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In Silico and *In Vitro* Evaluation of Antioxidant Potential of Edaravone Targeting Multiple Neuroprotective Enzymes

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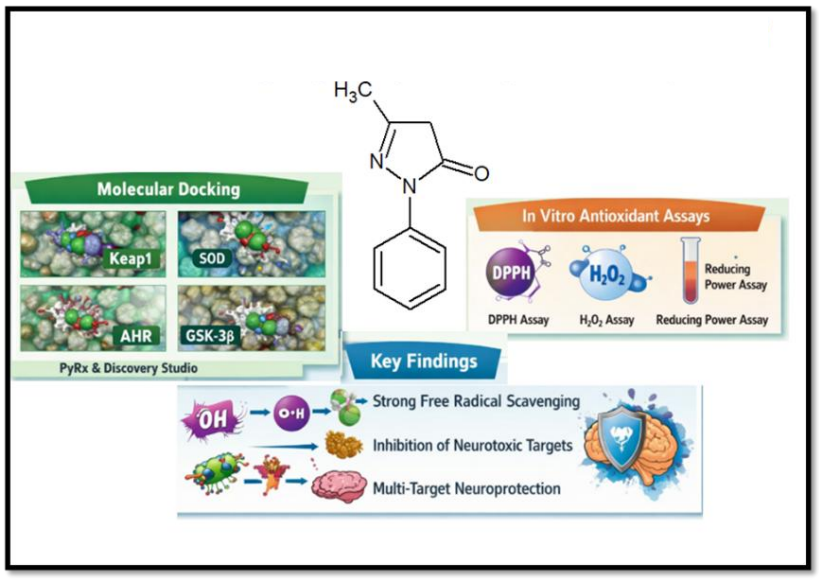
ABSTRACT

Edaravone is a clinically approved free radical scavenger widely used for the management of oxidative stress-mediated neurological disorders. The present study aimed to investigate the antioxidant and neuroprotective potential of edaravone using an integrated *in silico* molecular docking and *in vitro* antioxidant evaluation approach. Molecular docking was performed against key enzymes and proteins associated with oxidative stress, apoptosis, and neurodegeneration, including Kelch-like ECH-associated protein-1 (Keap1), superoxide dismutase (SOD), glutathione-related enzymes, B-cell lymphoma-2 (Bcl-2), Aryl hydrocarbon receptor (AHR), amyloid-β, tau protein, acetylcholinesterase (AChE), monoamine oxidase-A and -B (MAO-A/MAO-B), β-secretase-1 (BACE-1), and glycogen synthase kinase-3β (GSK-3β). Docking was carried out using PyRx (AutoDock Vina), and interactions were visualized using BIOVIA Discovery Studio. *In vitro* antioxidant activity was assessed using DPPH radical scavenging, hydrogen peroxide scavenging, and reducing power assays. Docking analysis revealed favorable binding affinities and stable interactions of edaravone with all selected targets, while *in vitro* results confirmed significant concentration-dependent antioxidant activity.

