EVALUATING PROPHYLACTIC AND THERAPEUTIC EFFICACY OF VANILLIC ACID ON NEURODEGENERATIVE DISORDERS: A NARRATIVE REVIEW

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Abstract:
Neurodegenerative illnesses, including Parkinson's disease (PD), Alzheimer's disease (AD), and ischemic stroke (IS), afflict a substantial portion of the global population. These illnesses exhibit a shared characteristic, namely neuroinflammation. Vanillic acid (VA), a phenolic acid found in various plant species, offers several health advantages, notably neuroprotection achieved via anti-inflammatory mechanisms. Therefore, the objective of this review is to compile and analyse various data pertaining to the preventative and therapeutic effects of VA on models of neuroinflammatory and neurodegenerative diseases. The evidence reported in this study elucidated the neuroprotective and therapeutic effects of VA in various animal models, hence substantiating the notion of VA's potential as a viable pharmaceutical candidate for the treatment of neurodegenerative illnesses.

Keywords: Vanillic acid; Phenolic acid; Neurodegeneration; Neuroinflammation; Antioxidant; Anti-inflammatory; Alzheimer’s disease; Brain Ischemia

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Introduction

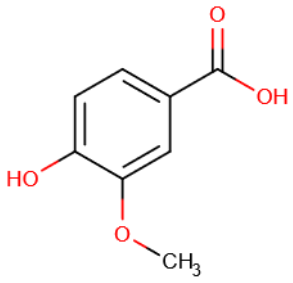
Millions of individuals worldwide experience neurodegenerative disorders including multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), and ischemic stroke (IS). For instance, the global prevalence of people with dementia including AD has increased to 160.84% in 2019 compared to 1990 (Li et al., 2022). Not only AD, but also the prevalence of PD has increased dramatically by 159.73% for the same period (Ou et al., 2021). Moreover, MS prevalence has risen globally to 10.4% in 2016 compared to 1990 (Collaborators, 2019). Besides, stroke was considered as second-leading cause of death in 2019 with an increased prevalence of 70.0% compared to 1990 (Collaborators, 2021). The underlying mechanisms of these disorders' pathogenesis are numerous, such as neuroinflammation and oxidative stress, leading to neurodegeneration. Therefore, inflammatory markers release, demyelination, and synaptic loss are features of these neurodegenerative disorders (Jellinger, 2010).

Vanillic acid (VA) is a pale-yellow phenolic with a creamy and pleasant aroma and is derived from benzoic acid. It possesses properties including antioxidant, antifungal, antidepressant, antinociceptive, anticancer, anti-inflammatory, and neuroprotective activity (Ingole et al., 2021). However, little is known about the underlying molecular processes by which VA exerts neuroprotection.

Sources of VA in plants including but not limited to *Angelica sinensis* (Lü et al., 2009), vanilla beans (Ranadive, 1992), pumpkin seeds (Mitić et al., 2020), papaya, mango, and banana (Siriamornpun & Kaewseejan, 2017), potatoes (Kim et al., 2019), olive oil (Papadopoulos & Boskou, 1991), berries such as strawberry, bilberry, lingonberry, raspberry, cranberry, red, and black currant, red, and yellow gooseberry, rowanberry, and blue berry (Mattila et al., 2006). Also, human consumption of vanilla-flavored product, coffee, tea, and chocolate can produce VA as a metabolic byproduct in urine (Wishart et al., 2022).

The potent antioxidant and anti-inflammatory impact of phenolics have been linked to their beneficial effects on neurodegenerative disorders. Thus, the aim of this review is to gather and assess different research papers concerned with the prophylactic and therapeutic impact of VA on nervous tissue in vitro and vivo.

Table 1. Chemical Structure and Synonyms of Vanillic Acid

Chemical Structure of Vanillic Acid	Vanillic Acid Synonyms
	4-hydroxy-3-methoxy-benzoic acid
	4-hydroxy-3-methoxy-benzoate
	Vanillate
	3-methoxy-4-hydroxybenzoate
	3-methoxy-4-hydroxybenzoic acid
	4-hydroxy-m-anisate
	4-hydroxy-m-anisic acid
	P-vanillate
	P-vanillic acid
	Protocatechuic acid 3-methyl ester
	P-hydroxy-m-methoxy-benzoic acid
	2-methoxy-4-carboxyphenol
	Methylprotocatechuic acid

Adopted from (Wishart et al., 2022)

