UNIVERSITI PUTRA MALAYSIA

NEUROPROTECTIVE EFFECT OF 7-GERANYLOXYCINNAMIC ACID ISOLATED FROM Melicope lunu-ankenda (Gaertn.) T.G. HARTLEY LEAVES In Vitro

ZEINAB ABDULWANIS MASAOUD MOHAMED

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ZEINAB ABDULWANIS MASAOUD MOHAMED

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

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December 2020

Chairman : Associate Professor Ahmad Faizal Abdull Razis, PhD
Institute : Bioscience

Neurodegenerative diseases (NDDs) are chronic and incurable conditions and have drawn robust attention of researchers due to their social and economic burdens. Lately, approximately 55 million people in the world were reported to suffer from one or more NDDs, notably a larger percentage suffers from AD because their longevity have increased. In Malaysia, the number of people with NDDs is projected to increase from 123,000 people in 2015 to be 261,000 by 2030 and will continue to increase to 590,000 people in 2050. Therefore, the strategies of using phytotherapeutic agents as alternative sources for NDDs therapy has become necessary. Several secondary metabolites have been isolated from *Melicope lunu-ankenda* (Gaertn.) T.G. Hartley plant (known in Malaysia as "tenggek burung") leaves such as phenolic acid derivatives including 7-geranyloxycinnamic acid. However, the neuroprotective activity of 7-geranyloxycinnamic acid not studied till date. Thus, the aim of present study was to elucidate the *in vitro* neuroprotective activity of 7-geranyloxycinnamic acid isolated from *M. lunu-ankenda* leaves. In this regard, 7-geranyloxycinnamic acid was tested for neuroprotection on retinoic acid (RA)-induced differentiation of human neuroblastoma (SH-SY5Y) cell lines, and compared with curcumin, which was used as positive control in this study. SH-SY5Y cells were treated with 10 µM RA for 7-days, and then observed under a fluorescence microscope (phase contrast) to monitor differentiation and measure neurite length of undifferentiated and differentiated SH-SY5Y cell line. The differentiation of SH-SY5Y cell line was further ascertained by immunocytochemistry assay, whereby III β-tubulin (tuj-1) expression was detected by an Alexa fluorophore- 488 secondary antibody conjugate. Cell viability and neuroprotection were first assayed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reagent to determine the highest cell viability concentration of 7-geranyloxycinnamic acid, whereby the differentiated cells were pre-treated with serially diluted concentrations of 7-geranyloxycinnamic acid for

24, 48 and 72 hours before being exposed for 4 hours to H_2O_2 (300 μM). Annexin V-FITC assay by using flow cytometry and fluorescence microscopy by means of acridine orange and propidium iodide (AO/PI) double staining were employed to analyze the apoptotic inhibition ability of the compound on the differentiated cells. Surface morphological assessment and ultrastructural analysis were then conducted using scanning and transmission electron microscopy to evaluate the effect of the compound on surface morphology and internal features of the cells. The results showed that treatment of SH-SY5Y cells with RA for 7-days differentiated the cells into neurons and showed extended neurites, which was confirmed by the expression of class III β-tubulin (tuj-1) neuronal marker. Pre-treatment of neuronal cells with 7-geranyloxycinnamic acid (2.08 μM), particularly after 72 hours of treatment, significantly protected the differentiated SH-SY5Y cells against H_2O_2-induced apoptotic cell death, which was similar to the treatment of cells with 5.97 μM Curcumin plus 4 h exposure to H_2O_2 (300 μM). fluorescence microscopy after AO/PI staining showed neuroprotective activity of 2.08 μM 7-geranyloxycinnamic acid against nuclei damages due to H_2O_2 exposure that perhaps leads to cellular death via apoptosis, this figure is similar to what was observed when the cells were treated with curcumin prior to H_2O_2. The neuroprotective activity of 2.08 μM 7-geranyloxycinnamic acid against H_2O_2-induced apoptosis was ascertained by annexin V-FITC, whereby the cells pre-treated with either 7-geranyloxycinnamic acid or curcumin showed a low level of apoptosis and high cell viability. Surface morphology and internal features of the cells were appeared protected by 7-geranyloxycinnamic acid treatment, which were similar to those pre-treated with curcumin before H_2O_2 insult. The present finding suggested the neuroprotective potential of 7-geranyloxycinnamic acid on neuronal cells against H_2O_2-induced neurotoxicity, which was the first study discovered neuroprotective effect of 7-geranyloxycinnamic acid via mitochondrial pathway. Further analysis is recommended to assess the modulatory effect of 7-geranyloxycinnamic acid on gene and protein expression for genes and markers involved in Nrf2/ARE, IkB-α/NF-kB, MAPK and mitochondrial signaling pathways. Also, *In vivo* study in rats is recommended to further explain the neuroprotective effect of the compound.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

KESAN PERLINDUNGAN NEURO ASID 7-GERANILOKSISINAMIK YANG DIPENCILKAN DARIPADA DAUN *Melicope lunu-ankenda* (Gaertn.) T.G. Hartley *In Vitro*

Oleh

ZEINAB ABDULWANIS MASAOUD MOHAMED

Disember 2020

Pengerusi : Profesor Madya Ahmad Faizal Abdull Razis, PhD
Institut : Biosains

Penyakit neurodegeneratif (NDDs) adalah penyakit kronik dan tidak dapat diubati, dan dengan itu telah mendapat perhatian para penyelidik kerana beban sosial dan ekonominya. Sejak kebelakangan ini, lebih kurang 55 juta manusia di dunia dilaporkan menderita dari satu atau lebih NDDs, terutamanya peratusan yang lebih besar menderita AD kerana jangka hayat mereka telah meningkat. Di Malaysia, jumlah penderita NDDs diunjurkan meningkat daripada 123,000 orang pada tahun 2015 menjadi 261,000 pada tahun 2030 dan akan terus meningkat ke 590,000 orang pada tahun 2050. Oleh itu, strategi menggunakan agen fitoterapeutik sebagai sumber alternatif untuk terapi NDDs telah menjadi satu keperluan. Pelbagai metabolit sekunder telah diasingkan daripada daun pokok *Melicope lunu-ankenda ankenda* (Gaertn.) T.G. Hartley (yang dikenali sebagai pokok tenggek burung di Malaysia seperti derivatif asid fenolik termasuk asid 7-geraniloksisinamik. Walau bagaimanapun, aktiviti perlindungan neuronya masih tidak dikaji hingga hari ini. Oleh itu, tujuan kajian ini adalah untuk menjelaskan aktiviti perlindungan neuro asid 7- geraniloksisinamik yang diperolehi daripada daun *M. lunu-ankenda*. Dalam hal ini, asid 7-geraniloksisinamik diuji perlindungan neuronya ke atas asid retinoik (RA) yang mengaruhi pembezaan sel neuroblastoma manusia (SH-SY5Y) dan dibandingkan dengan kurkumin, yang digunakan sebagai kawalan positif dalam kajian ini. Sel SH-SY5Y dirawat dengan 10 µM RA selama 7 hari, dan kemudian diperhatikan di bawah mikroskop pendarfluor (kontras fasa) untuk memantau pembezaan dan mengukur panjang neurit garis sel SH-SY5Y yang tidak dibezakan dan dibezakan. Pembezaan garis sel SH-SY5Y dipastikan dengan lebih teliti melalui pemeriksaan imunokimia, di mana ekspresi III β-tubulin (tuj-1) dikesan oleh konjugat antibodi sekunder Alexa fluorophore- 488. Daya tahan sel dan sitotoksisiti telah diuji menggunakan reagen 3- (4,5-dimetilthiazol-2-yl) -2,5-diphenyltetrazolium bromida (MTT) untuk menentukan kepekatan asid 7-geraniloksisinamik yang tertinggi di mana sel-sel yang dibezakan itu diawetkan

dengan kepekatan asid 7- geraniloksisinamik yang dicairkan secara bersiri selama 24, 48 dan 72 jam sebelum terdedah selama 4 jam kepada H_2O_2 (300 μM). Ujian Annexin V-FITC dengan menggunakan aliran sitometri dan pendarfluor mikroskopi melalui pewarna akridin oren dan propidium iodida (AO / PI) telah digunakan untuk menganalisis keupayaan perencatan apoptotik pada sel yang dibezakan. Penilaian morfologi secara permukaan dan analisis ultrastruktur telah dilakukan menggunakan pengimbasan dan transmisi mikroskop elektron untuk menilai kesan sebatian ke atas morfologi permukaan dan ciri-ciri dalaman sel. Hasil kajian menunjukkan bahawa rawatan sel SH-SY5Y dengan RA selama 7 hari membezakan sel menjadi neuron yang mempunyai neurit yang diperpanjang, yang disahkan oleh ekspresi penanda neuron kelas III β-tubulin (tuj-1). Pra-rawatan sel-sel neuron dengan asid 7-geraniloksisinamik (2.08 μM) terutamanya selepas rawatan selama 72 jam telah melindungi sel-sel SH-SY5Y yang dibezakan terhadap kematian sel apoptotik yang disebabkan oleh H_2O_2, yang serupa dengan rawatan sel dengan 5.97 μM Kurkumin ditambah 4 jam pendedahan kepada H_2O_2 (300 μM). mikroskopi pendarluor setelah pewarnaan AO/PI menunjukkan aktiviti neuroprotektif 2.08 μM 7-geraniloksisinamik asid terhadap kerosakan nukleus akibat pendedahan H_2O_2 yang mungkin menyebabkan kematian sel melalui apoptosis, angka ini mirip dengan apa yang diperhatikan ketika sel-sel dirawat dengan kurkumin sebelum H_2O_2. Kegiatan neuroprotektif 2.08 μM 7-geraniloksisinamik asid terhadap H_2O_2-disebabkan apoptosis dipastikan oleh annexin V-FITC, di mana sel-sel yang dirawat sebelumnya dengan 7-geraniloksisinamik asid atau kurkumin menunjukkan tahap rendah apoptosis dan daya maju sel yang tinggi. Morfologi permukaan dan ciri dalaman sel nampak dilindungi oleh rawatan asid 7-geraniloksisinamik, yang serupa dengan rawatan pra-kurkumin sebelum serangan H_2O_2. Penemuan ini menunjukkan potensi neuroprotektif asid 7-geraniloksisinamik pada sel-sel neuron terhadap neurotoksisitas yang disebabkan oleh H_2O_2, yang merupakan kajian pertama mendapati kesan neuroprotektif asid 7-geraniloksisinamik melalui jalur mitokondria. Analisis lebih lanjut disyorkan untuk menilai kesan modulasi asid 7-geraniloksisinamik pada ekspresi gen dan protein untuk gen dan penanda yang terlibat dalam jalur isyarat Nrf2/ARE, IkB-α/NF-kB, MAPK dan mitokondria. Di samping itu, kajian *in vivo* pada tikus disyorkan untuk menjelaskan lebih lanjut kesan neuroprotektif sebatian.

