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# بسم الله الرحمن الرحيم

مركز الشبكات وتكنولوجيا المعلومات

قسم التوثيق الإلكتروني



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# جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

## قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها  
على هذه الأقراص المدمجة قد أعدت دون أية تغييرات





**Department of Biochemistry**  
**The effect of the flavonoid quercetin on the modulation of the  
amyloid pathway in Aluminum chloride-induced Alzheimer  
disease in rats**

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## **Abstract**

Alzheimer's disease (AD) is a neurodegenerative disease clinically characterized by progressive cognitive impairment. Exposure to aluminum (Al), a potent neurotoxin, causes oxidative stress and initiates the development of Alzheimer's disease. Quercetin (Q), a bioflavonoid, has been reported to slow down AD progression. The aim of this study was to look into the role of Q in treating and protecting  $\text{AlCl}_3$ -induced AD rats by looking into the molecular processes that underpin its neuroprotective and therapeutic effects. In this study, male Wistar rats were subjected to a two independent experiments; experiment I (effect of post treatment with quercetin) in which the rats were distributed into; a normal control group which induced with saline for 56 days, two quercetin doses groups that is orally administrated with Q (25 and 50 mg/kg) for 28 days after induction with saline for 28 days, AD group, that is IP(Intraperitoneally) administrated with  $\text{AlCl}_3$ (50 mg/kg) for 28 days followed by saline for 28 days, and the treated groups :( $\text{AlCl}_3$  followed by Q25), and ( $\text{AlCl}_3$  followed by Q50) for 28 days, as well as, experiment II (Coadministration of  $\text{AlCl}_3$  with quercetin) that divided into a normal control (NC) group, two quercetin doses (both 25 and 50 mg/kg) groups,  $\text{AlCl}_3$  (AD) group, co-administration with  $\text{AlCl}_3$  + Q25 group, and co-administration with  $\text{AlCl}_3$  + Q50 group for 56 consecutive days. Behavioral assessments were carried out on rats in the final week of both experiments. Hippocampi were collected for neurochemical and histological evaluations, as well as gene expression assessment. The results of experiment 1 demonstrated that administration of Q to an  $\text{AlCl}_3$ -induced AD rat model reduced behavioral impairments, improved cholinergic and dopaminergic dysfunctions, and decreased the formation of insoluble amyloid plaques in the hippocampus. In the hippocampus, these beneficial effects of Q were linked to downregulation of

APP, BACE1, APOE, and PSEN1 and upregulation of ADAM10 and ADAM17 gene expression levels. Moreover, experiment 2 resulted in; the co-administration of quercetin (50 mg/kg) has a substantial effect on learning and memory deficits by reducing eosinophilic plaques and  $\beta$ -amyloid plaque deposits, as well as restoring the activity of Acetylcholine esterase (AChE) and increasing dopamine (DA) level. Furthermore, it significantly decreased levels of amyloid precursor protein (APP),  $\beta$ -amyloid converting enzyme 1 (BACE1), and Presenilin I (PSEN1) and increased the expression of ADAM17 in the hippocampus tissue compared to  $AlCl_3$  group. Conclusion: Q treatment might attenuate neurotransmission impairment,  $A\beta$  aggregation in the hippocampus, and behavioral deficits in the  $AlCl_3$ -induced AD rat model via up-regulating and stimulating the non-amyloidogenic pathway leading to the inhibition of the amyloidogenic pathway in the mild Alzheimer. In addition, co-administration of quercetin with the  $AlCl_3$ -induced AD rats could also inhibit the progression of cognitive impairment in the hippocampus tissue in the severe AD through inhibition of the genes of the amyloidogenic pathway.

