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

Rasha M. Alderbi[1,2], Mohammad Z. Alam[3,4], Badrah S. Alghamdi[3,5], Ulfat M. Omar[2,6], Faisal S. Al-Shehri[7], Maryam A. Al-Ghamdi[2,8,9]

[1]Research Centre, King Faisal Specialist Hospital and Research Centre, Jeddah, 21499, Saudi Arabia
[2]Biochemistry Department, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia
[3]Neuroscience and Geroscience Research Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia
[4]Department of Medical Laboratory Sciences, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah 21589, Saudi Arabia
[5]Department of Physiology, Neuroscience Unit, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[6]Princess Dr. Najlaa Bint Saud Al-Saud Center of Excellence Research in Biotechnology, King Abdulaziz University, Jeddah, Saudi Arabia
[7]Medical Student, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[8]Vitamin D Pharmacogenomics Research Group, King Abdulaziz University, Saudi Arabia
[9]Experimental Biochemistry Unit, King Fahd Medical Research Center, King Abdulaziz University, Saudi Arabia

Correspondence: Maryam A. Al-Ghamdi
Email: maaalghamdi3@ kau.edu.sa, **Mobile no.:** +966555683221

ABSTRACT: *A considerable number of individuals globally suffer from neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), and ischemic stroke (IS). These disorders share a common feature which is neuroinflammation. The phenolic acid vanillic acid (VA), which is present in a variety of plants, provides many health benefits including neuroprotection through anti-inflammatory processes. Hence, the purpose of this review is to assemble and discuss different studies regarding VA prophylactic and therapeutic potential on neuroinflammatory and neurodegenerative disease models. The data presented in this review highlighted the neuroprotective and therapeutic impact of VA on variable experimental models, supporting the idea of considering VA as a promising drug candidate in neurodegenerative disorders.*

Key words: Vanillic acid; Phenolic acid; Neurodegeneration; Neuroinflammation; Antioxidant; Anti-inflammatory; Alzheimer's disease; Brain Ischemia

INTRODUCTION

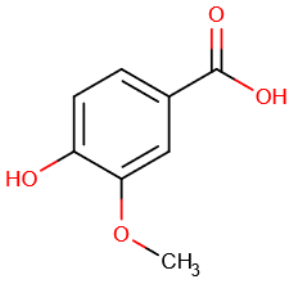
Millions of individuals worldwide experience neurodegenerative disorders including multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), and ischemic stroke (IS). For instance, the global prevalence of people with dementia including AD has increased to 160.84% in 2019 compared to 1990 [1]. Not only AD but also the prevalence of PD has significantly increased by 159.73% for the same period [2]. Moreover, MS prevalence has risen globally to 10.4% in 2016 compared to 1990 [3]. Besides, stroke was considered as second-leading cause of death in 2019 with an increased prevalence of 70.0% compared to 1990 [4]. The underlying mechanisms of these disorders' pathogenesis are numerous, such as neuroinflammation and oxidative stress, leading to neurodegeneration. Therefore, inflammatory marker release, demyelination, and synaptic loss are features of these neurodegenerative disorders [5].

Vanillic acid (VA) is a pale-yellow phenolic with a creamy and pleasant aroma derived from benzoic acid. It possesses properties including antioxidant, antifungal, antidepressant, antinociceptive, anticancer, anti-inflammatory, and neuroprotective activity [6]. However, little is known about the underlying molecular processes by which VA exerts neuroprotection.

Sources of VA in plants include but not limited to *Angelica sinensis* [7], vanilla beans [8], pumpkin seeds [9], papaya, mango, and banana [10], potatoes [11], olive oil [12], berries such as strawberry, bilberry, lingonberry, raspberry, cranberry, red, and black currant, red, and yellow gooseberry, rowanberry, and blueberry [13]. Also, human consumption of vanilla-flavored products, coffee, tea, and chocolate can produce VA as a metabolic byproduct in urine [14].

The potent antioxidant and anti-inflammatory impact of phenolics have been linked to their beneficial effects on neurodegenerative disorders. Thus, this review aims 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)

The 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 the 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 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 [15].

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 enzyme 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 levels, 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 the phenolic compounds 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 [16].

The 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 plaque 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 [17].