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This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

Ahmad Faizal Abdull Razis, PhD
Associate Professor
Institute of Bioscience/ Faculty of Food Science and Technology
Universiti Putra Malaysia
(Chairman)

Norshariza Nordin, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

ZALILAH MOHD SHARIFF, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 08 April 2021

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Signature:	_____
Name of Member of Supervisory Committee:	Associate Professor Dr. Norshariza Nordin

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LIST OF ABBREVIATIONS

AD	Alzheimer’s disease
ALS	Amyotrophic lateral sclerosis
AO	Acridine orange
Aβ	Beta amyloid
Bad/Bax	BCL2-associated agonist of cell death/ BCL2-associated X protein
Bcl-2	B-cell lymphoma 2
BSA	Bovine serum albumin
CDs	Cyclodextrins
COX-2	Cyclooxygenase-2
CysDA	5-S-cysteinyl-dopamine
DA	Dopamine
DAT	Dopamine transporters
DMEM/Hams' F12	Dulbecco Modified Eagle Medium and Ham’s F12
DMSO	Dimethyl sulfoxide
FBS	Fetal bovine serum
GPX1	Glutathione peroxidase
GSK-3β	Glycogen synthase kinase-3β
H_2O_2	Hydrogen peroxide
HD	Huntington’s disease
HPLC	High Performance Liquid Chromatography
ICC	Immunocytochemistry
JNK	C-Jun N-terminal kinase
LSs	Liposomes
MCs	Micelles
MDA	Malondialdehyde
MS	Multiple sclerosis
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NDDs	Neurodegenerative diseases

NMR	Nuclear magnetic resonance
NSs	Nanospheres
PBS	Phosphate buffer saline
PC12	Pheochromocytoma
PD	Parkinson's disease
PGE2	Prostaglandin E2
PGK1	Phosphoglycerate kinase-1
PI	Propidium iodide
PS	Phosphatidylserine
RA	Retinoic acid
ROS	Reactive oxygen species
SD	Standard deviation
SH-SY5Y	Human neuroblastoma
SLNs	Solid lipid nanoparticles
SOD	Superoxide dismutase
Tuj-1	Class III β-tubulin

CHAPTER 1

INTRODUCTION

1.1 Research Background

Neurodegenerative diseases namely Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD) and Amyotrophic lateral sclerosis (ALS) can be recognized by the sluggish loss of capabilities of the neuronal cells (Singh et al., 2019; Ratheesh et al., 2017) and their pathogenesis are related to oxidative stress, a condition initiated by inordinate creation of responsive oxygen species (ROS) such as hydrogen peroxide (H_2O_2) (Kim et al., 2015). H_2O_2 is created as a defense against cellular metabolism aerobic respiration and pathogens (Niedzielska et al., 2016). However, uncontrolled increased intracellular H_2O_2 level will harm proteins and lipids, and incite apoptosis or necrosis (Sajjad et al., 2018; Lukiw et al., 2012). The brain is profoundly affected by excessive oxidation because it contains lipid-rich substance, high demand for oxygen and low antioxidant (Salim, 2017). Mitochondrial dysfunction often includes aberrant H_2O_2 which is related to the pathogenesis of neurological disorders.

Examinations of the brain of patients suffering from neuronal disorders show elevated oxidative stress (Liu et al., 2017; Chen et al., 2018). In most cases of neurodegenerative diseases, biological molecules are subjected to oxidative injury due to loss of the antioxidant system's function or excessive production of H_2O_2. This then initiates a cascade of events that eventually cause cell death. As such, any excess of H_2O_2 necessitates antioxidant activity to have proper protection (Angelova & Abramov, 2018; Popa-Wagner et al., 2013).

Symptoms of neuronal disease have always been treated by using phytochemicals, which are known to possess anti-inflammatory and anti-oxidant effects (Kumar & Khanum, 2012; Perez-Hernandez et al., 2016). *Melicope lunu-ankenda* (*Rutaceae*) or "tenggek burung" (as commonly known as in Malaysia) have been the source of several secondary metabolites. This includes hydroxybenzoic acid and hydroxycinnamic acid derivatives (Al-Zuaidy et al., 2016; Eliaser et al., 2018). Polyphenols such as phenolic acids exert their neuroprotective activity via anti-inflammatory and anti-apoptotic activities. In addition, they also act via the prevention of generation of ROS and protein oxidation (Hong & Jeong, 2012; Vauzour et al., 2010). There is a wide distribution of hydroxycinnamic acid derivatives in plants (Teixeira et al., 2013). Furthermore, they appear to contain great amounts of antioxidants and anti-inflammatory activity, thus conferring the ability to protect neuronal cells (Zhang et al., 2018). Being the two hallmarks of NDDs, these aforementioned pharmacological functions are associated with the therapy for neurological disorders via alleviation of oxidative stress and inflammation (Zhang et al., 2018).

Past *in vitro* investigations proved that hydroxycinnamic acid derivatives have antioxidant function against ROS and confers some protection to neurons from the effects of oxidative stress due to H_2O_2 (Garrido et al., 2012; Jeong et al., 2011). The compound (7-geranyloxycinnamic acid) is basically a cinnamic acid derivative of *M. lunu-ankenda* leaves (*Rutaceae*) (Ramli et al., 2004). An assessment was made in the SH-SY5Y neuroblastoma cell line on the 7-geranyloxycinnamic acid's neuroprotective function against toxicity caused by H_2O_2. Furthermore, in order to explore potential mechanism of action, there were also studies on the impact of this hydroxycinnamic acid derivative on the surface ultrastructural (cells surface's composition and topography) and internal morphological characteristics (cytoplasmic inclusion).

1.2 Problem Statement and Justification

The main challenge currently to the healthcare system worldwide is the rapid increase in incidence of neurodegenerative disease (NDDs) which relates to increase in life expectancy worldwide particularly in developed countries. There are over 9.9 million new cases of NDDs every year worldwide, or 1 new case every 3.2 seconds. NDDs become a global concern due to their economic cost and causing human suffering. The available treatment used currently for NDDs is only to manage the symptoms and improve quality of life of affected persons and it is associated with severe side effects. Therefore, the need for cost effective and safer ways of medication become necessary, and so using phytotherapeutic products could be the best approach to fill that gap. Phenolic acids isolated from *M. lunu-ankenda* plant such as caffeic acid, sinapic acid, coumaric acid and ferulic acid showed neuroprotective activities on various models of NDDs via anti-apoptotic pathway. Despite being cinnamic acid derivatives, the anti-apoptotic effects of 7-geranyloxycinnamic acid were not studied for its neuroprotective activities till date. However, conducting research to discover neuroprotective agents such as 7-geranyloxycinnamic acid can help in the development of safer therapies to provide protection and treatment for NDDs.

1.3 Hypothesis

1.3.1 Null hypothesis (H_0)

7-geranyloxycinnamic acid isolated from *M. lunu-ankenda* does not show neuroprotective activity in *in vitro* model of NDDs.

1.3.2 Alternate hypothesis (H_A)

7-geranyloxycinnamic acid isolated from *M. lunu-ankenda* exert neuroprotective activity *in vitro.*

1.4 Research objectives

1.4.1 General objective

To evaluate the *in vitro* neuroprotective activity of 7-geranyloxycinnamic acid and elucidate the anti-apoptotic mechanism through which it elicits the neuroprotection on SH-SY5Y cell line.

1.4.2 Specific objectives

1.4.2.1 To confirm the generation of human neuroblastoma (SH-SY5Y) cells-derived terminally differentiated neurons.

1.4.2.2 To evaluate the anti-apoptotic potential of 7-geranyloxycinnamic acid against H_2O_2-induced apoptosis on differentiated SH-SY5Y cell line.

1.4.2.3. To assess the surface morphology and internal inclusion preservation ability of 7-geranyloxycinnamic acid against H_2O_2-induced apoptotic features on differentiated SH-SY5Y cell line.

REFERENCES

Abeliovich, A., & Gitler, A. D. (2016). Defects in trafficking bridge Parkinson's disease pathology and genetics. *Nature, 539*(7628), 207-216.

Adam-Vizi, V. (2005). Production of reactive oxygen species in brain mitochondria: contribution by electron transport chain and non–electron transport chain sources. *Antioxidants & Redox Signaling, 7*(9-10), 1140-1149.

