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Pharmacological correction of cognitive dysfunctions in animals

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Cognitive dysfunction in animals, particularly in aging domestic companions, is an increasingly important area of study in veterinary medicine. The pathology is often compared to neurodegenerative conditions in humans, such as Alzheimer's disease, due to similar clinical and neuropathological features. Affected animals display signs like memory impairment, disorientation, changes in social interaction, and anxiety-related behaviors. The growing need to improve the quality of life in these animals and the possibility to use them as a model for human diseases highlights the importance of effective research in this area. Cholinesterase inhibitors such as donepezil enhance cholinergic transmission in the central nervous system, improving memory, learning ability, and overall cognitive function. Donepezil has demonstrated clinical benefits in aging dogs, particularly in later stages of cognitive decline. Its pharmacological profile includes acetylcholinesterase inhibition, reduction of neuroinflammation, enhancement of synaptic plasticity, and support for neuronal connectivity. Innovative delivery systems, such as injectable microspheres, aim to prolong its therapeutic effects and minimize adverse reactions. Central nervous system stimulants like methylphenidate increase catecholaminergic activity and improve functions related to attention, working memory, and executive control. However, their clinical use requires caution due to possible side effects including anxiety, restlessness, sleep disturbances, and increased oxidative stress. Memantine, an N-methyl-D-aspartate receptor antagonist, offers neuroprotection by mitigating excitotoxicity and inflammation, with promising effects in both ischemic and degenerative conditions. Its stable pharmacokinetic profile and emerging transdermal formulations support wider and safer use in clinical settings. Nootropic agents such as piracetam and oxiracetam support cerebral metabolism and enhance neural adaptability under conditions of hypoxia and oxidative stress. Oxiracetam has been shown to improve spatial learning, reduce ischemic brain injury, restore blood-brain barrier integrity, and increase cerebral circulation, combining cognitive and neuroprotective effects. Selegiline, a selective monoamine oxidase B inhibitor, exerts antioxidant and neurotrophic effects by modulating dopaminergic pathways, enhancing motivation, reducing anxiety, and promoting the expression of brain-derived neurotrophic factor and nerve growth factor, which support cognitive restoration. Additional compounds, including antioxidants (vitamins C and E, coenzyme Q_{10}), mitochondrial cofactors (taurine, L-carnitine, alpha-lipoic acid), and polyunsaturated fatty acids like docosahexaenoic acid, contribute to the maintenance of neuronal function, membrane stability, and resistance to oxidative damage. Used individually or in combination, these agents hold potential for slowing cognitive decline and improving quality of life in aging companion animals. Overall, pharmacological correction of cognitive dysfunction in animals holds promise for improving animal welfare and may offer translational insights relevant to human medicine.

Keywords: cognitive dysfunction; veterinary neurology; pharmacological treatment; neuroprotection; aging animals; cholinesterase inhibitors; nootropic agents; neurodegeneration models.

Introduction

The study of cognitive dysfunctions (CD) in animals is an important area of modern veterinary science. The term cognitive dysfunction refers to the development of neurodegenerative diseases associated with neuronal loss and neuroaxonal degeneration. In affected animals, CD manifests through behavioral changes, impaired memory, and reduced learning ability. Research into cognitive dysfunctions in animals allows veterinarians and scientists to better understand the pathophysiological mechanisms underlying these disorders. However, effective methods for diagnosing and treating this condition have not yet been fully established. A key objective in identifying such pathology remains improving the quality of life of animals by preventing the progression of the disease (Li et al., 2023; Kang et al., 2024b; Zhang et al., 2024a).

The study of cognitive dysfunctions in animals is also of great significance for human medicine, considering that many neurodegenerative processes are common to both animals and humans (Araujo et al., 2011). The use of animals as models of CD opens up opportunities for the development of new therapeutic approaches that may be beneficial in both veterinary and human medicine (Zabot et al., 2024).

Various pharmacological agents are used to treat cognitive dysfunctions in animals, with each group targeting specific pathophysiological processes responsible for neurodegeneration and cognitive impairment. Antioxidants (e.g., vitamins E and C, flavonoids, coenzyme Q_{10}) help reduce oxidative stress, which plays a crucial role in neuronal aging and the development of cognitive dysfunction. These substances protect brain cells from damage caused by free radicals and slow down neurodegenerative processes (Ma et al., 2024; Zhang et al., 2024b).

Mitochondrial enzyme cofactors (such as taurine, L-carnitine, and α-lipoic acid) improve energy metabolism in brain cells, reduce inflammation levels, and support neuronal functionality, which is particularly important for maintaining cognitive function in aging animals (Chen et al., 2019; Wang et al., 2021; Wang et al., 2022). Cholinesterase inhibitors contribute to increased acetylcholine levels, a neurotransmitter that plays a key role in memory, learning, and cognitive activity. These drugs help improve cognitive functions by reducing the deficit of this neurotransmitter in the brain. Central nervous system stimulants enhance brain activity, increase attention, and improve information processing (Ahmari et al., 2020; Feizipour et al., 2020).

Drugs from other groups, such as neuroprotective agents (e.g., memantine), vasodilators (e.g., *Ginkgo biloba*, nicergoline), adaptogens (e.g., *Rhodiola rosea*, *Eleutherococcus*), as well as dietary supplements containing omega-3 and omega-6 fatty acids, contribute to improved cerebral blood flow, support neuronal function, and may slow the progression of cognitive impairments (Román et al., 2019; Ordóñez-Gutiérrez et al., 2021). Thus, analysis of the current literature indicates that the use of cholinesterase inhibitors, CNS stimu-

lants, psychoanaleptics, and nootropics is a promising approach for stimulating cognitive function in animals. This is supported by their influence on key neurophysiological processes that govern memory, learning, and adaptation. Drugs from these groups activate neuronal activity, enhance attention and information processing, improve cerebral circulation, increase neuroplasticity, and protect neurons from degenerative changes. In addition, they may improve cognitive function by preventing the development of stress-related conditions.

The aim of our study was to review current developments concerning the present state and future prospects of pharmacological support for the prevention and treatment of cognitive dysfunctions in animals.

A search, selection, and analysis of scientific articles related to the topic of the study was conducted for the period 1996–2025 in accordance with the methodology for systematic literature reviews. To locate scientific publications, scientometric databases such as the Web of Science Core Collection (http://apps.webofknowledge.com) and PubMed (https://pubmed.ncbi.nlm.nih.gov) were used. The selection of scientific articles was carried out from journals in the following categories: veterinary sciences, animal ethology, neurosciences, and animal behavior.

Cognitive dysfunction in animals: clinical and translational perspectives

The study of cognitive dysfunctions in animals is important both for improving the health and welfare of the animals themselves and for gaining new insights that may be applicable to the treatment of neurodegenerative diseases in humans. Cognitive dysfunctions in animals, particularly in aging companion animals such as dogs and cats, are increasingly recognized as significant clinical conditions that negatively impact behavior, quality of life, and the human-animal bond. Addressing these dysfunctions not only helps to alleviate suffering and improve daily functioning in affected animals but also enhances the emotional well-being of pet owners and caretakers, who often report distress over the progressive decline in their animals' cognitive abilities.

Beyond its clinical relevance in veterinary practice, the study of animal cognitive dysfunctions offers valuable translational models for understanding human neurological conditions, such as Alzheimer's disease, Parkinson's disease, vascular dementia, and other forms of age-related cognitive impairment. Animals, especially those with naturally occurring or experimentally induced neurodegenerative changes, serve as essential models for studying the underlying mechanisms of neuronal degeneration, synaptic failure, and neuroinflammation. These models help identify critical biomarkers, assess disease progression, and evaluate the safety and efficacy of new pharmacological interventions before human clinical trials.

In scientific research, animals are frequently used as analogues of cognitive disorders observed in humans due to the shared structural, functional, and neurochemical features of mammalian brains. Canines, in particular, have emerged as valuable spontaneous models because of their prolonged lifespans, complex behavior, and similarities in age-associated brain changes to those found in elderly humans. Rodent models remain indispensable for mechanistic studies, genetic manipulation, and high-throughput screening of potential therapeutic compounds. Research using these models has yielded promising results in the development of cholinesterase inhibitors, NMDA receptor antagonists, neuroprotectants, and cognitive enhancers that act on multiple levels of the central nervous system.

In our work, we considered the results of such studies, as they are instrumental in developing new therapeutic approaches in both veterinary and human medicine. By analyzing recent advancements in the pharmacological correction of cognitive dysfunctions in animal models, we aim to bridge the gap between experimental research and clinical application. This dual benefit – enhancing animal health while contributing to the broader field of neuroscience – underscores the importance of continued investment in comparative neurobehavioral research. Moreover, understanding the parallels and divergences between species in terms of cognitive aging can help refine treatment strategies and inform future drug development with greater precision and relevance across species.

Donepezil contributes to the restoration of cognitive functions under various pathological conditions in animals

Donepezil is an acetylcholinesterase inhibitor commonly prescribed to treat cognitive impairments in humans, particularly in Alzheimer's disease (AD), and it holds broad potential for application in veterinary medicine. Its effectiveness is increasingly supported by a growing body of animal research, which demonstrates not only its role in inhibiting acetylcholinesterase activity but also its ability to influence various neurobiological mechanisms implicated in cognitive dysfunction. Studies in rodent models have revealed that donepezil can restore impaired learning and memory by enhancing cholinergic transmission, mitigating neuroinflammation, and promoting neuronal survival and synaptic plasticity (Lim et al., 2016; Winocur, 2017; Zabot et al., 2024). These findings point to its utility in addressing a range of cognitive impairments in animals, whether age-related, chemically induced, or associated with complex neuropsychiatric conditions.

