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SHORT REVIEW

Oxyresveratrol: A Potential Pharmacological Prospective Against Neurodegenerative Diseases

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Abstract

Oxyresveratrol (OXY) is a polyphenolic compound found in various plants, including the heartwood of *Artocarpus lakoocha*, mulberry wood, mulberry twigs, and *Smilacis chinae* rhizome. Numerous reports have highlighted its pharmacological activities, such as antioxidant, anti-inflammatory, and neuroprotective effects. In this review, we specifically focus on the neuroprotective effects of oxyresveratrol in both *in vitro* and *in vivo* models. To conduct this review, we adopted a systematic approach and utilized search engines to explore online databases, covering publications from 2000 to 2021. We carefully analyzed the data and synthesized the findings into a comprehensive table and figure. Our review underscores the application of oxyresveratrol in the context of neurodegenerative diseases, with particular emphasis on conditions such as Alzheimer's Disease (AD), Parkinson's Disease (PD), ischemic strokes, and traumatic brain injury. The findings of our review suggest that oxyresveratrol holds significant promise as a natural compound for the prevention and management of neurodegenerative diseases. However, it is important to note that the clinical application of oxyresveratrol is still limited. Consequently, further research is warranted to explore the potential development of innovative health-promoting products utilizing oxyresveratrol, particularly in the context of protecting against neurodegenerative diseases in ageing populations.

Keywords: Neurodegenerative Diseases, Oxyresveratrol, Pharmacology

1. Introduction

Oxyresveratrol, an OH group of 4-substituted resorcinol, has been discovered in various plants, particularly in the heartwood of *Artocarpus lakoocha*, known as "Ma-Haad" in Thai[1,2]. This plant is indigenous to South and Southeast Asian regions, including Bangladesh, Cambodia, India, Laos, Malaysia, Myanmar, Nepal, Vietnam, and Thailand[3]. Oxyresveratrol exhibits a wide range of pharmacological activities[4]. In traditional Thai medicine, the grey bark of this herb is utilized as an anthelmintic agent for treating tapeworm and scars, while the roots and stem bark are used as antipyretic agents[3,4]. Oxyresveratrol, possessing tyrosinase inhibition, belongs to the stilbene family, like resveratrol, and is often found in its trans-form[5]. This bioactive compound has been traditionally employed as an anthelmintic drug in Thai medicine.

Nowadays, research on herbal plants and their bioactive compounds is gaining significant interest due to their safety profile and minimal side effects. Many researchers have shifted their focus towards exploring the potential use of herbal plants, which are abundant in diverse

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bioactive compounds and have shown neuroprotective properties. These plants contain phenolic compounds and flavonoids that can effectively reduce the activities of Reactive Oxygen Species (ROS) and Nitric Oxide (NO), thus mitigating oxidative stress, which is considered one of the primary causes of neurodegenerative diseases. There are several reports on the phytopharmacological and phytochemical activities of oxyresveratrol, particularly its antioxidant, anti-inflammatory, and neuroprotective effects. However, despite the available literature, the specific details, and underlying mechanisms behind the neuroprotective effects of this compound remain relatively unknown. Therefore, the objective of this study is to provide a comprehensive overview and summary of the neuroprotective effects of oxyresveratrol in the context of neurodegenerative diseases.

2. Methodology

This systematic review followed key elements including utilizing search engines from reputable online databases, employing relevant search terms, and selecting high-quality research articles[6,7]. The review procedure involved describing the results obtained from the selected articles and summarizing the research findings.

2.1 Search Engine

The review team conducted searches on four major online databases: Google Scholar, ScienceDirect, Scopus, and PubMed. Google Scholar provides access to various sources such as websites, articles, book chapters, proceedings, and full-text content. ScienceDirect offers a comprehensive scientific database consisting of articles and book chapters. Scopus is an online database provided by Elsevier. PubMed, on the other hand, is a scientific database that hosts over 30 million papers and provides links to the publishers' sites or free PDFs.