Ahmed, R. M., Devenney, E. M., Irish, M., Ittner, A., Naismith, S., Ittner, L. M., ... & Kiernan, M. C. (2016). Neuronal network disintegration: common pathways linking neurodegenerative diseases. *Journal of Neurology, Neurosurgery & Psychiatry, 87*(11), 1234-1241.

Ali, M. Y., Jannat, S., Jung, H. A., Choi, R. J., Roy, A., & Choi, J. S. (2016). Anti-Alzheimer's disease potential of coumarins from Angelica decursiva and artemisia capillaris and structure-activity analysis. *Asian Pacific Journal of Tropical Medicine, 9*(2), 103-111.

Alonso, A. D. C., Li, B., Grundke-Iqbal, I., & Iqbal, K. (2008). Mechanism of tau-induced neurodegeneration in Alzheimer disease and related tauopathies. *Current Alzheimer Research, 5*(4), 375-384.

Alzheimer's Association. (2017). 2017 Alzheimer's disease facts and figures. *Alzheimer's & Dementia, 13*(4), 325-373.

Alzheimer's Association. (2019). 2019 Alzheimer's disease facts and figures. *Alzheimer's & Dementia, 15*(3), 321-387.

Alzheimer's Association. (2020). 2020 Alzheimer's disease facts and figures. *Alzheimer's & Dementia, 16*(3), 391-460.

AL-Zuaidy, M. H., Hamid, A. A., Ismail, A., Mohamed, S., Abdul Razis, A. F., Mumtaz, M. W., & Salleh, S. Z. (2016). Potent antidiabetic activity and metabolite profiling of *Melicope lunu-ankenda* Leaves. *Journal of Food Science, 81*(5), C1080-C1090.

Anand, P., Singh, B., & Singh, N. (2012). A review on coumarins as acetylcholinesterase inhibitors for Alzheimer's disease. *Bioorganic & Medicinal Chemistry, 20*(3), 1175-1180.

Andrabi, S. A., Umanah, G. K., Chang, C., Stevens, D. A., Karuppagounder, S. S., Gagné, J. P., ... & Dawson, T. M. (2014). Poly (ADP-ribose) polymerase-dependent energy depletion occurs through inhibition of glycolysis. *Proceedings of the National Academy of Sciences, 111*(28), 10209-10214.

Angelova, P. R., & Abramov, A. Y. (2018). Role of mitochondrial ROS in the brain: from physiology to neurodegeneration. *FEBS letters, 592*(5), 692-702.

Arthur, K. C., Calvo, A., Price, T. R., Geiger, J. T., Chio, A., & Traynor, B. J. (2016). Projected increase in amyotrophic lateral sclerosis from 2015 to 2040. *Nature Communications, 7*(1), 1-6.

Ascherio, A., & Schwarzschild, M. A. (2016). The epidemiology of Parkinson's disease: risk factors and prevention. *The Lancet Neurology, 15*(12), 1257-1272.

Azmi, N. H., Ismail, N., Imam, M. U., & Ismail, M. (2013). Ethyl acetate extract of germinated brown rice attenuates hydrogen peroxide-induced oxidative stress in human SH-SY5Y neuroblastoma cells: role of anti-apoptotic, pro-survival and antioxidant genes. *BMC complementary and Alternative Medicine, 13*(1), 177.

Baecher-Allan, C., Kaskow, B. J., & Weiner, H. L. (2018). Multiple sclerosis: mechanisms and immunotherapy. *Neuron, 97*(4), 742-768.

Bento-Silva, A., Koistinen, V. M., Mena, P., Bronze, M. R., Hanhineva, K., Sahlstrøm, S., ... & Aura, A. M. (2020). Factors affecting intake, metabolism and health benefits of phenolic acids: do we understand individual variability?. *European Journal of Nutrition, 59*(4), 1275-1293.

Bhat, A. H., Dar, K. B., Anees, S., Zargar, M. A., Masood, A., Sofi, M. A., & Ganie, S. A. (2015). Oxidative stress, mitochondrial dysfunction and neurodegenerative diseases; a mechanistic insight. *Biomedicine & Pharmacotherapy, 74*, 101-110.

Bhullar, K. S., & Rupasinghe, H. P. (2013). Polyphenols: multipotent therapeutic agents in neurodegenerative diseases. *Oxidative Medicine and Cellular Longevity, 2013*.

Bovolenta, T. M., de Azevedo Silva, S. M. C., Arb Saba, R., Borges, V., Ferraz, H. B., & Felicio, A. C. (2017). Systematic review and critical analysis of cost studies associated with Parkinson's disease. *Parkinson's Disease, 2017;2017:*3410946.

Bovolenta, T. M., de Azevedo Silva, S. M. C., Saba, R. A., Borges, V., Ferraz, H. B., & Felicio, A. C. (2017). Average annual cost of Parkinson's disease in São Paulo, Brazil, with a focus on disease-related motor symptoms. *Clinical Interventions in Aging, 12*, 2095.

Brownlee, W. J., Hardy, T. A., Fazekas, F., & Miller, D. H. (2017). Diagnosis of multiple sclerosis: progress and challenges. *The Lancet, 389*(10076), 1336-1346.

Burté, F., Carelli, V., Chinnery, P. F., & Yu-Wai-Man, P. (2015). Disturbed mitochondrial dynamics and neurodegenerative disorders. *Nature Reviews Neurology, 11*(1), 11-24.

Chan, J. C., Stout, J. C., & Vogel, A. P. (2019). Speech in prodromal and symptomatic Huntington's disease as a model of measuring onset and progression in dominantly inherited neurodegenerative diseases. *Neuroscience & Biobehavioral Reviews, 107*, 450-460.

Chaurio, R. A., Janko, C., Muñoz, L. E., Frey, B., Herrmann, M., & Gaipl, U. S. (2009). Phospholipids: key players in apoptosis and immune regulation. *Molecules*, *14*(12), 4892-4914.

Chen, H., Kwong, J. C., Copes, R., Tu, K., Villeneuve, P. J., Van Donkelaar, A., ... & Wilton, A. S. (2017). Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study. *The Lancet*, *389*(10070), 718-726.

Chen, L., Liu, D. N., Wang, Y., Liu, X. Y., Han, S., Zhang, K., ... & Wang, J. H. (2019). Treatment with MQA, a derivative of caffeoylquinic acid, provides neuroprotective effects against cerebral ischemia through suppression of the p38 pathway and oxidative stress in rats. *Journal of Molecular Neuroscience*, *67*(4), 604-612.

Chen, R., Lai, U. H., Zhu, L., Singh, A., Ahmed, M., & Forsyth, N. R. (2018). Reactive oxygen species formation in the brain at different oxygen levels: the role of hypoxia inducible factors. *Frontiers in Cell and Developmental Biology*, *6*, 132.

Cheung, Y. T., Lau, W. K. W., Yu, M. S., Lai, C. S. W., Yeung, S. C., So, K. F., & Chang, R. C. C. (2009). Effects of all-trans-retinoic acid on human SH-SY5Y neuroblastoma as in vitro model in neurotoxicity research. *Neurotoxicology*, *30*(1), 127-135.

Chin-Chan, M., Navarro-Yepes, J., & Quintanilla-Vega, B. (2015). Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. *Frontiers in Cellular Neuroscience*, *9*, 124.

Cook, C., Stankowski, J. N., Carlomagno, Y., Stetler, C., & Petrucelli, L. (2014). Acetylation: a new key to unlock tau's role in neurodegeneration. *Alzheimer's Research & Therapy*, *6*(3), 29.

Coornaert, I., Hofmans, S., Devisscher, L., Augustyns, K., Van Der Veken, P., De Meyer, G. R., & Martinet, W. (2018). Novel drug discovery strategies for atherosclerosis that target necrosis and necroptosis. *Expert Opinion on Drug Discovery*, *13*(6), 477-488.

Coupé, P., Manjón, J. V., Lanuza, E., & Catheline, G. (2019). Lifespan changes of the human brain in Alzheimer's disease. *Scientific Reports*, *9*(1), 1-12.

Dajas, F. (2012). Life or death: neuroprotective and anticancer effects of quercetin. *Journal of Ethnopharmacology*, *143*(2), 383-396.

de Oliveira, N. K., Almeida, M. R. S., Pontes, F. M. M., Barcelos, M. P., Tomich, C. H., Rosa, J. M. C., ... & Izabel, L. (2019). Antioxidant effect of flavonoids present in Euterpe oleracea Martius and neurodegenerative diseases: A literature review. *Central Nervous System Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Central Nervous System Agents)*, *19*(2), 75-99.

Degterev, A., Boyce, M., & Yuan, J. (2003). A decade of caspases. *Oncogene*, *22*(53), 8543-8567.

Dok-Go, H., Lee, K. H., Kim, H. J., Lee, E. H., Lee, J., Song, Y. S., ... & Cho, J. (2003). Neuroprotective effects of antioxidative flavonoids, quercetin, (+)-dihydroquercetin and quercetin 3-methyl ether, isolated from Opuntia ficus-indica var. saboten. *Brain Research*, *965*(1-2), 130-136.

Dugger, B. N., & Dickson, D. W. (2017). Pathology of neurodegenerative diseases. *Cold Spring Harbor Perspectives in Biology*, *9*(7), a028035.

Egorova, P. A., & Bezprozvanny, I. B. (2019). Molecular mechanisms and therapeutics for spinocerebellar ataxia type 2. *Neurotherapeutics*, 1-24.

Eliaser, M.E., Hui Ho, J., Hashim, N.M., Rukayadi, Y., Lian Ee, G.C., & Abdull Razis, A.F. (2018). Phytochemical constituents and biological activities *of Melicope lunu-ankenda*. *Molecules*, *23*(10), 2708.