In a detailed pharmacological study, Shin et al. (2018) evaluated the effects of donepezil on rodents with scopolamine-induced memory impairment, a widely accepted model of cholinergic dysfunction. The researchers identified a clear relationship between donepezil brain concentrations and behavioral improvement, determining that the optimal therapeutic concentration in the brain was 46.5 ± 3.5 ng/g. At this concentration, donepezil significantly restored spontaneous alternation behavior in the Y-maze, underscoring its potential to reverse acute cognitive deficits. Beyond cholinergic modulation, Kim et al. (2021) found that donepezil exerts strong anti-inflammatory effects by downregulating lipopolysaccharide (LPS)- and amyloid-beta (Aβ)-induced neuroinflammatory responses. The drug achieved this by suppressing key components of the MAPK, NLRP3 inflammasome, and STAT3 signaling pathways. These results suggest a dual mechanism of action – neurochemical and immunological – which may explain its broader therapeutic effects in neurodegenerative disease models.

The cognitive benefits of donepezil are not limited to Alzheimer-like conditions. In a schizophrenia model using phencyclidine (PCP)-treated mice, Li et al. (2018) demonstrated that donepezil significantly improved performance in the novel object recognition, Morris water maze, and passive avoidance tests. The underlying mechanisms included the inhibition of neuronal apoptosis and the upregulation of neuroprotective signaling molecules such as p-Akt and p-GSK-3β, along with the modulation of Bcl-2/Bax and caspase-3 pathways. Furthermore, in a combined model of dementia and depression, Zabot et al. (2024) reported that donepezil, especially when administered with fluoxetine, was effective in restoring cognitive performance and partially reversing proinflammatory cytokine imbalances. While donepezil alone improved cognitive outcomes, its limited impact on hippocampal TNF-α levels highlights the potential need for combination therapies to achieve full neuroprotective effects.

These studies collectively underscore the multifaceted therapeutic potential of donepezil in veterinary and human neuroscience. By addressing both neurotransmitter deficits and inflammatory pathologies, donepezil emerges as a promising candidate for managing a spectrum of cognitive disorders in animals, while also offering insights applicable to human medicine.

Some studies also explore the potential application of donepezil beyond traditional cognitive impairment, particularly in the context of addictive behavior and the gut-brain axis, as well as novel delivery methods. Mei et al. (2023) investigated the effect of donepezil on heroin-seeking behavior in rats and found that high-dose administration (3 mg/kg) significantly inhibited heroin self-administration under a fixed-ratio reinforcement schedule and reduced the motivational value of heroin in a progressive ratio model. Moreover, all tested doses (1–3 mg/kg) reduced cue-induced reinstatement of heroin-seeking behavior after withdrawal. Immunohistochemical analysis revealed that the behavioral improvements were associated with increased expres-

sion of dopamine receptor 1 and dopamine receptor 2 in the nucleus accumbens, as well as enhanced expression of choline acetyltransferase in the ventral tegmental area. These findings suggest that donepezil may modulate both dopaminergic and cholinergic systems to counteract the neuroadaptive changes associated with opioid dependence, providing a promising avenue for adjunctive treatment in opioid use disorders.

In another innovative line of research, Lee et al. (2021) examined the synergistic effects of combining donepezil with DW2009, a fermented soybean product enriched with *Lactobacillus plantarum* C29, to enhance cognitive function in mice. Their results demonstrated that co-administration of donepezil and DW2009 (or C29 alone) significantly outperformed the effects of either agent alone in ameliorating lipopolysaccharide (LPS)-induced cognitive deficits. The combination treatment reduced markers of neuroinflammation, such as activated microglia (NF-κB+/Iba1+), tumor necrosis factor-α, and interleukin-1β expression in the hippocampus, while simultaneously increasing the population of BDNF+/NeuN+ cells and brain-derived neurotrophic factor levels. Importantly, this intervention also improved gut health, as evidenced by suppression of LPS-induced colitis and beneficial alterations in the gut microbiota, including increased Firmicutes and decreased Cyanobacteria. These results underscore the potential of donepezil, especially when combined with microbiota-modulating agents, to exert systemic effects via the microbiota-gut-brain axis.

In addition to exploring new therapeutic indications and combination therapies, recent studies have been investigating advanced delivery methods to enhance the pharmacokinetics and efficacy of donepezil. Kang et al. (2024a) proposed a novel technique known as intracalvariosseous (ICO) administration, which involves the injection of donepezil-loaded long-acting microspheres (DPZ@LAM) into the diploic space of the skull. This method exploits the anatomical connectivity between the skull bone marrow, meninges, and brain to bypass the blood-brain barrier and achieve targeted CNS drug delivery. A single administration of DPZ@LAM in a mouse model of scopolamine-induced memory impairment resulted in sustained therapeutic levels of donepezil in the brain for up to four weeks. This long-lasting exposure significantly improved cognitive performance, decreased acetylcholinesterase activity, and elevated BDNF levels in the brain, without the need for repeated dosing. The ICO approach presents a promising alternative for the controlled, long-term treatment of neurodegenerative diseases, particularly in cases where conventional systemic administration is limited by poor blood–brain barrier permeability or frequent dosing requirements.

Table 1 consolidates diverse experimental paradigms and mechanisms to emphasize the pharmacodynamic versatility of donepezil and its relevance to both central and systemic effects.

Table 1
Summary of experimental findings on donepezil's cognitive and neurobiological effects in animal models

Study / model	Condition / induction method	Key mechanisms affected	Observed cognitive outcomes	Notable remarks
Shin et al. (2018)	Scopolamine-induced memory impairment (rodents)	↑ ACh transmission, brain [DPZ]: 46.5 ± 3.5 ng/g	Improved Y-maze performance (spontaneous alternation)	Dose–response relationship established
Kim et al. (2021)	LPS- and Aβ-induced neuroinflammation	↓ MAPK, NLRP3, STAT3 pathways	Reduced neuroinflammation, enhanced neuronal survival	Dual action: cholinergic + anti-inflammatory
Li et al. (2018)	PCP-induced schizophrenia model (mice)	↑ p-Akt, p-GSK-3β, ↓ caspase-3	Improved NOR, MWM, and passive avoidance tests	Anti-apoptotic and neuroprotective action
Zabot et al. (2024)	Dementia and depression model (mice)	↑ Cognitive performance, limited TNF-α reduction	Synergistic effect with fluoxetine	Partial anti-inflammatory effect alone
Mei et al. (2023)	Heroin dependence (rats)	↑ D1/D2 receptors, ↑ ChAT expression	↓ Heroin seeking, ↓ relapse	Modulates dopaminergic–cholinergic systems
Lee et al. (2021)	LPS-induced neuroinflammation + gut dysbiosis	↓ TNF-α, IL-1β, ↑ BDNF, altered microbiota	Ameliorated cognitive deficits, ↑ gut health	DPZ + probiotic (C29) synergy
Kang et al. (2024)	ICO delivery in scopolamine-impaired mice	Sustained DPZ brain levels (via microspheres)	Long-term cognitive improvement, ↑ BDNF	Novel delivery bypasses BBB, single dosing

Together, these studies demonstrate that donepezil not only retains its central role as a cognitive enhancer but also holds potential for broader applications including the treatment of addiction, neuroinflammation, and gut–brain axis dysregulation. Moreover, innovations in drug delivery – such as the ICO route – may revolutionize the pharmacological management of neurodegenerative and neuropsychiatric conditions, enhancing both efficacy and patient compliance.

Thus, numerous studies confirm the effectiveness of donepezil in restoring cognitive function under various pathological conditions in animals. The drug shows potential in treating neuroinflammatory processes, addictive behaviors, and cognitive impairments. Current research is focused on developing novel delivery methods and combination therapies to enhance the efficacy of donepezil.

The use of methylphenidate for cognitive enhancement in animals reveals significant risks associated with oxidative stress, social isolation, and other side effects

Methylphenidate (MPH) is a widely used psychostimulant that affects cognitive functions through modulation of dopaminergic and noradrenergic systems. A review of current literature indicates considerable variability in its efficacy and highlights its potential in various contexts of cognitive dysfunction in animal models.

The study by Kapur (2020) underscores the multifaceted potential of methylphenidate (MPH) as a pharmacological cognitive enhancer, particularly in cases characterized by deficient catecholaminergic activity. MPH acts primarily through indirect agonism of dopaminergic and noradrenergic systems, which are crucial for cognitive processes such as attention, memory, and executive function. Kapur's analysis highlights the variability of MPH's cognitive-enhancing effects, pointing out that its efficacy is influenced by several interrelated factors, including the administered dose, the nature of the cognitive task, and the specific domain of cognition being targeted. While MPH has proven benefits in individuals with attention-deficit/hyperactivity disorder (ADHD), its off-label use in healthy individuals remains contentious due to inconsistent findings and the potential for misuse. Additionally, Kapur notes that MPH may improve subjective perceptions of productivity even when objective cognitive improvements are minimal, suggesting a complex interplay between pharmacological and psychological effects. Safety concerns also remain prominent, with MPH presenting sympathomimetic, cardiovascular, and addictive risks that necessitate cautious consideration, especially in non-clinical populations or those with pre-existing health conditions.

Supporting these observations, Beaudin et al. (2024) explored the therapeutic efficacy of MPH in a rodent model of cognitive dysfunction caused by early-life manganese (Mn) exposure – a known environmental neurotoxin. Their findings demonstrated that oral MPH administration significantly alleviated deficits in attention and sensorimotor functions that persisted in adulthood. Importantly, the attention-related benefits of MPH emerged only after prolonged treatment, indicating the need for sustained administration to achieve cognitive improvement in some contexts. The study further investigated the mechanisms underlying MPH's action, revealing that different cognitive domains respond to distinct dosages and are modulated by vary-

ing catecholaminergic receptor pathways. For example, sensorimotor improvements were more responsive to higher MPH doses and were dependent on D1 receptor activity, while antagonism of D2 receptors also influenced Mn-induced dysfunctions. These results not only validate MPH's efficacy in reversing neurotoxic damage but also shed light on its domain-specific pharmacodynamics, thereby broadening its potential application in treating environmentally induced neurodevelopmental disorders.