2.2 Search Terms

To gather articles relevant to the pharmacological effects of oxyresveratrol in neurodegenerative diseases, the search was conducted using keywords such as oxyresveratrol, neurodegenerative diseases, Parkinson's disease, Alzheimer's disease, neuroprotective effects, pharmacology, and related terms. The search terms were carefully selected to ensure the relevance of the articles to the study's topic. Articles published between the years 2000 and 2021 were included, focusing on the pharmacological effects of oxyresveratrol in neurodegenerative diseases from various impactful journals. The data pertaining to neuroprotective effects were analyzed and presented in a table and figure format.

3. Oxyresveratrol

3.1 Characteristics of Oxyresveratrol

Oxyresveratrol is a derivative of resveratrol. Its structure consists of a trans-1,2-diphenylethylene nucleus, with each aromatic ring containing OH groups and a dihedral angle of 9.39 degrees[8]. It has a molecular formula of $C_{14}H_{12}O_4$ and a molecular weight of 244.249. Oxyresveratrol exists as a yellow powder with a purity greater than 98% (melting point of 199-204°C), while it appears as an off-white powder with a purity greater than 99%[1]. Oxyresveratrol exhibits good solubility in organic solvents such as methanol, ethanol, acetonitrile, dimethylsulfoxide (DMSO), dimethylformamide, ether, as well as water. When subjected to Thin Layer Chromatography (TLC) analysis with UV light, oxyresveratrol shows blue fluorescence due to its aromaticity. However, it is chemically unstable under basic conditions. Additionally, oxyresveratrol is prone to oxidation by prooxidant agents. To maintain its stability, it is recommended to store oxyresveratrol in a dark room at -40°C[9].

3.2 Pharmacological Activities

Various pharmacological activities of oxyresveratrol, both *in vitro* and *in vivo*, have been reported, including antioxidant activities[10], anti-inflammatory activities[11-13], and notably, neuroprotective effects in the context of Alzheimer's disease, Parkinson's disease, and ischemia models[14-17]. It has also demonstrated anti-apoptotic effects[18] and other beneficial properties[4,19,20].

Oxyresveratrol has exhibited strong antioxidant activity[10] and has shown potential as a scavenger of free radicals, as demonstrated by its effects on 2,2-diphenyl-1-pieryl-hydrazyl (DPPH) and 2,2'-Azinobis-(3-ethylbenzthiazoline-6-sulphonate) (ABTS) with a TEAC assay[21]. In comparison to resveratrol, Oxyresveratrol has been found to be a more effective scavenger in the DPPH radical-scavenging model and has also been shown to reduce the levels of reactive nitrogen and oxygen species under oxidative stress[22]. Furthermore, Oxyresveratrol has displayed anti-inflammatory activities,

as evidenced by the reduction in the levels of IL-4, IL-5, and IL-13 through Th2 inhibition[23].

Oxyresveratrol has potential effects on age-related diseases[10]. It has shown significant neuroprotection against neuronal injury induced by MCAO or brain ischemia[15] and may provide protection after mild traumatic brain injury[17]. Oxyresveratrol has been found to distinctly reduce 6-OHDA-induced phosphorylation of c-Jun N-terminal kinases (JNKs), which are stress-activated kinases, and enhance SIRT1 levels, indicating its potential for neuroprotection[14].

4. Pathology of Neurodegenerative Diseases

Neurodegenerative diseases have emerged as significant health challenges in recent years. The global population affected by neurological disorders is estimated to exceed 1 billion, including conditions such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, dementia, ischemic strokes, and other age-related diseases due to the increasing geriatric population[24-26]. These diseases exhibit diverse pathologies and are characterized by cognitive impairments, memory loss, and other symptoms that affect movement, speech, and overall quality of life associated with health[26].

4.1 Alzheimer's Disease

Alzheimer's Disease (AD) is an age-related neurodegenerative disorder characterized by a progressive loss of cognitive abilities and functions[27,28]. Ageing is the primary risk factor for AD, and genetics, particularly the apolipoprotein E4 gene (APOE-e4), also play a significant role. The prevalence of AD increases with age, with approximately 5.3% of individuals aged 65-74 years, 13.8% of those aged 75-84 years, and 34.6% of those aged ≥ 85 years being affected[29].