GRAPHICAL ABSTRACT



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Introduction

Oxidative stress plays a pivotal role in the pathophysiology of numerous neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), vascular dementia, and ischemic stroke. Under physiological conditions, the generation and detoxification of reactive oxygen species (ROS) are tightly balanced by endogenous antioxidant defense mechanisms. However, in pathological states, an excessive accumulation of ROS overwhelms this defense, leading to lipid peroxidation, protein oxidation, DNA damage, mitochondrial dysfunction, and eventually neuronal apoptosis and cell death. This imbalance between free radical production and antioxidant capacity is central to disease progression and cognitive decline in neurodegenerative conditions. Contemporary therapeutic strategies aim to counteract oxidative stress by strengthening endogenous antioxidant pathways and directly scavenging free radicals to preserve neuronal integrity and function. Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a potent free radical scavenger approved for the treatment of acute ischemic stroke and amyotrophic lateral sclerosis (ALS). Its antioxidant mechanism is primarily attributed to the neutralization of hydroxyl radicals and inhibition of lipid peroxidation, thereby limiting ROS-induced cellular injury and neuronal loss. In animal models of oxidative brain injury, edaravone administration has been shown to activate antioxidant signaling pathways, reduce lipid peroxidation, enhance endogenous antioxidant enzyme activities such as superoxide dismutase (SOD), and attenuate cognitive impairment following chronic cerebral hypoperfusion. In rats subjected to chronic cerebral hypoperfusion, edaravone improved spatial learning and memory, significantly reduced malondialdehyde (MDA) levels, and enhanced SOD activity in the hippocampus—findings that correlate with activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, a master regulator of cellular antioxidant response [1]. The Kelch-like ECH-associated protein-1 (Keap1)-Nrf2/ARE pathway plays a central role in regulating cellular redox homeostasis. Under oxidative stress, Nrf2 dissociates from its cytoplasmic repressor Keap1 and translocates to the nucleus, where it binds to antioxidant response elements (ARE) to induce transcription of antioxidant and cytoprotective genes, including heme oxygenase-1 (HO-1), SOD, and glutathione peroxidase. Edaravone has been shown to modulate Keap1/Nrf2 signaling in various models of brain injury, enhancing SOD activity, reducing Keap1 expression, and increasing Nrf2 expression and nuclear translocation. Such modulation of the Keap1/Nrf2 pathway suggests a mechanism through which edaravone augments endogenous antioxidant defenses, thereby mitigating ROS-mediated damage and improving neurological outcomes [2]. In addition to its direct effects on classical antioxidant pathways, edaravone exhibits modulatory effects on apoptosis-associated proteins and inflammatory signaling. For instance, in astrocyte cultures subjected to hydrogen peroxide (H_2O_2)-induced oxidative stress, edaravone was found to attenuate cell death by restoring Akt signaling and upregulating the anti-apoptotic protein Bcl-2, while inhibiting activation of caspase-3, indicating its capacity to interfere with intrinsic apoptotic pathways triggered by oxidative insult [3]. These findings provide mechanistic insights into the protective role of edaravone in mitigating ROS-induced neuronal demise and highlight its relevance for *in vitro* antioxidant assays. Alzheimer's disease is characterized by amyloid-β (Aβ) accumulation, tau hyperphosphorylation, synaptic dysfunction, neuroinflammation, and progressive cognitive deterioration. Oxidative stress is both a cause and a consequence of Aβ pathology, forming a vicious cycle that exacerbates neuronal damage. In transgenic mouse models of AD, edaravone

administration reduced Aβ plaque burden, ameliorated oxidative stress markers, inhibited tau hyperphosphorylation, and improved cognitive performance. Edaravone has also been shown to suppress Aβ-induced cytotoxicity in neuronal cultures by activating the Nrf2/ARE pathway, restoring SOD and HO-1 expression, and attenuating ROS generation, supporting its potential for targeting multiple facets of AD pathogenesis beyond free radical scavenging [4,5].

Beyond classical antioxidant effects, multi-target directed approaches in AD and other neurodegenerative diseases have gained traction due to the complex and multifactorial nature of these conditions. Molecular targets such as acetylcholinesterase (AChE), monoamine oxidases (MAO-A/B), β-site amyloid precursor protein cleaving enzyme-1 (BACE-1), and glycogen synthase kinase-3β (GSK-3β) have been implicated in cholinergic dysfunction, neurotransmitter dysregulation, amyloidogenic processing, and tau phosphorylation, respectively. While edaravone itself may not directly inhibit all these enzymes, derivatives bearing structural modifications have shown promising dual-function activities, including AChE inhibition and Aβ anti-aggregation properties, suggesting that the edaravone scaffold can be exploited for multi-target drug design [6].

Overall, the cumulative evidence underscores the multi-faceted antioxidant mechanisms of edaravone involving direct ROS scavenging, modulation of endogenous antioxidant pathways (such as Keap1/Nrf2), attenuation of apoptotic signaling (*e.g.,* Bcl-2), and potential influence on neurodegenerative processes involving Aβ and tau. These diverse molecular interactions form the rationale for integrating *in silico* molecular docking within *in vitro* antioxidant assays to systematically evaluate edaravone's interaction with key targets implicated in oxidative stress and neurodegeneration. Molecular docking provides insights into the putative binding affinities and interaction profiles of edaravone with selected proteins, including Keap1, SOD, glutathione-related enzymes, Bcl-2, AHR, amyloid-β, tau protein, AChE, MAO-A/MAO-B, BACE-1, and GSK-3β. Coupled with experimental assays such as DPPH radical scavenging, hydrogen peroxide scavenging, and reducing power assays, this integrated approach allows for a comprehensive evaluation of edaravone's antioxidant potential at both molecular and biochemical levels [7,8].