Epifano, F., Curini, M., Menghini, L., & Genovese, S. (2009). Natural coumarins as a novel class of neuroprotective agents. *Mini Reviews in Medicinal Chemistry*, *9*(11), 1262-1271.

Esparza, T. J., Zhao, H., Cirrito, J. R., Cairns, N. J., Bateman, R. J., Holtzman, D. M., & Brody, D. L. (2013). Amyloid-beta oligomerization in Alzheimer dementia versus high-pathology controls. *Annals of Neurology*, *73*(1), 104-119.

Farrokhi, M., Beni, A. A., Etemadifar, M., Rezaei, A., Rivard, L., Zadeh, A. R., ... & Ghadimi, M. (2015). Effect of fingolimod on platelet count among multiple sclerosis patients. *International Journal of Preventive Medicine*, 6, 125.

Finicelli, M., Squillaro, T., Di Cristo, F., Di Salle, A., Melone, M. A. B., Galderisi, U., & Peluso, G. (2019). Metabolic syndrome, mediterranean diet, and polyphenols: evidence and perspectives. *Journal of Cellular Physiology. 2019*, 234, 5807–5826.

Finkbeiner, S. (2011). Huntington's disease. *Cold Spring Harbor Perspectives in Biology*, *3*(6), a007476.

Frank, S. (2010). Tetrabenazine: the first approved drug for the treatment of chorea in US patients with Huntington disease. *Neuropsychiatric Disease and Treatment*, *6*, 657.

Frazzitta, G., Maestri, R., Bertotti, G., Riboldazzi, G., Boveri, N., Perini, M., ... & Ghilardi, M. F. (2015). Intensive rehabilitation treatment in early Parkinson's disease: a randomized pilot study with a 2-year follow-up. *Neurorehabilitation and Neural Repair*, *29*(2), 123-131.

Fürstenau, C. R., de Souza, I. C. C., & de Oliveira, M. R. (2019). The effects of kahweol, a diterpene present in coffee, on the mitochondria of the human neuroblastoma SH-SY5Y cells exposed to hydrogen peroxide. *Toxicology in Vitro*, *61*, 104601.

Furukawa, Y., Watanabe, S., Okuyama, S., & Nakajima, M. (2012). Neurotrophic effect of citrus auraptene: neuritogenic activity in PC12 cells. *International Journal of Molecular sciences*, *13*(5), 5338-5347.

Gandhi, S., & Abramov, A. Y. (2012). Mechanism of oxidative stress in neurodegeneration. *Oxidative Medicine and Cellular Longevity*, *2012*.

García-Morales, G., Huerta-Reyes, M., González-Cortazar, M., Zamilpa, A., Jiménez-Ferrer, E., Silva-García, R., ... & Aguilar-Rojas, A. (2015). Anti-inflammatory, antioxidant and anti-acetylcholinesterase activities of Bouvardia ternifolia: potential implications in Alzheimer's disease. *Archives of Pharmacal Research*, *38*(7), 1369-1379.

Garrido, J., Gaspar, A., Garrido, E. M., Miri, R., Tavakkoli, M., Pourali, S., ... & Firuzi, O. (2012). Alkyl esters of hydroxycinnamic acids with improved antioxidant activity and lipophilicity protect PC12 cells against oxidative stress. *Biochimie*, *94*(4), 961-967.

Ghanbarabadi, M., Iranshahi, M., Amoueian, S., Mehri, S., Motamedshariaty, V. S., & Mohajeri, S. A. (2016). Neuroprotective and memory enhancing effects of auraptene in a rat model of vascular dementia: Experimental study and histopathological evaluation. *Neuroscience Letters*, *623*, 13-21.

Gitler, A. D., Dhillon, P., & Shorter, J. (2017). Neurodegenerative disease: models, mechanisms, and a new hope. *Disease Models & Mechanisms*, *2017*,10: 499-502

González-Sarrías, A., Núñez-Sánchez, M. A., Tomás-Barberán, F. A., & Espín, J. C. (2017). Neuroprotective effects of bioavailable polyphenol-derived metabolites against oxidative stress-induced cytotoxicity in human neuroblastoma SH-SY5Y cells. *Journal of Agricultural and Food Chemistry*, *65*(4), 752-758.

Guo, F., Zhao, W., Yang, L., Yang, Y., Wang, S., Wang, Y., ... & Wang, J. (2017). Truncated apolipoprotein CI induces apoptosis in neuroblastoma by activating caspases in the extrinsic and intrinsic pathways. *Oncology Reports*, *38*(3), 1797-1805.

Guven, M., Sehitoglu, M. H., Yuksel, Y., Tokmak, M., Aras, A. B., Akman, T., ... & Cosar, M. (2015). The neuroprotective effect of coumaric acid on spinal cord ischemia/reperfusion injury in rats. *Inflammation*, *38*(5), 1986-1995.

Han, J., Miyamae, Y., Shigemori, H., & Isoda, H. (2010). Neuroprotective effect of 3, 5-di-O-caffeoylquinic acid on SH-SY5Y cells and senescence-accelerated-prone mice 8 through the up-regulation of phosphoglycerate kinase-1. *Neuroscience*, *169*(3), 1039-1045.

Hardiman, O., Al-Chalabi, A., Chio, A., Corr, E. M., Logroscino, G., Robberecht, W., ... & Van Den Berg, L. H. (2017). Amyotrophic lateral sclerosis. *Nature Reviews Disease Primers*, *3*(1), 1-19.

He, W., Goodkind, D., & Kowal, P. R. (2016). An aging world: 2015. *International Population Reports*, P95/16-1.

Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. (2013). Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology*, *80*(19), 1778-1783.

Hewlings, S. J., & Kalman, D. S. (2017). Curcumin: a review of its' effects on human health. *Foods*, *6*(10), 92.

Holland, D., McEvoy, L. K., Desikan, R. S., Dale, A. M., & Alzheimer's Disease Neuroimaging Initiative. (2012). Enrichment and stratification for predementia Alzheimer disease clinical trials. *PloS One*, *7*(10).

Hong, S. Y., Jeong, W. S., & Jun, M. (2012). Protective effects of the key compounds isolated from Corni fructus against β-amyloid-induced neurotoxicity in PC12 cells. *Molecules*, *17*(9), 10831-10845.

Hong-Qi, Y., Zhi-Kun, S., & Sheng-Di, C. (2012). Current advances in the treatment of Alzheimer's disease: focused on considerations targeting Aβ and tau. *Translational Neurodegeneration*, *1*(1), 21.

Hou, Y., Dan, X., Babbar, M., Wei, Y., Hasselbalch, S. G., Croteau, D. L., & Bohr, V. A. (2019). Ageing as a risk factor for neurodegenerative disease. *Nature Reviews Neurology*, *15*(10), 565-581.

Hou, Z., Imam, M. U., Ismail, M., Azmi, N. H., Ismail, N., Ideris, A., & Mahmud, R. (2015). Lactoferrin and ovotransferrin contribute toward antioxidative effects of Edible Bird's Nest against hydrogen peroxide-induced oxidative stress in human SH-SY5Y cells. *Bioscience, Biotechnology, and Biochemistry*, *79*(10), 1570-1578.

Hussain, G., Rasul, A., Anwar, H., Aziz, N., Razzaq, A., Wei, W., ... & Li, X. (2018). Role of plant derived alkaloids and their mechanism in neurodegenerative disorders. *International Journal of Biological Sciences*, *14*(3), 341.

Ishola, I. O., Osele, M. O., Chijioke, M. C., & Adeyemi, O. O. (2019). Isorhamnetin enhanced cortico-hippocampal learning and memory capability in mice with scopolamine-induced amnesia: Role of antioxidant defense, cholinergic and BDNF signaling. *Brain Research*, *1712*, 188-196.

Islam, M. T. (2017). Oxidative stress and mitochondrial dysfunction-linked neurodegenerative disorders. *Neurological Research*, *39*(1), 73-82.

Ismail, N., Ismail, M., Azmi, N. H., Bakar, A., Firdaus, M., Basri, H., & Abdullah, M. A. (2016). Modulation of hydrogen peroxide-induced oxidative stress in human neuronal cells by thymoquinone-rich fraction and thymoquinone via transcriptomic regulation of antioxidant and apoptotic signaling genes. *Oxidative Medicine and Cellular Longevity*, *2016*.

Ismail, N., Ismail, M., Imam, M. U., Azmi, N. H., Fathy, S. F., Foo, J. B., & Bakar, M. F. A. (2014). Mechanistic basis for protection of differentiated SH-SY5Y cells by oryzanol-rich fraction against hydrogen peroxide-induced neurotoxicity. *BMC Complementary and Alternative Medicine*, *14*(1), 467.

Jaafaru MS, Nordin N, Shaari K, Rosli R, Razis AFA. (2018). Isothiocyanate from Moringa oleifera seeds mitigates hydrogen peroxide-induced cytotoxicity and preserved morphological features of human neuronal cells. *PloS One 2018, 13*(5), e0196403.

Jaafaru, M. S., Nordin, N., Rosli, R., Shaari, K., Noor, N. M., & Razis, A. F. A. (2019). Prospective role of mitochondrial apoptotic pathway in mediating GMG-ITC to reduce cytotoxicity in H_2O_2-induced oxidative stress in differentiated SH-SY5Y cells. *Biomedicine & Pharmacotherapy, 119*, 109445.

Jaafaru, MS. 2019. *Elucidating the neuroprotective pathways of Glucomoringin Isothiocyanate isolated from Moringa oleifera Lam seeds on differentiated (SH-SY5Y) cells*, PhD Thesis, Universiti Putra Malaysia.