The major hallmark of AD is the deposition of amyloid-beta (Ab) protein and the occurrence of aberrant neuronal cell death in the brain. AD is characterized by symptoms such as memory disorders, language impairments, difficulties in learning, and other impairments that significantly impact daily life[25].

4.2 Parkinson's Disease

Parkinson's Disease (PD) is the second most common neurodegenerative disease, following Alzheimer's disease[14,30-36]. James Parkinson first described PD in 1817 as an age-related neurodegenerative disorder affecting elderly individuals[24]. The incidence rates of PD range from 1.5 to 22 cases per 100,000 populations per year, with an overall mortality rate of 2.14 per 100,000 populations[37]. PD is predominantly considered an ageing-associated disease that primarily affects the elderly[38].

PD is characterized by various signs and symptoms. Motor symptoms of PD are typically characterized by rest tremors, bradykinesia, rigidity, and movement disorders, while non-motor symptoms include olfactory impairment, cognitive dysfunction, autonomic dysfunction, and psychiatric manifestations[31]. PD has significant effects on the daily life of patients, resulting in a loss of identity and dignity. It significantly impacts the quality of life and diminishes the ability of patients to maintain social connections[39,40]. Furthermore, with the ageing population and the development of new treatments, the economic impact of PD is expected to increase[37].

The primary pathological hallmark of PD is the loss and death of dopaminergic neurons in the substantia nigra of the human brain. This leads to striatal dopamine deficiency and the formation of α-synuclein protein aggregates known as Lewy bodies. Other contributing factors include oxidative stress and mitochondrial dysfunction[41]. Clinical studies have demonstrated that the loss of dopaminergic neurons, particularly in a moderate to severe state, is associated with the development of motor symptoms. The dopaminergic system, originating from the substantia nigra and ventral tegmental areas, plays a crucial role in cognitive function and language through two projection systems[42].

4.3 Ischemic Stroke

Currently, the World Health Organization (WHO) reports that stroke is the leading cause of death and long-term disability. A stroke occurs when the blood flow to brain tissue is interrupted or reduced. It can be classified into two main types: ischemic and hemorrhagic strokes. Ischemic stroke occurs when there is a blockage in a blood vessel supplying the brain, resulting in a lack of oxygen and glucose in the affected area. On the other hand, hemorrhagic stroke is caused by the rupture of a blood vessel, leading to bleeding into the brain[43,44].

4.4 Traumatic Brain Injury

Traumatic Brain Injury (TBI) is the leading cause of disability and death among individuals under the age of 45 worldwide[45,46]. In the United States alone, it is estimated that nearly 2.5-6.5 million people have experienced TBI[47]. The mortality rates associated with TBI range from 30% to 40%, and more than 60% of cases result in physical, psychosocial, and social impairments[48]. The pathophysiology of TBI involves two stages. In the first stage, there is tissue damage and impairment of cerebral blood flow and metabolism. The second stage is characterized by the excessive release of excitatory neurotransmitters, activation of N-methyl-D-aspartate (NMDA) receptors and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptors, and accumulation of cytosolic Ca^{2+} and Na^{+}[46].

5. Neuroprotective Activity of Oxyresveratrol

Oxyresveratrol has demonstrated neuroprotective effects, as depicted in Figure 1 and Table 1. In widely used AD models, such as Aβ (25-35)-induced neurotoxicity, and PD models using neurotoxins like 6-OHDA and rotenone, oxyresveratrol has shown efficacy in mitigating oxidative stress and neuronal mitochondrial dysfunction[14,34,36,49,50]. The neuroprotective effects of oxyresveratrol include reducing LDH release, inhibiting caspase-3-like activity, and suppressing the JNK pathway in response to 6-OHDA induction.

