 mg/kg of cedrol versus control group, suggesting the role of brain monoaminergic system in anxiolytic effects of cedrol (Zhang and Yao 2019).

Memory and cognitive deficits associated with aging have been understood to be as a result of loss of neuronal function (Zhou et al. 2025). Inflammation and oxidative stress have an outstanding role in induction of aging and damage of neurons (Chai et al. 2026; Nagarajan et al. 2025). In old rats, cedrol at 5 and 10 mg/kg doses was injected for 30 consecutive days. Memory retention was checked using passive avoidance test. In addition, oxidative stress indicators including MDA and thiol in the cortex, hippocampus, heart, liver and kidney tissues and liver enzymes were measured. Cedrol administration ameliorated memory retention and lowered the level of MDA and liver enzymes and elevated thiol concentration, showing the alleviating effects of cedrol on aging-related injuries through modulation of oxidative stress (Ghorbani et al. 2025).

Neuropathic pain is nerve pain resulting from nervous system injuries. This chronic pain can be induced in both peripheral and central nervous systems (Xie et al. 2026). Sakhaee et al evaluated the cedrol influence at 20 and 40 mg/kg doses on neuropathic pain evoked by chronic constriction injury (CCI) model of sciatic nerve in rats. The results suggested that the alleviating impact of cedrol on neuropathic pain was associated with attenuation of oxidative damage and inflammation in spinal cord (Sakhaee et al. 2020). Administration of cedrol at 10 and 20 mg/kg doses also attenuated pain in complete Freund's adjuvant -induced arthritis in rats. In this study, analgesic impact of cedrol was mediated by decrease of MDA and TNF-α and increase of thiol, SOD and glutathione peroxidase (Forouzanfar et al. 2022). Figure 3 demonstrates the mechanisms of neuroprotective effect of cedrol. Table 1 shows the effects of cedrol on the nervous system.

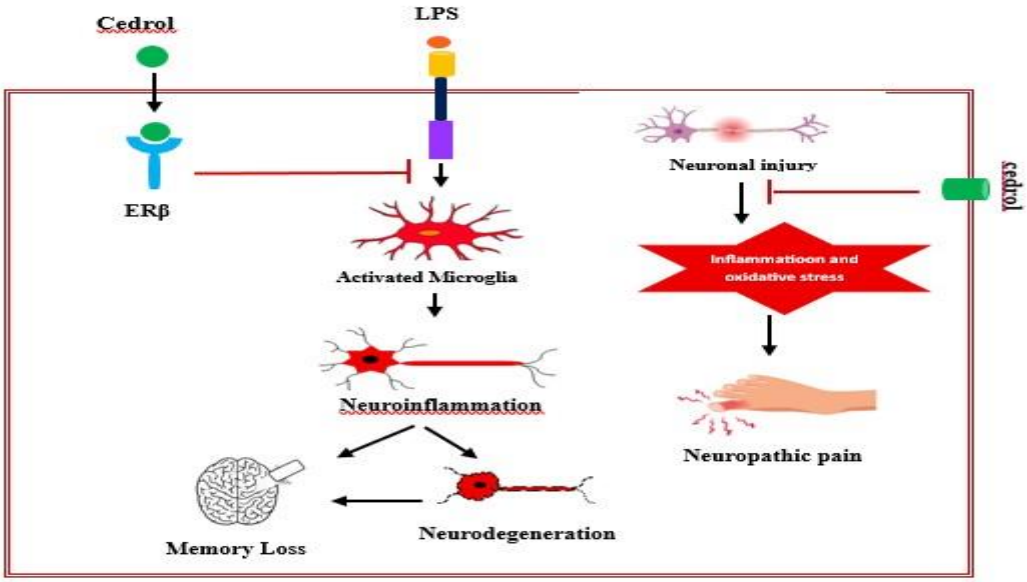

Figure 3. The mechanisms of neuroprotective effect of cedrol. LPS: lipopolysaccharide, ERβ: estrogen receptor β

Table 1. The protective effects of cedrol on the nervous system.

