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Review

Promising Neuroprotective Effects of *Dracocephalum* Species: Mechanistic Perspectives

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Abstract

Neurological diseases have important effects on morbidity and mortality rates. Natural products offer various health benefits, and *Dracocephalum* species, belonging to the Lamiaceae family, have been traditionally used for several therapeutic values. The genus *Dracocephalum* and its metabolites have demonstrated numerous pharmacological activities such as antioxidative, anti-inflammatory, antiviral, antiparasitic, antibacterial, antifungal, nephroprotective, hepatoprotective, neuroprotective, gastroprotective, cardioprotective, antiapoptotic, and anticancer effects. *Dracocephalum* spp. contain phytosterols, polysaccharides, coumarins, alkaloids, phenolic acids, flavonoids, and terpenes. This review explores the potential neuroprotective effects of *Dracocephalum* spp. by evaluating the mechanisms and signaling pathways involved. The role of the genus *Dracocephalum* was investigated in relation to various neurological conditions such as Alzheimer's disease, insomnia, Parkinson's disease, vascular dementia, cerebral ischemia, pain, depression, and glioblastoma. These findings suggest that *Dracocephalum* spp. and their phytochemicals have neuroprotective effects by targeting the regulation of various pathways. Therefore, clinical trials should be performed to confirm the *in vitro* and animal findings.

Keywords: *Dracocephalum*; Flavonoids; Lamiaceae; Neurological disorders; Neurodegenerative diseases; Traditional Medicine

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Introduction

Medicinal plants play a crucial role in treating various disorders owing to their possession of specific phytochemical compounds that can target diverse biological mechanisms. Phytochemical analyses have revealed natural bioactive metabolites with potential protective functions that participate in two therapeutic approaches: a) one molecule-one target, and b) multi-target directed ligands. The intricate and structurally diverse nature of natural products makes them suitable for serving as leads in drug discovery because of their appropriate selectivity and specificity [1-3].

The Lamiaceae family is considered to be one of the most significant flowering plant families due to its vast number of species and diverse characteristics. The family consists of seven subfamilies distributed worldwide [4], approximately 240 genera, and 7000 species. Most of these species are fragrant and are used as cosmeceuticals, flavors, nutraceuticals, teas, and hydrolates [5]. Plants belonging to this family have shown a vast variety of biological and pharmacological effects [5-9]. The Lamiaceae family encompasses a genus known as *Dracocephalum* L., commonly referred to as "Dragonheads," which includes over 60 species [4,10,11]

The majority of *Dracocephalum* species are aromatic herbaceous perennials, commonly found inhabiting high-altitude and semi-arid regions [12-16].

A great number of secondary metabolites have been isolated and identified in the aforementioned genus. The difference in the expression of particular genes involved in the biosynthesis pathways of available metabolites in various species of a genus is one of the hypotheses related to the observation of diverse metabolite profiling in them. However, medicinal plants belonging to the same genus have numerous similarities in their secondary metabolites due to the same metabolic pathways. Metabolite analyses show that the main constituents isolated from the extracts, essential oils, and hydrolats of *Dracocephalum* spp. consist of phytosterols, vitamins, amino acids, proteins, oxylipins, fatty acids, naphthalene derivatives, cyanogenic glucosides, polysaccharides, coumarins and furanocoumarins, carotenes, alkaloids, lignans, tannins, stilbenes, phenolic acids, flavonoids, aliphatic/aromatic carboxylic acids, phenols, phenylpropanoids, diterpenoids, triterpenoids, sesquiterpenes, and oxygenated and hydrocarbonated monoterpenes [17-33]. These main groups of phytochemicals are accounts for neuroprotective, antihyperlipidemic, hepatoprotective, anti-inflammatory, antimicrobial [34,35], gastroprotective, anticancer, sedative, antinociceptive [36], antispasmodic, antioxidant, and cardioprotective effects of the genus [37].

In this review, the pharmacological properties of the *Dracocephalum* genus are extensively studied. Following this, we investigated the neuroprotective effects of various species of *Dracocephalum* in the context of neurological disorders.

Methods

This review is based on experimental data from studies regarding the use of *Dracocephalum* species and their metabolites as neuroprotective agents. The articles' publication dates were not restricted, as both older and more recent scientific findings reinforce the discussed matter. For this study, various scientific databases such as PubMed, Scopus, Google Scholar, SID, Embase, and Web of Science were used, employing specific keywords including "*Dracocephalum*", "neuro*", "Alzheimer's disease", "Parkinson's disease", "vascular dementia", "cerebral ischemia", "pain", "insomnia", "neurotoxicity", and "glioblastoma. The search was conducted until June 6, 2024. To be considered eligible, research articles had to meet certain criteria, namely that they presented results attributing the function of *Dracocephalum* species or their bioactive compounds in neuroprotection. Contrariwise, certain exclusion criteria were established, for example ignoring articles in languages other than English and Persian. Furthermore, missing full-text access and articles deprived of a concise description of their purpose were not included in our study.

Applications in Ecology and Food Technology

It has been demonstrated that *Dracocephalum* plants contain essential oils (EO) that possess insecticidal properties. The essential oil derived from *D. kotschyi* was found to effectively combat green peach aphids, whereas the essential oils of *D. foetidum*, *D. fruticztlosum*, *D. moldavica*, *D. peregrinum*, and *D. ruyschiana* showed strong insecticidal effects on mosquito larvae [38,39].