Several studies have reported that oxyresveratrol has a significant impact on inhibiting the transcription of Activating Transcription Factor 4 (ATF4) in the 6-OHDA

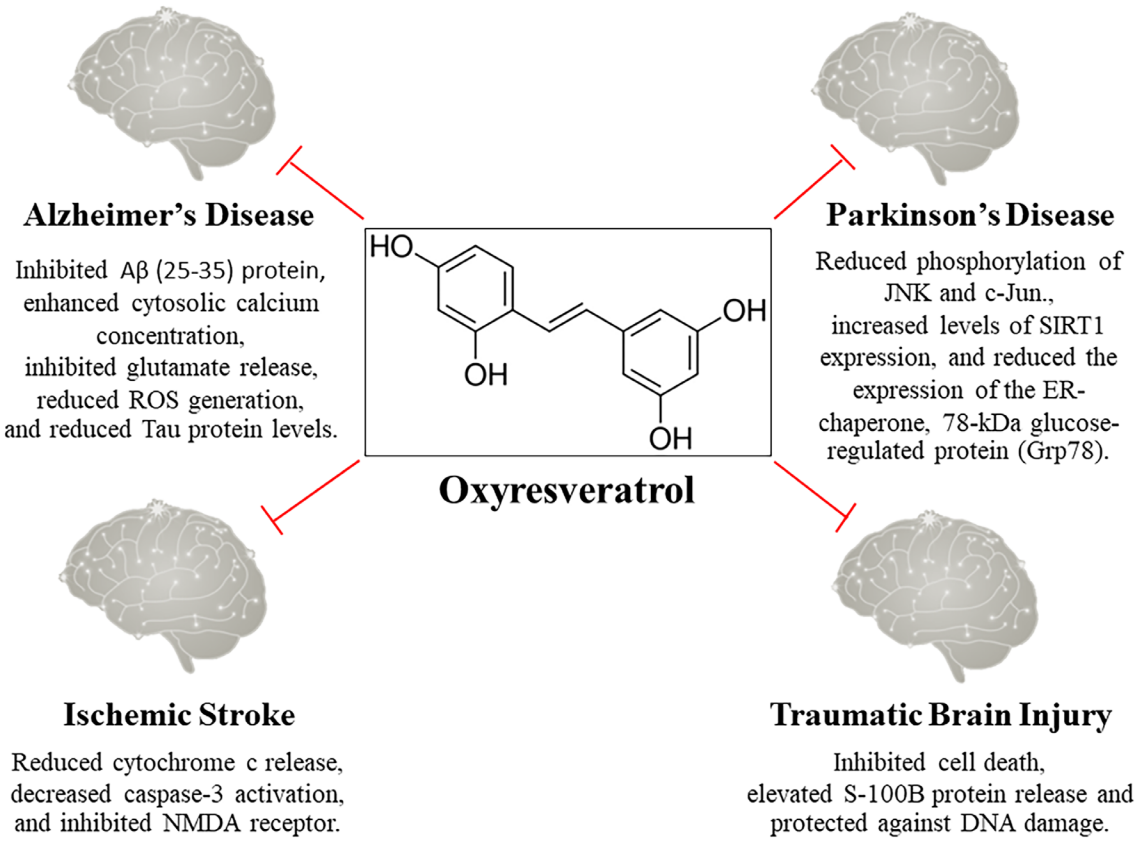

Figure 1. Effects of oxyresveratrol on neuroprotective activities.

Table 1. Model, effects, and mechanism involved in neurodegenerative diseases of oxyresveratrol (OXY)