Does	Duration and rout of administration	Type of study	Type of rodent	Relevant disease	Effects	Reference
7.5, 15 and 30 mg/kg	One week, intraperitoneal	*In vivo*	rat	Brain injury	Improvement of the behavioral performance, reduction in level of MDA and NO and increase of content of thiol and BDNF	(Asgharzade et al. 2025)
20 and 50 µM 40 mg/kg	3 days, oral	*In vitro* *In vivo*	mice	acute cerebral ischemia	Downregulation of IL-1β, IL-6, TNFα and COX-2 expression, reduction of infarct size and mNSS, and improvement of behavioral responses	(Bi et al. 2024)
7.5, 15 and 30 mg/kg	Two weeks, oral	*In vivo*	rat	Cognitive impairment	Amelioration of memory deficits, mitigation of TNF-α, IL-1β and MDA concentration and AChE activity and elevation of thiol and SOD level	(Farimani et al. 2024)
10 and 20 mg/kg	6 weeks, oral	*In vivo*	rat	Parkinson's disease	Alleviation of cognitive and motor deficits, decline of MDA level and increment of thiol concentration and SOD activity in the striatum	(Forouzanfar et al. 2025)
1200 mg/kg	Single injection, intraperitoneal	*In vivo*	mice	Anxiety	Amelioration of behavioral responses, decrease of DA and norepinephrine concentration in stratum, hippocampus and hypothalamus	(Zhang et al. 2020)
1200 and 1600 mg/kg	Single injection, intraperitoneal	*In vivo*	mice	Anxiety	Exertion of anxiolytic effect. Decrease of 5-HIAA and DA level and ration 5HIAA/5-HT, and increase of 5-HT level and ration 3,4-DOPAC/DA	(Zhang and Yao 2019)
5 and 10 mg/kg	30 days, intraperitoneal	*In vivo*	rat	Cognitive Impairment	Amelioration of memory retention and reduction of MDA level and elevation of thiol concentration and liver enzymes	(Ghorbani et al. 2025)
20 and 40 mg/kg	14 days, intraperitoneal	*In vivo*	rat	Neuropathic pain	Alleviation of neuropathic pain and attenuation of oxidative damage and inflammation in spinal cord	(Sakhaee et al. 2020)
10 and 20 mg/kg	21 days, oral	*In vivo*	rat	Arthritis	Inhibition of pain by decreasing MDA and TNF-α and increasing thiol, SOD and glutathione peroxidase	(Forouzanfar et al. 2022)

MDA: malondialdehyde, IL: interleukin, TNFα: tumor necrosis factor alpha, COX-2: cyclooxygenase-2, mNSS: modified neurologic severity score, AChE: acetylcholinesterase, SOD: superoxide dismutase, DA: dopamine, 5HIAA: 5-hydroxyindoleacetic acid, 5HT: 5-hydroxytryptamine, DOPAC: dihydroxyphenyl acetic acid

Protective effect of cedrol on the cardiovascular, respiratory, renal, gastrointestinal, and musculoskeletal systems

Cardiac fibrosis resulting from deposition of collagen in cardiac muscle is a damaging event to the heart and induces cardiac arrythmia (Shiel et al. 2025). Compounds causing oxidative stress such as LPS also can induce cardiac dysfunction (Han et al. 2025). Pathological assessments have been also demonstrated that LPS exerts structural alterations including cardiac fibrosis (Marefati et al. 2023). In a rat model of LPS-induced inflammation, administration of LPS for two weeks caused myocardial fibrosis. Injection of cedrol at 7.5, 15 and 30 mg/kg doses before LPS treated cardiac fibrosis in rats. This cardioprotective effects of cedrol were attributed to the ability of cedrol in mitigating the level of MDA and enhancing thiol content and SOD and catalase (CAT) activity in heart tissue of rats (Rastegar-Moghaddam et al. 2024). In rats exposed to LPS, the protective impact of cedrol against lung damages resulting from LPS injection was examined. In this research, cedrol at 7.5, 15 and 30 mg/kg doses was used for 14 constative days. Then, bronchoalveolar lavage fluid (BALF) and lung tissue specimens were gathered for histopathological and biochemical evaluations. The results elucidated that cedrol at 30 mg/kg dose corrected the LPS-induced lung turbulences and mitigated the white blood cell (WBC) counts, level of MDA, NO, TNF-α and IL-1β and increased total thiol content and SOD and CAT activities (Behrouz et al. 2025). In an LPS-triggered systemic inflammation model, the reno- and hepato-protective impact of cedrol at 75, 15 and 30 mg/kg doses was studied. Biochemical measurements revealed that the level of urea, creatinine, liver enzymes and MDA was lower and the concentration of thiol and the activity of SOD and CAT were higher in rats treated by 15 and 30 mg/kg of cedrol with respect to those of control group. This protective effect of cedrol against LPS also was attributed to its antioxidant properties (Hosseini et al. 2025).