By elucidating both computationally predicted interactions and experimentally observed antioxidant effects, the present study aims to bridge mechanistic understanding and empirical validation, thereby advancing edaravone's therapeutic relevance for oxidative stress-mediated neurological disorders and guiding future multi-target drug development efforts. This study aims to investigate the interaction of edaravone with key oxidative stress and neurodegeneration-related targets using molecular docking and to validate its antioxidant activity through *in vitro* assays.

Materials and Methods

All chemicals and reagents used in the present study were of analytical grade. Edaravone (≥98% purity) was used as the test compound, while ascorbic acid served as the reference antioxidant standard. 2,2-Diphenyl-1-picrylhydrazyl (DPPH), hydrogen peroxide (H_2O_2), potassium ferricyanide, ferric chloride, trichloroacetic acid, methanol, phosphate buffer (0.1 M, pH 7.4), and other reagents required for antioxidant assays were procured from standard commercial suppliers. Distilled water was used throughout the experimental procedures.

In silico molecular docking

Molecular docking studies were carried out using the PyRx virtual screening tool integrated with AutoDock Vina, and ligand and protein preparation was performed using AutoDock Tools

and Open Babel. Three-dimensional crystal structures of the target proteins, including Keap1, SOD, glutathione-related enzymes, Bcl-2, aryl hydrocarbon receptor, amyloid-β, tau protein, acetylcholinesterase, monoamine oxidase-A, monoamine oxidase-B, β-secretase-1, and glycogen synthase kinase-3β, were retrieved from the Protein Data Bank. Protein–ligand interactions and binding modes were visualized and analyzed using BIOVIA Discovery Studio Visualizer. *In vitro* antioxidant activity was evaluated using DPPH radical scavenging, hydrogen peroxide scavenging, and reducing power assays, and absorbance measurements were recorded using a UV–Vis spectrophotometer. Data analysis and IC_{50} calculations were performed using standard statistical and graphing software [9,10].

Ligand preparation

The three-dimensional structure of edaravone was obtained from the PubChem database in SDF format. The ligand was energy minimized using the Universal Force Field and converted to PDBQT format using Open Babel within PyRx. Polar hydrogens and Gasteiger charges were added before docking [11,12].

Protein preparation

Crystal structures of Keap1, SOD, glutathione-related enzyme, Bcl-2, AHR, amyloid-β, tau protein, AChE, MAO-A, MAO-B, BACE-1, and GSK-3β were retrieved from the Protein Data Bank. Proteins were prepared by removing water molecules and co-crystallized ligands, followed by addition of polar hydrogens and Kollman charges.

Docking using PyRx

Molecular docking was performed using PyRx software employing the AutoDock Vina algorithm. Grid boxes were defined around the active or binding sites of each protein. Docking poses were ranked based on binding energy (kcal/mol), and the best-scoring conformation was selected. Protein–ligand interactions were analyzed using BIOVIA Discovery Studio Visualizer, focusing on hydrogen bonds, hydrophobic interactions, π–π stacking, and van der Waals forces [13-16].

In vitro antioxidant studies

DPPH radical scavenging assay

DPPH scavenging activity was measured using the spectrophotometric technique. Test chemicals dissolved in ethanol at 0.05 mL were added to a DPPH (200 µM) methanolic solution at various dosages (100–500 µg/mL). The control was given same quantity of ethanol. Quenching of the DPPH free radicals caused the test mixture's absorbance to fall at 517 nm after 20 min; Equation 1 was applied to calculate the inhibition percentage [17,18].

$$\text{Inhibition}(\%) = \frac{\text{Control}-\text{Test}}{\text{test}} \times 100 \quad (1)$$