In Vitro Effect of Vanillic Acid on Neuronal Cells

An in vitro study by Siddiqui and colleagues was designed to determine the anti-inflammatory impact of the VA and gallic acid (GA) on an inflammation model caused by lysolecithin (LPC, 0.003%). Glial cells and neurons from hippocampus were co-cultured, and LPC was introduced to cause inflammation. Software for morphometry was used to quantify neurite outgrowth. Different antibodies were used in immunostaining, sodium dodecyl sulfate polyacrylamide gel electrophoresis, and western blotting methods to determine the degree of myelination and demyelination. The steady repetitive firing pattern was observed using whole-cell patch clamp recordings. It was shown that, after 48 hours in culture, GA, and VA greatly increased neurite outgrowth. In the LPC inflammation's model, both drugs substantially decreased the expression of COX-2, NF-κβ, tenascin-C, chondroitin sulfate proteoglycans, and glial fibrillary acidic protein in astrocytes. Neurites and oligodendrocyte cell bodies treated with GA and VA had their myelin protein levels markedly increased. Both GA and VA treatment restored

prolonged repetitive firing in the LPC inflammation model. These results have demonstrated that VA and GA have anti-inflammatory properties and might be used to treat neurological diseases (Siddiqui et al., 2019).

Another study where Fe^{2+}- induced oxidative toxicity in brain tissue was used to investigate the neuroprotective impact of Vanillin (V) and VA on dysregulated metabolic pathways, cholinergic and nucleotide-hydrolyzing enzymes activities, and oxidative imbalance. Firstly, cytotoxicity of V and VA was tested on HT22 cells. Secondly, treatment of tissue with V and VA has improved GSH level, SOD, and CAT functions, and reduced MDA and nitric oxide (NO) levels that were affected by Fe^{2+}. Thirdly, they increased ATPase function while simultaneously inhibiting AChE and butyrylcholinesterase (BChE). The pentose phosphate and purine metabolism pathways were restored after treatment with V, and the pathways for histidine and selenoamino metabolisms were also simultaneously activated. While VA did not activate any new pathways, it recovered and reactivated oxidatively decreased metabolites and pathways. Both phenolics demonstrated strong catalase binding affinity, but VA had a greater binding energy of about 7.0 kcal/mol. On HT22 cells, neither of phenolic compound was cytotoxic, and their expected toxicity class was 4. These findings imply that vanillin and vanillic acid, with vanillin being the most potent, impart a neuroprotective effect on oxidative brain damage (Salau et al., 2020).

Effect of Vanillic Acid on Alzheimer's Disease Animal Models

Several studies were concerned with AD, a neurodegenerative condition brought on by the accumulation of a protein plaques called amyloid beta (Aβ) in the extracellular space of neurons, that yields to oxidative stress and the demise of neural cells by activating the production of active oxygen species (Berkeley & O'Brien, 2009).

One of the widely used animal models of AD is Aβ-induced rodent model, where an aggregated Aβ is being injected into rodent's brain through intracerebroventricular (ICV) injection to induce a similar pathogenic consequence seen in AD (Poon et al., 2020). A progressive reduction in cognitive ability is one of AD characteristics. For this reason, Ahmadi and colleagues evaluated the impact of VA on learning and memory deficits on $A\beta_{1-40}$-induced AD in rat model by conducting behavioral tests such as Open field (OF) test, novel object recognition (NOR) test, Morris water maze (MWM) test, and passive avoidance learning (PAL). Moreover, they analyzed oxidative stress markers like total antioxidant capacity (TAC), malondialdehyde (MDA) levels, and total oxidant status (TOS). In the diseased group (Aβ-injected group), a reduced cognitive memory, spatial memory, and passive avoidance memory were observed by using NOR, MWM, and PAL respectively. A 50 mg/kg/day of VA treatment, on the other hand, has shown an enhanced recall and learning ability. Moreover, VA dramatically decreased TAC, TOS, and MDA levels compared to Aβ alone group. Therefore, VA can be viewed as a neuroprotective agent in AD because it reduced the impacts of Aβ on learning beside memory via inhibiting oxidative stress (Ahmadi, Safari, et al., 2021). Another study on the same rat model and similar VA dose was conducted to evaluate the neuroprotective impact of VA on the hippocampus' long-term potentiation (LTP). Following stereotaxic surgery, population spike (PS) amplitude as well as excitatory postsynaptic potential (EPSP) slope were measured in dentate gyrus of hippocampus. LTP was elicited by stimulating the perforate pathway at a high frequency. Blood samples were collected to measure the plasma concentrations of MDA and total thiol group (TTG). After inducing LTP, the EPSP slope and PS amplitude in the Aβ -injected rats were both greatly decreased. Accordingly, the results showed that VA lessened the effects of Aβ on LTP. Additionally, using VA showed neuroprotective effects which adverse the damage of Aβ on the hippocampus plasticity both substantially reduce MDA and raise TTG levels. Thus, VA has neuroprotective and antioxidant impact against the Aβ mediated inhibition of LTP, according to this trial on male rats (Ahmadi, Mirazi, et al., 2021). Amin and colleagues used an equivalent model which is $A\beta_{1-42}$-induced mouse model to assess the potential antioxidant influence of VA on oxidative stress and neuroinflammation mediated cognitive impairment. As $A\beta_{1-42}$ ICV injection caused synaptic deficits, memory impairment, increased reactive oxygen species (ROS), neuroinflammation, and neurodegeneration, treatment with VA with a dose of 30mg/kg/day for three weeks reversed ROS synthesis and improved glutathione (GSH) levels in mice brain. Also, VA therapy reduced neuroinflammation, apoptosis of neurons, and alleviated cognitive impairment and synaptic deficits. Additionally, safety of VA treatment was proven on HT22 cells beside improved cell viability upon exposure to $A\beta_{1-42.}$ This research showed that VA has the potential to be a new,