Jaiswal, M. K. (2019). Riluzole and edaravone: A tale of two amyotrophic lateral sclerosis drugs. *Medicinal Research Reviews, 39*(2), 733-748.

Jameel, E., Umar, T., Kumar, J., & Hoda, N. (2016). Coumarin: a privileged scaffold for the design and development of antineurodegenerative agents. *Chemical Biology & Drug Design*, *87*(1), 21-38.

Janko, C., Jeremic, I., Biermann, M., Chaurio, R., Schorn, C., Muñoz, L. E., & Herrmann, M. (2013). Cooperative binding of Annexin A5 to phosphatidylserine on apoptotic cell membranes. *Physical Biology*, *10*(6), 065006.

Jantas, D., Chwastek, J., Grygier, B., & Lasoń, W. (2020). Neuroprotective Effects of Necrostatin-1 Against Oxidative Stress–Induced Cell Damage: an Involvement of Cathepsin D Inhibition. *Neurotoxicity Research*, 1-18.

Jembrek, M. J., Vlainić, J., Čadež, V., & Šegota, S. (2018). Atomic force microscopy reveals new biophysical markers for monitoring subcellular changes in oxidative injury: Neuroprotective effects of quercetin at the nanoscale. *PloS One*, *13*(10).

Jeong, C. H., Jeong, H. R., Choi, G. N., Kim, D. O., Lee, U. K., & Heo, H. J. (2011). Neuroprotective and antioxidant effects of caffeic acid isolated from Erigeron annuus leaf. *Chinese Medicine*, *6*(1), 25.

Jia, J., Wei, C., Chen, S., Li, F., Tang, Y., Qin, W., ... & Zhou, A. (2018). The cost of Alzheimer's disease in China and re-estimation of costs worldwide. *Alzheimer's & Dementia*, *14*(4), 483-491.

Jiang, X. W., Bai, J. P., Zhang, Q., Hu, X. L., Tian, X., Zhu, J., ... & Zhao, Q. C. (2017). Caffeoylquinic acid derivatives protect SH-SY5Y neuroblastoma cells from hydrogen peroxide-induced injury through modulating oxidative status. *Cellular and Molecular Neurobiology*, *37*(3), 499-509.

Jin, F., Wu, Q., Lu, Y. F., Gong, Q. H., & Shi, J. S. (2008). Neuroprotective effect of resveratrol on 6-OHDA-induced Parkinson's disease in rats. *European Journal of Pharmacology*, *600*(1-3), 78-82.

Jin, Y., & Wang, H. (2019). Naringenin Inhibit the Hydrogen Peroxide-Induced SH-SY5Y Cells Injury Through Nrf2/HO-1 Pathway. *Neurotoxicity Research*, *36*(4), 796-805.

Johnson, A. J., Kumar, A., Rasheed, S. A., Chandrika, S. P., Chandrasekhar, A., Baby, S., & Subramoniam, A. (2010). Antipyretic, analgesic, anti-inflammatory and antioxidant activities of two major chromenes from *Melicope lunu-ankenda*. *Journal of Ethnopharmacology*, *130*(2), 267-271.

Kanski, J., Aksenova, M., Stoyanova, A., & Butterfield, D. A. (2002). Ferulic acid antioxidant protection against hydroxyl and peroxyl radical oxidation in synaptosomal and neuronal cell culture systems in vitro: structure-activity studies. *The Journal of Nutritional Biochemistry*, *13*(5), 273-281.

Kao, E. S., Hsu, J. D., Wang, C. J., Yang, S. H., Cheng, S. Y., & Lee, H. J. (2009). Polyphenols extracted from Hibiscus sabdariffa L. inhibited lipopolysaccharide-induced inflammation by improving antioxidative conditions and regulating cyclooxygenase-2 expression. *Bioscience, Biotechnology, and Biochemistry*, *73*(2), 385-390.

Kaur, M., Prakash, A., & Kalia, A. N. (2016). Neuroprotective potential of antioxidant potent fractions from Convolvulus pluricaulis Chois. in 3-nitropropionic acid challenged rats. *Nutritional Neuroscience*, *19*(2), 70-78.

Kaur, N., Kumar, P., Jamwal, S., Deshmukh, R., & Gauttam, V. (2016). Tetrabenazine: spotlight on drug review. *Annals of Neurosciences*, *23*(3), 176-185.

Keogh-Brown, M. R., Jensen, H. T., Arrighi, H. M., & Smith, R. D. (2016). The impact of Alzheimer's disease on the Chinese economy. *EBioMedicine*, *4*, 184-190.

Khachanova, N. V., & Gorokhova, T. V. (2017). Extending the potential of the treatment of multiple sclerosis with a new agent for oral use–teriflunomide (Aubagio). *Neuroscience and Behavioral Physiology*, *47*(1), 112-116.

Kim, D. W., Lee, K. T., Kwon, J., Lee, H. J., Lee, D., & Mar, W. (2015). Neuroprotection against 6-OHDA-induced oxidative stress and apoptosis in SH-SY5Y cells by 5, 7-Dihydroxychromone: Activation of the Nrf2/ARE pathway. *Life Sciences*, *130*, 25-30.

Kim, G. H., Kim, J. E., Rhie, S. J., & Yoon, S. (2015). The role of oxidative stress in neurodegenerative diseases. *Experimental Neurobiology*, *24*(4), 325-340.

Kim, J. H., Quilantang, N. G., Kim, H. Y., Lee, S., & Cho, E. J. (2019). Attenuation of hydrogen peroxide-induced oxidative stress in SH-SY5Y cells by three flavonoids from Acer okamotoanum. *Chemical Papers*, *73*(5), 1135-1144.

Klockgether, T., Mariotti, C., & Paulson, H. L. (2019). Spinocerebellar ataxia. *Nature Reviews Disease Primers*, *5*(1), 1-21.

Koeppen, A. H. (2018). The neuropathology of spinocerebellar ataxia type 3/Machado-Joseph disease. In *Polyglutamine Disorders* (pp. 233-241). Springer, Cham.

Korecka, J. A., van Kesteren, R. E., Blaas, E., Spitzer, S. O., Kamstra, J. H., Smit, A. B., ... & Bossers, K. (2013). Phenotypic characterization of retinoic acid differentiated SH-SY5Y cells by transcriptional profiling. *PloS One*, *8*(5).

Kostova, I., Bhatia, S., Grigorov, P., Balkansky, S., S Parmar, V., K Prasad, A., & Saso, L. (2011). Coumarins as antioxidants. *Current Medicinal Chemistry*, *18*(25), 3929-3951.

Kovalevich, J., & Langford, D. (2013). Considerations for the use of SH-SY5Y neuroblastoma cells in neurobiology. In *Neuronal Cell Culture* (pp. 9-21). Humana Press, Totowa, NJ.

Kroemer, G., El-Deiry, W. S., Golstein, P., Peter, M. E., Vaux, D., Vandenabeele, P., ... & Piacentini, M. (2005). Classification of cell death: recommendations of the Nomenclature Committee on Cell Death. *Cell Death and Differentiation*, *12*(12), 1463-1467.

Kumar, A., & Singh, A. (2015). A review on Alzheimer's disease pathophysiology and its management: an update. *Pharmacological Reports, 67*(2), 195-203.

Kumar, G. P., & Khanum, F. (2012). Neuroprotective potential of phytochemicals. *Pharmacognosy Reviews*, *6*(12), 81.

Lal, B., Bhise, N. B., Gidwani, R. M., Lakdawala, A. D., Joshi, K., & Patvardhan, S. (2005). Isolation, synthesis and biological activity of Evolitrine and analogs. *Arkivoc*, *11*, 77-97.

Langa, K. M. (2015). Is the risk of Alzheimer's disease and dementia declining? *Alzheimer's Research & Therapy*, *7*(1), 34.

Larson, T. C., Kaye, W., Mehta, P., & Horton, D. K. (2018). Amyotrophic lateral sclerosis mortality in the United States, 2011–2014. *Neuroepidemiology*, *51*, 96-103.

Lee, B., Weon, J. B., Eom, M. R., Jung, Y. S., & Ma, C. J. (2015). Neuroprotective compounds of Tilia amurensis. *Pharmacognosy Magazine*, *11*(Suppl 2), S303.

Li Z, Pang L, Fang F, Zhang G, Zhang J, Xie M, Wang L (2012) Resveratrol attenuates brain damage in a rat model of focal cerebral ischemia via up-regulation of hippocampal Bcl-2. *Brain Res, 2012*, 1450, 116-124.

Li, M., Fan, Y., Zhong, T., Yi, P., Fan, C., Wang, A., ... & Xu, Y. (2019). The protective effects of vernicilignan A, a new flavonolignan isolated from Toxicodendron vernicifluum on SH-SY5Y cells against oxidative stress-induced injury. *Fitoterapia, 134*, 81-87.

Lim, K. Y., Sasmita, A. O., Ling, A. P. K., Koh, R. Y., Voon, K. G. L., Say, Y. H., & Wong, Y. P. (2018). Neuroprotective mechanisms of orientin against hydrogen peroxide-induced oxidative damage in SH-SY5Y cells. *Journal of Biochemistry, Microbiology and Biotechnology*, *6*(1), 10-18.

Limbocker, R., Mannini, B., Perni, M., Chia, S., Heller, G., Ruggeri, F. S., ... & Knowles, T. P. (2017). Attenuating the Toxicity of Amyloid-beta aggregation with specific species. *Biophysical Journal, 112*(3), 494a.