Inflammatory bowel disease (IBD) as an inflammatory ailment of gastrointestinal tract possesses symptoms including diarrhea, abdominal pain, bleeding and weight loss (Steinwurz et al. 2023). In this inflammatory disease, intestinal epithelial damage and disruption of its protective barrier leads to the entry of toxins and pathogens into the intestinal lumen and evoke inflammatory processes (Hyun 2021). Intestinal epithelial cells have a large number of mitochondria and evidence shows that mitochondrial malfunction is involved in IBD pathogenesis (Mancini et al. 2020). Xu et al evaluated the impact of 100 mg/kg dose of cedrol in a mice model of IBD caused by dextran sulfate sodium. They checked the alteration in mitochondrial biogenesis and tight junction proteins by Western blotting technique and assessed the condition gut microbiota and their metabolites. Results indicated that cedrol ameliorated mitochondrial action via enhancing ATP generation, elevating the expression of protective factors such as Nrf2, SIRT 1, PGC-1α, and mitochondrial transcription factor A (TFAM). Additionally, cedrol recovered gut microbiota and intestinal barrier integrity (Xu et al. 2026). In a study programmed by Zhao et al, cedrol at 10 mg/kg dose also alleviated dextran sulfate sodium-caused ulcerative colitis in mice. Protective impacts of cedrol were mediated through downregulating the IL-1β mRNA and repairing intestinal barrier damage by overexpression of tight junction proteins including zonula occludens 1, claudin-1and occluding (Zhao et al. 2026).

Non-alcoholic fatty liver disease (NAFLD) is a liver disorder characterized by accumulation lipids including triglyceride in liver tissue (Ghosh et al 2026). Dexamethasone as a glucocorticoid drug has been found to deposit lipids in liver tissue and to induce symptoms of NAFLD when it is administered chronically

(Liu et al. 2021). Researchers reported that cedrol at 20 mg/kg dose could exert protective effect against dexamethasone-triggered liver injuries in mice. Mitigation of lipid accumulation in liver of mice by cedrol was accompanied with downregulation of glucocorticoid receptor and genes affecting lipide metabolism including *Cd36, C/ebpβ,* and *Srebp* (Shu et al. 2025).

Sarcopenia is an age-linked musculoskeletal disorder which is characterized by loss of muscle mass and strength (Cigrovski and Ruzic 2025). Sarcopenia mainly affects elderly and sedentary individuals (do Amaral et al., 2025). Myostatin is a protein from transforming growth factor beta (TGF-β) protein family that can reduce muscle strength (Akhter et al. 2025). Therefore, myostatin can be a suitable thematic target for preventing the progression of sarcopenia (Lee 2021). In addition, muscle RING-finger protein 1 (MuRF1) has been known as a ubiquitin ligase causing protein destruction and myofibril degeneration (Ulla et al. 2024). It has been also recognized that increased level of calcium concentration exerts positive effects on maintenance of muscle mass via activating calcium/calmodulin-dependent kinase (CaMK)- FoxO3a signaling pathway (Lim et al. 2025). Kang and et al. programed a study on effect of cedrol derivative against muscle atrophy in twenty-month-old mice. For this purpose, the mice were fed by 125 mg/kg of cedrol derivative for 16 consecutive days. Besides the evaluation of muscle strength of the mice by the grip strength tests, the expression of myostatin, MuRF1 and FoxO3a and intracellular calcium concentration were assessed. *In vitro* and *in vivo* data indicated that cedrol derivative decreased the myostatin, and MuRF1 expression, and FoxO3a, and increased level of calcium and muscle strength. Overall, it was concluded that cedrol derivative prevents muscle weakness by reducing myostatin and MuRF1 expression and affecting the activation of CaMKII signaling pathway (Kang et al. 2025). Figure 4 exhibits the mechanism of therapeutic effects of cedrol on the cardiovascular, respiratory, renal, gastrointestinal and musculoskeletal systems. The protective effects of cedrol on the cardiovascular, respiratory, renal, gastrointestinal and musculoskeletal systems are collected in Table 2.