hopeful, and easily available neuroprotective treatment that can be used in neurodegenerative diseases (Amin et al., 2017).

A further commonly used animal model for neuroinflammatory diseases such as AD is lipopolysaccharide (LPS)-induced mouse model. Briefly, LPS injection stimulate neuroinflammation in rodent by activating microglia and astrocytes causing neuronal damage similar to that in AD (Dutta et al., 2008). The pattern recognition receptor signaling event known as receptor for advanced glycation endproducts (RAGE) has been linked to a number of human illnesses, including AD. Thus, this study was aimed to evaluate VA's neuroprotective properties on LPS-induced mouse model via different biochemical, immunofluorescence, and behavioral studies. Firstly, VA co-treated group greatly reduced the expression of RAGE and its downstream phospho-c-Jun n-terminal kinase (p-JNK), which was increased in the LPS-alone treated group. Secondly, VA co-treated group showed reduced pro-inflammatory cytokines release like interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), and cyclooxygenase (COX-2). Moreover, microglia and astrocytes activation decreased in VA treated group. Furthermore, it was found that VA treatment greatly reduced the expression of β-site amyloid precursor protein (APP)-cleaving enzyme 1 (BACE1), and amyloid-β that were induced by LPS and considered as markers of AD. Also, VA treatment enhanced memory and substantially decreased synaptic loss that was caused by LPS-induction via increasing the expression level of presynaptic marker (SYP) and postsynaptic marker (PSD-95). Together, these findings raise the possibility that VA might have neuroprotective effects against LPS-induced neurotoxicity by inhibiting the LPS/RAGE-mediated JNK signaling pathway (Ullah et al., 2020).

Equally important is Streptozotocin (STZ)-induced neurodegeneration rodent model of AD. In this model, STZ injections intracerebroventricularly in mice alter brain chemistry, free radical production, cerebral energy metabolism, and cholinergic transmission, eventually resulting in cognitive deficits. When taken as a whole, these results resemble AD dementia in humans. With this intention, Singh and colleagues' research examined the neuroprotective impact of VA on STZ mouse model via biochemical and behavioral tests. The OF habituation memory test and the Y-maze were used to evaluate the behavioral effects. Superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) were evaluated for oxidative stress evaluation, TNF-α, and acetylcholinesterase (AChE) levels were measured in brain tissue, and plasma corticosterone was measured as well. The five animal groups employed were control, negative control, and three distinct groups of animals each given 25, 50, and 100 mg/kg of VA over the course of 28 days. All groups, except the control group, received ICV injections of STZ on days 14 and 16 of the 28-day VA treatment. Compared to control rats, VA enhanced spatial learning and memory retention by reducing oxidative damage. The habituation memory was greatly improved by VA at doses of 50 and 100 mg/kg, whereas AChE, corticosterone, and TNF-α were lowered and antioxidants SOD, GPx, and CAT were raised. All metrics showed a dose-dependent response to VA (100 mg/kg). Besides, AChE, TNF-a, and corticosterone were reduced in VA (Singh et al., 2015).

Effect of Vanillic Acid on Brain Ischemia Animal Model

Bilateral Common Carotid Artery Occlusion (BCCAO) is a contemporary method for inducing global cerebral ischemia in experimental animals to study brain ischemia. In this model, common carotid artery is being ligated for a certain time depending on the used protocol to induce cerebral ischemia, followed by reperfusion (BCCAO/R) period (Handayani et al., 2019).