A recent study conducted by Pouresmaeil et al., 2022 discovered that the EO of *D. moldavica* has the potential to be used in the bio-herbicides industry because of its notable phytotoxic and weed-killing effects [40]. The principal components found in *D. integrifolium* EO, namely eucalyptol and sabinene, are considered to be the key active ingredients responsible for insecticidal activity [41]. *D. moldavica* EO revealed convincing fumigant toxicity against *Sitophilus zeamais* and *Tribolium castaneum* adults [41]. *D. polychaetum* EO and its components can be advantageous as acaricides in managing the populations of *Tetranychus urticae* mites [42].

The utilization of HPMC-based films encompassing alginate and *D. moldavica* EO presents a promising alternative to synthetic packaging due to their superior antioxidant potential, enhanced water barrier characteristics, and applicable mechanical properties [43]. The novel biopolymer derived from *D. moldavica* seed

mucilage is also a viable option for the production of biodegradable edible films with antioxidant properties and no visible defects [44].

The potential use of *Dracocephalum* spp. as preservatives in food/cosmetics or as functional components in nutraceuticals is worth considering [45]. The incorporation of *D. moldavica* seed bagasse in ice cream formulations results in an increase in dry matter, fat, and protein content while simultaneously improving physical properties such as hardness, adhesiveness, viscosity, and reducing melting rate [46].

In comparison to the control sample made entirely of semolina, pasta containing defatted flour of *D. moldavica* (Moldavian dragonhead), a by-product that is derived from the process of oil extraction, cooks more slowly and loses less moisture during the cooking process. However, *D. moldavica* can be added to the pasta at a concentration of 10 g/100 g to produce a high-nutrient and sensory-acceptable product. *D. moldavica* offers a nutritional boost of 145% in dietary fiber, 5.8% in proteins, and 50% in minerals at this level of addition without impairing the cooking or sensory qualities of the pasta. A sensory acceptance index of 88% is obtained from this formulation. Linolenic (62.21%) and linoleic (20.39%) acids are highly present in the beneficial fatty acid composition of *D. moldavica*. Therefore, consumers looking for a healthier diet can use pasta that has been fortified with *D. moldavica* [47].

Fried snacks fortified with a seed composition of 22% exhibited the most elevated levels of polyphenolic compounds and free phenolic acids as well as the highest degree of radical scavenging activity [48]. Crisps were enriched with 5-20% dragonhead leaves, causing ameliorated nutritional value and augmented dietary fiber content. The presence of rosmarinic acid resulted in the demonstration of potent antioxidant properties and effectively scavenged free radicals in the test snacks with higher amounts of additives. The inclusion of the additive also impacted the physical characteristics of the snacks, attenuating water absorption, expansion coefficients, and solubility, while enhancing cutting strength, bulk density, and breaking index. The maximum viscosity was witnessed at 5 and 10% additions. The snacks exhibited reduced brightness and increased greenness as dragonhead leaves were incorporated in greater amounts. Sensory evaluation revealed favorable acceptance for snacks enriched with up to 15% dried *D. moldavica* leaves [49].

Compared to the control, adding 6 g/100 g *D. moldavica* to the bread recipe led to notable increases in dietary fiber (59%), fat (32%), and minerals (50%), accompanied by significant alleviations in the contents of carbohydrates and energy [50].

Enriching wheat flour with *D. moldavica* powder affected an upsurge in the flour water absorption resulting in attenuation of the dough's tolerance. Nonetheless, the bread yield augmented while the crumb volume declined as a consequence. Interestingly, the bread's textural properties remained principally unaltered by the addition of *D. moldavica*. Due to the inclusion of *D. moldavica*, the crumb's lightness decreased; while its greenness and yellowness increased. Additionally, the total phenol content and antioxidant activity of the bread increased due to the presence of *D. moldavica* [51].

Traditional and Pharmacological Uses

Dragonheads have a long history regarding individual ethnopharmacological applications as medicinal herbs and have played an important role in traditional Uyghur medicine for centuries [4,52]. Some species of *Dracocephalum* are employed as traditional Chinese medicine (TCM) for the treatment of hepatitis, throat-swelling diseases, lymphadenitis, flu fever, and acute/chronic tracheitis [53].

D. moldavica is commonly used in TCM to treat liver-related conditions, headaches, digestive problems, and respiratory congestion. A clinical trial in the TCM field demonstrated that the aqueous extract of *D. moldavica* effectively treated cardiovascular diseases, insomnia, asthma, fatigue, and neurasthenia [54]. In Tibet, *D. nutans* has been traditionally used to treat liver and stomach diseases [15].

In traditional Persian medicine (TPM), hydrolate and decoction of *D. moldavica* are used as a heart tonic, antiflatulent, diaphoretic, sedative, anti-emetic, and vermifuge [55]. In TPM and native culture, *D. kotschyi* is cast off as an additive to enhance the taste and fragrance of drinks and foods, in addition to its use as antinociceptive, antipyretic, tonic, decongestant, carminative, and anti-inflammatory in the form of decoction and infusion [55-58]. *D. moldavica* has been utilized in the ethnomedicine of Europe for the treatment of hypertension and heart disease [15].