Table 2. The protective effects of cedrol on other body systems

Type of system	Duration and route administration	Does	Type of rodent	Type of study	Effects	Reference
Cardiovascular	two weeks, Intraperitoneal	7.5, 15 and 30 mg/kg	rat	*In vivo*	Alleviation of cardiac fibrosis through lowering the MDA level and elevating thiol content and CAT and SOD activity	(Rastegar-Moghaddam et al. 2024)
Respiratory	two weeks, oral	30 mg/kg	rat	*In vivo*	Mitigation of WBC counts, and MDA, NO, TNF-α and IL-1β level and increase of total thiol content and SOD and CAT activates	(Behrouz et al. 2025)
Urinary and gastrointestinal	two weeks, oral	75, 15 and 30 mg/kg	rat	*In vivo*	Reduction of urea, creatinine, liver enzymes and MDA level and enhancement of thiol concentration and of SOD and CAT activity	(Hosseini et al. 2025)
Gastrointestinal	13 days, oral	100 mg/kg	mice	*In vivo*	Amelioration of mitochondrial action via enhancing ATP generation, elevating the expression of protective factors such as Nrf2, SIRT 1, PGC-1α, and TFAM and modulation of gut microbiota and intestinal barrier integrity	(Xu et al. 2026)
Gastrointestinal	9 days, oral	10 mg/kg	mice	*In vivo*	Downregulation of IL-1β mRNA and repairment of intestinal barrier damage by overexpression of tight junction proteins including zonula occludens 1, claudin-1and occluding	(Zhao et al. 2026)
Gastrointestinal	16 days, Intraperitoneal	20 mg/kg	mice	*In vivo*	Mitigation of lipid accumulation in liver, downregulation of glucocorticoid receptor and genes affecting lipide metabolism including *Cd36, C/ebpβ, and Srebp*	(Shu et al. 2025)
Musculoskeletal	16 days, oral	125 mg/kg 3 μM	mice	*In vivo* *In vitro*	Decrease of myostatin, and MuRF1 and FoxO3a expression and increase intracellular calcium and muscle strength	(Kang et al. 2025)

MDA: malondialdehyde, CAT: catalase, SOD: superoxide dismutase, WBC: white blood cell, NO: nitric oxide, TNFα: tumor necrosis factor alpha, IL: interleukin, Nrf2: nuclear factor erythroid 2-related factor 2, SIRT1: silent information regulator sirtuin 1

