STUDIES ON PHYTOBIOACTIVE INHIBITORS FOR ALZHEIMER'S DISEASE AND THEIR ENCAPSULATION IN LIPOSOMES FOR EFFECTIVE DELIVERY

SUKRITI SRIVASTAVA

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY DELHI

NEW DELHI-110016

JULY-2025

STUDIES ON PHYTOBIOACTIVE INHIBITORS FOR ALZHEIMER'S DISEASE AND THEIR ENCAPSULATION IN LIPOSOMES FOR EFFECTIVE DELIVERY

by

SUKRITI SRIVASTAVA

DEPARTMENT OF CHEMISTRY

Submitted

in fulfilment of the requirements of the degree of

Doctor of Philosophy

to the

INDIAN INSTITUTE OF TECHNOLOGY DELHI

NEW DELHI-110016

JULY-2025

Dedicated to my,

Parents & Husband

CERTIFICATE

This is to certify that the thesis entitled **"Studies on phytobioactive inhibitors for Alzheimer's disease and their encapsulation in liposomes for effective delivery"** being submitted by **Ms. SUKRITI SRIVASTAVA** to the Indian Institute of Technology Delhi for the award of the degree of **Doctor of Philosophy** in Chemistry is a record of Bonafide research work carried out by her. Ms. Sukriti Srivastava has worked under my guidance and supervision and has fulfilled the requirements for the thesis submission, which, to my knowledge, has reached the requisite standard.

The results contained in this dissertation have not been submitted in part or full to any other University or Institute for the award of any degree or diploma.

Date: 21st July 2025
Place: New Delhi

Prof. Sunil K. Khare
Professor
Department of Chemistry
Indian Institute of Technology Delhi

Prof. Shashank Deep
Professor
Department of Chemistry
Indian Institute of Technology Delhi

ACKNOWLEDGEMENTS

My Ph.D. journey, which began in July 2019 with the goal of contributing to Alzheimer's research, has been a transformative experience. The process taught me invaluable lessons- scientific, managerial, and personal. It strengthened my resilience, patience, and ability to navigate challenges, from a global pandemic to personal hurdles like a fractured ankle and marriage. Through every setback, I learned to persevere, adapt, and face life's challenges with a positive outlook.

I am grateful to ***God*** for guiding me through this journey. I also want to thank my late grandparents, ***Smt. Sheila Srivastava***, ***Shri. Rajendra Shankar Srivastava***, and ***Shri. Krishna Nand Lal***, whose blessings and prayers continue to light my path. They may not have fully understood my work, but their unwavering support and selfless joy in my achievements meant the world to me. Their presence remains a source of strength and guidance.

I am immensely grateful to my supervisor, ***Prof. Sunil Kumar Khare***, for his unwavering support and guidance throughout my PhD. Beyond scientific training, he imparted invaluable life lessons on resilience, teamwork, and perseverance. His mentorship was especially crucial during the challenges of my fourth year when setbacks and lost time due to COVID felt overwhelming. His encouragement helped me regain confidence and move forward. His insightful advice on analyzing data on weekly basis, making reports and blue file all proved meaningful in the end. I truly cherish the bond we share, hoping it remains strong in the years to come.

I am sincerely grateful to my co-supervisor, ***Prof. Shashank Deep***, for his invaluable guidance and support. His expertise in computational biology and aggregation studies greatly enriched my understanding. Always approachable, he readily provided solutions, reviewed my

manuscripts, and offered insightful suggestions. His trust and encouragement have been instrumental in my journey, and I deeply appreciate his mentorship.

I sincerely thank my SRC members, ***Prof. N.G. Ramesh***, ***Prof. Tanmay Dutta***, and ***Prof. Preeti Srivastava***, for their critical evaluation of my work and their steadfast support, guidance, and insightful feedback throughout my doctoral journey. I am also deeply grateful to ***Prof. Selvarajan Nagendran***, Head of the Department of Chemistry, and the former Heads of the Department- ***Prof. Siddharth Pandey***, ***Prof. Narayanan D. Kurur***, ***Prof. Anil J. Elias***, ***Prof. Ashok K. Ganguli***, and ***Prof. Ravi Shankar***, for ensuring that I had access to all the necessary resources to carry out my research seamlessly.