Hence, one study was designed to examine the effect of VA on hippocampus LTP injuries brought on using transient bilateral common carotid artery occlusion (tBCCAO) procedure for 30 min to create a model of hypoperfusion before reperfusion (tBCCAO/R) for 72 hours in rats, which was resulted in histological and locomotor abnormalities. VA (100mg/kg/day) was given for 14 days before tBCCAO induction. After BCCAO/R, behavioral, histological, and electrophysiological variables were assessed. According to the data, pretreatment with VA significantly enhanced mobility and memory impairment in contrast to untreated BCCAO/R group. Moreover, the results showed that the field EPSP amplitude and slope were higher in VA-pretreated group than those of the BCCAO/R untreated group. Additionally, when compared to untreated rats, histopathological analysis of VA-pretreated rats revealed significantly less CA1 neuron pattern and cell loss. These findings support the idea that VA protects rodents from transient cerebral ischemia and reperfusion. Also, it suggests that VA can be helpful in cases of

cerebrovascular dysfunction (Khoshnam et al., 2017).

A similar study by Khoshnam and colleagues using same animal model of tBCCAO and tBCCAO/R and experimental design to examine the neuroprotective potential of VA has been carried out. Hippocampi were taken out for TUNEL staining tests, ELISA, and their cognitive function was assessed by MWM test. The outcomes demonstrated that tBCCAO greatly decreased MWM's spatial memory performance. However, pretreatment with VA for 14 days straight greatly improved spatial memory, reduced IL-6 and TNF-α levels, and decreased the number of TUNEL positive cells. Also, it increased the amount of IL-10 in the hippocampi of rats. These findings suggested that VA can be considered as a new, promising, and easily available neuroprotective agent against vascular dementia and states of cerebrovascular inadequacy (Khoshnam, Sarkaki, et al., 2018).

Moreover, a study conducted on the same model to evaluate VA effect on blood-brain barrier (BBB) disfunction, anxiety, cerebral hyperemia, and neurological deficits caused by BCCAO/R. After two weeks of pretreatment with VA, chronic cerebral hypoperfusion was induced. Next to BCCAO, elevated plus maze (EPM) tests, sensorimotor scores, BBB disruption, and cerebral hyperemia were assessed. When compared to untreated rats, pretreatment with VA enhanced the sensory motor indications and anxiety. Besides, VA reduced reactive hyperemia and BBB disfunction in contrast to untreated rats. According to the researchers, these findings were novel on this cerebral hypoperfusion's model and imply that VA might be an effective preparation for cerebral hypoperfusion (Khoshnam, Farbood, et al., 2018).

Effect of Vanillic Acid on Multiple Sclerosis Animal Model

The Cuprizone (CPZ) mouse model is known as an MS model where a copper-chelating agent is used orally to induce either acute or chronic demyelination which is then followed by a period of remyelination. In this study, acute demyelination was induced by feeding mice with 0.3% CPZ-mixed chow for five consecutive weeks. After that, 30 mg/kg of VA was given intraperitoneally to one of the treated groups during remyelination period. Locomotion and anxiety were evaluated using OF test. The results showed that VA promoted locomotion compared to untreated group, and anxiety behaviors were enhanced as well (Alderbi et al., 2022). Another study was conducted on the same CPZ-model to examine the prophylactic effect of a number of medicinal mushrooms on the motor activity and weight of the experimental mice. Pretreatment with a 5% of each mushroom for five weeks has shown both improved motor dysfunction which was assessed by rotarod and recovery of weight loss that were caused by CPZ. Interestingly, those mushrooms *Pleurotus eryngii*, *Ganoderma lucidum*, and *Hericium. Erinaceus* share VA in their phenolic composition and could be used for avoidance and easing of MS manifestations. (Yamashina et al., 2022).

Effect of Vanillic Acid on Parkinson's Disease Animal Model

Rotenone-induced PD model is a well-known model in which rotenone administration is causing a syndrome in rats that mimics the neuropathological results and behavioral signs of PD (von Wrangel et al., 2015). Accordingly, the therapeutic effect of three different doses of VA (12, 25, and 50 mg/kg) given orally as a co-treatment to rotenone of a dose of 2 mg/kg subcutaneously was investigated on rotenone-induced PD model. Rotenone was given continuously for 35 days, which caused the brain to experience oxidative stress by raising the thiobarbituric acid reactive substances (TBARS), and superoxide anion generation (SAG) level and reducing CAT, and GSH levels.

