UNIVERSITI TEKNOLOGI MARA

NEUROPROTECTIVE EFFECTS OF BIOGENIC GOLD NANOPARTICLES FROM *FAGONIA ARABICA* IN SK-N-SH CELLS AND IN VIVO ICV-STZ MOUSE MODEL: ANTIOXIDANT, ANTI-INFLAMMATORY, AND COGNITIVE ENHANCEMENT POTENTIAL IN ALZHEIMER'S DISEASE

IBRAHIM AHMED SHAIKH

Thesis submitted in fulfilment
of the requirements for the degree of
Doctor of Philosophy
(Pharmacology)

Faculty of Pharmacy

January 2026

ABSTRACT

Neurodegenerative diseases, such as Alzheimer's disease (AD) pose significant challenges to modern medicine. Its global prevalence is rising sharply, primarily among older adults. AD pathology is multifactorial, involving amyloid-β, tau dysfunction, oxidative stress, and neuroinflammation, making therapy challenging. Green-synthesized nanoparticles offer a promising targeted approach to enhance cognition and mitigate AD pathology. This study aimed to explore the neuroprotective potential of *Fagonia arabica* and its green-synthesized gold nanoparticles (AuNPs). The research focused on evaluating the anti-inflammatory, antioxidant, and neuroprotective potential of *F. arabica* through in silico, in vitro, and in vivo animal models. The dried plant material underwent sequential solvent extraction with hexane, ethyl acetate, ethanol, and distilled water. The resulting extracts were subjected to phytochemical analyses, identifying important classes of phytochemicals like flavonoids, alkaloids, and phenols. The aqueous extract was further analyzed for total phenols and flavonoids, with contents found to be 2450.35 µg GAE/g and 1980.29 µg QE/g, respectively. In silico analysis revealed strong binding affinities of the plant's phytochemicals to key inflammatory and neuroprotective targets, particularly the compound veridiflorol. The AuNPs were characterized using ultraviolet-visible (UV-Vis), x-ray diffraction (XRD), particle size analysis (PSA), scanning electron microscopy with energy dispersive x-ray spectroscopy (SEM-EDX), Fourier transform infrared spectroscopy (FTIR), and zeta potential techniques, confirming their stability and optimal characteristics, including a crystalline nature, an average size of 111.4 nm, and a zeta potential value of -2.1 mV. In vitro assays demonstrated significant anti-inflammatory activity by protein denaturation (IC_{50} 118.65 µg/mL) and cyclooxygenase-2 (COX-2) inhibition (IC_{50} 109.67 µg/mL), as well as antioxidant activity confirmed by 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging assay (IC_{50} 115.01 µg/mL). The AuNPs exhibited minimal toxicity on normal L929 cell lines (IC_{50} 246.57 µg/mL), indicating good biocompatibility. The AuNPs showed significant neuroprotective activity against trimethyltin (TMT)-induced neurotoxicity in SK-N-SH neuroblastoma cells, with cell viability of 78.53% at 50 µg/mL concentration ($p < 0.001$) compared to cisplatin (cell viability 13.35%). The AuNPs exhibited significant neuroprotective effects in the Intracerebroventricular Streptozotocin (ICV-STZ)-induced mouse model of AD. Treatment with the AuNPs led to notable improvements in cognitive performance, as evidenced by behavioural assessments, which showed significant ($p < 0.001$) decrease in the escape latency in the AuNPs treated animals compared to the ICV-STZ group in the Morris water maze test. Similarly, there was an increase ($p < 0.001$) in the percentage of alternations in the AuNPs treated group compared to the ICV-STZ group in the Y-maze test. This was accompanied by a marked reduction in acetylcholinesterase activity and enhancement of endogenous antioxidant defense mechanisms including CAT and SOD. Collectively, these results highlight the multifaceted efficacy of *F. arabica* AuNPs in ameliorating pathological hallmarks of AD, supporting their potential as a promising candidate for further development in the treatment of neurodegenerative disorders. Future studies should investigate the mechanisms underlying these neuroprotective potentials and assess the clinical usefulness of these nanoparticles in relevant in vivo models.

Keywords: Alzheimer’s disease; gold nanoparticles (AuNPs); neuroinflammation and oxidative stress; cognitive function and behavioural assessment.

ACKNOWLEDGEMENT

Firstly, I wish to thank Allah Almighty for giving me the opportunity to embark on my Ph.D. journey and completing it successfully. I extend my heartfelt gratitude to my supervisor, Assoc. Prof. Dr. Gurmeet Kaur Surindar Singh, for her invaluable guidance, encouragement, and unwavering support throughout this research.

My sincere appreciation also goes to my Co-Supervisors Assoc. Prof. Dr. Hanish Singh Jayasingh Chellammal, and Dr. Noordin Othman for their constant support and guidance. Special thanks to my colleagues and friends for helping me during the course of this project.

Finally, this thesis is lovingly dedicated to my beloved parents, my wife, and my children, whose vision, prayers, and determination have been the foundation of my education and success. This achievement is as much theirs as it is mine. **Alhamdulillah**.

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CHAPTER 1
INTRODUCTION

1.1. Research Background

Alzheimer's disease (AD) is a gradual, irreversible neurological diseases that damages critical brain functions such as memory, cognitive intelligence, thinking, and reasoning skills, eventually impairing the capacity to perform everyday tasks. Progressive memory loss and cognitive impairment define AD; it is also known to cause motor function decline and personality changes, hence ultimately leading to mortality. AD causes a steady neuronal degeneration and death, especially in the hippocampus, the part of the brain involved in forming memories (Shineman and Fillit, 2009). According to the World Health Organization (WHO), the number of people living with dementia globally is projected to triple from 50 million in 2017 to 152 million by 2050, with AD accounting for 60–70% of these cases (WHO, 2025). This escalation in cases will result in increased financial burdens and additional strain on both public health and society as a whole. AD is primarily characterized by the presence of extracellular senile plaques (SPs) and intracellular neurofibrillary tangles (NFTs). NFTs are generated through the regulation of the excessively phosphorylated and glycosylated microtubule-associated tau protein, while SPs are linked to the aggregation and deposition of amyloid β peptides (Zhang et al. 2023).

Lack of cure and limited treatment effectiveness are the major treatment challenges faced by AD patients. Currently, there is no cure for AD. Available treatments focus on managing symptoms and slowing down the progression of the disease but cannot stop or reverse it completely (Abeysinghe et al., 2020). While some medications can temporarily improve cognitive function and manage behavioural symptoms in some individuals, the effects vary, and not everyone responds to treatment. These medications do not work for everyone and may have side effects. Currently, the marketed nootropic drugs like piracetam and cholinesterase inhibitors like galantamine, donepezil, and rivastigmine are the mainstays for treating the symptoms in patients with AD. However, these drugs have certain drawbacks such as short half-lives and serious adverse effects like hepatotoxicity, bronchitis, anorexia,