Lionaki, E., Markaki, M., Palikaras, K., & Tavernarakis, N. (2015). Mitochondria, autophagy and age-associated neurodegenerative diseases: New insights into a complex interplay. *Biochimica et Biophysica Acta (BBA)-Bioenergetics*, *1847*(11), 1412-1423.

Liu, J., Jiang, X., Zhang, Q., Lin, S., Zhu, J., Zhang, Y., ... & Zhao, Q. (2017). Neuroprotective effects of Kukoamine A against cerebral ischemia via antioxidant and inactivation of apoptosis pathway. *Neurochemistry Iinternational*, *107*, 191-197.

Liu, Z., Zhou, T., Ziegler, A. C., Dimitrion, P., & Zuo, L. (2017). Oxidative stress in neurodegenerative diseases: from molecular mechanisms to clinical applications. *Oxidative Medicine and Cellular Longevity*, *2017*.

Lopes, F. M., Schröder, R., da Frota Júnior, M. L. C., Zanotto-Filho, A., Müller, C. B., Pires, A. S., ... & Moreira, J. C. F. (2010). Comparison between proliferative and neuron-like SH-SY5Y cells as an in vitro model for Parkinson disease studies. *Brain Research*, *1337*, 85-94.

Lu, Z., Nie, G., Belton, P. S., Tang, H., & Zhao, B. (2006). Structure–activity relationship analysis of antioxidant ability and neuroprotective effect of gallic acid derivatives. *Neurochemistry International*, *48*(4), 263-274.

Lukiw, W. J., Bjattacharjee, S., Zhao, Y., Pogue, A. I., & Percy, M. E. (2012). Generation of reactive oxygen species (ROS) and pro-inflammatory signaling in human brain cells in primary culture. *Journal of Alzheimer's Disease & Parkinsonism*, Suppl 2 *(*001).

Majno, G., & Joris, I. (1995). Apoptosis, oncosis, and necrosis. An overview of cell death. *The American Journal of Pathology*, *146*(1), 3.

Mancuso, C., & Santangelo, R. (2014). Ferulic acid: pharmacological and toxicological aspects. *Food and Chemical Toxicology*, *65*, 185-195.

Mandel, S., & Youdim, M. B. (2004). Catechin polyphenols: neurodegeneration and neuroprotection in neurodegenerative diseases. *Free Radical Biology and Medicine*, *37*(3), 304-317.

Mandelkow, E. M., & Mandelkow, E. (2012). Biochemistry and cell biology of tau protein in neurofibrillary degeneration. *Cold Spring Harbor Perspectives in Medicine*, *2*(7), a006247.

Mansouri, M. T., Farbood, Y., Sameri, M. J., Sarkaki, A., Naghizadeh, B., & Rafeirad, M. (2013). Neuroprotective effects of oral gallic acid against oxidative stress induced by 6-hydroxydopamine in rats. *Food Chemistry*, *138*(2-3), 1028-1033.

Martin, L., Latypova, X., & Terro, F. (2011). Post-translational modifications of tau protein: implications for Alzheimer's disease. *Neurochemistry International*, *58*(4), 458-471.

Masato, A., Plotegher, N., Boassa, D., & Bubacco, L. (2019). Impaired dopamine metabolism in Parkinson's disease pathogenesis. *Molecular Neurodegeneration*, *14*(1), 35.

Matos, M. J., Santana, L., Uriarte, E., Abreu, O. A., Molina, E., & Yordi, E. G. (2015). Coumarins—an important class of phytochemicals. *Phytochemicals-Isolation, Characterisation and Role in Human Health*, 113-140.

Matthews, F. E., Arthur, A., Barnes, L. E., Bond, J., Jagger, C., Robinson, L., ... & Medical Research Council Cognitive Function and Ageing Collaboration. (2013). A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the cognitive function and ageing Study I and II. *The Lancet*, *382*(9902), 1405-1412.

Maya, S., Prakash, T., & Madhu, K. (2018). Assessment of neuroprotective effects of Gallic acid against glutamate-induced neurotoxicity in primary rat cortex neuronal culture. *Neurochemistry International*, *121*, 50-58.

McColgan, P., & Tabrizi, S. J. (2018). Huntington's disease: a clinical review. *European Journal of Neurology*, *25*(1), 24-34.

McKee, A. C., Stein, T. D., Nowinski, C. J., Stern, R. A., Daneshvar, D. H., Alvarez, V. E., ... & Riley, D. O. (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain*, *136*(1), 43-64.

Migliore, L., & Coppedè, F. (2009). Genetics, environmental factors and the emerging role of epigenetics in neurodegenerative diseases. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, *667*(1-2), 82-97.

Mirshekar, M. A., Sarkaki, A., Farbood, Y., Naseri, M. K. G., Badavi, M., Mansouri, M. T., & Haghparast, A. (2018). Neuroprotective effects of gallic acid in a rat model of traumatic brain injury: behavioral, electrophysiological, and molecular studies. *Iranian journal of Basic Medical Sciences*, *21*(10), 1056.

Mitchell, J. D., & Borasio, G. D. (2007). Amyotrophic lateral sclerosis. *The lancet*, *369*(9578), 2031-2041.

Morroni, F., Sita, G., Graziosi, A., Turrini, E., Fimognari, C., Tarozzi, A., & Hrelia, P. (2018). Neuroprotective effect of caffeic acid phenethyl ester in a mouse model of Alzheimer's disease involves Nrf2/HO-1 pathway. *Aging and Disease*, *9*(4), 605.

Murillo, J. R., Goto-Silva, L., Sánchez, A., Nogueira, F. C., Domont, G. B., & Junqueira, M. (2017). Quantitative proteomic analysis identifies proteins and pathways related to neuronal development in differentiated SH-SY5Y neuroblastoma cells. *EuPA open Proteomics*, *16*, 1-11.

Nakanishi, E., & Takahashi, R. (2019). Side Effects, Contraindications, and drug-drug interactions in the Use of Antiparkinsonian Drugs. *NeuroPsychopharmacotherapy*, 1-10.

Nam, M. N., Lee, A. Y., Sin, S. M., Goo, Y. M., Choi, J. M., & Cho, E. J. (2019). Protective Effects of Paeonia lactiflora and Its Active Compound, Paeoniflorin, against Neuronal Oxidative Stress in H_2O_2-Treated SH-SY5Y Cells. *International Journal of Gerontology*, s39-44.

Nerius, M., Fink, A., & Doblhammer, G. (2017). Parkinson's disease in Germany: prevalence and incidence based on health claims data. *Acta Neurologica Scandinavica*, *136*(5), 386-392.

Neumann, M., Bentmann, E., Dormann, D., Jawaid, A., DeJesus-Hernandez, M., Ansorge, O., ... & Yokota, O. (2011). FET proteins TAF15 and EWS are selective markers that distinguish FTLD with FUS pathology from amyotrophic lateral sclerosis with FUS mutations. *Brain*, *134*(9), 2595-2609.

Nićiforović, N., & Abramovič, H. (2014). Sinapic acid and its derivatives: natural sources and bioactivity. *Comprehensive Reviews in Food Science and Food Safety*, *13*(1), 34-51.

Niedzielska, E., Smaga, I., Gawlik, M., Moniczewski, A., Stankowicz, P., Pera, J., & Filip, M. (2016). Oxidative stress in neurodegenerative diseases. *Molecular Neurobiology*, *53*(6), 4094-4125.

Niu, H., Álvarez-Álvarez, I., Guillén-Grima, F., & Aguinaga-Ontoso, I. (2017). Prevalence and incidence of Alzheimer's disease in Europe: A meta-analysis. *Neurología (English Edition)*, *32*(8), 523-532.

Oakley, P. A. (2018). On the side effects of 'pain'and 'dehydration'in the top 20 selling pharmaceuticals of 2017. *Journal of Pharmaceutical Research International*, 1-9.

Oboh, G., Agunloye, O. M., Akinyemi, A. J., Ademiluyi, A. O., & Adefegha, S. A. (2013). Comparative study on the inhibitory effect of caffeic and chlorogenic acids on key enzymes linked to Alzheimer's disease and some pro-oxidant induced oxidative stress in rats' brain-in vitro. *Neurochemical Research*, *38*(2), 413-419.

Okuyama, S., Minami, S., Shimada, N., Makihata, N., Nakajima, M., & Furukawa, Y. (2013). Anti-inflammatory and neuroprotective effects of auraptene, a citrus coumarin, following cerebral global ischemia in mice. *European Journal of Pharmacology*, *699*(1-3), 118-123.

Ono, K., Hirohata, M., & Yamada, M. (2005). Ferulic acid destabilizes preformed β-amyloid fibrils in vitro. *Biochemical and Biophysical Research Communications*, *336*(2), 444-449.

Othman, A., Mukhtar, N. J., Ismail, N. S., & Chang, S. K. (2014). Phenolics, flavonoids content and antioxidant activities of 4 Malaysian herbal plants. *International Food Research Journal*, *21*(2), 759.

Park, S. A., Ahn, S. I., & Gallo, J. M. (2016). Tau mis-splicing in the pathogenesis of neurodegenerative disorders. *BMB Reports*, *49*(8), 405.

Paşayeva, L., Arslan, A. K. K., & Kararenk, A. C. (2019). Viburnum opulus L. Fruit Extracts Protect Human Neuroblastoma SH-SY5Y Cells against hydrogen peroxide-induced cytotoxicity. *Multidisciplinary Digital Publishing Institute Proceedings, 40*(1), 5.

Perez-Garcia, M. J., Kong, L., Sumner, C. J., & Tizzano, E. F. (2017). Developmental aspects and pathological findings in spinal muscular atrophy. *In Spinal Muscular Atrophy* (pp. 21-42). Academic Press.