Neurodegenerative Diseases	Model	Sources of OXY	Effects Summary and Mechanism Involved	References
Alzheimer's disease	Rat cerebral cortical neurons induced by Amyloid β Protein (25-35)	*Smilacis chinae* Rhizome	OXY exhibited significant inhibition of Aβ (25-35)-induced neuronal cell death and enhanced the concentration of cytosolic calcium. Additionally, it effectively inhibited the release of glutamate into the medium and the production of Reactive Oxygen Species (ROS).	53
	Mouse cortical neurons induced by chloroquine diphosphate salt	Standard from Sigma	OXY activates autophagy signalling and alleviates the generation of Amyloid Precursor Protein (APP) in primary cortical astrocytes.	54
	Drosophila fly models induced by human-Tau protein	heartwood of *Artocarpus lakoocha*	OXY, when combined with alkoxy glycerols, reduced the Tau protein level in flies and promoted the function of learning and memory. Additionally, the climbing ability of flies with Tau pathology was examined.	52
Parkinson's disease	SH-SY5Y neuroblastoma cells induced by 6-OHDA	mulberry twigs	OXY significantly reduced the phosphorylation of JNK and c-Jun, which were induced by 6-OHDA. Furthermore, it increased the level of SIRT1.	14
	Supercoiled pBR322 plasmid DNA induced by photosensitized riboflavin	heartwood of *Artocarpus lakoocha*	OXY exhibited a protective effect against DNA damage when compared to the standard antioxidants Trolox and ascorbic acid.	55
	SH-SY5Y neuroblastoma cells induced by H_2O_2	heartwood of *Artocarpus lakoocha*	OXY improved mitochondrial dysfunction, decreased lipid peroxidation release, and reduced ROS production.	16
	Mes23.5 hybrid murine neuroblastoma-glioma cells (N18TG2) induced by 6-OHDA and rat embryonic mesencephalic neurons induced by α-syn model	Standard from Sigma	OXY is markedly shown to protect in the 6-OHDA model by inhibiting the transcription of the ATF4 gene. On the contrary, in the α-syn model, it inhibits the formation of mutant A30P oligomers, leading to a reduction in the expression of the ER-chaperone, 78-kDa glucose-regulated protein (Grp78).	50
	Rat induced by rotenone	heartwood of *Artocarpus lakoocha*	OXY reduced MDA levels and increased catalase activity. The dopaminergic neurons in OXY rats were not different from the control group, while the PD rats showed a low level of dopaminergic neurons compared to the controls.	56
	Rat induced by 6-OHDA	Standard from Sigma	OXY significantly attenuated motor deficits as examined by the apomorphine-induced rotation test, cylinder asymmetric test, and rotarod test.	57
Ischemic stroke	Rat induced by MCAO	mulberry wood	OXY reduced the release of cytochrome c and decreased caspase-3 activity in MCAO rats. Furthermore, it reduced the number of apoptotic nuclei in the ischemic brain compared to the control.	15
	Cortical neurons induced by NMDA	*Smilacis chinae* Rhizome	OXY inhibited NMDA-induced neuronal cell death, reduced intracellular Ca2+ concentration, and decreased ROS production in cortical neurons.	58
Traumatic brain injury	neurons and glia induced trauma by stretch	mulberry wood	OXY significantly inhibited cell death and reduced S-100B protein release.	17
	Mice induced by kainic acid	mulberry wood	OXY reduced the expression levels of FoxO3a and pFoxO3a proteins in the hippocampal CA3 region.	59

model. Conversely, in the α-syn model, oxyresveratrol inhibits A30P oligomer aggregation, thereby reducing the expression of ER-chaperone, 78-kDa glucose-regulated protein (Grp78), in the PD model[50].

In recent years, oxyresveratrol has been found to activate autophagy signalling and alleviate Amyloid Precursor Protein (APP) generation in primary cortical astrocytes. APP is dependent on secretase enzymes, including β-secretase and γ-secretase[51]. By reducing Tau protein levels in flies and promoting learning and memory function during Tau flies' climbing ability tests, oxyresveratrol combined with alkoxy glycerols has shown promising effects[52].

6. Conclusion

This review highlights the immense potential of oxyresveratrol as a highly promising compound for the prevention and improvement of neurodegenerative diseases, including AD, PD, and ischemic stroke. Oxyresveratrol has shown significant effectiveness in targeting various pathological mechanisms associated with these diseases. For instance, in AD models, oxyresveratrol has demonstrated its ability to inhibit Aβ (25-35)-induced neuronal cell death and enhance cytosolic calcium concentration. In PD models, oxyresveratrol has exhibited inhibitory effects on Activating Transcription Factor 4 (ATF4) transcription and increased the expression of genes or proteins related to anti-apoptotic and antioxidant enzymes. Furthermore, oxyresveratrol may have additional preventive effects on other neurodegenerative diseases. However, it is important to note that the efficacy and utility of oxyresveratrol in treating specific neurodegenerative pathologies may vary depending on the models studied. Further research is warranted to explore and develop innovative health-promoting products utilizing oxyresveratrol for the benefit of the elderly population.

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