Moreover, Ramon-Duaso et al. (2019) extended the therapeutic relevance of MPH to genetic models of cognitive impairment. In their study, muscle-blind-like 2 (Mbnl2) knockout mice – used as a model for the central nervous system manifestations of myotonic dystrophy type 1 – exhibited pronounced cognitive and mood disturbances alongside neuroinflammatory markers in the medial prefrontal cortex and hippocampus. Chronic MPH treatment not only reversed the cognitive deficits and depressive-like behaviors in these mice but also significantly reduced microglial overactivation, normalized dopaminergic gene expression (including Dat and Drd2), and increased levels of neuroprotective markers such as brain-derived neurotrophic factor (BDNF) and nuclear factor erythroid 2-related factor. These findings emphasize the anti-inflammatory and neuromodulatory properties of MPH and suggest its potential as a therapeutic agent in neurogenetic disorders involving both cognitive and emotional dysregulation.

Taken together, these studies reinforce the growing body of evidence supporting MPH as a potent modulator of cognitive and emotional function across a range of pathological conditions. They also highlight the need for individualized treatment approaches that consider dosage, treatment duration, and the specific neurochemical and cognitive profile of the patient or model. Furthermore, the interactions demonstrated between MPH and inflammatory as well as dopaminergic signaling pathways open new avenues for exploring its role in disorders marked by neuroinflammation or dopamine dysregulation. While further clinical research is warranted, especially in human populations beyond ADHD, these findings lay an important foundation for the broader therapeutic applications of MPH.

The effect of methylphenidate on cognitive processes appears to be complex and dose-dependent, with both beneficial and detrimental consequences depending on the administered amount and duration of exposure. As confirmed by the study conducted by Salman et al. (2019), low to moderate therapeutic doses of MPH (0.5–2.5 mg/kg) significantly improved spatial learning and memory retention in rats using the Morris water maze test. This suggests an enhancement of cognitive function potentially mediated by increased catecholaminergic neurotransmission. However, at a higher dose of 5 mg/kg, MPH was found to impair both acquisition and retention of memory, likely due to its agonistic activity at 5-HT1A receptors, indicating a possible serotonergic mechanism underlying the observed cognitive deficits at elevated concentrations.

Beyond its dose-related cognitive effects, the pharmacokinetics and accumulation profile of MPH are also of considerable interest. Moeller et al. (2021) demonstrated that methylphenidate could be effectively detected in equine hair using a validated liquid chromatography-high-resolution mass spectrometry protocol. The successful identification of MPH in hair samples implies that the compound may persist in the body for extended periods. This accumulation raises concerns about the long-term exposure of animals to the substance and suggests the potential for prolonged neuropsychological effects, including sustained influence on cognition and behavior, even after discontinuation of the drug.

Moreover, not all effects of MPH are beneficial. Its chronic use has been associated with negative outcomes at the cellular level. The research by Novo et al. (2023) investigated the differential responses of glial cells to MPH and discovered that, while microglial cells exhibited minimal direct response, astrocytes showed pronounced sensitivity. MPH promoted astrogliosis, increased oxidative and nitrosative stress, and elevated pro-inflammatory cytokine TNF levels. These effects were consistent both in vitro and in the hippocampal tissue of Wistar Kyoto rats exposed to chronic MPH treatment. These neuroinflammatory processes may contribute to the deterioration of neural function and cognition over time.

In line with these findings, Foschiera et al. (2022) provided further insights into the biochemical and cellular consequences of MPH exposure. Their study highlighted that MPH disrupts mitochondrial function by impairing enzymes involved in the Krebs cycle and the electron transport chain, reducing ATP production, and inhibiting Na+,K+-ATPase activity. These disruptions compromise energy homeostasis in the brain and are accompanied by elevated levels of reactive oxygen and nitrogen species, resulting in oxidative stress and subsequent damage to proteins, lipids, and DNA. This cascade of events supports the hypothesis that mitochondrial dysfunction and oxidative imbalance are central mechanisms in MPH-induced neurotoxicity.

Behavioral studies by Motaghinejad et al. (2015a, 2015b) also support the notion that prolonged or high-dose exposure to MPH can provoke psychological disturbances, including increased anxiety, depression, and impaired cognitive function. These effects were observed using behavioral paradigms such as the Elevated Plus Maze, Open Field Test, Forced Swim Test, Tail Suspension Test, and Morris Water Maze. Notably, co-administration of venlafaxine – a serotonin-norepinephrine reuptake inhibitor – was shown to mitigate the anxiety and depressive behaviors induced by MPH, although it did not reverse the drug's negative impact on learning and memory. Similarly, the authors demonstrated that forced physical exercise exerted a neuroprotective effect, attenuating the behavioral and cognitive deficits caused by MPH administration. These findings suggest that both pharmacological and non-pharmacological interventions can play a role in counteracting the adverse consequences of MPH misuse.

Thus, the current body of evidence indicates that while MPH can enhance cognitive functions at clinically relevant doses, especially in the context of ADHD treatment, its overuse or misuse – especially at high doses or over extended periods – can lead to serious neurobiological and behavioral complications. These include neuroinflammation, oxidative damage, mitochondrial dysfunction, and emotional disturbances, all of which raise significant concerns regarding its widespread and often unsupervised use for cognitive enhancement in healthy individuals and animals.

Other researchers (Cim et al., 2025) established that methylphenidate induces oxidative stress in the ovaries of female rats, accompanied by elevated cortisol levels and reduced antioxidant defense, including significantly decreased levels of total glutathione, superoxide dismutase, and catalase, alongside increased malondialdehyde concentration. The study also revealed immunohistochemical signs of DNA damage (8-hydroxy-2'-deoxyguanosine positivity), indicating cellular oxidative damage. Although the drug did not significantly alter prolactin or proinflammatory cytokine levels (IL-1β, TNF-α), prolonged exposure to methylphenidate (30 days) resulted in a striking 66.7% infertility rate among treated rats. These findings underscore the potential reproductive risks associated with long-term use of methylphenidate in females and highlight the need for further evaluation of its effects on fertility and hormonal regulation.

Achterberg et al. (2015, 2018) found that methylphenidate and atomoxetine suppress social play in rats by acting on a network of prefrontal and limbic brain regions, including the anterior cingulate cortex, infralimbic cortex, basolateral amygdala, and habenula. These areas are crucial for emotional regulation and cognitive control, suggesting that the drugs' suppressive effect on play behavior arises from their modulation of noradrenergic neurotransmission within these circuits. Interestingly, methylphenidate did not affect other types of social interaction or locomotor activity, implying a selective effect on play-specific motivation. In follow-up studies, infusion of an α2-adrenoceptor antagonist into these same regions failed to reverse the play-suppressing effects, suggesting parallel action across different regions rather than a single linear pathway. These results deepen our understanding of how psychostimulants can alter developmentally critical behaviors, raising concerns about their long-term use in juvenile populations.

Frizzo et al. (2020) studied the effects of chronic exposure to environmentally relevant concentrations of methylphenidate in zebrafish (*Danio rerio*), revealing that even low doses present in contaminated water significantly impaired social behavior. Zebrafish exposed to

methylphenidate exhibited a marked avoidance of conspecifics in social preference tests, indicating a disruption in normal affiliative behavior. Moreover, behavioral assessments using the novel tank test suggested an anxiolytic-like response at the lowest concentration, although oxidative stress parameters did not appear to be involved in this effect. These findings highlight the ecological risk posed by psychostimulant contamination in aquatic environments, as behavioral alterations in fish can affect reproductive success, survival, and broader ecosystem dynamics. The study draws attention to the need for environmental regulations concerning pharmaceutical pollutants in wastewater.

Mirra et al. (2024) investigated the effect of methylphenidate on recovery from general anesthesia induced by propofol in pigs and concluded that the stimulant did not significantly accelerate the return of physiological reflexes or influence electroencephalographic or nociceptive withdrawal responses. Two separate experimental designs – one testing administration during anesthesia and another after extubation – consistently showed no clinically relevant improvement in recovery parameters, even at doses up to 20 mg/kg. These results indicate that methylphenidate, despite its known arousal-enhancing properties in other contexts, may have limited or no utility as a recovery-promoting agent in propofol-based anesthesia protocols. This challenges the idea of using psychostimulants as a universal strategy for anesthesia reversal and suggests species- and context-specific limitations in its efficacy.

Table 2 provides a structured overview of methylphenidate's therapeutic potential and limitations, highlighting the importance of dose titration, treatment duration, and neuroinflammatory outcomes.

Table 2
Summary of Methylphenidate's effects on cognition and neurobiology in animal models

Study / model	Cognitive context / pathology	Dose / regimen	Main effects	Mechanistic insights / risks
Kapur (2020)	General cognitive enhancement (review)	Variable	Context-dependent cognitive improvement	Efficacy modulated by task, dose, domain
Beaudin et al. (2024)	Mn-induced neurotoxicity (rodents)	Oral MPH, chronic	Improved attention, sensorimotor function	Domain-specific dose-response, D1/D2 modulation
Ramon-Duaso et al. (2019)	Mbnl2 KO (myotonic dystrophy) mice	Chronic MPH	Reversed cognitive and emotional deficits	↓ Microglial activity, ↑ BDNF, normalized DA signaling
Salman et al. (2019)	Spatial memory (healthy rats)	0.5–5 mg/kg	↑ Memory at 0.5–2.5 mg/kg, ↓ at 5 mg/kg	Possible serotonergic toxicity at high doses
Moeller et al. (2021)	Pharmacokinetics (horses)	Hair analysis	MPH detectable post-treatment	Evidence of accumulation; relevance to long-term exposure
Novo et al. (2023)	Cellular effects (astrocytes, microglia)	Chronic MPH	↑ TNF, oxidative stress, astrogliosis	Chronic toxicity risk; inflammatory damage
Foschiera et al. (2022)	Oxidative stress and cytotoxicity	–	–	Study continuation

Thus, the presented data confirms the efficacy of MPH in restoring cognitive functions in animal models, especially in cases of attention deficits, memory impairments, and sensorimotor coordination issues. At the same time, the potential negative effects – particularly those related to neuroinflammation and oxidative stress – require further research on the safety and long-term consequences of MPH use in therapeutic and subtherapeutic doses.