Pérez-Hernández, J., Zaldívar-Machorro, V. J., Villanueva-Porras, D., Vega-Ávila, E., & Chavarría, A. (2016). A potential alternative against neurodegenerative diseases: Phytodrugs. *Oxidative Medicine and Cellular Longevity, 2016*.

Petersen, C., Nolan, A. L., Resende, E. D. P. F., Miller, Z., Ehrenberg, A. J., Gorno-Tempini, M. L., ... & Miller, B. L. (2019). Alzheimer's disease clinical variants show distinct regional patterns of neurofibrillary tangle accumulation. *Acta Neuropathologica, 138*(4), 597-612.

Pokusa, M., & Kráľová Trančíková, A. (2017). The central role of biometals maintains oxidative balance in the context of metabolic and neurodegenerative disorders. *Oxidative Medicine and Cellular Longevity, 2017*.

Popa-Wagner, A., Mitran, S., Sivanesan, S., Chang, E., & Buga, A. M. (2013). ROS and brain diseases: the good, the bad, and the ugly. *Oxidative Medicine and Cellular Longevity, 2013*.

Prince, M. B. (2013). R.; Albanese, E. et al. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimer's & Dementia*, *9*(1), 63-75.

Prince, M., Comas-Herrera, A., Knapp, M., Guerchet, M., & Karagiannidou, M. (2016). World Alzheimer report 2016: improving healthcare for people living with dementia: coverage, quality and costs now and in the future. *Alzheimer's Disease International, 2016*.

Prince, M., Wimo, A., Guerchet, M., Ali, G. C., Wu, Y. T., & Prina, M. (2015). The global impact of dementia. *World Alzheimer Report*, 1-82.

Pringsheim, T., Jette, N., Frolkis, A., & Steeves, T. D. (2014). The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Movement Disorders, 29*(13), 1583-1590.

Przedborski, S., Vila, M., & Jackson-Lewis, V. (2003). Series Introduction: Neurodegeneration: What is it and where are we? *The Journal of Clinical Investigation, 111*(1), 3-10.

Qiu, C., von Strauss, E., Bäckman, L., Winblad, B., & Fratiglioni, L. (2013). Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. *Neurology*, *80*(20), 1888-1894.

Ramli, I., Kamarulzaman, N. H., Shaari, K., & Ee*, G. C. L. (2004). p-O-geranylcoumaric acid from Melicope lunu-ankenda. *Natural Product Research*, *18*(4), 289-294.

Ratheesh, G., Tian, L., Venugopal, J. R., Ezhilarasu, H., Sadiq, A., Fan, T. P., & Ramakrishna, S. (2017). Role of medicinal plants in neurodegenerative diseases. *Biomanufacturing Reviews*, *2*(1), 2.

Ratheesh, M., Sindhu, G., & Helen, A. (2013). Anti-inflammatory effect of quinoline alkaloid skimmianine isolated from *Ruta graveolens* L. *Inflammation Research*, *62*(4), 367-376.

Sadigh-Eteghad, S., Sabermarouf, B., Majdi, A., Talebi, M., Farhoudi, M., & Mahmoudi, J. (2015). Amyloid beta: a crucial factor in Alzheimer's disease. *Medical Principles and Practice, 24*(1), 1-10.

Sahebkar, A. (2011). Citrus auraptene: a potential multifunctional therapeutic agent for nonalcoholic fatty liver disease. *Annals of Hepatology*, *10*(4), 575-577.

Sajjad, N., Ali, R., Hassan, S., Ganai, B. A., & Hamid, R. (2018). Oxidative stress in Neurodegenerative diseases. *International Journal of Management, Technology And Engineering, Issn*, *8*, 2249-7455.

Salim, S. (2017). Oxidative stress and the central nervous system. *Journal of Pharmacology and Experimental Therapeutics*, *360*(1), 201-205.

Satizabal, C. L., Beiser, A., Chêne, G., Chouraki, V. A., Himali, J. J., Preis, S. R., ... & Seshadri, S. (2014). Temporal trends in dementia incidence in the Framingham Study. Alzheimer's & Dementia: *The Journal of the Alzheimer's Association*, *10*(4), P296.

Scapagnini, G., Foresti, R., Calabrese, V., Stella, A. G., Green, C. J., & Motterlini, R. (2002). Caffeic acid phenethyl ester and curcumin: a novel class of heme oxygenase-1 inducers. *Molecular Pharmacology, 61*(3), 554-561.

Scoto, M., Finkel, R. S., Mercuri, E., & Muntoni, F. (2017). Therapeutic approaches for spinal muscular atrophy (SMA). *Gene Therapy*, *24(*9), 514-519.

Serdar, B. S., Erkmen, T., Ergür, B. U., Akan, P., & Koçtürk, S. (2018). Which medium and ingredients provide better morphological differentiation of SH-SY5Y cells?. In *Multidisciplinary Digital Publishing Institute Proceedings* (Vol. *2*, No. 25, p. 1577).

Sevigny, J., Chiao, P., Bussière, T., Weinreb, P. H., Williams, L., Maier, M., ... & O'Gorman, J. (2016). The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature, 537*(7618), 50-56.

Sgarbossa A, Giacomazza D, Di Carlo M (2015) Ferulic acid: a hope for Alzheimer's disease therapy from plants. *Nutrients 2015*, 7, 5764–5782.

Sharma, K. (2019). Cholinesterase inhibitors as Alzheimer's therapeutics. *Molecular Medicine Reports, 20*(2), 1479-1487.

Shaw, C. Y., Chen, C. H., Hsu, C. C., Chen, C. C., & Tsai, Y. C. (2003). Antioxidant properties of scopoletin isolated from Sinomonium acutum. *Phytotherapy Research*, *17*(7), 823-825.

Singh, A., Kukreti, R., Saso, L., & Kukreti, S. (2019). Oxidative stress: a key modulator in neurodegenerative diseases. *Molecules*, *24*(8), 1583.

Skodda, S., Grönheit, W., Lukas, C., Bellenberg, B., von Hein, S. M., Hoffmann, R., & Saft, C. (2016). Two different phenomena in basic motor speech performance in premanifest Huntington disease. *Neurology*, *86*(14), 1329-1335.

Solanki, I., Parihar, P., & Parihar, M. S. (2016). Neurodegenerative diseases: from available treatments to prospective herbal therapy. *Neurochemistry international*, *95*, 100-108.

Song, J. X., Sun, Y. R., Peluso, I., Zeng, Y., Yu, X., Lu, J. H., ... & Chen, L. L. (2016). A novel curcumin analog binds to and activates TFEB in vitro and in vivo independent of MTOR inhibition. *Autophagy*, *12*(8), 1372-1389.

Song, X. J., Zhou, H. Y., Sun, Y. X., & Huang, H. C. (2020). Inhibitory effects of curcumin on H 2 O 2-induced cell damage and APP expression and processing in SH-SY5Y cells transfected with APP gene with Swedish mutation. *Molecular Biology Reports*, *47*(3), 2047-2059.

Sospedra, M., & Martin, R. (2005). Immunology of multiple sclerosis. Annu. *Rev. Immunol.*, *23*, 683-747.

Sousa, R. M., Ferri, C. P., Acosta, D., Albanese, E., Guerra, M., Huang, Y., ... & Rodriguez, M. C. (2009). Contribution of chronic diseases to disability in elderly people in countries with low and middle incomes: a 10/66 Dementia research group population-based survey. *The Lancet*, *374*(9704), 1821-1830.

Spagnuolo, C., Moccia, S., & Russo, G. L. (2018). Anti-inflammatory effects of flavonoids in neurodegenerative disorders. *European Journal of Medicinal Chemistry*, *153*, 105-115.

Squillaro, T., Cimini, A., Peluso, G., Giordano, A., & Melone, M. A. B. (2018). Nano-delivery systems for encapsulation of dietary polyphenols: An experimental approach for neurodegenerative diseases and brain tumors. *Biochemical Pharmacology*, *154*, 303-317.

Squillaro, T., Schettino, C., Sampaolo, S., Galderisi, U., Di Iorio, G., Giordano, A., & Melone, M. A. (2018). Adult-onset brain tumors and neurodegeneration: Are polyphenols protective?. *Journal of Cellular Physiology*, *233*(5), 3955-3967.

Sugarman, E. A., Nagan, N., Zhu, H., Akmaev, V. R., Zhou, Z., Rohlfs, E. M., ... & Allitto, B. A. (2012). Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of> 72 400 specimens. *European Journal of Human Genetics*, *20*(1), 27-32.

Sul, D., Kim, H. S., Lee, D., Joo, S. S., Hwang, K. W., & Park, S. Y. (2009). Protective effect of caffeic acid against beta-amyloid-induced neurotoxicity by the inhibition of calcium influx and tau phosphorylation. *Life Sciences*, *84*(9-10), 257-262.

Sveinbjornsdottir, S. (2016). The clinical symptoms of Parkinson's disease. *Journal of Neurochemistry*, *139*, 318-324.

Szwajgier, D., Borowiec, K., & Pustelniak, K. (2017). The neuroprotective effects of phenolic acids: molecular mechanism of action. *Nutrients*, *9*(5), 477.

Teixeira, J., Gaspar, A., Garrido, E. M., Garrido, J., & Borges, F. (2013). Hydroxycinnamic acid antioxidants: an electrochemical overview. *BioMed Research International*, *2013*.

Tian, X., Gao, L., An, L., Jiang, X., Bai, J., Huang, J., ... & Zhao, Q. (2016). Pretreatment of MQA, a caffeoylquinic acid derivative compound, protects against H2O2-induced oxidative stress in SH-SY5Y cells. *Neurological Research*, *38*(12), 1079-1087.