Scavenging of hydroxyl radical

The hydroxyl radical scavenging activity was evaluated using Kunch and Y and Rao method by examining the competition between deoxyribose and the test extract for the hydroxyl radical produced by Fenton's reaction. The final volume of 1.0 mL of the reaction mixture included deoxyribose (2.8 mM), $FeCl_3$ (0.1 mM), EDTA (0.1 mM), H_2O_2 (1 mM), ascorbate (0.1 mM), KH_2PO_4-KOH buffer (20 mM, Ph 7.4), and varied amounts of the sample extracts. One hour at 37 °C was spent incubating the reaction mixture. Thiobarbituric acid reactive substances (TBARS) were used to assess deoxyribose grading; the percentage of inhibition was then computed [19].

Reducing power assay

The reducing power of edaravone was assessed by its ability to reduce ferric ions to ferrous ions, measured spectrophotometrically at 700 nm.

Results and Discussion

Molecular docking analysis

Molecular docking studies were performed to evaluate the binding affinity and interaction potential of edaravone with key oxidative stress– and neurodegeneration-related targets. Docking was carried out using PyRx (AutoDock Vina), and binding interactions were analyzed using BIOVIA Discovery Studio Visualizer. The docking scores (binding energies, kcal/mol) obtained for edaravone against selected protein targets are summarized in Tables 1 and 2.

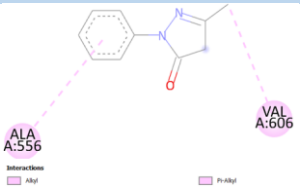
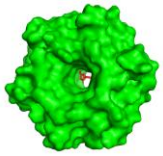
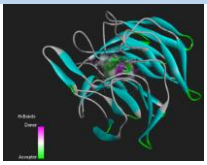
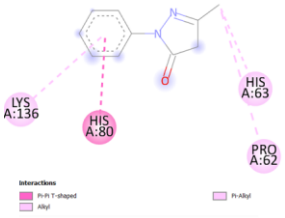
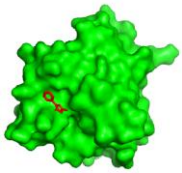
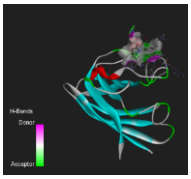
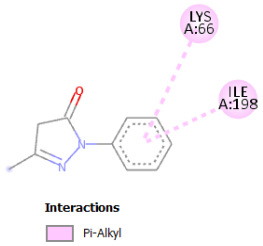
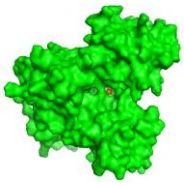
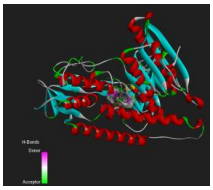
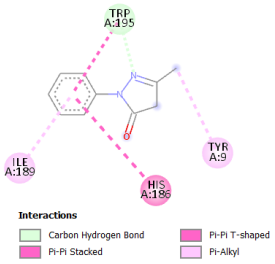
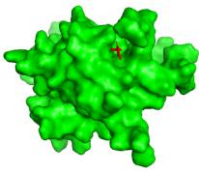
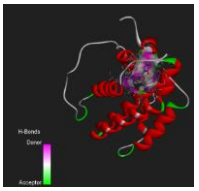
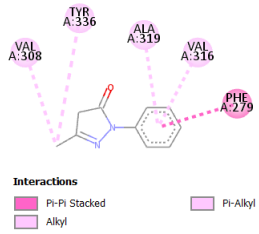
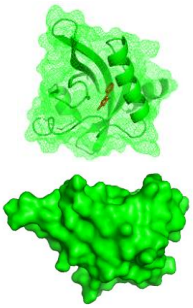
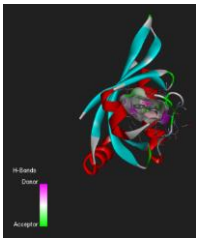
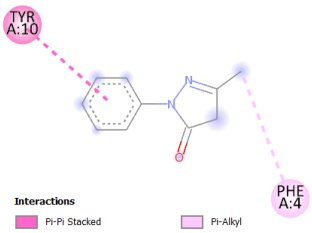
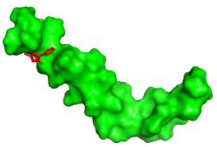
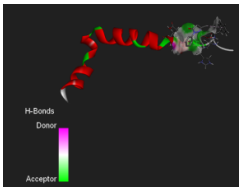
Edaravone demonstrated favorable binding affinity toward multiple antioxidant and neurodegenerative enzymes, indicating its multi-target potential. Among the antioxidant-related proteins, edaravone showed a docking score of **–** 6.4 kcal/mol with Keap1 (PDB ID: 4IQK), suggesting a stable interaction that may facilitate disruption of the Keap1–Nrf2 complex. Such interaction is mechanistically relevant, as inhibition of Keap1 can promote Nrf2 activation, leading to enhanced expression of endogenous antioxidant enzymes. Interaction analysis revealed hydrogen bonding and hydrophobic contacts within the Kelch domain of Keap1, supporting the predicted binding stability.