Increasing evidence demonstrates that *Dracocephalum* spp. possess health-promoting effects, including neuroprotective (anti-dementia, sedative, antinociceptive, and antidepressant effects), antioxidant, anti-complementary, antigenotoxic, antibacterial, antifungal, hepatoprotective, nephroprotective, antifibrotic, bronchodilator, virucidal, anti-inflammatory, anti-arthritis, hypotensive, cardioprotective, antihyperlipidemic, antidiabetic, anti-toxoplasma, anti-trichomonas, and anticancer effects [59].

Neuroprotective Effects

The genus *Dracocephalum* has protective effects against neurological conditions such as vascular dementia, Alzheimer's disease, insomnia, Parkinson's disease, cerebral ischemia, pain, and glioblastoma (Figure 1 and Table 1). The structural formula of

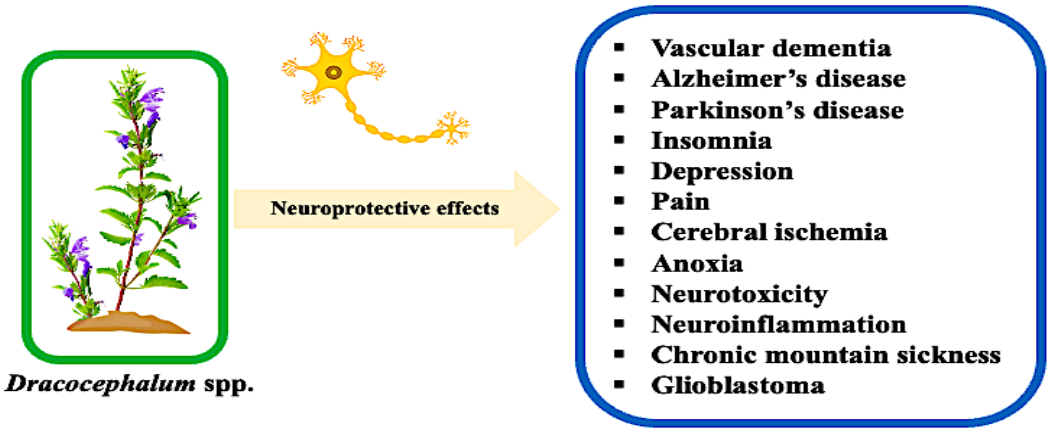

Figure 1. Neuroprotective effects of *Dracocephalum* species.

chemical compounds with neuroprotective effects which are derived from the *Dracocephalum* genus is shown in figure 2.

Vascular Dementia

Vascular dementia (VaD) is a type of dementia that exhibits heterogeneity concerning both clinical phenotype and pathogenic mechanisms. Although VaD has a slightly higher mortality rate and slower progression than Alzheimer's disease, it is still a significant public health problem. In a study conducted on rats with vascular dementia induced by oxygen-glucose deprivation (OGD), the administration of *D. moldavica* at doses of 20 and 40 mg/kg orally for a period of four weeks resulted in an increase in superoxide dismutase (SOD) and glutathione peroxidase (GPx) levels, as well as a decrease in malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), and 3-nitrotyrosine (3-NT) levels. The treatment also restored the hippocampal phosphorylated calcium/calmodulin-dependent protein kinase II

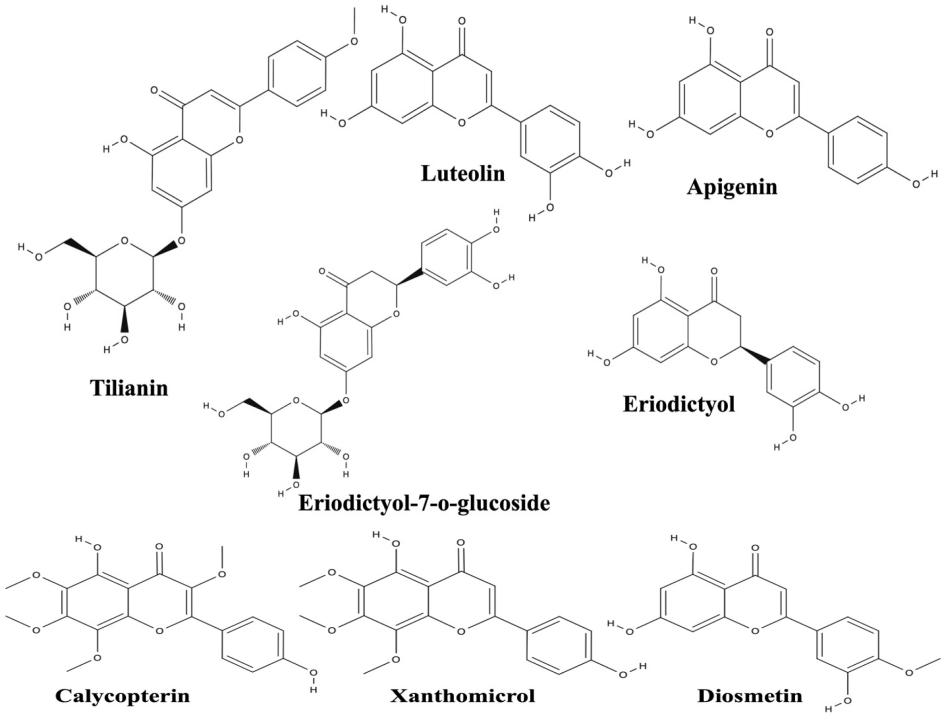

Figure 2. Chemical structures of neuroprotective compounds isolated from *Dracocephalum* spp.