Tisdale, S., & Pellizzoni, L. (2015). Disease mechanisms and therapeutic approaches in spinal muscular atrophy. *Journal of Neuroscience*, *35*(23), 8691-8700.

Tysnes, O. B., & Storstein, A. (2017). Epidemiology of Parkinson's disease. *Journal of Neural Transmission*, *124*(8), 901-905.

Uzun, K., & Arslan, A. K. K. (2020). Turkish endemic achillea species protect human neuroblastoma SH-SY5Y cells against hydrogen peroxide-induced cytotoxicity. *Multidisciplinary Digital Publishing Institute Proceedings*, *40*(1), 43.

Van Es, M. A., Hardiman, O., Chio, A., Al-Chalabi, A., Pasterkamp, R. J., Veldink, J. H., & Van den Berg, L. H. (2017). *Amyotrophic lateral sclerosis. The Lancet*, *390*(10107), 2084-2098.

Vauzour, D., Corona, G., & Spencer, J. P. (2010). Caffeic acid, tyrosol and p-coumaric acid are potent inhibitors of 5-S-cysteinyl-dopamine induced neurotoxicity. *Archives of Biochemistry and Biophysics*, *501*(1), 106-111.

Venugopala, K. N., Rashmi, V., & Odhav, B. (2013). Review on natural coumarin lead compounds for their pharmacological activity. *BioMed research international*, *2013*, *1*.

Vucic, S., Rothstein, J. D., & Kiernan, M. C. (2014). Advances in treating amyotrophic lateral sclerosis: insights from pathophysiological studies. *Trends in Neurosciences*, *37*(8), 433-442.

Wang, C., Pei, A., Chen, J., Yu, H., Sun, M. L., Liu, C. F., & Xu, X. (2012). A natural coumarin derivative esculetin offers neuroprotection on cerebral ischemia/reperfusion injury in mice. *Journal of Neurochemistry*, *121*(6), 1007-1013.

Wansi, J. D., Devkota, K. P., Tshikalange, E., & Kuete, V. (2013). Alkaloids from the medicinal plants of Africa. In *Medicinal Plant Research in Africa* (pp. 557-605). *Elsevier*.

Waziri, P. M., Abdullah, R., Yeap, S. K., Omar, A. R., Abdul, A. B., Kassim, N. K., ... & Imam, M. U. (2016). Clausenidin from Clausena excavata induces apoptosis in hepG2 cells via the mitochondrial pathway. *Journal of Ethnopharmacology*, *194*, 549-558.

Weekman, E. M., Sudduth, T. L., Caverly, C. N., Kopper, T. J., Phillips, O. W., Powell, D. K., & Wilcock, D. M. (2016). Reduced efficacy of anti-Aβ immunotherapy in a mouse model of amyloid deposition and vascular cognitive impairment comorbidity. *Journal of Neuroscience, 36*(38), 9896-9907.

Weinstock-Guttman, B. (2013). An update on new and emerging therapies for relapsing-remitting multiple sclerosis. *The American Journal of Managed Care, 19*(17 Suppl), s343-54.

Westmark, C. J., Sokol, D. K., Maloney, B., & Lahiri, D. K. (2016). Novel roles of amyloid-beta precursor protein metabolites in fragile X syndrome and autism. *Molecular Psychiatry, 21*(10), 1333-1341.

Williamson, J. M., & Lyons, D. A. (2018). Myelin dynamics throughout life: an ever-changing landscape? *Frontiers in Cellular Neuroscience, 12*, 424.

Wimo, A., Guerchet, M., Ali, G. C., Wu, Y. T., Prina, A. M., Winblad, B., ... & Prince, M. (2017). The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimer's & Dementia, 13*(1), 1-7.

Winblad, B., Amouyel, P., Andrieu, S., Ballard, C., Brayne, C., Brodaty, H., ... & Fratiglioni, L. (2016). Defeating Alzheimer's disease and other dementias: a priority for European science and society. *The Lancet Neurology, 15*(5), 455-532.

Wu, Y. T., Fratiglioni, L., Matthews, F. E., Lobo, A., Breteler, M. M., Skoog, I., & Brayne, C. (2016). Dementia in western Europe: epidemiological evidence and implications for policy making. *The Lancet Neurology, 15*(1), 116-124.

Xie, H. R., Hu, L. S., & Li, G. Y. (2010). SH-SY5Y human neuroblastoma cell line: in vitrocell model of dopaminergic neurons in Parkinson's disease. *Chinese Medical Journal, 123*(8), 1086-1092.

Ye, Q., Ye, L., Xu, X., Huang, B., Zhang, X., Zhu, Y., & Chen, X. (2012). Epigallocatechin-3-gallate suppresses 1-methyl-4-phenyl-pyridine-induced oxidative stress in PC12 cells via the SIRT1/PGC-1α signaling pathway. *BMC complementary and Alternative Medicine, 12*(1), 82.

Zaitone, S. A., Ahmed, E., Elsherbiny, N. M., Mehanna, E. T., El-Kherbetawy, M. K., ElSayed, M. H., ... & Moustafa, Y. M. (2019). Caffeic acid improves locomotor activity and lessens inflammatory burden in a mouse model of rotenone-induced nigral neurodegeneration: Relevance to Parkinson's disease therapy. *Pharmacological Reports, 71*(1), 32-41.

Zare, K., Eidi, A., Roghani, M., & Rohani, A. H. (2015). The neuroprotective potential of sinapic acid in the 6-hydroxydopamine-induced hemi-parkinsonian rat. *Metabolic Brain Disease, 30*(1), 205-213.

Zhang, R., Yi, R., Bi, Y., Xing, L., Bao, J., & Li, J. (2017). The effect of selenium on the Cd-induced apoptosis via NO-mediated mitochondrial apoptosis pathway in chicken liver. *Biological Trace Element Research, 178*(2), 310-319.

Zhang, X., He, X., Chen, Q., Lu, J., Rapposelli, S., & Pi, R. (2018). A review on the hybrids of hydroxycinnamic acid as multi-target-directed ligands against Alzheimer's disease. *Bioorganic & Medicinal Chemistry*, *26*(3), 543-550.

Zhang, Z. J., Cheang, L. C. V., Wang, M. W., & Lee, S. M. Y. (2011). Quercetin exerts a neuroprotective effect through inhibition of the iNOS/NO system and pro-inflammation gene expression in PC12 cells and in zebrafish. *International Journal of Molecular Medicine*, *27*(2), 195-203.

Zhao, J. J., Song, J. Q., Pan, S. Y., & Wang, K. (2016). Treatment with isorhamnetin protects the brain against ischemic injury in mice. *Neurochemical Research*, *41*(8), 1939-1948.

Zhao, X., Fang, J., Li, S., Gaur, U., Xing, X., Wang, H., & Zheng, W. (2019). Artemisinin attenuated hydrogen peroxide (H2O2)-induced oxidative injury in SH-SY5Y and hippocampal neurons via the activation of AMPK pathway. *International Journal of Molecular Sciences*, *20*(11), 2680.

Zhao, X., Li, R., Jin, H., Jin, H., Wang, Y., Zhang, W., ... & Chen, W. (2018). Epigallochin-3-gallate confers protection against corticosterone-induced neuron injuries via restoring extracellular signal-regulated kinase 1/2 and phosphatidylinositol-3 kinase/protein kinase B signaling pathways. *PloS One*, *13*(1).

Zheng, C., Zhou, M., Sun, J., Xiong, H., Peng, P., Gu, Z., & Deng, Y. (2019). The protective effects of liraglutide on AD-like neurodegeneration induced by oxidative stress in human neuroblastoma SH-SY5Y cells. *Chemico-Biological Interactions*, *310*, 108688.

BIODATA OF STUDENT

Zeinab Abdulwanis Masoud Mohamed is a Libyan citizen from Tripoli, she obtained her bachelor's degree in 2009 from Tripoli University, specializing in pharmaceutical science. She has extensive experience in the pharmaceutical industry gained from working in variable roles.

Since graduation in 2009 she worked in her own pharmacy, providing medicine and medical advice to a large number of customers. She also worked in a local hospital pharmacy in Tripoli between 2010 and 2016, advising on the science of medicines and their clinical use to improve patient care through safe and effective use of medicines, developing clinical pharmacy programs, reviewing patients records to determine the appropriate medical therapy, and evaluating patients conditions to ensure effective treatment.

She also worked as a consultant for a large pharmaceutical distributor in Tripoli, directing quality control operations, selection of medicines, quantification, import, storage, stock management and distribution.

Zeinab has started her master's degree course in Medical Biotechnology at Universiti Putra Malaysia (UPM) in 2018, with the research is focusing on elucidating neuroprotective effect of 7-Granyloxycinnamic Acid isolated from Melicope lunu-ankenda leaves. She is expected to complete her degree course before the end of 2020.

LIST OF PUBLICATIONS

Abdulwanis Mohamed, Z., Mohamed Eliaser, E., Mazzon, E., Rollin, P., Cheng Lian Ee, G., & Abdull Razis, A. F. (2019). Neuroprotective potential of secondary metabolites from melicope lunu-ankenda (rutaceae). *Molecules*, *24*(17), 3109.

Abdulwanis Mohamed, Z., Mohamed Eliaser, E., Jaafaru, M. S., Nordin, N., Ioannides, C., & Abdull Razis, A. F. (2020). Neuroprotective Effects of 7-Geranyloxycinnamic Acid from Melicope lunu ankenda Leaves. *Molecules*, *25*(16), 3724.

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