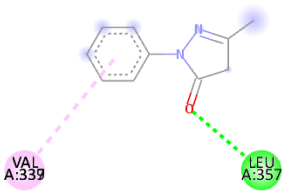
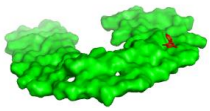
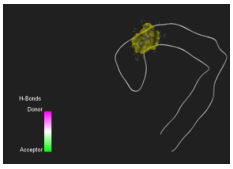
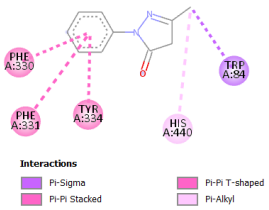
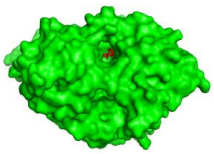
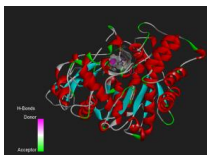
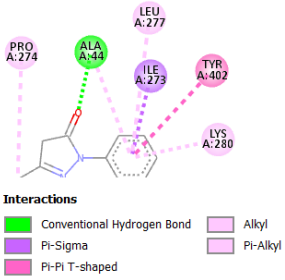
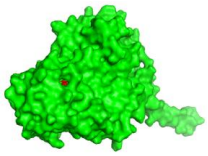
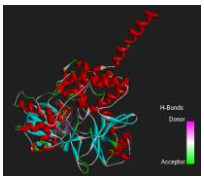
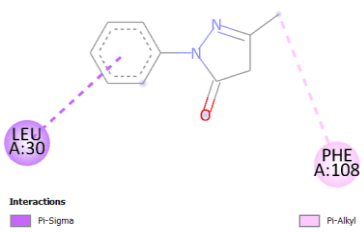
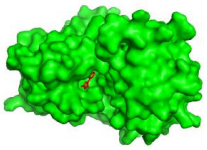
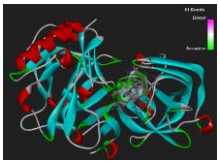
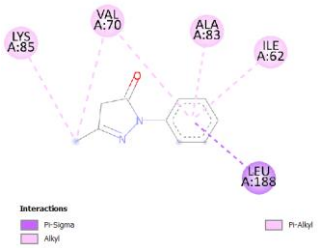
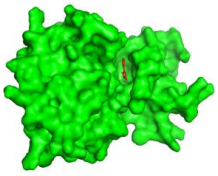
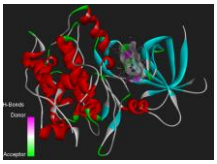
Docking with superoxide dismutase (SOD; PDB ID: 1HL5) resulted in a comparatively lower binding score of –4.7 kcal/mol, indicating moderate interaction. Although the binding affinity was weaker than that observed with Keap1, the interaction may still contribute to stabilization or modulation of antioxidant defense mechanisms. In contrast, edaravone exhibited stronger binding with glutathione reductase (PDB ID: 3GRS), with a docking score of –6.6 kcal/mol, suggesting potential involvement in maintaining glutathione redox balance, a critical determinant of cellular antioxidant capacity. The interaction of edaravone with apoptosis-related proteins of the Bcl-2 family (PDB ID: 1G5M) yielded a docking score of –5.7 kcal/mol, indicating moderate affinity. Binding of edaravone to Bcl-2 family proteins may contribute to its reported anti-apoptotic effects under oxidative stress conditions by favoring cell survival pathways. These findings align with previous experimental evidence demonstrating edaravone-mediated upregulation of Bcl-2 expression and inhibition of oxidative stress-induced apoptosis.