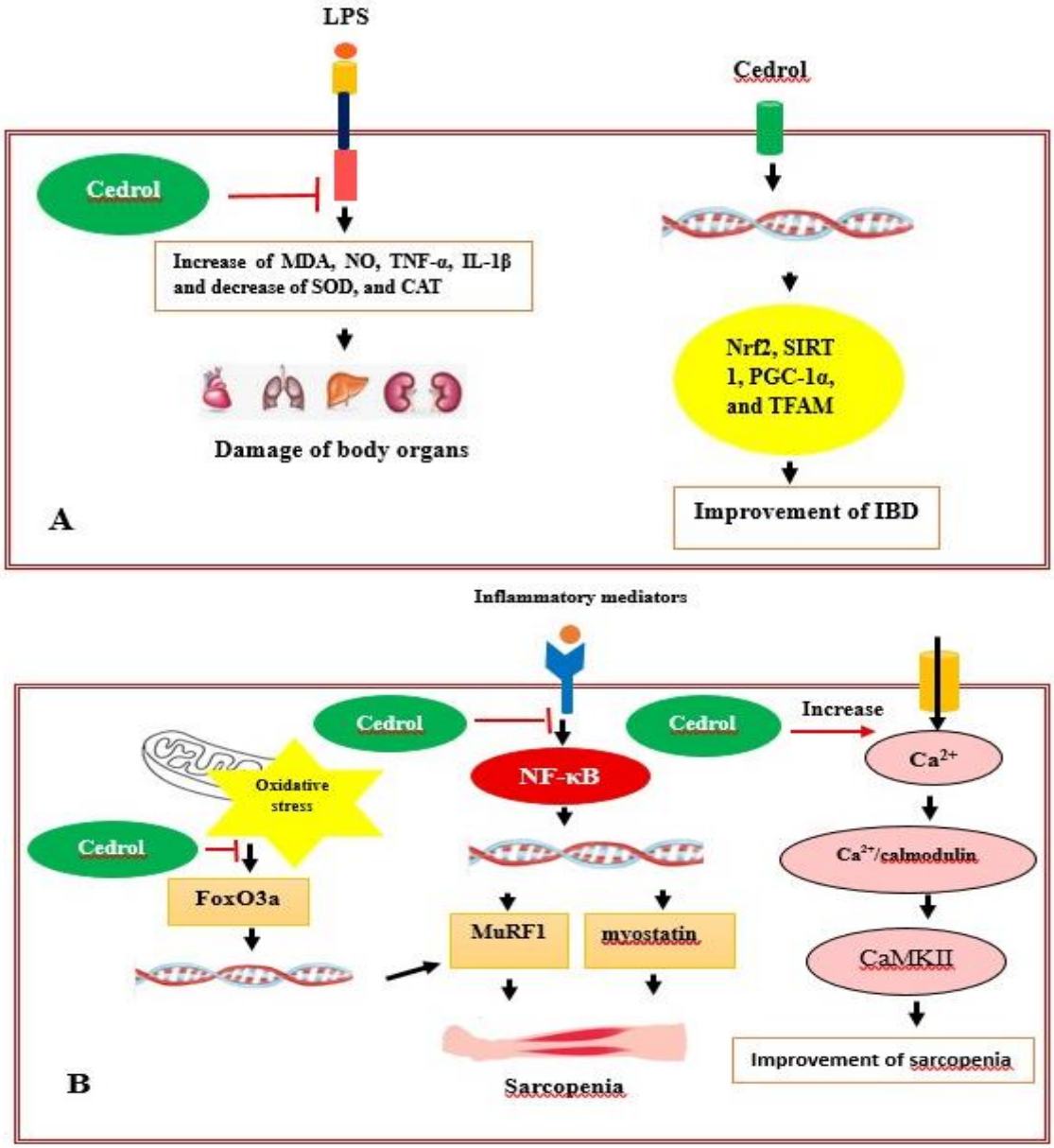

Figure 4. Mechanisms of therapeutic effects of cedrol on cardiovascular, respiratory, renal and gastrointestinal systems (A) and musculoskeletal system (B). LPS: Lipopolysaccharide, MDA: malondialdehyde, NO: nitric oxide, TNFα: tumor necrosis factor alpha, IL: interleukin, SOD: superoxide dismutase, CAT: catalase, IBD: inflammatory bowel disease, Nrf2: nuclear factor erythroid 2-related factor 2, SIRT1: silent information regulator sirtuin 1, TFAM: mitochondrial transcription factor A, NF-κB: nuclear factor kappa B, CaMK: calcium/calmodulin-dependent kinase

Anticancer effects of cedrol

Cancer is a consequence of uncontrolled growth and proliferation of cells with the potential to spread to the other organs of the body (Matsunuma et al. 2025). The target of the most of therapeutic procedures to suppress the proliferation of cancer cell is to induce apoptosis-related intracellular signaling pathways (Yang et al. 2025). Some mechanisms involved in apoptosis that are targeted by anticancer drugs include inhibition of DNA replication, halting cell cycle, modulation of redox balance and reduction of antiapoptotic molecules such as Bcl2 (Yilmaz et al. 2010). Natural compounds have been listed as one of therapeutic strategies for treating the cancer cells (Roohi et al. 2023). As a natural product, cedrol has been shown to be as an attractive

candidate for treatment of cancer in both *in vitro* and *in vivo* studies. Mishra et al., in an *in vitro* study exposed the human leukemia K562 and colon cancer HT-29 cell line to cedrol at 100 and 200 µM doses for 48 hr. Cedrol effectively triggers apoptosis in both cancer cell lines through the intrinsic (mitochondrial) and extrinsic (death receptor) pathways. Molecular results showed that cedrol increased apoptosis by activating pro-apoptosis proteins such as BID and BAX, and inhibiting anti-apoptotic molecules including Bcl-2, XIAP and Bcl-XL, and upregulating caspase 9. Cedrol also inhibited cell survival by affecting PI3/AKT/mTOR/ERK1/2 and NF-κB signaling pathways (Mishra et al. 2021). Anticancer impact of cedrol at 5, 20 and 40 µM on A549 human lung carcinoma cells was evaluated. In order to evaluate the cell viability, mitochondrial transmembrane potential (MTP) and lactate dehydrogenase (LDH) assessments were carried out. Morphological changes of cells were also checked using an inverted phase contrast microscope. In this study, cedrol triggered autophagy in a dose-dependent manner by decreasing MTP, downregulating PI3K and Akt, and upregulating ROS (Zhang et al. 2016). In *in vitro* study conducted by Chien et al, the HT-29 (human colorectal adenocarcinoma) cells and CT-26 cells were treated by cedrol at 0, 14, 28, 56, 112, 225, and 450 µM or 5-fluorouracil at 0, 24, 48, 96, 192, and 384 µM doses for 24, 48 and 72 hr. Then MTT (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide), TUNEL and flow cytometry assays were used to evaluate cell viability, cell cycle arrest, and apoptosis and western blotting was employed to assess the expression of protein. Cedrol time- and dose-dependently suppressed cell proliferation of HT-29 and CT-26, stoped cell cycle at the G0/G1 phase through affecting CDK4 and cyclin D1 and induced apoptosis by activating extrinsic (FasL/caspase-8) and intrinsic (Bax/caspase-9) pathways. In this study, the simultaneous use of cedrol with 5-fluorouracil resulted in a stronger inhibitory impact on cell proliferation of colorectal cancer (Chien et al. 2022).