Table 1. Neuroprotective potential of *Dracocephalum* spp.

Neurological disorder	Plant	Used part	Study characteristics	Model	findings	Ref.
Vascular dementia	*D. moldavica*	Tilianin	20 and 40 mg/kg, p.o. 4 weeks	OGD-induced vascular dementia in rats	↑SOD, ↑GPx, ↓MDA, ↓4-HNE, ↓3-NT, restored hippocampal p-CaMKII/ERK1/2/CREB signaling, repressed ox-CaMKII/p38 MAPK/JNK/NF-κB connected inflammatory response	[60]
Vascular dementia	*D. moldavica*	Total flavonoids, tilanin	TFDM (25–100 μg/ml), tilianin (8–32 μM), luteolin (2.5–10 μM), and apigenin (2.5–10 μM)	SH-SY5Y, *in vitro* OGD model	Upregulated miR-3184-3p and downregulated miR-6875-5p in OGD-injured cells, ↑cell viability	[61]
Alzheimer's disease	*D. moldavica*	Total flavonoids extract	200 mg/kg, p.o., 12 weeks	APP and PS1 double transgenic mice and copper-injured APP Swedish mutation overexpressing SH-SY5Y cells	↓Cognitive impairments and neurodegeneration, ↑antioxidant defense system in APP/PS1 mice, ↓Aβ burden, preserved the ERK/CREB/BDNF pathway both in vitro and in vivo	[62]
Alzheimer's disease	*D. moldavica*	EtOH extract	12.5, 25, 50, 100 mg/kg, p.o., 24 h	Scopolamine-induced cognitive impairment in mice	Ameliorated the step-through latency reduction in the PAT, ↓memory impairment in the MWM task, ↑phosphorylation levels of ERK and CREB in the hippocampus	[63]
Alzheimer's disease	*D. moldavica*	Hydroalcoholic extract	1, 10, and 100 μg/mL	Aβ-induced toxicity in PC12 cells	↓MDA, ↑GPX, ↓ROS	[64]
Alzheimer's disease	*D. moldavica*	Total flavonoids extract	TFDM	$A\beta_{1-42}$-activated C8-D1A astrocytes	Inhibited inflammatory secretion in reactive astrocytes	[65]
Alzheimer's disease	*D. multicaule*	MeOH extract	5 μg/mL	In vitro	AChE inhibition=78.5 ± 3.7%	[66]
Alzheimer's disease	*D. rupestre*	Eriodictyol	20, 40, and 80 μM	$A\beta_{25-35}$-induced oxidative cell death in primary neurons	↓JNK/p38 apoptotic signaling pathway, activated Nrf2/ARE signaling pathway	[67]
Alzheimer's disease	*D. heterophyllum*	Samwinol	1–80 μM	$A\beta_{25-35}$-induced neuroinflammation in PC-12 cells	Suppressed ERK/AKT phosphorylation, activated Nrf2/HO-1 signaling pathway	[68]
Parkinson's disease	*D. moldavica*	Tilianin	3, 10, 30 μM	MPP^+-stimulated MES23.5 cells	↓IL-6, IL-1β, and TNF-α mRNA expression, ↓ROS, ↓MnSOD, and CAT protein expression levels, inhibited the MAPK signaling pathway	[69]
Sleep disorder	*D. moldavica*	Aqueous extract of DM	1, 10, 50, 100, 200 mg/kg, i.p., 60 min	Sodium pentobarbital-induced sleeping time in mice	↓Animals' general activity, motor coordination, and exploration	[70]
Depression	*D. moldavica*	EtOH extract	80, 100 mg/kg, p.o.	Immobility-induced depression in CD-1 mice	Antidepressive effects	[71]