I am deeply grateful to everyone I collaborated with during my Ph.D. journey. I conducted part of my nano-delivery work in ***Prof. Prashant Mishra***'s lab at IIT Delhi, where his guidance and support were invaluable. Special thanks to his Ph.D. scholar, ***Ms. Surbhi Chauhan***, for her constant help and kindness. I also had the privilege of working at Sorbonne University, Paris, under ***Prof. Stéphanie Daumas***, who hosted me for a research internship, providing training in animal handling and allowing me to test my compound on a mouse model. I am extremely grateful to her for giving me this opportunity. Her Ph.D. scholar, ***Ms. Elisa Kabli***, became a dear friend and mentor throughout my work. Her warmth and support made my stay in France feel like home. Additionally, I extend my sincere gratitude to ***Dr. Shilpa Sharma*** for her patience and invaluable guidance in teaching me simulations. I am forever thankful to all faculty members, fellow Ph.D. scholars, and staff who supported me in any way.

I want to extend my gratitude to ***central research facility***, ***nano research facility***, ***instrumentation facility of Chemistry Department***, and ***high-performance computing*** of ***supercomputing facility*** at IIT Delhi, for providing the resources and instruments as and when required throughout the Ph.D.

I am immensely grateful to ***Dr. Amrik Bhattacharya***, whose selfless support greatly benefited my Ph.D. journey. Despite not being directly involved in my work, he generously reviewed my manuscripts and thesis, providing invaluable feedback with kindness and encouragement. I also thank ***Dr. Razi Ahmad***, with whom I published my first two review papers. His unwavering positivity and guidance have been a source of motivation during difficult times.

Dr. Sumit Kumar played a crucial role in my early days at the lab, guiding me through report writing and lab culture. His discipline and commitment, alongside our supervisor, kept us focused. ***Dr. Shivani Chaturvedi***'s motivational talks gave me the strength to believe in God's will and correct timing, which I needed the most at a particular time when everything seemed unachievable. ***Dr. Sunaina***'s practical advice on time management, goal setting, and critical reading strategies helped me stay organized and prepared throughout my Ph.D. Their insights and support contributed significantly to my growth.

I am deeply grateful to my seniors for their guidance and support. ***Dr. Shubhrima Ghosh*** inspired me with her hard work, time management, and versatility, always offering help despite leaving the lab early in my journey. ***Dr. Neerja Yadav*** demonstrated the power of discipline and dedication, while ***Dr. Syeda Warisul Fatima*** and ***Dr. Shahnawaz Alam*** created a welcoming and enjoyable lab environment. ***Dr. Nitin Srivastava*** was a valuable critic, constantly pushing me to improve and supporting me through challenges. I also extend my thanks to ***Dr. Nikky***, ***Ms. Pooja***, ***Ms. Deeksha***, ***Ms. Saniya***, ***Ms. Simran***, and ***Ms. Tanisha*** for fostering a lively and encouraging atmosphere. I also want to acknowledge ***Mr. Bibhuti*** who is not just a junior but also a good friend, his practical approach to life is truly inspiring. Mentoring M.Sc. students, ***Ms. Alka*** and ***Ms. Heena***, was a rewarding experience, and I appreciate their enthusiasm and cooperation. I have had some amazing moments with each one of them, that I will forever cherish.

I am indebted to my 2 wonderful lab mates who turned into friends for a lifetime, ***Dr. Ankita Maurya*** and ***Ms. Huma Fatima*****,** who made this journey so beautiful. I am out of words, but mere talking to both of them kept me going. At times, just the idea of having lunch and tea together pushed me through the day. We experienced pretty much everything together, from taking up courses, working on projects, and studying for the exams to bunking classes together. We have witnessed each other's entire Ph.D. journey, our highs and lows, our achievements and failures. And since both of them did everything a little before me, they also kept setting examples for me to follow. They knew my speed and always waited for me to catch up. Made my birthdays special and conferences exciting. I will always cherish our bond.

I also want to acknowledge the support of my husband ***Mr. Sahil Jain***, during this entire period. It is needless to say that I could not have done this without his unwavering support. Since, we got married all our plans revolved around my schedule. He never questioned the unreasonable working hours, me coming late from the lab, or working on weekends, because if anything is important to me, it is important to him. He always understood the amount of stress I was going through, and never complained about my grumpiness and mood swings. He has cancelled our plans last minute without a tinge of irritation on his face. He is not from biology background but he always made it a point to understand what I am doing, and asks the best questions I don't know the answers to. So much so that now when I prepare a presentation, I ask myself what would Sahil ask. He is my cheerleader and he pushes me to work hard more than anyone else. He really gets on my nerve sometimes and annoys me with that, but I know he is the one person who would be the happiest to see me succeed, along with my mother.

I am truly grateful to have my family, who have stood by me unwaveringly throughout this journey. Many people have supported me at different phases of my Ph.D., but the reason I dreamt of becoming a researcher and working on neurodegenerative disorders was my siblings.