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### **List of Abbreviations**

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>AD</b>                               | Alzheimer's disease                          |
| <b>AChE</b>                             | Acetylcholine Esterase                       |
| <b>ADAM</b>                             | Membrane-bound disintegrin metalloproteinase |
| <b>AICD</b>                             | APP intracellular domain                     |
| <b>AlCl<sub>3</sub></b>                 | Aluminum chloride                            |
| <b>Alum</b>                             | Aluminum sulphate                            |
| <b>Aph1</b>                             | Anterior pharynx-defective 1                 |
| <b>APOE</b>                             | Apolipoprotein E                             |
| <b>APP</b>                              | Amyloid precursor protein                    |
| <b>APP CTF83/<math>\alpha</math>CTF</b> | APP C-terminal fragment 83                   |
| <b>APP <math>\beta</math>CTF /C99</b>   | membrane-associated C-terminal APP fragment  |
| <b>A<math>\beta</math></b>              | Amyloid-Beta                                 |
| <b>BACE1</b>                            | $\beta$ -secretase 1                         |
| <b>BBB</b>                              | Blood Brain Barrier                          |
| <b>BChE</b>                             | Butyryl cholinesterase                       |
| <b>CAA</b>                              | Cerebral Amyloid Angiopathy                  |
| <b>CDK5</b>                             | Cyclin dependent kinase                      |
| <b>COX-2</b>                            | cyclo oxygenase 2                            |
| <b>DA</b>                               | Dopamine                                     |
| <b>DTNB</b>                             | 5,5'-dithio-bis-2-nitrobenzoic acid          |
| <b>EOAD</b>                             | Early-Onset Alzheimer Disease                |
| <b>ep</b>                               | eosinophilic plaques                         |
| <b>GSK-3<math>\beta</math></b>          | Glycogen synthase kinase 3 beta              |
| <b>H &amp; E</b>                        | Hematoxylin and eosin stain                  |
| <b>HC</b>                               | Habenular Commissure                         |
| <b>HD</b>                               | Huntington's disease                         |
| <b>IL-6</b>                             | Interleukin 6                                |
| <b>iNOS</b>                             | inducible nitric oxide synthase              |
| <b>IP</b>                               | Intraperitoneally                            |
| <b>IRE</b>                              | Iron responsive element                      |
| <b>LB</b>                               | Lewy bodies                                  |

## *List of Abbreviations*

|                                        |                                                                             |
|----------------------------------------|-----------------------------------------------------------------------------|
| <b>LBD</b>                             | Lewy Body Dementia                                                          |
| <b>LOAD</b>                            | late-onset Alzheimer's disease                                              |
| <b>MAPKs</b>                           | Mitogen Activated Protein Kinase                                            |
| <b>MCI</b>                             | Mild cognitive impairment                                                   |
| <b>MD</b>                              | Mixed Dementia                                                              |
| <b>Nct</b>                             | Nicestrin                                                                   |
| <b>NF-<math>\kappa</math>B</b>         | Nuclear factor kappa B                                                      |
| <b>NFT</b>                             | Neurofibrillary tangles                                                     |
| <b>NMDA</b>                            | N-methyl-d-aspartate                                                        |
| <b>Nrf-2</b>                           | Nuclear factor (erythroid-derived 2)-like 2                                 |
| <b>PD</b>                              | Parkinson's disease                                                         |
| <b>PDD</b>                             | Parkinson's disease dementia                                                |
| <b>Pen-2</b>                           | Presenilin enhancer 2                                                       |
| <b>PI3K/Akt/GSK3<math>\beta</math></b> | phosphoinositide3 kinase/protein kinase B/Glycogen synthase kinase3 $\beta$ |
| <b>pn</b>                              | pyramidal neuron                                                            |
| <b>PON2</b>                            | paraoxonase 2                                                               |
| <b>PP2A</b>                            | protein phosphatase 2A                                                      |
| <b>PSEN1</b>                           | Presenilin 1                                                                |
| <b>Q</b>                               | Quercetin                                                                   |
| <b>ROS</b>                             | Reactive Oxygen Species                                                     |
| <b>SAP97</b>                           | Synapse-associated protein 97                                               |
| <b>sAPP</b>                            | soluble APP-fragment                                                        |
| <b>SE</b>                              | Standard error of mean                                                      |
| <b>SOD</b>                             | superoxide dismutase                                                        |
| <b>SP</b>                              | Senile plaques                                                              |
| <b>TACE</b>                            | Tumor necrosis factor-alpha converting enzyme                               |
| <b>TBI</b>                             | Traumatic brain injury                                                      |
| <b>TNF-alpha</b>                       | tumor necrosis factor-alpha                                                 |
| <b>VaD</b>                             | Vascular Dementia                                                           |
| <b>WHO</b>                             | World Health Organization                                                   |

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