One of the widely used animal models of AD is the Aβ-induced rodent model, where an aggregated Aβ is injected into a rodent's brain through intracerebroventricular (ICV) injection to induce a similar pathogenic consequence seen in AD [18]. A progressive reduction in cognitive ability is one of AD characteristics. For this reason, Ahmadi and colleagues [19], evaluated the impact of VA on learning and memory deficits on $A\beta_{1-40}$-induced AD in a rat model by conducting behavioral tests such as the 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), 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 reduces the impacts of Aβ on learning besides memory via inhibiting oxidative stress [20]. 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 the dentate gyrus of the 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 reducing MDA and raising TTG levels. Thus, VA has a neuroprotective and antioxidant impact against the Aβ mediated inhibition of LTP, according to this trial on male rats [21]. Amin and colleagues used an equivalent model which is the $A\beta_{1-42}$-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, and 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 [22].

A further commonly used animal model for neuroinflammatory diseases such as AD is the lipopolysaccharide (LPS)-induced mouse model. Briefly, LPS injection stimulates neuroinflammation in rodents by activating microglia and astrocytes causing neuronal damage similar to that in AD [23]. The pattern recognition receptor signalling event known as a receptor for advanced glycation end products (RAGE) has been linked to some human illnesses, including AD. Thus, this study was aimed at evaluating VA's neuroprotective properties in an LPS-induced mouse model via different biochemical, immunofluorescence, and behavioral studies. Firstly, the 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, the 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 astrocyte 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 the 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 signalling pathway [24].

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 controlled, negative control, and three distinct groups of animals each given 25, 50, and 100 mg/kg of VA over 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 [25]

The 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 [24].

Hence, one study was designed to examine the effect of VA on hippocampus LTP injuries brought on using a 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 the untreated BCCAO/R group. Moreover, the results showed that the field EPSP amplitude and slope were higher in the 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 the VA protects rodents from transient cerebral ischemia and reperfusion. Also, it suggests that VA can be helpful in cases of cerebrovascular dysfunction [26].

A similar study by Khoshnam and colleagues using the 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, and 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 [27]

Moreover, a study was conducted on the same model to evaluate the VA effect on blood-brain barrier (BBB) dysfunction, 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 sensory motor indications and anxiety. Besides, VA reduced reactive hyperemia and BBB dysfunction in contrast to untreated rats. According to the researchers, these findings were novel in this cerebral hypoperfusion model and imply that VA might be an effective preparation for cerebral hypoperfusion [28].

The 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 the remyelination period. Locomotion and anxiety were evaluated using the OF test. The results showed that VA promoted locomotion compared to the untreated group, and anxiety behaviors were enhanced as well [29]. Another study was conducted on the same CPZ model to examine the prophylactic effect of many medicinal mushrooms on the motor activity and weight of the experimental mice. Pretreatment with 5% of each mushroom for five weeks has shown both improved motor dysfunction which was assessed by rotarod and recovery of weight loss which was 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. [30].

The Effect of Vanillic Acid on Parkinson's Disease Animal Model

Rotenone-induced PD model is a well-known model in which rotenone administration causes a syndrome in rats that mimics the neuropathological results and behavioral signs of PD [31]. 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) levels 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 [32].

Table 2. The 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 ↓ COX-2 ↓	TNF-α ↓ IL-6 ↓		
		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's content has no conflicts of interest.

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} Ferrous 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 end products
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

REFERENCES

1. Li, X., Feng, X., Sun, X., Hou, N., Han, F., & Liu, Y. (2022). Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2019. *Front Aging Neurosci*, *14*, 937486. https://doi.org/10.3389/fnagi.2022.937486
2. Ou, Z., Pan, J., Tang, S., Duan, D., Yu, D., Nong, H., & Wang, Z. (2021). Global Trends in the Incidence, Prevalence, and Years Lived With Disability of Parkinson's Disease in 204 Countries/Territories From 1990 to 2019. *Front Public Health*, *9*, 776847. https://doi.org/10.3389/fpubh.2021.776847
3. Collaborators, G. B. D. M. S. (2019). Global, regional, and national burden of multiple sclerosis 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*, *18*(3), 269-285. https://doi.org/10.1016/S1474-4422(18)30443-5
4. Collaborators, G. B. D. S. (2021). Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*, *20*(10), 795-820. https://doi.org/10.1016/S1474-4422(21)00252-0
5. Jellinger, K. A. (2010). Basic mechanisms of neurodegeneration: a critical update. *J Cell Mol Med*, *14*(3), 457-487. https://doi.org/10.1111/j.1582-4934.2010.01010.x
6. Ingole, A. S., Kadam, M. P., Dalu, A. P., Kute, S. M., Mange, P. R., Theng, V. D., Lahane, O. R., Nikas, A. P., Kawal, Y. V., Nagrik, S. U., & Patil, P. A. (2021). A Review of the Pharmacological Characteristics of Vanillic Acid. *Journal of Drug Delivery and Therapeutics*, *11*, 200-204. https://doi.org/10.22270/JDDT.V11I2-S.4823
7. Lü, J.-L., Zhao, J., Duan, J.-A., Yan, H., Tang, Y.-P., & Zhang, L.-B. (2009). Quality Evaluation of Angelica sinensis by Simultaneous Determination of Ten Compounds Using LC-PDA. *Chromatographia*, *70*(3), 455-465. https://doi.org/10.1365/s10337-009-1222-9
8. Ranadive, A. S. (1992). Vanillin and related flavor compounds in vanilla extracts made from beans of various global origins. *Journal of Agricultural and Food Chemistry*, *40*(10), 1922-1924. https://doi.org/10.1021/jf00022a039
9. Mitić, M., Janković, S., Mašković, P., Arsić, B., Mitić, J., & Ickovski, J. (2020). Kinetic models of the extraction of vanillic acid from pumpkin seeds. *Open Chemistry*, *18*(1), 22-30. https://doi.org/doi:10.1515/chem-2020-0001
10. Siriamornpun, S., & Kaewseejan, N. (2017). Quality, bioactive compounds and antioxidant