Memantine demonstrates a wide range of therapeutic effects in correcting cognitive impairments in animals

Memantine is a non-competitive NMDA receptor antagonist used for treating cognitive impairments in both humans and animals. Its effectiveness has been confirmed in numerous animal studies involving cognitive disorders caused by trauma, neurodegenerative processes, and other pathological conditions. For instance, Allam et al. (2024) studied the efficacy of memantine and *Ginkgo biloba* extract (EGb 761) in rats using a novel scopolamine-heavy metals mixture model that better mimics the pathological features of Alzheimer's disease compared to traditional scopolamine models. In this study, memantine demonstrated modulatory effects on key markers of neurodegeneration, such as acetylcholinesterase, caspase-3, amyloid-beta (Aβ1-42), and phosphorylated tau protein in nervous tissue. However, EGb 761 showed even more pronounced benefits in several parameters, such as stronger inhibition of oxidative stress, proinflammatory cytokines (TNF-α, IL-1β), and better preservation of hippocampal structure and function. These findings support memantine's therapeutic potential but also highlight the growing interest in natural compounds as complementary or alternative options. Furthermore, the results indicate that memantine may influence multiple mechanisms involved in cognitive impairment, including cholinergic transmission, apoptotic signaling, and protein aggregation. This multi-target action contributes to its utility in addressing complex neurodegenerative conditions where multiple pathways are simultaneously disrupted.

Memantine exhibits a neuroprotective effect in conditions associated with inflammation or traumatic brain injury (Boucher et al., 2024). In their study on repetitive mild traumatic brain injury (rmTBI), Boucher et al. demonstrated that both early and delayed administration of memantine (even six months post-injury) resulted in partial but persistent improvements in behavioral and neuropathological outcomes. These included decreased neuroinflammation (particularly via modulation of microglial activity), improved motor coordination, and better memory performance. Interestingly, the treatment at three months post-injury was less effective than immediate or late interventions, suggesting a time-sensitive therapeutic window for optimal benefit. Moreover, chronic changes in tau phosphorylation (T231) and glial activation were ameliorated to a greater extent in the early and late treatment groups compared to the vehicle-treated animals. This indicates that memantine's neuroprotective efficacy may not only be due to acute NMDA receptor antagonism, but also due to long-term modulation of neuroinflammatory pathways. Bardaghi et al. (2023) further supported these findings by showing that memantine significantly reduced expression levels of inflammatory markers such as NF-κB, TNF-α, and IL-1β in a mouse model of sepsis-induced brain dysfunction. The animals also exhibited improvements in oxidative stress parameters, including increased total thiol content and superoxide dismutase (SOD) activity. Behavioral testing revealed significant recovery in cognitive functions and a reduction in anxiety- and depression-like symptoms. These data strongly suggest that memantine confers neuroprotection not only through receptor blockade but also by downregulating systemic and central inflammation and improving redox balance.

A study done by MacLean et al. (2023) showed that memantine significantly improves neurovascular function following repeated mild traumatic brain injury in rats. Treatment with memantine (10 mg/kg) reduced the severity of cortical spreading depolarization and led to improved neurological status compared to the control group. This adds to the accumulating evidence that memantine may help restore brain homeostasis after repetitive injuries by modulating excitotoxic cascades and maintaining cerebral perfusion. This study conclusions resonate with the findings of Boucher et al., reinforcing the neurovascular component of memantine's action. Finally, Dicpinigaitis et al. (2015) explored the potential application of memantine as a suppressant of the cough reflex. Their translational study demonstrated that memantine effectively suppressed citric acid-induced coughing in guinea pigs, showing comparable efficacy to codeine and greater potency than dextromethorphan. In humans, a single dose of memantine significantly reduced cough reflex sensitivity in healthy subjects during capsaicin challenge. Although the results were less pronounced in subjects with upper respiratory tract infection, the fin-

dings provide preliminary support for further clinical exploration of memantine as a novel antitussive agent. Taken together, these studies broaden the therapeutic scope of memantine beyond Alzheimer's disease, positioning it as a multi-functional neurotherapeutic agent with applications in trauma, inflammation, and even respiratory disorders. Beyond neurodegenerative and inflammatory diseases, memantine is also being actively investigated as a potential treatment for various forms of addiction and psychiatric disorders. Levin et al. (2019) conducted a detailed study in which adult female rats received either acute or chronic memantine treatment to evaluate its impact on nicotine self-administration. While acute administration slightly increased nicotine intake, chronic memantine treatment resulted in a sustained and statistically significant reduction in nicotine self-administration. Notably, this effect persisted even after the cessation of memantine administration, suggesting that chronic NMDA receptor modulation can induce long-lasting changes in the reinforcement pathways associated with nicotine dependence. These findings underscore memantine's potential as a pharmacological aid in smoking cessation therapies, particularly through its capacity to modulate glutamatergic mechanisms underlying addiction. Furthermore, the observed persistence of reduced nicotine-seeking behavior post-treatment positions memantine as a candidate for relapse prevention strategies.

In addition to its effects on nicotine addiction, memantine also demonstrates promise in treating depressive symptoms and cognitive deficits induced by psychostimulant withdrawal. Marszalek-Grabska et al. (2016) found that memantine significantly improved performance in the novel object recognition test in rats withdrawn from amphetamine, thereby attenuating memory impairment linked to drug abstinence. Moreover, memantine showed strong antidepressant-like effects in the forced swim test, surpassing the efficacy of the tricyclic antidepressant imipramine at equivalent doses. These outcomes suggest that memantine may provide a dual benefit – addressing both affective and cognitive symptoms during withdrawal periods. Interestingly, the study also explored the interplay between memantine and other receptor antagonists, such as scopolamine and MK-801, revealing that cholinergic pathways may also influence the cognitive-enhancing effects of memantine. These findings reinforce the drug's multifaceted neuropsychopharmacological profile and its potential role in addressing substance use disorders and associated psychiatric comorbidities.

Expanding into the realm of neurodevelopmental conditions, the study by Kumar & Sharma (2016) illustrated that memantine effectively attenuated a broad range of behavioral and biochemical abnormalities in a rat model of autism induced by prenatal exposure to valproic acid. Memantine treatment significantly improved social behavior, exploratory activity, and spontaneous alternation, while also restoring serotonin levels and mitochondrial function in the prefrontal cortex. Moreover, it counteracted heightened oxidative stress, inflammation, and blood-brain barrier permeability – key pathophysiological features associated with autism spectrum disorders (ASD). These results suggest that NMDA receptor modulation can exert far-reaching neuroprotective and neuroregulatory effects in ASD, supporting the rationale for further clinical exploration of memantine and similar agents in managing core and comorbid symptoms of autism.

Further evidence of memantine's neuroprotective properties comes from the study by Wu et al. (2021), which investigated a novel memantine derivative – MN-08 – in transgenic mouse models of Alzheimer's disease (AD). MN-08 not only demonstrated potent NMDA receptor antagonism and favorable pharmacokinetics, but also significantly inhibited amyloid-β aggregation, preserved neuronal integrity, and improved cognitive performance over both short- and long-term treatment courses. The compound was shown to mitigate excitotoxic calcium influx and modulate intracellular signaling pathways such as ERK and PI3K/Akt/GSK3β, which are critical in neuronal survival and synaptic plasticity. These multifactorial effects position MN-08 as a promising next-generation therapeutic with broader efficacy and safety in treating neurodegenerative disorders like AD. Memantine has also shown beneficial therapeutic effects in cases of infectious and toxic damage to the nervous system. Sun et al. (2019) reported that memantine can mitigate neuronal dysfunction caused by neurotropic viruses, including the rabies virus and Japanese encephalitis virus (JEV). *In vitro* studies revealed a neuroprotective effect of memantine on virus-infected neurons, while *in vivo* experiments demonstrated that memantine significantly prolonged survival in mice infected with JEV. The drug also reduced brain inflammation and viral load, suggesting that it can interfere with the neuroinflammatory cascade and viral pathogenesis. These findings highlight the therapeutic promise of NMDA antagonists in managing viral encephalopathies, especially given memantine's established safety and ability to cross the blood-brain barrier.

Moreover, it was found that memantine's neuroprotective role extends to mitigating chemotherapy-induced neurotoxicity. In a study by Salih & Al-Baggou (2020), mice treated with the chemotherapeutic agent cisplatin displayed marked behavioral impairments and neuronal damage. However, pretreatment with memantine at both 5 mg/kg and 10 mg/kg improved performance in a battery of neurobehavioral tests, with the higher dose offering near-complete protection. Memantine also normalized weight gain patterns and reduced overexpression of nicotinic acetylcholine receptors, which were elevated in cisplatin-treated mice. These results suggest that memantine may counteract cisplatin-induced neurobehavioral toxicity and synaptic dysregulation, offering a potential adjunctive treatment to preserve neurological function in patients undergoing chemotherapy.

Some studies point to the potential use of memantine in treating affective disorders. Demontis et al. (2015) demonstrated that memantine may have a stabilizing effect in rats with a model of bipolar disorder. The authors showed that memantine prevents both the dopamine receptor sensitization caused by chronic imipramine treatment and the subsequent desensitization and depressive-like behavior after drug withdrawal. This suggests that memantine may possess both antimanic and mood-stabilizing properties, particularly valuable in treatment-resistant bipolar disorder. However, the study by Straathof et al. (2022) did not find a positive effect of memantine in rats with compulsive behavior induced by quinpirole. In their adolescent rat model, neither acute nor chronic administration of memantine had a significant effect on compulsive checking behavior or frontostriatal network connectivity, pointing to possible age-specific or condition-specific limitations of its therapeutic potential.