These changes lead to the development of stiff muscles as well as decreased locomotion, weight, and rearing behavior. In comparison to the rotenone group, co-treatment of VA remarkably increased weight, rearing, and locomotor activity, and significantly reduced muscle rigidity and catalepsy in a dose dependent manner. Additionally, it demonstrated enhanced oxidative stress parameters, thereby lowering neuronal oxidative stress. Dopamine (DA) levels were also estimated, and it was discovered that they were higher in the VA treated animals than in the rotenone group. Based on histopathology results, the VA co-treated group had significantly fewer eosinophilic lesions than the rotenone group did. In conclusion, the research demonstrated that levodopa-carbidopa and VA co-treatment greatly reduced motor defects and protected neurons against oxidative stress, suggesting that VA may have therapeutic potential as a neuroprotective in PD (Sharma et al., 2021).

Table 2. Effect of Vanillic Acid on Animal Models of Neurodegenerative Disorders

Affected Parameters	Neurodegenerative Disorders			
	AD	**IS**	**MS**	**PD**
Locomotion		↑	↑	↑
Cognitive Memory	↑			
Spatial Memory	↑	↑		
Habituation Memory	↑	↑		
Sensorimotor Deficit		↓		
Anxiety		↓	↓	
Weight Loss			↓	↓
Catalepsy				↓
Long-Term Potentiation	↑	↑		
Oxidative Stress Markers	TAC ↓ TOS ↓ ROS ↓ MDA ↓			TBARS ↓ SAG ↓
	SOD ↑ CAT ↑ GPx ↑ TTG ↑ GSH ↑			GSH ↑ CAT ↑
Inflammatory Markers	IL-1 ↓ TNF-α ↓	TNF-α ↓ IL-6 ↓		
	COX-2 ↓	IL-10 ↑		
Biochemical Parameters	Corticosterone ↓ AChE ↓			
Synaptic Deficit	↓			
Blood-Brain Barrier Dysfunction		↓		
Cerebral Hyperemia		↓		
Hippocampus Neuronal Damage		↓		
Microglia and Astrocyte Activation	↓			
Apoptosis	↓	↓		
RAGE Expression	↓			
BACE-1 Expression	↓			

Conclusion

The data gathered in this review appears to suggest that VA has a promising neuroprotective and anti-inflammatory activity both in vitro and vivo. More research is needed to better understand the underlying mechanism of VA and involved molecular pathways. We also encourage further research into VA as a potential neuro-prophylactic and neurotherapeutic candidate for treating a range of neurological disorders in humans.

Conflict Of Interest

The authors confirm that this article content has no conflicts of interest.

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List of Abbreviations

AChE Acetylcholinesterase
AD Alzheimer's disease
APP β-amyloid precursor protein
Aβ Amyloid beta
BACE-1 β-site amyloid precursor protein cleaving enzyme 1
BBB Blood-brain barrier
BCCAO Bilateral common carotid artery occlusion
BCCAO/R Bilateral common carotid artery occlusion reperfusion
BChE Butyrylcholinesterase
CAT Catalase
COX-2 Cyclooxygenase

CPZ Cuprizone
DA Dopamine
ELISA Enzyme-linked immunosorbent assay
EPM Elevated plus maze
EPSP Excitatory postsynaptic potential
Fe^{+2} Ferros ion
GA Gallic acid
GPx Glutathione peroxidase
GSH Glutathione
ICV Intracerebroventricular
IL-1 Interleukin-1
IL-10 Interleukin-10
IL-6 Interleukin-6
IS Ischemic stroke
JNK The c-Jun N-terminal kinase pathway
LPS Lipopolysaccharide
LTP Long term potentiation
MDA Malondialdehyde
MS Multiple sclerosis
MWM Morris water maze
Neuro-2A Neuro-2A neuroblastoma
NF-κβ Nuclear factor kappa-light-chain-enhancer of activated B cells
NO Nitric oxide
NOR Novel object recognition
OF Open field
PAL Passive avoidance
PD Parkinson's disease
p-JNK phospho-c-Jun n-terminal kinase
PS Population spike
PSD-95 Post synaptic dense protein 95
RAGE Receptor for advanced glycation endproducts
ROS Reactive oxygen species
SAG Superoxide anion generation
SOD Superoxide dismutase
STZ Streptozotocin
SYP Synaptophysin
TAC Total antioxidant capacity
TBARS Thiobarbituric acid reactive substances
tBCCAO transient bilateral common carotid artery occlusion
tBCCAO/R transient bilateral common carotid artery occlusion reperfusion
TNF-α Tumor necrosis factor alpha
TOS Total oxidant status
TTG Total thiol group
TUNEL Terminal deoxynucleotidyl transferase dUTP nick end labeling
V Vanillin
VA Vanillic acid

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