capacity of selected climacteric fruits with relation to their maturity [Research Paper]. *Scientia Horticulturae*, *221*(14 July 2017), 33-42. https://doi.org/10.1016/j.scienta.2017.04.020

11. Kim, J., Soh, S. Y., Bae, H., & Nam, S.-Y. (2019). Antioxidant and phenolic contents in potatoes (Solanum tuberosum L.) and micropropagated potatoes. *Applied Biological Chemistry*, *62*(1), 17. https://doi.org/10.1186/s13765-019-0422-8
12. Papadopoulos, G., & Boskou, D. (1991). Antioxidant effect of natural phenols on olive oil. *Journal of the American Oil Chemists' Society*, *68*(9), 669-671. https://doi.org/https://doi.org/10.1007/BF02662292
13. Mattila, P., Hellström, J., & Törrönen, R. (2006). Phenolic Acids in Berries, Fruits, and Beverages. *Journal of Agricultural and Food Chemistry*, *54*(19), 7193-7199. https://doi.org/10.1021/jf0615247
14. Wishart, D. S., Guo, A., Oler, E., Wang, F., Anjum, A., Peters, H., Dizon, R., Sayeeda, Z., Tian, S., Lee, B. L., Berjanskii, M., Mah, R., Yamamoto, M., Jovel, J., Torres-Calzada, C., Hiebert-Giesbrecht, M., Lui, V. W., Varshavi, D., Varshavi, D., . . . Gautam, V. (2022). HMDB 5.0: the Human Metabolome Database for 2022. *Nucleic Acids Res*, *50*(D1), D622-d631. https://doi.org/10.1093/nar/gkab1062
15. Siddiqui, S., Kamal, A., Khan, F., Jamali, K. S., & Saify, Z. S. (2019). Gallic and vanillic acid suppress inflammation and promote myelination in an in vitro mouse model of neurodegeneration. *Molecular Biology Reports*, *46*(1), 997-1011. https://doi.org/10.1007/s11033-018-4557-1
16. Ahmadi, N., Safari, S., Mirazi, N., Karimi, S., & Komaki, A. (2021). Effects of vanillic acid on Aβ1-40-induced oxidative stress and learning and memory deficit in male rats. *Brain Research Bulletin*, *170*, 264-273. https://doi.org/https://doi.org/10.1016/j.brainresbull.2021.02.024
17. Berkeley, J. L., & O'Brien, R. J. (2009). CHAPTER 14 - Neurodegenerative and Movement Disorders. In D. N. Irani (Ed.), *Cerebrospinal Fluid in Clinical Practice* (pp. 115-119). W.B. Saunders. https://doi.org/https://doi.org/10.1016/B978-141602908-3.50017-0
18. Poon, C. H., Wang, Y., Fung, M. L., Zhang, C., & Lim, L. W. (2020). Rodent Models of Amyloid-Beta Feature of Alzheimer's Disease: Development and Potential Treatment Implications. *Aging Dis*, *11*(5), 1235-1259. https://doi.org/10.14336/ad.2019.1026
19. Ahmadi, N., Mirazi, N., Komaki, A., Safari, S., & Hosseini, A. (2021). Vanillic acid attenuates amyloid beta1-40-induced long-term potentiation deficit in male rats: an in vivo investigation. *Neurol Res*, *43*(7), 562-569.
20 Ahmadi, N., Safari, S., Mirazi, N., Karimi, S., & Komaki, A. (2021). Effects of vanillic acid on Aβ1-40-induced oxidative stress and learning and memory deficit in male rats. *Brain Research Bulletin*, *170*, 264-273. https://doi.org/https://doi.org/10.1016/j.brainresbull.2021.02.024 https://doi.org/10.1080/01616412.2021.1893565
21. Amin, F. U., Shah, S. A., & Kim, M. O. (2017). Vanillic acid attenuates Abeta(1-42)-induced oxidative stress and cognitive impairment in mice. *Sci Rep*, *7*, 40753. https://doi.org/10.1038/srep40753
22. Dutta, G., Zhang, P., & Liu, B. (2008). The lipopolysaccharide Parkinson's disease animal model: mechanistic studies and drug discovery. *Fundam Clin Pharmacol*, *22*(5), 453-464. https://doi.org/10.1111/j.1472-8206.2008.00616.x
23. Ullah, R., Ikram, M., Park, T. J., Ahmad, R., Saeed, K., Alam, S. I., Rehman, I. U., Khan, A., Khan, I., Jo, M. G., & Kim, M. O. (2020). Vanillic Acid, a Bioactive Phenolic Compound, Counteracts LPS-Induced Neurotoxicity by Regulating c-Jun N-Terminal Kinase in Mouse Brain. *Int J Mol Sci*, *22*(1). https://doi.org/10.3390/ijms22010361
24. Singh, J. C., Kakalij, R. M., Kshirsagar, R. P., Kumar, B. H., Komakula, S. S., & Diwan, P. V. (2015). Cognitive effects of vanillic acid against streptozotocin-induced neurodegeneration in mice. *Pharm Biol*, *53*(5), 630-636. https://doi.org/10.3109/13880209.2014.935866
25 Handayani, E. S., Susilowati, R., Setyopranoto, I., & Partadiredja, G. (2019). Transient Bilateral Common Carotid Artery Occlusion (tBCCAO) of Rats as a Model of Global Cerebral Ischemia. *Bangladesh Journal of Medical Science*.
26. Khoshnam, S. E., Sarkaki, A., Khorsandi, L., Winlow, W., Badavi, M., Moghaddam, H. F., & Farbood, Y. (2017). Vanillic acid attenuates effects of transient bilateral common carotid occlusion and reperfusion in rats. *Biomed Pharmacother*, *96*, 667-674. https://doi.org/10.1016/j.biopha.2017.10.052
27. Khoshnam, S. E., Sarkaki, A., Rashno, M., & Farbood, Y. (2018). Memory deficits and hippocampal inflammation in cerebral hypoperfusion and reperfusion in male rats: Neuroprotective role of vanillic acid. *Life Sci*, *211*, 126-132.