Pharmacokinetic studies by Lee et al. (2016) revealed that memantine has good oral bioavailability (41%) and an even more favorable pharmacokinetic profile when administered transdermally (bioavailability of 63%). The patch formulation led to more stable and prolonged plasma concentrations, reduced interindividual variability, and a lower risk of drug accumulation compared to oral administration. These findings suggest that transdermal delivery of memantine may be particularly advantageous for chronic treatment scenarios, potentially enhancing therapeutic outcomes and minimizing side effects related to peak plasma levels.

Furthermore, research by Li et al. (2021) demonstrated that memantine improves the functioning of the entorhinal cortex to CA1 projection in APP/PS1 mouse models of Alzheimer's disease. Memantine not only enhanced synaptic transmission in this circuit but also promoted dendritic spine regeneration of entorhinal cortex neurons, which are crucial for spatial memory. The authors concluded that this mechanism may underline the beneficial cognitive effects in neurodegenerative conditions. This highlights the multifaceted nature of memantine's actions, encompassing both affective and cognitive domains, with effects modulated by dosage, route of administration, and the specific neurobiological context of the disorder being treated.

Thus, memantine demonstrates a broad spectrum of therapeutic effects in correcting cognitive impairments caused by traumatic, neurodegenerative, infectious, and toxic damage to the nervous system in animals. Its multifunctionality opens new perspectives for further research and clinical application.

Piracetam is an effective nootropic drug that demonstrates improvement in cognitive functions in animals

Piracetam is the first nootropic agent in its class, developed in 1964. It remains relevant in modern pharmacotherapy due to its neu-

roprotective, antioxidant, and metabolic activity. Its chemical structure is closely related to other racetams; however, it possesses unique pharmacological properties that significantly affect the functioning of the nervous system in both humans and animals. Piracetam is widely used in veterinary medicine for the treatment of cognitive disorders of various origins in animals (Genton & Van Vleymen, 2020).

The mechanism of action of piracetam is associated with the stimulation of metabolic processes in neurons, improvement of interneuronal communication, and enhancement of cerebral blood flow and oxygen exchange. Piracetam positively influences the function of mitochondria – key structures for neuronal energy supply. Stockburger et al. (2013) highlighted the drug's ability to improve mitochondrial dynamics in brain cells. Thanks to its neuroprotective, metabolic, and antioxidant properties, piracetam can be used to improve memory, attention, correct cognitive impairments, and treat consequences of traumatic brain injuries, hypoxia, strokes, neurotoxicity, and other pathological conditions in animals (Stockburger et al., 2013; Genton & Van Vleymen, 2020; Liu et al., 2024).

Numerous studies on dogs, rats, and other models confirm the therapeutic potential of piracetam. In the study by Liu et al. (2024) there was used a model of vascular dementia in vitro. It was revealed that piracetam significantly reduces oxidative stress and improves mitochondrial function. The authors emphasized that this effect was crucial for the prevention of hypoxic-ischemic brain damage. Piracetam's antioxidant effect on the nervous system through improved mitochondrial function, reduced oxidative stress, and increased ATP levels in neurons was confirmed by Niknahad et al. (2023).

It has been also shown that piracetam enhances memory, learning, and cognitive function. In studies on rats, Genton & Van Vleymen (2000) noted that piracetam's therapeutic effect was most pronounced in animals that experienced hypoxia, drug intoxication, electric shock injury, and aging. Wolthuis (cited by Genton & Van Vleymen, 2000) conducted an experiment in which rats received 100 mg/kg intraperitoneally, followed by training in a Y-maze. After 10 days, rats treated with piracetam showed significantly better performance in avoiding electric shock compared to the control group. This suggests enhanced learning and memory under the influence of piracetam.

Piracetam exhibits a pronounced neuroprotective effect – it helps reduce inflammatory cytokines and improves motor activity in animals (Tripathi et al., 2017; Niknahad et al., 2023). Tripathi et al. (2017) conducted a study on rats with neuroinflammation induced by lipopolysaccharide (LPS). Piracetam administration led to decreased expression of pro-inflammatory factors such as TNF-α and IL-1β, as well as improved behavioral indicators – exploratory activity and spatial memory. The drug also reduces cell death under hypoxic and toxic conditions (Genton & Van Vleymen, 2000).

The results of many experimental studies indicate that piracetam can positively affect cognitive functions themselves in various animal species. Elbeltagy et al. (2024) demonstrated significant memory improvement and enhanced antioxidant protection in mice treated with piracetam alongside with cisplatin, a drug that impairs cognitive function. Mice were tested using a novel location recognition task. Those treated with piracetam performed better, showing reduced neurotoxicity and preserved cognitive functions. Ahmad et al. (2017) confirmed that piracetam improves navigational memory in rats using the Morris water maze test. However, its effect was weaker compared to other nootropics such as modafinil and citicoline. Jawaid et al. (2020) studied the combined neuroprotective effect of piracetam and selegiline in animals with cognitive disorders induced by scopolamine and streptozotocin (simulation of Alzheimer's disease). It was found that the combination was more effective than either drug administered alone. Studies show that piracetam has a high safety profile. Even at high doses (up to 10,000 mg/kg in rats), no fatalities or serious side effects were reported (Genton & Van Vleymen, 2000).

Thus, piracetam is an effective nootropic drug that improves cognitive functions, learning, memory, and behavioral responses in animals. It has neuroprotective, antioxidant, and antidepressant properties, making it a promising agent for correcting cognitive disorders in veterinary practice. Table 3 provides a comparative overview of the pharmacological properties and therapeutic applications memantine and piracetam. Memantine primarily acts as an NMDA receptor antagonist with significant anti-inflammatory and neuroplasticity-promoting properties, making it suitable for complex conditions such as Alzheimer's disease, traumatic brain injury, and addiction. Piracetam, on the other hand, exerts its effects by enhancing neuronal metabolism and membrane function, and is commonly used to improve cognitive deficits associated with vascular and post-traumatic brain injuries, as well as age-related decline.

Table 3

Comparative overview of the pharmacological properties and therapeutic applications of memantine and piracetam

Parameter	Memantine	Piracetam
Mechanism of action	Non-competitive NMDA receptor antagonist; modulates glutamatergic neurotransmission	Enhances neuronal metabolism, mitochondrial function, and membrane fluidity; promotes neuroplasticity
Main effects	Neuroprotection, cognitive enhancement, anti-inflammatory, antidepressant, anti-addictive, antitussive	Cognitive stimulation, improvement of memory and attention, neuroprotection, antioxidant and anti-hypoxic action
Indications in animals	Cognitive disorders, traumatic brain injury, sepsis-induced encephalopathy, Alzheimer's models, addiction, ASD	Vascular and post-traumatic cognitive impairment, stroke, hypoxia, neurotoxicity, age-related cognitive decline
Anti-inflammatory properties	Suppresses TNF-α, IL-1β, NF-κB; reduces microglial activation and glial reactivity	Reduces oxidative stress and lipid peroxidation; moderate anti-inflammatory activity
Neuroplasticity and neurorepair	Enhances synaptic transmission, dendritic spine regeneration, neurogenesis	Improves neuronal membrane structure, increases mitochondrial biogenesis and energy metabolism
Experimental models used	Alzheimer's, TBI, sepsis, autism, drug withdrawal, viral encephalitis, bipolar disorder	Vascular dementia, TBI, ischemic stroke, toxic encephalopathy, cognitive aging
Additional applications	Cough suppression, nicotine addiction, mood stabilization, neuroprotection in chemotherapy	Prevention of post-hypoxic encephalopathy, improvement of motor coordination, support in aging-related decline
Pharmacokinetics	Oral bioavailability ~41%; transdermal ~63%; long half-life; low risk of accumulation with patch use	High oral bioavailability; rapid brain penetration; short half-life; requires multiple doses per day
Limitations	Effect may depend on timing; limited efficacy in compulsive disorders; dose sensitivity	Lower potency in advanced degenerative conditions; fewer effects on neuroinflammation
Therapeutic potential	Broad-spectrum neurotherapeutic agent; promising for complex disorders with multiple pathogenic mechanisms	Effective cognitive enhancer; suitable for early interventions and mild to moderate neurological dysfunction

Thus, this comparison highlights key differences in mechanisms of action, experimental indications, and pharmacokinetic profiles, facilitating an informed understanding of their respective therapeutic potentials and limitations in veterinary and biomedical research contexts.

Oxiracetam exhibits pronounced nootropic and neuroprotective effects on cognitive function in animals

Oxiracetam is a derivative of piracetam and belongs to the group of nootropics used for the treatment of memory and cognitive disorders. Compared to piracetam, oxiracetam demonstrates a stronger stimulating effect on neuroplasticity and the speed of information processing. It possesses vasoprotective, neuroprotective, and anti-inflammatory properties. In veterinary medicine, it is most used for treating cognitive impairments associated with cerebrovascular diseases, ischemic strokes, and traumatic brain injuries (Yao et al., 2016; Li et al., 2017; Fan et al., 2021).

Some of the primary effects of oxiracetam in animals include improvement in learning, memory, and cognitive recovery, which has been confirmed by multiple studies. For example, Fan et al. (2021) demonstrated in studies on rats following ischemic stroke that the drug not only improves cognitive functions but also enhances the morphological condition of neuronal structures, reducing necrosis and activating intracellular protective mechanisms. Oxiracetam promoted the restoration of the blood-brain barrier, reduced neuronal tissue loss, and improved spatial learning in animals. Other researchers also confirmed improvements in cognitive functions, memory, and learning in rats with vascular dementia under oxiracetam treatment (Xu et al., 2019). Li et al. (2017) studied the efficacy of oxiracetam in rats with cognitive impairments caused by chronic cerebral hypoperfusion. Administration of 100–200 mg/kg significantly improved spatial memory, learning, and orientation, and supported the restoration of brain white matter and synaptic transmission in the hippocampus. The drug also enhanced the functional activity of neurons.