Pain	*D. polychaetum*	Aqueous extract	25, 50, 100 and 200 mg/kg, i.p.	Formalin-induced pain in rats	Analgesic effects	[72]
Pain	*D. kotschyi*	Essential oil	3.125, 6.25, 12.5, 25, 50, 75, 100, and 400 mg/kg, i.p.	Acetic acid-induced pain in mice	Anti-nociceptive effects	[73]
Pain	*D. moldavica*	Essential oil	5, 10, 20 mg/kg, i.p.	Acetic acid and formalin-induced pain in mice	Analgesic properties	[74]
Cerebral ischemia-reperfusion	*D. moldavica*	Hydroalcoholic extract of DM	25, 50, 100 mg/kg, p.o., 5 days	MCAO rats	↑Neurobehavioral scores, ↓cerebral edema and infarction, ↓MDA, ↑SOD and GSH-Px, ↓IL-6, IL-8, and TNF-α	[75]
Cerebral ischemia reperfusion	*D. moldavica*	Total flavonoids	25, 50, 100 mg/kg, p.o., 5 days	MCAO rats	↑Number of viable neurons, ↓gene expression levels of p53 and protein expression levels Bax, ↑protein expression levels of Bcl-2	[76]
Cerebral ischemia-reperfusion	*D. moldavica*	Total flavones	25, 50, 100 mg/kg, p.o., 5 days	MCAO rats	↓TNF-α and IL-6, ↓protein expression levels of caspase-3 and AMPK	[77]
Cerebral ischemia	*D. moldavica*	Total flavonoids	12.5, 50. 25 mg/kg, p.o., 5 days	MCAO rats	↑GSH/GSSG ratio, ↑SOD, CAT, GPX, ↓MDA, carbonyl, and 8-OHdG contents	[78]
Cerebral ischemia	*D. rupestre*	Eriodictyol-7-O-glucoside	30 mg/kg, 5 days 20, 40, 80 μM	MCAO rats, primary cultured astrocytes exposed to transient OGD	Upregulated Nrf2, NQO-1, HO-1 and γ-GCS	[79]
Cerebral ischemia	*D. rupestre*	Eriodictyol	1, 2, and 4 mg/kg, p.o. 5 days	MCAO mice	Prevented neuronal death, ↓infarct area and memory deficits, ↓MPO activity and TNF-α, iNOS, and GFAP expression	[80]
Ischemic brain injury	*D. rupestre*	Eriodictyol	20, 40, 80 mg/kg, p.o., 14 days	MCAO rats	↓IL-6, TNF-α, IL-10, and TGF-β1, inhibited the reduction of p62 and increased ATG5, Beclin1, and LC3 protein conversion, altered LC3, Bax, and cleaved-caspase-3, ↑Bcl-2 and Ki67	[81]
Cerebral ischemia	*D. tanguticum*	BuOH-soluble fraction	30 mg/kg, p.o., 7 days	MCAO rats	Modulated the mRNA expression and protein synthesis of BDNF and NT-3, MDA, ↑SOD, CAT, and GSH-Px, facilitated the neurobehavioral recovery	[82]
Cerebral ischemia	*D. moldavica*	Tilianin	1, 3, 10, 30 μM	OGD-induced neuro-cytotoxic injury in SH-SY5Y cells	↓CaMKII-linked signaling mediated *via* mitochondria and p38/JNK/NF-κB cascades	[83]
Cerebral ischemia	*D. moldavica*	Effective parts	-	Z-VAD-FMK plus OGD/R injury in HBMECs	Inhibited RIP3/MLKL/PGAM5 pathway	[84]

Anoxia	*D. tanguticum*	Aqueous extract	i.p.	Mice model	Prolonged duration of gasping following decapitation in mice, as well as the survival time of mice with bilateral ligation of the carotid artery, exhibited protective effects against brain pathology in rats subjected to high-altitude hypoxic conditions	[85]
Oxidative stress	*D. rupestre*	Eriodictyol	20, 40, and 80 μM	H_2O_2-induced neurotoxicity in PC12 cells	upregulated HO-1 and γ-GCS expression *via* activation of the Nrf2/ARE pathway	[86]
Oxidative stress	*D. kotschyi*	Calycopterin	25, 50, and 100 μM	H_2O_2-induced neurotoxicity in PC12 cells	Prevented the MMP decrease, suppressed cytochrome C release to the cytosol, inhibited decrease in GSH level and SOD activity, ↑γ-GCS and HO-1 levels modulated the level of CREB phosphorylation and Nrf2 pathway	[87]
Glioblastoma	*D. kotschyii*	Xanthomicrol	200 mg/mL	A172 cells	Cytotoxic effects	[88]
Glioblastoma	*D. tanguticum*	Chloroform extract	90 μg/mL	T98G cells	Cytotoxic effects, induced cell apoptosis via Caspase-3 and Bax pathways, inhibited p21	[89]
Glioblastoma	*D. moldavica*	Total flavones	100, 50, 25, 12.5, 6.25, 3.13, and 1.56 μg/mL	H_2O_2-induced apoptosis in astrocytes, human glioma cell line U87	↓MDA, ↓LDH, ↓mRNA expression of Bax, Caspases-9 and -12, p38MAPK, and CaMKII ↑mRNA expression of mTOR	[90]
Glioblastoma	*D. peregrinum*	Diosmetin	5, 10, 20 μg/mL, i.v.	Human glioma cell lines U251, U138, and T98, BALB/c nude mice	↑Expression of E-cadherin via the TGF-β signaling cascade effectively hampers the malignant metastasis and invasion of glioma cells.	[91]
Chronic mountain sickness	*D. moldavica*	Total flavonoids	100, 200, 400 mg/kg, p.o.	Rats model of CMS	Improved pathological changes in brain tissue, such as expansion of the meninges, heightened blood flow, swelling of the brain's parenchyma, infiltration of inflammatory cells within the perivascular region, and augmentation of pyramidal cells	[92]