My younger brother, ***Mr. Ashutosh Srivastava***, who is 21 years old today, has suffered from epilepsy since he was seven and has been on medication ever since. I have witnessed people advising my parents not to send him to school because his classmates were scared of his condition. My elder sister, ***Ms. Medhavi Srivastava***, now 28 years old, has been battling depression for the past seven years and initially experienced seizures and anxiety attacks. I have seen both my parents and siblings suffer from conditions that, to this day, have no definitive cure. The limitations of medical science in dealing with brain-related disorders often lead to multiple side effects, making treatment itself another challenge. It was during my M.Tech. studies that I deeply engaged with this subject, and I decided that I wanted to contribute to this field further. Despite my dedication, there were times when my stance wavered. Relatives often told my parents that I had already studied enough and should start working. However, my father, ***Mr. Sharad Kumar Srivastava***, always reassured me, saying that I could always work after earning my Ph.D., but once I started working, I would not be able to go back and pursue a Ph.D. even if I wanted to. He joked that a Ph.D. was the best deal- I'd get paid and earn a degree, so no losses, only gains! Lastly, whatever motivation I had and still have to achieve something in life comes from my mother, ***Mrs. Mona Srivastava***. Whenever I feel like giving up or get too comfortable, I remember her childhood advice, to never rely on others because your self-worth influences how you're treated, always strive to stand out. These words continue to push me forward every single day.

I am indebted to all those people who have helped me at any phase of this journey. Every little help mattered.

Sukriti Srivastava

New Delhi

ABSTRACT

Alzheimer's disease remains one of the most challenging neurodegenerative disorders, characterized by cholinergic imbalance in neuromuscular region, amyloid-beta (Aβ) plaque accumulation, tau protein hyperphosphorylation, oxidative stress, and neuroinflammation. The past research on Alzheimer's was focussed on acetylcholinesterase inhibition to maintain the level of neurotransmitter, acetylcholine in the brain. The major available commercial drugs (Donepezil, Rivastigmine, Galantamine) against Alzheimer's are acetylcholinesterase inhibitors. Current therapies also focus on symptomatic relief without addressing the disease's underlying mechanisms. This necessitates a multi-target-directed approach using plant-derived bioactive compounds known for their neuroprotective properties. These compounds can modulate key pathways in disease progression, offering the potential for holistic treatment strategies.

The study began with the identification of acetylcholinesterase and beta-site amyloid precursor protein cleaving enzyme 1 inhibitors, enzymes pivotal to cholinergic dysfunction and $A\beta_{42}$ aggregation. Computational screening was employed to assess the binding affinity and pharmacological potential of various bioactive compounds, followed by enzyme inhibition assays to validate the findings. The rationale was to target these enzymes to simultaneously mitigate neurotransmitter degradation and $A\beta_{42}$ formation. Results demonstrated that selected bioactive compounds acted as dual inhibitors, paving the way for further exploration of their therapeutic potential. After *in vitro* analysis, withanolide A, obtained from *Withania somnifera* was identified to have dual role, as acetylcholinesterase and beta-site amyloid precursor protein cleaving enzyme 1 inhibitor. Withanolide A inhibited acetylcholinesterase (IC_{50} value 107 μM) and showed mixed-type inhibition. At this concentration, it inhibited beta-site amyloid precursor protein cleaving enzyme 1 activity by 57.10% and was stated most effective. Both

the compounds, as well as their crude extracts, were found to have no cytotoxic effect on the SH-SY5Y cell line.

Insoluble $A\beta_{42}$ peptides form neurotoxic plaques that disrupt synaptic transmission and contribute to Alzheimer's disease pathology. *In vitro* aggregation studies of $A\beta_{42}$ exhibited a sigmoidal growth curve, highlighting distinct nucleation, elongation, and fibril maturation phases. The anti-amyloidogenic potential of bacoside A and withanolide A was assessed at different aggregation stages. Docking studies confirmed that both compounds specifically interact with the KLVFFA stretch of $A\beta_{42}$, a critical region for monomer self-association and fibril formation. A 500 ns molecular dynamics simulation to study the interaction of these compounds with disordered $A\beta_{42}$ (2MXU.pdb) revealed stable binding to monomers, with reduced stability during fibril elongation. Bacoside A and withanolide A inhibited α-helix conversion during nucleation, preventing key intermediates required for fibril growth, leading to the formation of non-toxic amorphous aggregates. Additionally, a 100 ns simulation with native helical $A\beta_{42}$ (1Z0Q.pdb) provided insights into their preventive action, reinforcing their early-stage aggregation inhibitory potential. These findings suggest that bacoside A and withanolide A act as promising anti-amyloidogenic agents, stabilizing $A\beta_{42}$ monomers while preventing fibril growth, thereby offering a potential therapeutic strategy for Alzheimer's disease.