The recovery of cognitive functions in animals under the influence of oxiracetam also occurs due to improved cerebral circulation and microcirculation, which in turn reduces neuroinflammation (Li et al., 2017).

Similar results were obtained by Yao et al. (2016), who investigated the effects of oxiracetam in rats with chronic ischemia. Their study showed cognitive recovery through behavioral tests and morphological improvements, including reduced neuronal damage in the hippocampus.

Researchers Youn et al. (2023) confirmed the neuroprotective properties of oxiracetam. They showed that the drug reduced brain edema, intracellular reactive oxygen species, and neuronal apoptosis, contributing to faster recovery of cognitive functions in mice with traumatic brain injuries (TBI). The study also investigated the drug's effect on inflammation during the early phase of TBI. The animal model revealed that oxiracetam decreased pro-inflammatory cytokines (IL-6, TNF-α), reduced gliosis, and prevented cognitive deficits. Behavioral tests demonstrated improvements in spatial memory and orientation, which holds significant clinical relevance for treating brain injury consequences.

The study by Xu et al. (2019) using a rat model of vascular dementia demonstrated that oxiracetam regulates the expression of genes associated with neuronal apoptosis and autophagy. Treatment activated the protective Akt/mTOR signaling pathway, which inhibited cell death processes and promoted neuron survival. This confirms the neuroprotective action of the drug at the molecular level.

The drug is considered safe for use in animals. Liu et al. (2019) conducted toxicokinetic studies of oxiracetam in dogs and found that doses up to 100 mg/kg were safe though temporary gastrointestinal disturbances may occur at high doses in some animals. Long-term administration does not cause clinically significant changes in liver, kidney, or cardiovascular function. This allows oxiracetam to be considered safe even when administered at high doses.

Thus, oxiracetam demonstrates strong nootropic and neuroprotective activity under conditions of cognitive dysfunction. Animal studies have shown that oxiracetam improves learning and memory (as proven in tests such as the Morris water maze and passive avoidance test); increases levels of neurotrophic factors that support neuron survival and regeneration; and protects against oxidative stress and hypoxia, which is important in age-related cognitive decline and neurodegeneration. Due to these effects, oxiracetam is a promising agent for the treatment of cognitive disorders associated with aging, vascular pathologies, and neurodegenerative processes.

Selegiline (deprenyl) is an effective agent for correcting cognitive dysfunctions in animals

Selegiline (L-deprenyl) is a selective monoamine oxidase-B (MAO-B) inhibitor used to treat cognitive impairments in animals, particularly in dogs and rodents. Its neuroprotective and antioxidant properties help reduce cognitive deficits associated with aging, neurodegenerative processes, and ischemic brain injury (Ahmari et al., 2020).

One of the key mechanisms of selegiline's cognitive action is its ability to reduce the breakdown of dopamine and other neurotransmitters as an MAO-B inhibitor (Feizipour et al., 2020). It also has a proven antidepressant effect, likely due to its ability to increase dopamine levels, which in turn enhances motivation for tasks requiring significant effort (Yohn et al., 2018). In a model where animals had to choose between an easy and a challenging way to obtain food, rats treated with selegiline more often chose the effortful task. This indicates an increase in motivational drive, which may be beneficial in treating cognitive dysfunctions associated with apathy or depressive states caused by dopamine deficiency. Feizipour et al. (2020) also confirmed the neuroprotective effects of selegiline even in cases of methamphetamine-induced neurotoxicity.

Additionally, the literature includes several studies examining selegiline's antioxidant activity and its effectiveness in neurodegeneration models in rodents. Ahmari et al. (2020) demonstrated that selegiline, in doses of 1.2–4.0 mg/kg, reduces oxidative stress in neurons, preventing degeneration and significantly improving cognitive function in rats with a model of temporary global ischemia.

Mohamadpour et al. (2024) showed that 30-day administration of selegiline (0.5 mg/kg/day) in a rat model of Alzheimer's disease improved memory, spatial orientation (e.g., in the Morris water maze), reduced anxiety, and normalized the oxidative-antioxidant balance. These findings highlight selegiline's potential as a neuroprotective agent in the context of neurodegeneration.

One of selegiline's mechanisms of action involves its impact on neurotrophic factors – proteins that play a crucial role in neuronal survival, growth, and plasticity. Selegiline increases the levels of brain-derived neurotrophic factor, which promotes neuroplasticity, recovery, and neuron protection, enhancing cognitive functions (Head et al., 1996). It also raises the level of nerve growth factor, supporting neuronal survival and regeneration.

Other researchers have also presented data on selegiline's effectiveness in animals with cognitive dysfunction. Campbell et al. (2001) evaluated the clinical effectiveness of selegiline for cognitive dysfunction in dogs. The study involved 641 dogs with clinical signs of cognitive impairment, including age-related dementia. The dogs received selegiline for 8 weeks. Behavioral changes were assessed using rating scales covering memory, orientation, sleep, and social interaction. After 60 days of treatment with 0.5–1.0 mg/kg, significant improvement was observed in 77.2% of animals. Additionally, 80% of the dogs showed improvement in at least three behavioral domains. The most notable effects were a reduction in disorientation and improved interaction with owners (77.8%). Remarkable changes were already evident after 4 weeks of treatment.

An interesting study by Mills & Ledger (2001) assessed selegiline's impact on dogs' learning ability in the context of training. It was found that selegiline facilitated faster formation of conditioned reflexes, attributed to better concentration and reduced emotional reactivity. Dogs treated with selegiline performed better in tasks requiring motivational effort and were less easily distracted compared to the control group. This is particularly relevant not only for treating cognitive dysfunctions but also for use in working dog training, where effective learning is crucial.

Head et al. (1996) conducted research on the effects of L-deprenyl on spatial short-term memory in young and aged dogs. The drug was administered in doses of 0.5 and 1.0 mg/kg. The results showed no complications in young dogs, while older dogs experienced improved spatial memory, increased activity, and reduced behavioral issues typical of aging.

Clinical studies indicate that selegiline is safe for use in dogs and rodents. Cohn et al. (2002) demonstrated that selegiline administration in healthy dogs caused no major physiological changes or significant effects on cardiovascular, renal, or hepatic function, except for minor fluctuations in heart rate, and was generally well tolerated by animals. Thus, selegiline (deprenyl) is an effective and promising agent for correcting cognitive dysfunction in animals, particularly in cases of aging, ischemic brain injury, and neurodegenerative disorders. Research has shown its effectiveness in improving memory, learning, reducing anxiety, oxidative stress, and neurodegeneration.

Conclusions

Cognitive dysfunction in animals, especially in dogs and rodents, is a significant clinical issue associated with aging, neurodegeneration, and cerebrovascular disorders. Given the parallels with human conditions, research on pharmacological intervention in animals represents a promising area of both human and veterinary relevance. Various drugs are under study for preventing and treating cognitive decline in animals. These include antioxidants, mitochondrial cofactors, cholinesterase inhibitors, CNS stimulants, neuroprotectants, vasodilators, adaptogens, and nutritional supplements. Each targets specific mechanisms: antioxidants and cofactors combat oxidative stress; cholinesterase inhibitors enhance memory; stimulants improve attention and processing.

Donepezil has shown the most promise, acting via acetylcholinesterase inhibition, neuroinflammation reduction, and support for synaptic plasticity. It may also aid in addiction treatment. Innovative delivery methods like intracerebral microspheres aim to extend its effects. Methylphenidate improves focus and memory, especially under catecholaminergic deficits, but carries risks of oxidative stress, anxiety, and behavioral changes. These highlight the need for careful dosing and further safety research. Memantine, an NMDA antagonist, offers wide neuroprotective benefits across various cognitive disorders. It reduces inflammation, prevents neuronal death, and enhances brain function. Its favorable pharmacokinetics and new transdermal forms support broader clinical use. Oxiracetam improves spatial learning, reduces ischemic damage, restores the blood-brain barrier, and enhances circulation, combining cognitive and neuroprotective benefits. Selegiline, a selective MAO-B inhibitor, shows antioxidant and neurotrophic effects, boosting motivation and anxiety control while stimulating brain-derived neurotrophic factor and nerve growth factor production, which aids cognitive recovery in aging and neurodegeneration.

In summary, pharmacological strategies targeting diverse mechanisms show clear potential for treating cognitive dysfunction in animals. Further research should refine dosing, assess long-term effects, explore combination therapies, and be more open to conducting tests in naturally aging models. This is key for both improving animal health and informing treatments for human neurodegenerative disorders.

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References

Achterberg, E. J. M., Damsteegt, R., & Vanderschuren, L. J. M. J. (2018). On the central noradrenergic mechanism underlying the social play-suppressant effect of methylphenidate in rats. Behavioural Brain Research, 347, 158–166.

Achterberg, E. J., van Kerkhof, L. W., Damsteegt, R., Trezza, V., & Vanderschuren, L. J. (2015). Methylphenidate and atomoxetine inhibit social play behavior through prefrontal and subcortical limbic mechanisms in rats. Journal of Neuroscience, 35(1), 161–169.

Ahmad, F., Nayak, V., Malalur, C., Mathew, R. Tripathy, A., & Bairy, K. L. (2017). Relative efficacy of piracetam, modafinil and citicoline on cognitive function in an animal model. Journal of Clinical and Diagnostic Research, 11(11), FC01–FC03.

Ahmari, M., Sharafi, A., Mahmoudi, J., Jafari-Anarkoli, I., Gharbavi, M., & Hosseini, M. J. (2020). Selegiline (L-deprenyl) mitigated oxidative stress, cognitive abnormalities, an histopathological change in rats: Alternative therapy in transient global ischemia. Journal of Molecular Neuroscience, 70(10), 1639–1648.