Minichromosome maintenance (MCM) proteins are a group of essential regulatory proteins for DNA replication in eukaryotic cells. These proteins have been known to be as an important biomarker for tracking and treating cancer cells (Cao et al. 2025). Yun et al examined the effect of different concentration of cedrol (0, 5. 10, 15, 20 and 25 µg/mL) on the expression of MCM, cell cycle arrest and apoptosis in human lung carcinoma A549 cells. Treatment with cedrol at 15, 20 and 25 µg/mL doses was associated with reduction of MCM proteins expression, decrement of cell viability, inhibition of cell cycle in G1 phase and induction of apoptosis (Yun et al., 2022). In a similar study, human colorectal cancer HT29 cells were incubated with concentration 0, 5. 10, 15, 20, 25 and 30 µg/mL of cedrol for 24 or 48 hr. According to the results, cedrol at 20, 25 and 30 µg/mL doses downregulated the expression of MCM proteins, stopped cell cycle in G1phase and stimulated programmed cell death (Jin et al. 2022).

Glioblastoma (GBM) is a kind of cancer that results from irregular growth of astrocytes in the brain or spinal cord that spreads rapidly and invades healthy organs (Durga and Pusapati 2026). Evidence shows that GBM can take place at different ages, however it usually occurs in old age. Reports also confirm that glioblastoma is resistant to chemotherapy drugs (Shirokov et al. 2025). Chang et al designed a study for estimating the antitumor activity of cedrol at 89.5 µM dose against GBM cells. Evaluations specified that cedrol applied its therapeutic effects via modulation of ROS generation, inhibition of cell cycle, induction of apoptosis and regulation of AKT/mTOR pathway activity. In this study, the anticancer impact of cedrol combined with temozolomide, an antineoplastic drug, was also checked. The results illuminated that cedrol amplified temozolomide effect through affecting the

androgen receptor and blocking cell growth caused by 5α-dihydrotestosterone (Chang et al. 2020).

Angiogenesis is a process in which new vessels grow from existing vessels. Angiogenesis is also considered an important marker in the process of tumor metastasis (Tan et al. 2025). Vascular endothelial growth factor (VEGF) has also been documented to be as a key factor of angiogenesis in GBM, colon, lung and breast cancers (Ghalehbandi et al., 2023). VEGF possesses two types receptors including VEGFR1 and VEGFR2 (Wang et al. 2025). The binding of VEGF to VEGFR2 leads to the activation of signaling pathways causing cell proliferation including PI3K/AKT/mTOR and MAPK/ERK pathways (Yu et al. 2020). In addition, downregulation of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and matrix metalloproteinases (MMPs) prevents angiogenesis and proliferation of cancer cells (Ansardamavandi et al. 2025; Allmang et al. 2025). In order to determine the mechanism of effects of cedrol against VEGF-induced angiogenesis, the human umbilical vein endothelial cells (HUVECs) were incubated by cedrol at 0-112 µM for 24 hr. The results indicated that treatment with cedrol suppressed dose-dependently VEGF-stimulated phosphorylation of ERK, AKT and P70S6K proteins and downregulated the expression of VCAM-1, ICAM-1 and MMP-9. This fining proposes that the antitumor impact of cedrol on HUVECs can be attributed to its ability in regulating the activity of MAPK/ERK and mTOR/PI3K/AKT signaling pathway (Chang et al. 2023). Figure 5 demonstrated anticancer effects of cedrol. The anticancer effects of cedrol are illustrated in Table 3.