Abbreviations: OGD: oxygen-glucose deprivation, 3-NT: 3-nitrotyrosine, 4-HNE: 4-hydroxynonenal, AChE: Acetylcholinesterase, Akt: Protein kinase, ARE: antioxidant response element, Aβ: Amyloid β , Bax: Bcl-2-associated X protein, Bcl-2: B-cell lymphoma 2, BDNF: brain-derived neurotrophic factor, CAT: Catalase, COX: cyclooxygenase, CREB: cAMP response element binding protein, ERK1/2: extracellular signal-regulated kinases ½, GPx: glutathione peroxidase
GSH: glutathione, GSH/GSSG: glutathione/glutathione disulfide ratio, GSK-3β: glycogen synthase kinase-3β, HO-1: heme oxygenase-1, I/R: Ischemia/reperfusion, IL-1β: Interleukin 1 beta, JNK: c-Jun N-terminal kinase, LDH: lactate dehydrogenase, MAPK: mitogen-activated protein kinase, MCAO: middle cerebral artery occlusion, MDA: malondialdehyde, MMP: mitochondrial membrane potential, NF-κB: nuclear factor kappa B, NQO-1: NAD(P)H:quinine oxidoreductase 1, Nrf2: nuclear factor erythroid-2-related factor 2, p-CaMKII: phosphorylated calcium/calmodulin-dependent protein kinase II, ROS: reactive oxygen species, SOD: superoxide dismutase, γ-GCS: gamma glutamate cysteine ligase.

(p-CaMKII)/extracellular signal-regulated kinases 1/2 (ERK1/2)/cAMP response element-binding protein (CREB) signaling and repressed oxidative CaMKII/p38 mitogen-activated protein kinase (MAPK)/c-Jun N-terminal kinase (JNK)/nuclear factor kappa B (NF-κB)-connected inflammatory response [60]. Furthermore, total flavonoids from *D. moldavica*, and tilanin, as well as luteolin and apigenin, were tested on an *in vitro* OGD model using SH-SY5Y cells. The findings led to miR-3184-3p upregulation and miR-6875-5p downregulation in OGD-injured cells [61].

Alzheimer's Disease

Alzheimer's disease is a type of neurodegenerative disease. The pathophysiological mechanism underlying the disease includes the manifestation of amyloid beta (Aβ) peptide, Tau protein, and oxidative stress, as well as an intensified neuro-inflammatory response. Various extracts and compounds derived from *Dracocephalum* species have been investigated for their potential therapeutic effects against Alzheimer's disease. A study found that administering a total flavonoid extract from *D. moldavica* at a dose of 200 mg/kg orally for 12 weeks resulted in improved cognitive function and reduced neurodegeneration in *APP* and *PS1* double transgenic mice, as well as decreased Aβ burden and increased antioxidant defense system. *In vitro*, studies also showed that this extract preserved the ERK/CREB/Brain-derived neurotrophic factor (BDNF) pathway [62]. Another study found that administering an ethanolic extract from *D. moldavica* at varying doses orally for 24 h improved cognitive impairment induced by scopolamine in mice, as evidenced by increased step-through latency and improved memory in the Morris water maze task, along with increased phosphorylation levels of ERK and CREB in the hippocampus [63]. A hydroalcoholic extract from *D. moldavica* was found to decrease MDA levels and increase GPx levels; while reducing ROS levels in PC12 cells exposed to Aβ-induced toxicity at varying doses [64]. Other *Dracocephalum* species, including *D. multicaule*, *D. rupestre*, and *D. heterophyllum* were also tested for their potential therapeutic effects against Alzheimer's disease [66].

Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative condition that progresses chronically and is characterized by both motor and non-motor symptoms. This condition has a significant clinical impact on patients, caregivers, and families due to its degenerative effects on mobility and muscle control. The loss of striatal dopaminergic neurons underlies the motor symptoms of PD, although the presence of nonmotor symptoms suggests a neuronal loss in nondopaminergic areas as well. The term parkinsonism refers to the symptom complex that describes the motor features of PD, including resting tremor, bradykinesia, and muscular rigidity. Oxidative stress, mitochondrial dysfunction, and inflammation are the common etiologies for PD. A study investigated the effects of tilianin, isolated from *D. moldavica*, on 1-Methyl-4-phenyl pyridinium (MPP^+)-stimulated MES23.5 cells concerning Parkinson's disease. The experiment involved exposing the cells to three different concentrations of tilianin (3, 10, 30 μM). The results indicated that tilianin administration led to a decrease in IL-6, IL-1β, and TNF-α mRNA expression levels as well as a reduction in ROS levels and MnSOD and CAT protein expression levels. Additionally, the MAPK signaling pathway was inhibited by tilianin administration [69].

Insomnia

Insomnia is a notable obstacle to the welfare of the population. It is a prevalent state connected to conspicuous limitations in operation and standard of living, psychiatric and physical diseases, and incidents. Therefore, clinical practice must offer successful therapy. A research study has investigated the effect of an aqueous extract of *D. moldavica* on sleep disorders. The extract was administered intraperitoneally at varying dosages of 1, 10, 50, 100, and 200 mg/kg, after which the mice were subjected to sodium pentobarbital-induced sleeping time. These results indicated a decrease in general activity, motor coordination, and exploration in the animals [70].