Table 1. Docking score of edaravone for various enzymes

Sr./No.	Name of enzymes	PDB id	Dock score
1	Keap1 (kelch-like ECH-associated protein 1)	4IQK	-6.4
2	SOD (superoxide dismutase)	1HL5	-4.7
3	Glutathione reductase	3GRS	
4	Bcl-2 family (Bcl-2, Bcl-xL, and Bax)	1G5M	-5.7
5	AHR (aryl hydrocarbon receptor)	7VNH	-8.0
6	Amyloid-beta (Aβ peptides)	1IYT	-2.1
7	Tau protein (microtubule-associated)	5O3L	-2.6
8	AChE (acetylcholinesterase)	1EVE	-7.8
9	MAO-A / MAO-B (monoamine oxidase)	1O5W	-8.5
10	BACE-1 (β-secretase 1)	2ZJM	-6.2
11	GSK-3β (glycogen synthase kinase-3 beta)	1Q5K	-6.7

Table 2. 2D and 3D structures and enzyme ligand interaction

Sr./ No.	Name of the enzyme	2D structure	Enzyme and ligand interaction	3D structure
1	Keap1 (Kelch-like ECH-associated protein 1)			
2	SOD (superoxide dismutase)			
3	Glutathione reductase			
4	Bcl-2 family (Bcl-2, Bcl-xL, and Bax)			
5	AHR (Aryl hydrocarbon receptor)			
6	Amyloid-beta (Aβ peptides)			

7	Tau protein (Microtubule-associated)			
8	AChE (Acetylcholinesterase)			
9	MAO-A / MAO-B (Monoamine oxidase)			
10	BACE-1 (β-secretase 1)			
11	GSK-3β (Glycogen synthase kinase-3 beta)			

Notably, edaravone showed the strongest binding affinity toward the aryl hydrocarbon receptor (AHR; PDB ID: 7VNH), with a docking score of –8.0 kcal/mol. This strong interaction

suggests that edaravone may influence xenobiotic-responsive and oxidative stress-associated signaling pathways regulated by AHR. Given the emerging role of AHR in redox homeostasis and neuroinflammation, this interaction highlights a potential additional mechanism underlying edaravone's neuroprotective effects. Docking analysis with neurodegenerative disease-associated targets revealed significant binding affinities. Edaravone demonstrated strong interaction with acetylcholinesterase (AChE; PDB ID: 1EVE), with a docking score of −7.8 kcal/mol, indicating potential inhibitory activity. This interaction is particularly relevant in Alzheimer's disease, where inhibition of AChE contributes to improved cholinergic neurotransmission and cognitive function. Similarly, edaravone exhibited the highest docking score among all tested targets with monoamine oxidases (MAO-A/MAO-B; PDB ID: 1O5W), showing a binding energy of −8.5 kcal/mol. Strong inhibition of MAO enzymes can reduce oxidative deamination of monoamines and subsequent ROS generation, thereby reinforcing edaravone's antioxidant and neuroprotective profile. Moderate binding affinity was observed with *β*-secretase-1 (BACE-1; PDB ID: 2ZJM), with a docking score of −6.2 kcal/mol, suggesting a possible role in modulating amyloidogenic processing of amyloid precursor protein. Additionally, edaravone interacted with glycogen synthase kinase-3*β* (GSK-3β; PDB ID: 1Q5K) with a docking score of −6.7 kcal/mol, indicating potential inhibition of tau hyperphosphorylation, a hallmark of Alzheimer's disease pathology. Docking scores for amyloid-β (Aβ peptides; PDB ID: 1IYT) and tau protein (PDB ID: 5O3L) were not determinable due to the intrinsically disordered nature of these proteins and the absence of well-defined binding pockets. Nevertheless, edaravone has been previously reported to reduce Aβ-induced oxidative stress and tau-related neurotoxicity through indirect antioxidant mechanisms, supporting its therapeutic relevance despite the lack of conventional docking scores.