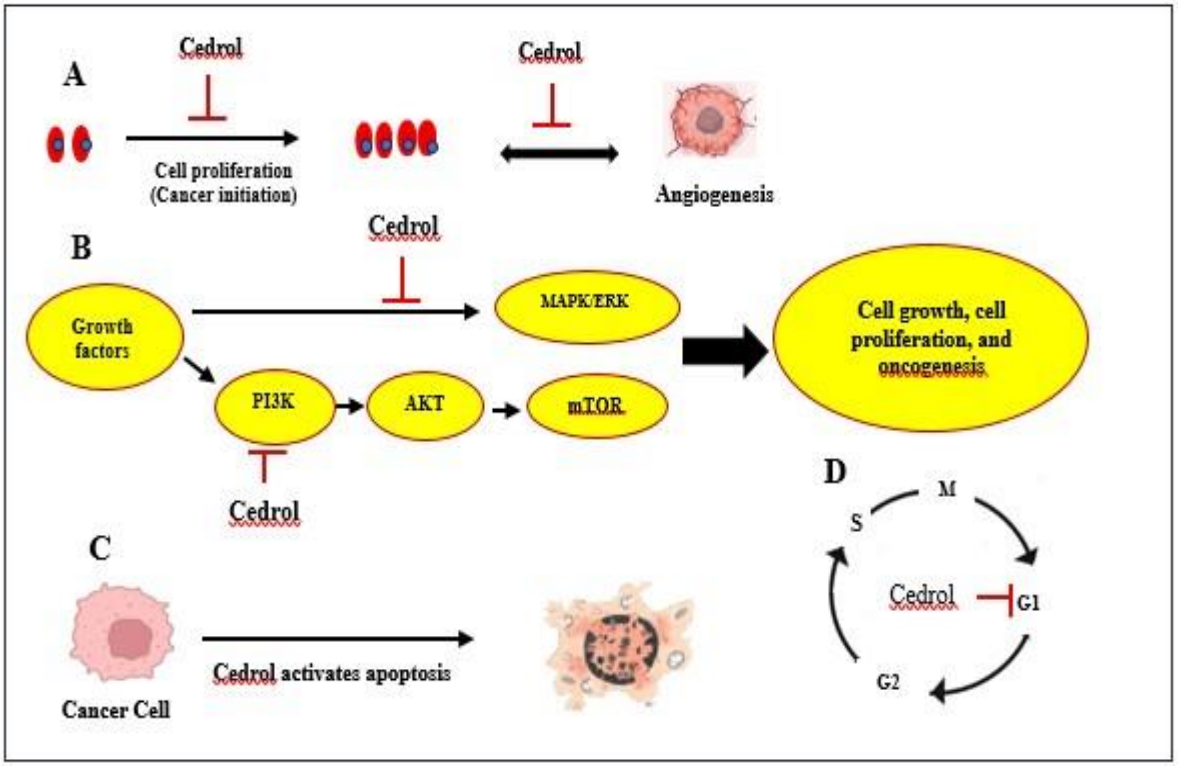

Figure 5. Mechanisms of anticancer effects of cedrol. A: inhibition of cell proliferation and angiogenesis, B: suppression of MAPK/ERK and PI3K/AKT/mTOR signaling pathways causing cell growth, cell proliferation and cancer, C: induction of apoptosis, and D: cell cycle arrest in G1 phase. MAPK: mitogen-activated protein kinase, ERK: extracellular-signal-regulated kinase, PI3K: phosphatidylinositol 3-Kinase, mTOR: mammalian target of rapamycin

Table 3. The anticancer effects of cedrol

Type of cells	Dose	Duration of treatment	Mechanism of effect	Reference
K562 and HT-29	100 and 200 µM	48 hr	Induction of apoptosis, upregulation of pro-apoptosis proteins such as BID and BAX, and downregulation of anti-apoptotic molecules such as Bcl-2, XIAP and Bcl-XL, upregulation of caspase 9, and inhibition of cell survival by affecting PI3/AKT/mTOR/ERK1/2 and NF-κB signaling pathways	(Mishra et al. 2021)
A549	5, 20 and 40 µM		Decrease of MTP, downregulation of PI3K and Akt, and upregulation of ROS	(Zhang et al. 2016)
HT-29 and CT-26	14, 28, 56, 112, 225, and 450 µM	24, 48 and 72 hr	Suppression of cell proliferation, inhibition of cell cycle at the G0/G1 phase, and induction of apoptosis	(Chien et al. 2022)
A549	15, 20 and 25 µg/mL	48 hr	Reduction of MCM proteins expression, and cell viability, inhibition of cell cycle in G1 phase and induction of apoptosis	(Yun et al. 2022)
HT29	20, 25 and 30 µg/mL	24 and 48 hr	Downregulation of MCM expression, stop of cell cycle in G1phase and stimulation of programmed cell death	(Jin et al. 2022)
GBM	89.5 µM	24 and 48 hr	Modulation of ROS generation, inhibition of cell cycle, induction of apoptosis and regulation of AKT/mTOR pathway activity	(Chang et al. 2020)
HUVEC	0-112 µM	24 and 48 hr	Suppression of VEGF-stimulated phosphorylation of ERK, AKT and P70S6K proteins and downregulation of VCAM-1, ICAM-1 and MMP-9 expression.	(Chang et al. 2023)