https://doi.org/10.1016/j.lfs.2018.08.065

28. Khoshnam, S. E., Farbood, Y., Fathi Moghaddam, H., Sarkaki, A., Badavi, M., & Khorsandi, L. (2018). Vanillic acid attenuates cerebral hyperemia, blood-brain barrier disruption and anxiety-like behaviors in rats following transient bilateral common carotid occlusion and reperfusion. *Metab Brain Dis*, *33*(3), 785-793. https://doi.org/10.1007/s11011-018-0187-5
29. Alderbi, R. M., Alshahrany, G. A., Alyami, K. A., Alsufiani, H. M., Omar, U. M., & Al-Ghamdi, M. A. (2022). Anti-Inflammatory Compounds Ameliorate Locomotion and Anxiety Behaviors in Cuprizone Mouse Model of Multiple Sclerosis [Abstract]. *MULTIPLE SCLEROSIS AND RELATED DISORDERS*, *59*(103618), 2. https://doi.org/10.1016/j.msard.2022.103618
30. Yamashina, K., Yamamoto, S., Matsumoto, M., Iwasa, K., Takeda, N., Haruta, C., Maruyama, K., Shimizu, K., & Yoshikawa, K. (2022). Suppressive Effect of Fruiting Bodies of Medicinal Mushrooms on Demyelination and Motor Dysfunction in a Cuprizone-Induced Multiple Sclerosis Mouse Model. *Int J Med Mushrooms*, *24*(9), 15-24. https://doi.org/10.1615/IntJMedMushrooms.2022044840
31. von Wrangel, C., Schwabe, K., John, N., Krauss, J. K., & Alam, M. (2015). The rotenone-induced rat model of Parkinson's disease: behavioral and electrophysiological findings. *Behav Brain Res*, *279*, 52-61. https://doi.org/10.1016/j.bbr.2014.11.002
32. Sharma, N., Khurana, N., Muthuraman, A., & Utreja, P. (2021). Pharmacological evaluation of vanillic acid in rotenone-induced Parkinson's disease rat model. *Eur J Pharmacol*, *903*, 174112. https://doi.org/10.1016/j.ejphar.2021.174112