An efficient high-yielding process was developed to obtain purified bacoside A from *Bacopa monnieri*. The purification protocol constituted a sequential solvent polarity-gradient extraction method followed by gradient silica-gel column chromatography. The bacoside A content was quantified by HPTLC, and a yield of 34.6 mg bacoside A per gram of crude Brahmi extract was obtained with 93% purity. Purified bacoside A exhibited high acetylcholinesterase inhibition (IC_{50} value 9.91µg/mL) and DPPH radical scavenging activity (IC50 value 29.22

µg/mL). This was followed by *in vivo* experiments in a compulsive mouse model (p. T8I-VGLUT3), designed to mimic cholinergic dysfunction observed in Alzheimer's disease. The rationale was to validate bacoside A's role as an acetylcholinesterase inhibitor and its therapeutic potential in reducing compulsive behaviour. The results affirmed the compound's efficacy and safety, strengthening its candidacy as a viable therapeutic agent.

To overcome the limitations of poor bioavailability and environmental instability, nanotechnology-based delivery systems were developed. Nano-liposomes were synthesized using the thin-film hydration method to enhance encapsulation efficiency and achieve sustained release in the gastrointestinal fluid. Cholesterol was used to stabilize the liposomes and limit the release of bacoside A and withanolide A at lower pH. This approach was rationalized by the need to improve the pharmacokinetics of bioactive compounds, ensuring effective delivery across the blood-brain barrier. The liposomal formulations exhibited superior short-term storage stability at all the temperatures (-20 to 55 °C) and long-term storage stability at 4 °C. The liposomes did not exhibit any cytotoxicity on SH-SY5Y cell line as indicated by MTT assay and live cell-imaging.

In conclusion, this work integrates computational, experimental, and nanotechnological approaches to provide a comprehensive framework for the use of phytochemicals in Alzheimer's disease treatment. By addressing multiple aspects of disease pathology, the findings offer significant insights into developing effective and sustainable therapeutic strategies.

सार

अल्जाइमर रोग सबसे चुनौतीपूर्ण न्यूरोडीजेनेरेटिव विकारों में से एक है, जिसकी विशेषता न्यूरोमस्कुलर क्षेत्र में कोलीनर्जिक असंतुलन, एमिलॉयड-बीटा (Aβ) पट्टिका संचय, टाउ प्रोटीन हाइपरफॉस्फोराइलेशन, ऑक्सीडेटिव तनाव और न्यूरोइन्फ्लेमेशन है। अल्जाइमर पर पिछले शोध मस्तिष्क में न्यूरोट्रांसमीटर, एसिटाइलकोलाइन के स्तर को बनाए रखने के लिए एसिटाइलकोलिनेस्टरेज़ अवरोध पर केंद्रित थे। अल्जाइमर के खिलाफ प्रमुख उपलब्ध वाणिज्यिक दवाएं (डोनेपेज़िल, रिवास्टिग्माइन, गैलेंटामाइन) एसिटाइलकोलिनेस्टरेज़ अवरोधक हैं। वर्तमान उपचार भी रोग के अंतर्निहित तंत्र को संबोधित किए बिना लक्षणात्मक राहत पर ध्यान केंद्रित करते हैं। इसके लिए पौधों से प्राप्त बायोएक्टिव यौगिकों का उपयोग करके एक बहु-लक्ष्य-निर्देशित दृष्टिकोण की आवश्यकता होती है जो उनके न्यूरोप्रोटेक्टिव गुणों के लिए जाने जाते हैं। ये यौगिक रोग की प्रगति में प्रमुख मार्गों को संशोधित कर सकते हैं, जो समग्र उपचार रणनीतियों की क्षमता प्रदान करते हैं।