MAPK: mitogen-activated protein kinase, ERK: extracellular-signal-regulated kinase, PI3K: phosphatidylinositol 3-kinase, mTOR: mammalian target of rapamycin, NF-κB: nuclear factor kappa B, MTP: mitochondrial transmembrane potential, ROS: reactive oxygen species, MCM: minichromosome maintenance, VCAM: vascular cell adhesion molecule, ICAM: intercellular adhesion molecule-1, MMP: matrix metalloproteinase

Discussion

In recent reports, the protective and anticancer effects of cedrol and its intracellular signaling mechanisms have been evaluated. The protective mechanisms of cedrol on body systems are mainly mediated through alleviation of inflammation and amplification of antioxidant defense. The most important inflammatory pathway targeted by cedrol is NF-κB signaling pathway. Memory enhancing effect of cedrol is also attributed to its ability in decreasing AChE activity and increasing the level of BDNF. Activation of ERβ has been suggested to have protective impact against neuroinflammation. Evidence shows that a part of neuroprotective properties of cedrol is mediated through binding to ERβ and downregulating the expression of IL-1β, IL-6, TNF-α and COX2. Cedrol also alleviates IBD by increasing the expression of Nrf2, SIRT 1, PGC-1α, and TFAM. The scientific findings indicate that downregulation of myostatin, MuRF1, and FoxO3a and upregulation of CaMKII signaling pathway by cedrol can lead to improvement of sarcopenia. In addition, the anti-cancer mechanisms of cedrol include induction of intrinsic and extrinsic pathways of apoptosis, cycle cell arrest, inhibition of PI3K/AKT/mTOR/ERK1/2 pathway and angiogenesis, and stimulation of autophagy. Despite all these findings, the therapeutic impact of cedrol has not been understood in clinical studies. Therefore, preclinical researchers need to determine the safety of cedrol.

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Conflicts of interest

The authors had no competing interests.

Code of Ethics

IR.KMU.REC.1404.530

Authors' Contributions

Reza Nosratabadi: Data collection, writing manuscript draft, editing manuscript. Siyavash Joukar: Preparing and editing manuscript. Gholamreza Sepehri:

Preparing and editing manuscript. Akbar Anaeigoudari: Conceptualization, data collection, writing manuscript draft, editing manuscript.

Abbreviations

IL: interleukin
ROS: reactive oxygen species
NF-κB: nuclear factor kappa B
MAPK: mitogen-activated protein kinase
BDNF: brain-derived neurotrophic factor
GDNF: glial cell line derived neurotrophic factor
LPS: lipopolysaccharide
COX: cyclooxygenase
Erβ: estrogen receptor β
mNSS: modified neurologic severity score
TNF-α: tumor necrosis factor alpha
AChE**:** acetylcholinesterase
SOD: superoxide dismutase
MDA: malondialdehyde
PD: Parkinson's disease
DA: dopamine
5HT: 5-hydroxytryptamine
5HIAA: 5-hydroxyindoleacetic acid
DOPAC: dihydroxyphenyl acetic acid
CAT: catalase
IBD**:** inflammatory bowel disease
Nrf2: nuclear factor erythroid 2-related factor 2SIRT: silent information regulator sirtuin
TFAM: mitochondrial transcription factor A
NAFLD: non-alcoholic fatty liver disease
TGF-β: transforming growth factor beta
MURF1: muscle RING-finger protein-1
CaMK: calcium/calmodulin-dependent kinase
PI3K: phosphatidylinositol 3-kinase
mTOR: mammalian target of tapamycin
ERK: extracellular-signal-regulated kinase
MTP: mitochondrial transmembrane potential
MCM: minichromosome maintenance
GBM: Glioblastoma
VCAM: vascular cell adhesion molecule
ICAM: intercellular adhesion molecule
MMP**:** matrix metalloproteinase

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