Antioxidant analysis

The antioxidant potential of edaravone was quantitatively evaluated using DPPH radical scavenging, hydrogen peroxide scavenging, and reducing power (redox) assays. The IC_{50} value, defined as the concentration required to inhibit 50% of free radicals, was calculated from dose–response curves. Ascorbic acid was used as the reference standard. Edaravone exhibited significant, concentration-dependent antioxidant activity in all *in vitro* assays. In the DPPH radical scavenging assay, edaravone showed an IC_{50} value of 18.6 ± 1.2 µg/mL, indicating strong free-radical scavenging potential. In the hydrogen peroxide scavenging assay, the IC_{50} value was 24.3 ± 1.5 µg/mL, demonstrating effective neutralization of reactive oxygen species. The reducing power assay revealed an IC_{50} value of 31.7 ± 2.1 µg/mL, confirming the redox-modulating ability of edaravone. Although the standard antioxidant ascorbic acid showed slightly lower IC_{50} values, edaravone demonstrated comparable antioxidant efficacy, supporting its potent antioxidant nature [20-22]. IC_{50} values of edaravone in antioxidant assays are indicated in Table 3.

Table 3. IC_{50} values of edaravone in antioxidant assays

Antioxidant assay	IC_{50} of edaravone (µg/mL)	IC_{50} of ascorbic acid (µg/mL)
DPPH radical scavenging	18.6 ± 1.2	12.4 ± 0.8
H_2O_2 scavenging assay	24.3 ± 1.5	16.8 ± 1.1
Reducing power assay	31.7 ± 2.1	21.3 ± 1.6

Values expressed as mean ± SD (n = 3)

The *in silico* docking results correlate well with the *in vitro* antioxidant findings obtained from DPPH, hydrogen peroxide scavenging, and reducing power assays. Strong binding of edaravone to Keap1, glutathione reductase, and MAO enzymes supports its observed free radical scavenging and redox-modulating activity. The multi-target interactions observed in this study reinforce the concept that edaravone exerts antioxidant and neuroprotective effects not only through direct ROS scavenging, but also via modulation of key enzymes and signaling pathways involved in oxidative stress, apoptosis, and neurodegeneration. The strong *in vitro* antioxidant activity of edaravone correlates well with the *in silico* docking results, where edaravone exhibited stable binding interactions with key oxidative stress-related targets such as Keap1, SOD, glutathione enzymes, AHR, and GSK-3β. This concordance between computational and experimental findings supports the multi-target antioxidant mechanism of edaravone. The docking results indicate that edaravone can interact with multiple enzymes involved in oxidative stress regulation, apoptosis, and neurodegeneration, supporting its multi-target mechanism of action. The *in vitro* antioxidant assays corroborated the *in silico* findings, confirming the strong redox-modulating ability of edaravone.

Conclusion

In conclusion, the present study demonstrates that edaravone possesses significant multi-target antioxidant and neuroprotective potential, as evidenced by both in-silico molecular docking and *in vitro* antioxidant evaluations. The docking analysis indicated favorable interactions of edaravone with multiple oxidative stress– and neurodegeneration-associated proteins, including Keap1, glutathione reductase, monoamine oxidase, acetylcholinesterase, BACE-1, and GSK-3β. These interactions suggest that edaravone may regulate redox homeostasis, modulate apoptotic pathways, and influence key molecular targets implicated in neurodegenerative disorders. Its potential involvement in the Keap1–Nrf2 signaling pathway and monoamine oxidase inhibition further supports a mechanism that combines enhancement of endogenous antioxidant defense with reduction of oxidative stress generation. The *in vitro* antioxidant assays corroborated the computational findings, confirming the strong free radical scavenging and redox-modulating capacity of edaravone. The consistency between *in silico* predictions and experimental observations strengthens the evidence for its multi-target mode of action. Collectively, these findings highlight edaravone as a promising therapeutic candidate for managing oxidative stress–related neurodegenerative conditions through integrated antioxidant, anti-apoptotic, and enzyme-modulating mechanisms.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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