Allam, E. A. H., Assi, A. A., Badary, D. M., Farrag, M. M. Y., & Nicola, M. A. (2024). Memantine versus ginkgo biloba extract: a comparative study on cognitive dysfunction treatment in a novel rat model. Planta Medica, 90(4), 286–297.

Araujo, J. A., Greig, N. H., Ingram, D. K., Sandin, J., de Rivera, C., & Milgram, N. W. (2011). Cholinesterase inhibitors improve both memory and complex learning in aged beagle dogs. Journal of Alzheimer's Disease, 26(1), 143–155.

Bardaghi, Z., Rajabian, A., Beheshti, F., Arabi, M. H., Hosseini, M., & Salmani, H. (2023). Memantine, an NMDA receptor antagonist, protected the brain against the long-term consequences of sepsis in mice. Life Sciences, 323, 121695.

Beaudin, S. A., Howard, S., Santiago, N., Strupp, B. J., & Smith, D. R. (2024). Methylphenidate alleviates cognitive dysfunction caused by early manganese exposure: Role of catecholaminergic receptors. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 131, 110949.

Boucher, M. L., Conley, G., Morriss, N. J., Ospina-Mora, S., Qiu, J., Mannix, R., & Meehan, W. P. (2024). Time-dependent long-term effect of memantine following repetitive mild traumatic brain injury. Journal of Neurotrauma, 41(13–14), e1736–e1758.

Campbell, S., Trettien, A., & Kozan, B. (2001). A noncomparative open-label study evaluating the effect of selegiline hydrochloride in a clinical setting. Veterinary Therapeutics, 2(1), 24–39.

Chen, C., Xia, S., He, J., Lu, G., Xie, Z., & Han, H. (2019). Roles of taurine in cognitive function of physiology, pathologies and toxication. Life Sciences, 231, 116584.

Cim, N., Cim, B., Akyuz, Cim, E. F., Bulut, S., Mammadov, R., Suleyman, B., Yucel, N., Mendil, A. S., Coban, T. A., & Suleyman, H. (2025). The effect of methylphenidate on the reproductive function of female rats. Journal of Obstetrics and Gynaecology Research, 51(1), e16145.

Cohn, L. A., Dodam, J. R., & Szladovits, B. (2002). Effects of selegiline, phenylpropanolamine, or a combination of both on physiologic and behavioral variables in healthy dogs. The American Journal of Veterinary Research, 63(6), 827–832.

Demontis, F., Falconi, M., Canu, D., & Serra, G. (2015). Memantine prevents "bipolar-like" behavior induced by chronic treatment with imipramine in rats. European Journal of Pharmacology, 752, 49–54.

Dicpinigaitis, P. V., Canning, B. J., Garner, R., Paterson, B. (2015). Effect of memantine on cough reflex sensitivity: Translational studies in guinea pigs and humans. Journal of Pharmacology and Experimental Therapeutics, 352(3), 448–454.

Elbeltagy, M., Khraisat, B., AlZoubi, L., Hmoud, L., AlJeady, A., Yousef, M., & Salman, A. (2024). The neuroprotective effects of Piracetam on cisplatin-induced cognitive decline. International Journal of Neuroscience, 135(3), 337–344.

Fan, W., Zhang, Y., Li, X., & Xu, C. (2021). S-oxiracetam facilitates cognitive restoration after ischemic stroke by activating α7nAChR and the PI3K-mediated pathway. Neurochemical Research, 46(4), 888–904.

Feizipour, S., Sobhani, S., Mehrafza, S., Gholami, M., Motaghinejad, M., Motevalian, M., Safari, S., & Davoudizadeh, R. (2020). Selegiline acts as neuroprotective agent against methamphetamine-prompted mood and cognitive related behavior and neurotoxicity in rats: Involvement of CREB/BDNF and Akt/GSK3 signal pathways. Iranian Journal of Basic Medical Sciences, 23(5), 606–615.

Foschiera, L. N., Schmitz, F., & Wyse, A. T. S. (2022). Evidence of methylphenidate effect on mitochondria, redox homeostasis, and inflammatory aspects: Insights from animal studies. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 116, 110518.

Frizzo, I. B., Koakoski, G., Freddo, N., Maffi, V. C., Bertol, C. D., Barcellos, L. J. G., & Rossato-Grando, L. G. (2020). Chronic exposure to methylphenidate-contaminated water Elicits social impairment to zebrafish. Environmental Toxicology and Pharmacology, 80, 103473.

Genton, P., & Van Vleymen, B. (2000). Piracetam and levetiracetam: Close structuralsimilarities but different pharmacological and clinical profiles. Epileptic Disorders, 2(2), 99–105.

Head, E., Hartley, J., Kameka, A. M., Mehta, R., Ivy, G. O., Ruehl, W. W., & Milgram, N. W. (1996). The effects of L-deprenyl on spatial short term memory in young and aged dogs. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 20(3), 515–530.

Jawaid, T., Kalpana, Kamal, M., Verma, N., Alkhamees, O. A., Alaseem, A. M., & Alsanad, S. M. (2020). Neuroprotective effects of co-administration of selegiline with piracetam on cognitive impairment: Involvement of NR2B, NR1 and bax signaling pathway. International Journal of Pharmacology, 16(8), 529–541.

Kang, J. H., Yang, J. K., Cho, K. H., Lee, O. H., Kwon, H., Kim, S. Y., Kim, S., & Ko, Y. T. (2024a). Intracalvariosseous administration of donepezil microspheres protects against cognitive impairment by virtue of long-lasting brain exposure in mice. Theranostics, 14(17), 6708–6725.

