



**Investigating the Effects of Vanillin on the  
6-Hydroxydopamine Model of Parkinson's Disease**

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## نموذج التفويض

أنا رشا خالد علي ابوثوابه ، أفوض جامعة الاسراء بتزويد نسخ من رسالتي للمكتبات أو المؤسسات أو الهيئات أو الأشخاص عند طلبهم حسب التعليمات النافذة في الجامعة.

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## **Dedication**

My sincere gratitude first and foremost goes to the lord of the world, **God** for giving me the strength, knowledge, and the opportunity to move through this project successfully.

I dedicate this thesis to **my lovely parents**, who have always loved me unconditionally; this accomplishment would not have been possible without them.

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**Our challenges don't define us, our actions do**

*Rasha Abuthawabeh*

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**List of Abbreviations**

<b>MPTP</b>	1methyl-4-phenyl-1,2,3,6 tetrahydropyridine
<b>6-OHDA</b>	6-hydroxydopamine
<b>AAV</b>	Adeno-associated virus
<b>AC</b>	Adenylyl cyclase
<b><math>\alpha</math>-syn</b>	Alpha-synuclein
<b>AD</b>	Alzheimer's disease
<b>Bcl-2</b>	B-cell lymphoma-2
<b>COMT</b>	Catechol- <i>O</i> -methyl transferase
<b>CNS</b>	Central nervous system
<b>CT</b>	Computed tomography
<b>CRF</b>	Corticotropin-releasing factor
<b>DBS</b>	Deep brain stimulation
<b>DOPA</b>	Dihydroxyphenylalanine
<b>DA</b>	Dopamine agonists
<b>DAT</b>	Dopamine transporter
<b>Ex-4</b>	Exendin-4
<b>Fe<sup>2+</sup></b>	Ferrous iron
<b>Fe<sup>3+</sup></b>	Ferric iron
<b>GDNF</b>	Glial cell derived neurotrophic factor
<b>GPi</b>	Globus pallidus interna
<b>GLP-1</b>	Glucagon-like peptide 1
<b>GSH</b>	Glutathione
<b>HPLC-ECD</b>	High-Performance Liquid Chromatography-electrochemical detector
<b>H<sub>2</sub>O<sub>2</sub></b>	Hydrogen peroxide
<b>•OH</b>	Hydroxyl radical
<b>iPSC</b>	Induced Pluripotent Stem Cells
<b>IL</b>	Interleukin

<b>I.P</b>	Intraperitoneal
<b>LRRK-2</b>	Leucine-rich repeat kinase 2
<b>L-DOPA</b>	Levodopa
<b>LBs</b>	Lewy bodies
<b>LPS</b>	Lipopolysaccharide
<b>LUHMES</b>	Lund human mesencephalic
<b>MRI</b>	Magnetic resonance imaging
<b>MFB</b>	Medial forebrain bundle
<b>MAO-B</b>	Monoamine oxidase –B
<b>NINDS</b>	National Institute of Neurological Disorders and Stroke
<b>NIH</b>	National Institutes of Health
<b>NTN</b>	Neurturin
<b>NO</b>	Nitric oxide
<b>NMDA</b>	N-methyl-D-aspartate receptor
<b>NAT</b>	Noradrenaline transporter
<b>NFκB</b>	Nuclear Factor Kappa B
<b>PD</b>	Parkinson's disease
<b>PC12</b>	Pheochromocytoma 12
<b>Pc19</b>	Pheochromocytoma 19
<b>PET</b>	Positron emission tomography
<b>PSI</b>	Proteasome inhibitor 1
<b>ROS</b>	Reactive oxygen species
<b>Se</b>	Selenium
<b>SPECT</b>	Single photon emission tomography
<b>S.C</b>	Subcutaneous
<b>SN</b>	Substantia nigra
<b>SNpc</b>	Substantia nigra para compacta
<b>STN</b>	Subthalamic nucleus
<b>O<sub>2</sub>•</b>	Superoxide anion radical
<b>SOD</b>	Superoxide dismutase

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<b>UPS</b>	The ubiquitin–proteasome system
<b>TTP</b>	Tocopherol transfer protein
<b>TCS</b>	Transcranial sonography
<b>TNF-<math>\alpha</math></b>	Tumor necrosis factor- $\alpha$
<b>TH</b>	Tyrosine hydroxylase
<b>UOP</b>	University of Petra
<b>UCN</b>	Urocortin

## **Investigating the Effects of Vanillin on the 6-Hydroxydopamine Model of Parkinson's Disease**

By

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### **ABSTRACT**

**Introduction:** Parkinson's disease (PD) is a progressive neurodegenerative disorder belonging to a group of conditions called motor system disorders. PD is primarily characterized by loss of structure in dopaminergic neurons in the substantia nigra para compacta (SNpc). In recent years; neuroinflammation became one of the significant characteristics that may play a role in the progression of PD. Vanillin is a candidate compound for neuroprotection in PD, it has antioxidant, anti-inflammatory properties and an ability to cross the BBB.

**Aim:** The aim of this study is to investigate the effects of vanillin on the 6-hydroxydopamine (6-OHDA) rodent model of PD. This was done by comparing 6-OHDA lesioned rats in the presence and absence of vanillin. Also, 6-OHDA is very commonly used to induce rodent model of PD, where it produces pathogenesis, progression, motor impairments and creates degeneration of dopaminergic neurons in the SNpc with similarities to human PD. As an animal model of PD, 6-OHDA proved its ability in validating and understanding the role of cell death. Our supposed work demonstrated that vanillin attenuates 6-OHDA-induced cytotoxicity.

**Method:** Male rats weighing between (200-250) g were randomized and divided into groups of 6 rats per group. Group A was considered as control and injected with vehicle only, group B animals were subjected to 6-OHDA alone, and group C was given 6-OHDA + intraperitoneal (i.p) vanillin (20mg/kg) and 3 days later 6-OHDA surgery, group D was subjected to 6-OHDA + (i.p) vanillin 7 days after surgery. On the other hand, group E where 6-OHDA lesioned rats were treated with oral vanillin and 3 days later 6-OHDA surgery, and finally group F where 6-OHDA lesioned rats were treated with oral vanillin 7days after surgery. The lesion severity was assessed behaviorally by apomorphine rotation test, neurochemically, and through immunohistochemistry.

**Results:** Seven days after intracerebral injection of 6-OHDA and following apomorphine challenge, 6-OHDA lesioned rats receiving vanillin showed significantly lower tight contralateral circling in comparison to 6-OHDA only group. Consistent with these observations, striatal tissue dopamine concentrations were significantly higher in 6-OHDA + vanillin treated rats versus 6-OHDA only group, the assay of TH immunoreactivity production was greatly reduced in the substantia nigra (SN) of 6-OHDA rats. While rats co-administered with vanillin presented an increase of TH-positive cell bodies.

**Conclusion:** Initial expectations for vanillin (20mg/kg) showed a promising results aspect as a neuroprotective or neuropreservative and may have potential in the management of PD. In conclusion, our work identified that vanillin act as neuroprotective compound with a capacity to slow down the degeneration of dopaminergic neuron, regenerate lost dopaminergic neurons and protect dopaminergic neurons that have not yet been affected by the disease which if translated therapeutically would offer a significant advance in PD treatment and prevention.