Depression

Depression is a serious mental health condition that affects millions of people globally. The World Health Organization ranks it as the second leading cause of disability worldwide. Depression is defined by persistent feelings of sadness and a lack of pleasure in everyday activities [93]. Current antidepressants, typically including tricyclics and selective serotonin reuptake inhibitors (SSRIs), act on the serotonin and norepinephrine systems of the brain to exert their therapeutic effect against depression. However, these drugs take a relatively long time to act, have adverse effects, and may turn out to be unsuccessful in treating depression. This has been driving the search for new antidepressants with higher efficacy and fewer unwanted effects [94]. The ethanolic extract from *D. moldavica* notably reduced the duration of immobility observed in both the forced swim test and the tail suspension test in CD-1 mice with oral administration of 80 and 100 mg/kg [71].

Pain

Chronic pain is a prevalent and intricate issue that causes significant distress to both individuals and society. Often associated with disease or injury, it poses

a profound challenge for those affected. Aqueous extract from *D. polychaetum* was administered intraperitoneally at doses of 25, 50, 100, and 200 mg/kg to rats with formalin-induced pain, resulting in analgesic effects [72]. Meanwhile, essential oil from *D. kotschyi* was administered intraperitoneally at doses of 3.125, 6.25, 12.5, 25, 50, 75, 100, and 400 mg/kg to mice with acetic acid-induced pain, resulting in anti-nociceptive effects [73]. Additionally, intraperitoneal administration of essential oil from *D. moldavica* at doses of 5, 10, and 20 mg/kg to mice with acetic acid and formalin-induced pain resulted in analgesic properties [74].

Cerebral Ischemia

Cerebral ischemia is one of the prominent reasons for morbidity and mortality worldwide. Hydroalcoholic extract of *D. moldavica* administered orally at doses of 25, 50, and 100 mg/kg for five days was found to increase neurobehavioral scores, decrease cerebral edema and infarction, reduce MDA levels, and increase SOD and GSH-Px levels; while decreasing IL-6, IL-8, and TNF-α levels in rats subjected to cerebral ischemia-reperfusion [75]. In another study using total flavonoids from *D. moldavica* in middle cerebral artery occlusion (MCAO), rats with cerebral ischemia-reperfusion, an increase in the number of viable neurons was observed along with a decrease in gene expression levels of p53 and protein expression levels Bax; while protein expression levels of Bcl-2 were increased [76]. Administration of total flavones from *D. moldavica* to MCAO rats resulted in decreased protein expression levels of caspase-3 and AMPK [77].

A study investigated the effects of *D. moldavica*, a plant extract rich in total flavonoids and tilianin, on cerebral ischemia in rats and neuro-cytotoxic injury in human brain microvascular endothelial cells (HBMECs). In the rat model, administration of *D. moldavica* resulted in increased levels of antioxidant enzymes including GPx, SOD, and CAT, as well as a decreased level of MDA, carbonyl, and 8-hydroxy-2'-deoxyguanosine (8-OHdG) contents [78].

In human SH-SY5Y cells subjected to OGD-induced neuro-cytotoxic injury, tilianin was found to decrease CaMKII-linked signaling mediated through mitochondria and p38/JNK/NF-κB inflammatory pathways. Additionally, effective components of *D. moldavica* were found to inhibit the RIP3/MLKL/PGAM5 pathway in HBMECs subjected to Z-VAD-FMK plus OGD/R injury [83].

A previous study examined the effects of eriodictyol-7-O-glucoside, derived from *D. rupestre*, on cerebral ischemia in MCAO rats and primary cultured astrocytes exposed to transient OGD. The treatment resulted in the upregulation of Nrf2, NQO-1, HO-1, and γ-GCS [79,95].

Another experiment investigated the impact of eriodictyol, also from *D. rupestre*, on MCAO mice. The administration of 1, 2, and 4 mg/kg orally for five days prevented neuronal death and reduced infarct area and memory deficits; while decreasing MPO activity and TNF-α, iNOS, and GFAP expression [80]. Conclusively, an additional study explored the effects of eriodictyol on ischemic brain injury in MCAO rats for 14 days at doses of 20, 40, and 80 mg/kg orally. The treatment decreased IL-6, TNF-α, IL-10, and TGF-β1 levels; while also altering LC3, Bax, and cleaved-caspase-3 protein conversion. Additionally, it increased Bcl-2 and Ki67 expression; while inhibiting p62 reduction and increased ATG5, Beclin1, and LC3 protein conversion, altering LC3, Bax, and cleaved-caspase-3 [81].

Oxidative Stress-induced Neurotoxicity

Oxidative stress has been identified as a key factor in the aging process and various neurological disorders. In PC12 cells exposed to H_2O_2-induced neurotoxicity, treatment with 20, 40, and 80 μM eriodictyol resulted in the upregulation of HO-1 and γ-GCS expression through activation of the Nrf2/ARE pathway [86].

Similarly, treatment with 25, 50, and 100 μM calycopterin isolated from *D. kotschyi* prevented a decrease in MMP, suppressed cytochrome C release to the cytosol, inhibited a decrease in GSH level and SOD activity, elevated γ-GCS and HO-1 levels. Besides, treatment with calycopterin resulted in modulating the level of CREB phosphorylation and Nrf2 pathway activation in H_2O_2-exposed PC12 cells [87].