Kang, T., Zheng, J., Jiang, C., Jin, L., Li, C., Chen, B., & Shen, Y. (2024b). Amelioration of walnut, peony seed and camellia seed oils against D-galactose-induced cognitive impairment in mice by regulating gut microbiota. Journal of Functional Foods, 15(13), 7063–7080.
Kapur, A. (2020). Is methylphenidate beneficial and safe in pharmacological cognitive enhancement? CNS Drugs, 34(10), 1045–1062.
Kim, J., Lee, H. J., Park, S. K., Park, J. H., Jeong, H. R., Lee, S., Lee, H., Seol, E., & Hoe, H. S. (2021). Donepezil regulates LPS and Aβ-stimulated neuroinflammation through MAPK/NLRP3 inflammasome/STAT3 signaling. International Journal of Molecular Sciences, 22(19), 10637.
Kumar, H., & Sharma, B. (2016). Memantine ameliorates autistic behavior, biochemistry and blood brain barrier impairments in rats. Brain Research Bulletin, 124, 27–39.
Lee, D. Y., Kim, J. K., Yun, S. W., Han, M. J., & Kim, D. H. (2021). DW2009 elevates the efficacy of donepezil against cognitive impairment in mice. Nutrients, 13(9), 3273.
Lee, S. H., Kim, S. H., Noh, Y. H., Choi, B. M., Noh, G. J., Park, W. D., Kim, E. J., Cho, I. H., & Bae, C. S. (2016). Pharmacokinetics of memantine after a single and multiple dose of oral and patch administration in rats. Basic and Clinical Pharmacology and Toxicology, 118(2), 122–127.
Levin, E. D., Wells, C., Yao, L., Guo, W., Nangia, A., Howard, S., Pippen, E., Hawkey, A. B., Rose, J. E., & Rezvani, A. H. (2019). Chronic memantine decreases nicotine self-administration in rats. European Journal of Pharmacology, 861, 172592.
Li, J., Cao, Y., Xu, J., Li, J., Lv, C., Gao, Q., Zhang, C., Jin, C., Wang, R., Jiao, R., & Zhu, H. (2023). Vitamin D improves cognitive impairment and alleviates ferroptosis via the Nrf2 signaling pathway in aging mice. International Journal of Molecular Sciences, 24(20), 15315.
Li, P., Xu, J., Gu, H., Peng, H., Yin, Y., & Zhuang, J. (2021). Memantine ameliorates cognitive deficit in AD mice via enhancement of entorhinal-CA1 projection. BMC Neuroscience, 22(1), 41.
Li, W., Liu, H., Jiang, H., Wang, C., Guo, Y., Sun, Y., Zhao, X., Xiong, X., Zhang, X., Zhang, K., Nie, Z., & Pu, X. (2017). (S)-Oxiracetam is the active ingredient in oxiracetam that alleviates the cognitive impairment induced by chronic cerebral hypoperfusion in rats. Scientific Reports, 7(1), 10052.
Li, Y. X., Ye, Z. H., Chen T., Jia, X. F., & He, L. (2018). The effects of donepezil on phencyclidine-induced cognitive deficits in a mouse model of schizophrenia. Pharmacology Biochemistry and Behavior, 175, 69–76.
Lim, I., Joung, H-Y., Yu, A. R., Shim, I., & Kim, J. S. (2016). PET Evidence of the effect of donepezil on cognitive performance in an animal model of chemobrain. BioMed Research International, 2016, 6945415.
Liu, J., Yang, N., Wang, X., & Wang, W. (2024). Piracetam reduces oxidative stress and mitochondrial function impairment in an *in vitro* model of vascular dementia. Experimental Brain Research, 242(8), 1841–1850.
Liu, T. T., Guo, X. M., Rong, Z. Y., Ye, X. F., Wei, J. F., Wang, A. P., & Jin, H. T. (2019). Comparative toxicity and toxicokinetic studies of oxiracetam and (S)-oxiracetam in dogs. Xenobiotica, 49(9), 1054–1062.
Ma, Y. Y., Li, X., Yu, Z. Y., Luo, T., Tan, C. R., Bai, Y. D., Xu, G., Sun, B. D., Bu, X. L., Liu, Y. H., Jin, W. S., Gao, Y. Q., Zhou, X. F., Liu, J., & Wang, Y. J. (2024). Oral antioxidant edaravone protects against cognitive deficits induced by chronic hypobaric hypoxia at high altitudes. Translational Psychiatry, 14(1), 415.
MacLean, M. A., Muradov, J. H., Greene, R., Van Hameren, G., Clarke, D. B., Dreier, J. P., Okonkwo, D. O., & Friedman, A. (2023). Memantine inhibits cortical spreading depolarization and improves neurovascular function following repetitive traumatic brain injury. Science Advances, 9(50), eadj2417.
Marszalek-Grabska, M., Gibula-Bruzda, E., Jenda, M., Gawel, K., & Kotlinska, J. H. (2016). Memantine improves memory impairment and depressive-like behavior induced by amphetamine withdrawal in rats. Brain Research, 1642, 389–396.
Mei, D., Wang, F., Yuan, B., Lai, M., Zhou, Y., Cui, W., Liu, H., & Zhou, W. (2023). Cognitive enhancer donepezil attenuates heroin-seeking behavior induced by cues in rats. Journal of Integrative Neuroscience, 22(3), 76.
Mills, D., & Ledger, R. (2001). The effects of oral selegiline hydrochloride on learning and training in the dog: a psychobiological interpretation. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 25(8), 1597–1613.
Mirra, A., Micieli, F., Arnold, M., Spadavecchia, C., & Levionnois, O. L. (2024). The effect of methylphenidate on anaesthesia recovery: An experimental study in pigs. PLoS One, 19(4), e0302166.
Moeller, B. C., Flores, L., Clifford, A., Alarcio, G., Mosburg, M., & Arthur, R. M. (2021). Detection of methylphenidate in equine hair using liquid chromatography-high-resolution mass spectrometry. Molecules, 26(19), 5798.
Mohamadpour, B., Mirazi, N., Komaki, A., Basir, H. S., & Hosseini, A. (2024). Protective effects of selegiline against amyloid beta-induced anxiety-like behavior and memory impairment. Brain and Behavior, 14(6), e3599.
Motaghinejad, M., Motevalian, M., Ebrahimzadeh, A., Larijani, S. F., & Khajehamedi, Z. (2015a). Reduction of methylphenidate induced anxiety, depression and cognition impairment by various doses of venlafaxine in rat. International Journal of Preventive Medicine, 6, 52.
Motaghinejad, M., Motevalian, M., Larijani, S. F., & Khajehamedi, Z. (2015b). Protective effects of forced exercise against methylphenidate-induced anxiety, depression and cognition impairment in rat. Advanced Biomedical Research, 4, 134.
Niknahad, H., Mobasheri, A., Arjmand, A., Rafiei, E., Alidaee S., Razavi, H., Bagheri, S., Rezaei, H., Sabouri, S., Najibi, A., Khodaei, F., Mohammad, S., Kashani, A., Mehdi Ommati, M., & Heidari, R. (2023). Hepatic encephalopathy complications are diminished by piracetam via the interaction between mitochondrial function, oxidative stress, inflammatory response, and locomotor activity. Heliyon, 9(10), e20557.
Novo, J. P., Muga, M., Lourenço, T., Sanches, E. S., Leitão, R. A., & Silva, A. P. (2023). Dichotomous effect of methylphenidate on microglia and astrocytes: Insights from *in vitro* and animal studies. Toxicology Letters, 389, 1–10.
Ordóñez-Gutiérrez, L., Fábrias, G., Casas, J., & Wandosell, F. (2021). Diets with higher ω-6/ω-3 ratios show differences in ceramides and fatty acid levels accompanied by increased amyloid-beta in the brains of male APP/PS1 transgenic mice. International Journal of Molecular Sciences, 22(20), 10907.
Ramon-Duaso, C., Gener, T., Consegal, M., Fernández-Avilés, C., Gallego, J. J., Castarlenas, L., Swanson, M. S., de la Torre, R., Maldonado, R., Puig, M. V., & Robledo, P. (2019). Methylphenidate attenuates the cognitive and mood alterations observed in Mbnl2 knockout mice and reduces microglia overexpression. Cerebral Cortex, 29(7), 2978–2997.
Román, G. C., Jackson, R. E., Gadhia, R., Román, A. N., & Reis, J. (2019). Mediterranean diet: The role of long-chain ω-3 fatty acids in fish; polyphenols in fruits, vegetables, cereals, coffee, tea, cacao and wine; probiotics and vitamins in prevention of stroke, age-related cognitive decline, and Alzheimer disease. Revue Neurologique, 175(10), 724–741.
Salih, N. A., & Al-Baggou, B. K. (2020). Effect of memantine hydrochloride on cisplatin-induced neurobehavioral toxicity in mice. Acta Neurologica Belgica, 120(1), 71–82.
Salman, T., Nawaz, S., Ikram, H., & Haleem, D. J. (2019). Enhancement and impairment of cognitive behaviour in Morris water maze test by methylphenidate to rats. Pakistan Journal of Pharmaceutical Sciences, 32(3), 899–903.
Shin, C. Y., Kim, H-S., Cha, K-H., Won, D. H., Lee, J-Y., Jang, S. W., & Sohn, U. D. (2018). The effects of donepezil, an acetylcholinesterase inhibitor, on impaired learning and memory in rodents. Biomolecules and Therapeutics, 26(3), 274–281.
Stockburger, C., Kurz, C., Koch, K. A., Eckert, S. H. Leuner, K., & Müller, W. E. (2013). Improvement of mitochondrial function and dynamics by the metabolic enhancer piracetam. Biochemical Society Transactions, 41(5), 1331–1334.
Straathof, M., Blezer, E. L. A., Smeele, C. E., van Heijningen, C., van der Toorn, A., Buitelaar, J. K., Glennon, J. C., Otte, W. M., Dijkhuizen, R. M., & Consortium, T. (2022). Memantine treatment does not affect compulsive behavior or frontostriatal connectivity in an adolescent rat model for quinpirole-induced compulsive checking behavior. Psychopharmacology, 239(8), 2457–2470.
Sun, L., Zhou, M., Liu, C., Tang, Y., Xiao, K., Dai, J., Gao, Z., Siew, L., Cao, G., Wu, X., Li, L., & Zhang, R. (2019). Memantine can relieve the neuronal impairment caused by neurotropic virus infection. Journal of Medical Virology, 91(6), 935–940.
Tripathi, A., Paliwal, P., & Krishnamurthy, S. (2017). Piracetam attenuates LPS-induced neuroinflammation and cognitive impairment in rats. Cellular and Molecular Neurobiology, 37(8), 1373–1386.
Wang, D., Cao, L., Zhou, X., Wang, G., Ma, Y., Hao, X., & Fan, H. (2022). Mitigation of honokiol on fluoride-induced mitochondrial oxidative stress, mitochondrial dysfunction, and cognitive deficits through activating AMPK/PGC-1α/Sirt3. Journal of Hazardous Materials, 437, 129381.
Wang, K., Shi, Y., Liu, W., Liu. S., & Sun, M. Z. (2021). Taurine improves neuron injuries and cognitive impairment in a mouse Parkinson's disease model through inhibition of microglial activation. NeuroToxicology, 83, 129–136.
Winocur, G. (2017). Chemotherapy and cognitive impairment: An animal model approach. Canadian Journal of Experimental Psychology, 71(4), 265–273.
Wu, L., Zhou, X., Cao, Y., Mak, S. H., Zha, L., Li, N., Su, Z., Han, Y., Wang, Y., Man Hoi, M. P., Sun, Y., Zhang, G., Zhang, Z., & Yang, X. (2021). Therapeutic efficacy of novel memantine nitrate MN-08 in animal models of Alzheimer's disease. Aging Cell, 20(6), e13371.
Xu, J., Qi, Q., Lv, P., Dong, Y., Jiang, X., & Liu, Z. (2019). Oxiracetam ameliorates cognitive deficits in vascular dementia rats by regulating the expression of neuronal apoptosis/autophagy-related genes associated with the activation of the Akt/mTOR signaling pathway. Brazilian Journal of Medical and Biological Research, 52(11), e8371.

Yao, X. L., Yao, Z. H., Li, L., Nie, L., & Zhang, S. F. (2016). Oxiracetam can improve cognitive impairment after chronic cerebral hypoperfusion in rats. Psychiatry Research, 246, 284–292.
Yohn, S. E., Reynolds, S., Tripodi, G., Correa, M., & Salamone, J. D. (2018). The monoamine-oxidase B inhibitor deprenyl increases selection of high-effort activity in rats tested on a progressive ratio/chow feeding choice procedure: Implications for treating motivational dysfunctions. Behavioural Brain Research, 342, 27–34.
Youn, D. H., Han, S. W., Kim, J. T., Choi, H., Lee, A., Kim, N., Jung, H., Hong, E. P., Park, C. H., Lee, Y., Cho, S. M., & Jeon, J. P. (2023). Oxiracetam alleviates anti-inflammatory activity an ameliorates cognitive impairment in the early phase of traumatic brain injury. Acta Neurochirurgica, 165(8), 2201–2210.
Zabot, G. C., Medeiros, E. B., Macarini, B. M. N., Peruchi, B. B., Keller, G. S., Lídio, A. V., Boaventura, A., de Jesus, L. C., de Bem Silveira, G., Silveira, P. C. L., Chede, B. C., Réus, G. Z., & Budni, J. (2024). The involvement of neuroinflammation in an animal model of dementia and depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 133, 110999.
Zhang, W., Zhong, Y., Wang, Z., Tang, F., & Zheng, C. (2024a). Apple polysaccharide improves age-matched cognitive impairment and intestinal aging through microbiota-gut-brain axis. Scientific Reports, 14(1), 16215.
Zhang, Y. M., Wang, Y. T., Wei, R. M., Li X. Y., Luo, B. L., Zhang, J. Y., Zhang, K. X., Fang, S. K., Liu, X. C., & Chen, G. H. (2024b). Mitochondrial antioxidant elamipretide improves learning and memory impairment induced by chronic sleep deprivation in mice. Brain and Behavior, 14(5), e3508.