UNIVERSITI TEKNOLOGI MARA

ASTAXANTHIN NANOEMULSION ENHANCES COGNITIVE FUNCTION AND MITIGATES ALZHEIMER'S DISEASE PATHOLOGICAL MARKERS IN A STREPTOZOTOCIN-INDUCED RAT MODEL

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Thesis submitted in fulfilment
of the requirements for the degree of
Doctors of Philosophy
(Science)

Faculty of Pharmacy

January 2024

ABSTRACT

Malaysia's older adults is at risk of Alzheimer's disease (AD) as the country's population ages rapidly, making it an old-age nation by 2030. AD is characterized by neuronal degeneration, which impairs memory, behaviour, language, and visual-spatial skills. Astaxanthin, a keto-carotenoid molecule, is well-known for its antioxidant activity. Despite its low oral bioavailability, astaxanthin is significant research candidate due to its possible health-promoting qualities such as antioxidant and anti-inflammatory. As a result, numerous studies on the protective effect of astaxanthin in chronic diseases are available, but very few actually investigate the protective effects of astaxanthin in nano form (nano-formulated astaxanthin has improved bioavailability, solubility, and stability) against AD-like rodent model. The present study aimed to elucidate the neuroprotective effects of astaxanthin nanoemulsion treatment against a chemically-induced AD-like model as a preventive (astaxanthin nanoemulsion treatment before AD induction) and treatment (astaxanthin nanoemulsion treatment after AD induction) measure by assessing cognitive function, biochemical markers, and histopathological changes in the brain. First, the presence of astaxanthin was measured in distinct brain regions (hippocampus, cortex, and cerebellum) to indicate that the synthesized astaxanthin nanoemulsion could pass the blood-brain barrier and exert its putative neuroprotective benefits. Results indicated that the hippocampus showed a significantly higher concentration of astaxanthin compared to the cortex and cerebellum. Given that the hippocampus is related to memory, detecting astaxanthin in the hippocampus indicating its possible neuroprotective effects in neurological diseases that cause memory impairment. Following that, a chemically-induced AD model was established to imitate the pathophysiology of AD by injecting streptozotocin (STZ) intrahippocampally (bilaterally). STZ injection significantly induced memory impairment, elevated synaptosomal amyloid beta and paired helical filament tau (PHF-tau), malondialdehyde, and decreased acetylcholine levels in the hippocampus. The results of STZ injection closely mimic some of the important clinical and cognitive aspects of the disease, thus making it a feasible model for future research into the condition and potential treatments. Finally, the neuroprotective effects of astaxanthin nanoemulsion administration on chemically-induced AD-like rats were investigated as a preventive and treatment strategy. Astaxanthin nanoemulsion significantly improved spatial learning memory (AD treatment study), recognition memory (AD prevention study), and motor function ($p < 0.05$) in behavioural tests. Furthermore, in both preventive and treatment studies, astaxanthin nanoemulsion significantly decreased the levels of synaptosomal amyloid beta and PHF-tau. Treatment with astaxanthin nanoemulsion reduced lipid peroxidation (AD prevention and treatment studies), neuroinflammation (AD prevention and treatment studies), enhanced acetylcholine (AD treatment study), and neuronal plasticity (AD treatment study). In conclusion, the findings of this study suggest that astaxanthin nanoemulsions offer several potential advantages in the setting of AD. It appears to improve cognitive function, and motor performance while also lowering amyloid beta and PHF-tau levels, resulting in reduced neuroinflammation and acting as a radical scavenger. It also possesses antioxidant and anti-inflammatory properties, which help to treat some of the underlying causes of AD.

ACKNOWLEDGEMENT

Alhamdulillah, all praise and thanks to Allah for providing me with the opportunity to continue my PhD studies and the perseverance to complete this challenging and long journey. This research is made possible by the assistance and encouragement of those around me.

First and foremost, I would like to express my heartfelt gratitude and appreciation to my supervisor, Dr. Gurmeet Kaur Surindar Singh, for her constant guidance, support, and expertise during this research journey. Her mentorship, patience, passion, and constant assistance have greatly aided me in strengthening my study, developing important insights, and completing my research.

I would also like to express my gratitude to my co-supervisors, Associate Professor Dr. Meor Mohd Redzuan Meor Mohd Affandi and Dr. Nurul Aqmar Mohamad Nor Hazalin, for their essential insight and assistance throughout this research. Their experience and input on my work have improved its quality and depth.

I would like to express my heartfelt gratitude to my dear parents, Wan Chik bin Man and , for their unconditional support, understanding, and encouragement throughout my academic journey. Not to mention my lovely siblings Mazlia, Mazliana, Mazliani, Mardiana, and Mazzatol Azlin, who always cheer me up when I need it.

Special thanks to my colleagues and friends, Nur Farahani and Farahdina, for their continuous help throughout my studies. I am also grateful to all of the laboratory personnel especially Puan Hanim and Puan Azurah for their guidance and constant assistance.

Finally, this thesis would not have been possible without the help of my supervisor and co-supervisor, as well as my family, friends, and UiTM colleagues. Thank you for being a part of this adventure.

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CHAPTER 1
INTRODUCTION

1.1 Research Background

Alzheimer's disease (AD) is a neurodegenerative disease that is sometimes misunderstood as normal aging due to its prevalence in old age. Many physiological changes occur as we age, including loss of organ function and cognitive function, which progress gradually until they become severe enough to impede everyday tasks. There is currently no cure for AD. Previous treatments focus on symptomatic medications (donepezil, rivastigmine, galantamine, and memantine), which target counterbalancing the neurotransmitter disruption that delays disease progression during the early stages of AD (Mendiola-Precoma et al., 2016). The US Food and Drug Administration recently granted approval for two new drugs to target amyloid aggregates, aducanumab and lecanemab. Numerous promising new therapies for AD are currently being studied in clinical trials, including anti-tau therapy (bepranemab), neuroprotectors and cognitive enhancers (buntanetap, caffeine, hydralazine hydrochloride, metformin), and anti-inflammation therapy (masitinib) (L. K. Huang et al., 2023). Despite all of the available medications, substantial research into improved ways to treat the condition, delay its onset, and prevent it from developing is still ongoing. To explain the pathophysiology of AD, numerous existing ideas have been proposed, including the amyloid cascade theory, cholinergic hypothesis, dendritic hypothesis, mitochondrial cascade hypothesis, metabolic hypothesis, and additional hypotheses (neuroinflammation and oxidative stress) (Folch et al., 2016). However, further research is needed to understand and support the mechanisms underlying the aforementioned assumptions that occur in AD.

Extensive studies on astaxanthin utilizing an applicable AD model will be able to represent the complicated mechanisms of AD in humans and unravel the possible therapeutic benefit of astaxanthin in AD. To better understand AD and create effective therapies, a rodent model that replicates disease pathology must be developed. Intracerebroventricular (ICV) injection of streptozotocin (STZ) is a well-known method for establishing AD in non-genetic types of AD that account for more than 92% of cases worldwide (sporadic AD) (Grieb, 2016). Since sporadic AD in human is associated with an insulin-resistant brain state, STZ has been manipulated and injected in the