Glioblastoma

Glioblastoma multiforme (GBM) is classified as one of the most malignant types of tumors that occur in the central nervous system. The following studies have been conducted on the potential cytotoxic effects of various compounds on glioblastoma cells. In one study, xanthomicrol at a concentration of 200 mg/mL was found to have cytotoxic effects on A172 cells [88].

Another study found that a chloroform extract of *D. tanguticum* at a concentration of 90 μg/mL induced cell apoptosis via Caspase-3 and Bax pathways and inhibited p21 in T98G cells [89]. Furthermore, *D. moldavica* total flavones at concentrations varying from 1.56 μg/mL to 100 μg/mL were found to inhibit H_2O_2-induced apoptosis in astrocytes and human glioma cell line U87; while also resulting in decreased levels of MDA, LDH, and mRNA expression of Bax, Caspases-9 and -12, p38MAPK, and CaMKII and augmented mTOR mRNA expression [90].

Finally, diosmetin at concentrations of 5 μg/mL to 20 μg/mL was found to upregulate the expression of E-cadherin *via* the TGF-β signaling pathway in hu-

man glioma cell lines U251, U138, and T98 as well as BALB/c nude mice [91].

Pharmacokinetics and Toxicity

The hydroalcoholic extract of *D. kotschyi*, administered orally to rats for 30 days at doses of 50, 100, and 200 mg/kg, did not result in significant alterations in the deliberated biochemical and hematological factors. However, the highest dose of the extract led to a slight elevation in liver enzymes Alkaline phosphatase (ALP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT); while the lowest dose caused an increase in creatinine levels. Nevertheless, a microscopic examination of liver and kidney sections revealed no tissue damage [96].

Known polymethoxylated flavonoids present in the aerial parts of *D. kotschyi* are namely calycopterin and xanthomicrol. A new online SPE-HPLC technique was developed for determining their concentrations in rat plasma following intravenous administration. The pharmacokinetic analysis showed that both agents had a plasma half-life of approximately 4 hours; however, calycopterin had a volume of distribution around eight times greater than xanthomicrol due to its greater hydrophobicity, which resulted in much diminished maximum plasma concentration in comparison with its fewer methoxylated congener. In a preliminary toxicological analysis, repeated administrations of high doses of xanthomicrol failed to produce any adverse behavioral, histological, or biochemical effects [97].

Maham et al., 2013 discovered that the EO of *D. moldavica* was toxic (LD_{50}= 600 mg/kg) utilizing Lorke's method upon intraperitoneal administration [74]. Treatment with *D. moldavica* aqueous extract created deaths with LD_{50}=470 mg/kg when administered intraperitoneally [70].

Discussion

Neurological disorders are very extensive in public health and affect morbidity and mortality. Searching for effective and novel therapeutic agents applied to treat these diseases has forced researchers to focus on natural products derived from food/plants [98]. Particularly in this review, the *Dracocephalum* genus from the Lamiaceae family has been selected to comprehensively evaluate the illustration of neuroprotection due to its traditional therapeutic uses.

The pharmacological potential of *Dracocephalum* spp. is broad and involves antioxidant, anti-inflammatory, antiviral, antiparasitic, antibacterial, antifungal, nephroprotective, anti-complementary, hepatoprotective, neuroprotective, gastroprotective, cardioprotective, antiapoptotic, and anticancer activities. This complex profile originates from the rich phytochemical composition of *Dracocephalum* spp., which includes flavonoids, lignans, phenols, phenylpropanoids, glycosides, polysaccharides, terpenoids, and other compounds. Such bioactive compounds are supposed to interact with a variety of biological pathways, hence observing their therapeutic effects [59,99].

This review represents the neuroprotective potentials of *Dracocephalum* species in terms of mechanisms and signaling pathways. The genus has been implicated in a range of neurological conditions including Alzheimer's disease, insomnia, Parkinson's disease, vascular dementia, cerebral ischemia, pain, depression, and glioblastoma. Possible neuroprotective effects of *Dracocephalum* spp. have been considered mediated through their ability to modulate key pathways involved in neuronal survival, inflammation, and oxidative stress.

This may include inhibition of the aggregation of Aβ and reduction in neuroinflammation in Alzheimer's disease [62,64]. Anti-inflammatory and antioxidant effects of *D. moldavica* metabolite (tilianin) can protect dopaminergic neurons against oxidative damage in Parkinson's disease [69]. In cerebral ischemia, these neuroprotective effects can happen because of improved cerebral blood flow and reduced neuronal apoptosis [76].

Our findings in this review show *Dracocephalum* spp. as a source of neuroprotective agents; however, these findings must be understood in the context of mostly preclinical studies *in vitro* and animal models. Therefore, rigorous clinical trials are needed to translate these promising results into clinical practice, aimed at validating the safety and efficacy of the compounds derived from *Dracocephalum* in humans, while understanding the optimal dosages and treatment strategies under which they can be therapeutically effective.

Conclusions

In this paper, we discussed that *Dracocephalum* spp. have neuroprotective effects in vascular dementia, Alzheimer’s disease, Parkinson’s disease, insomnia, cerebral ischemia, pain, neurotoxicity, depression, and glioblastoma. Furthermore, we discussed the signaling pathways attributed to preclinical pharmacological characteristics which can assist in setting up future clinical trials.

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Competing Interests

The authors declare no competing interests.

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