अध्ययन की शुरुआत एसिटाइलकोलिनेस्टरेज़ और बीटा-साइट एमिलॉयड प्रीकर्सर प्रोटीन क्लीविंग एंजाइम 1 अवरोधकों की पहचान के साथ हुई, जो कोलीनर्जिक डिसफंक्शन और $Aβ_{42}$ एकत्रीकरण के लिए महत्वपूर्ण एंजाइम हैं। विभिन्न बायोएक्टिव यौगिकों की बंधन आत्मीयता और औषधीय क्षमता का आकलन करने के लिए कम्प्यूटेशनल स्क्रीनिंग का उपयोग किया गया, इसके बाद निष्कर्षों को मान्य करने के लिए एंजाइम अवरोध परख की गई। तर्क यह था कि इन एंजाइमों को एक साथ न्यूरोट्रांसमीटर गिरावट और $Aβ_{42}$ गठन को कम करने के लिए लक्षित किया जाए। परिणामों ने प्रदर्शित किया कि चयनित बायोएक्टिव यौगिक दोहरे अवरोधकों के रूप में कार्य करते हैं, जिससे उनकी चिकित्सीय क्षमता के आगे अन्वेषण का मार्ग प्रशस्त होता है। इन विट्रो विश्लेषण के बाद, विथानिया सोम्नीफेरा से प्राप्त विथानोलाइड

ए की दोहरी भूमिका की पहचान की गई, एसिटाइलकोलिनेस्टरेज़ और बीटा-साइट एमिलॉयड प्रीकर्सर प्रोटीन क्लीविंग एंजाइम 1 अवरोधक के रूप में। विथानोलाइड ए ने एसिटाइलकोलिनेस्टरेज़ (IC50 मान 107 μM) को बाधित किया और मिश्रित प्रकार का अवरोध दिखाया। इस सांद्रता पर, इसने बीटा-साइट एमिलॉयड प्रीकर्सर प्रोटीन क्लीविंग एंजाइम 1 गतिविधि को 57.10% तक बाधित किया और इसे सबसे प्रभावी बताया गया। दोनों यौगिकों, साथ ही उनके कच्चे अर्क का SH-SY5Y सेल लाइन पर कोई साइटोटॉक्सिक प्रभाव नहीं पाया गया।

अघुलनशील $A\beta_{42}$ पेप्टाइड्स न्यूरोटॉक्सिक प्लेक बनाते हैं जो सिनैप्टिक ट्रांसमिशन को बाधित करते हैं और अल्जाइमर रोग विकृति में योगदान करते हैं। $A\beta_{42}$ के इन विट्रो एकत्रीकरण अध्ययनों ने एक सिग्मोइडल वृद्धि वक्र प्रदर्शित किया, जो अलग-अलग न्यूक्लियेशन, बढ़ाव और फाइब्रिल परिपक्वता चरणों को उजागर करता है। बैकोसाइड ए और विथानोलाइड ए की एंटी-एमाइलॉयडोजेनिक क्षमता का मूल्यांकन विभिन्न एकत्रीकरण चरणों में किया गया था। डॉकिंग अध्ययनों ने पुष्टि की कि दोनों यौगिक विशेष रूप से $A\beta_{42}$ के KLVFFA खिंचाव के साथ परस्पर क्रिया करते हैं, जो मोनोमर स्व-संयोजन और फाइब्रिल गठन के लिए एक महत्वपूर्ण क्षेत्र है। अव्यवस्थित $A\beta_{42}$ (2MXU.pdb) के साथ इन यौगिकों की परस्पर क्रिया का अध्ययन करने के लिए 500 ns आणविक गतिशीलता सिमुलेशन ने फाइब्रिल बढ़ाव के दौरान कम स्थिरता के साथ मोनोमर्स के लिए स्थिर बंधन का खुलासा किया। बैकोसाइड ए और विथेनोलाइड ए ने न्यूक्लियेशन के दौरान α-हेलिक्स रूपांतरण को बाधित किया, जिससे फाइब्रिल वृद्धि के लिए आवश्यक प्रमुख मध्यवर्ती को रोका गया, जिससे गैर-विषाक्त अनाकार समुच्चय का निर्माण हुआ। इसके अतिरिक्त, मूल हेलिकल $A\beta_{42}$ (1Z0Q.pdb) के साथ 100 ns सिमुलेशन ने उनकी निवारक कार्रवाई में अंतर्दृष्टि प्रदान की, जिससे उनके प्रारंभिक चरण के एकत्रीकरण अवरोधक क्षमता को मजबूत किया गया। इन निष्कर्षों से पता चलता है कि बेकोसाइड ए और विथानोलाइड ए आशाजनक एंटी-एमाइलॉयडोजेनिक एजेंट के रूप में कार्य

करते हैं, जो फाइब्रिल वृद्धि को रोकते हुए $A\beta_{42}$ मोनोमर्स को स्थिर करते हैं, जिससे अल्जाइमर रोग के लिए संभावित चिकित्सीय रणनीति की पेशकश होती है।

बेकोपा मोनिएरी से शुद्ध बेकोसाइड ए प्राप्त करने के लिए एक कुशल उच्च उपज प्रक्रिया विकसित की गई थी, शुद्धिकरण प्रोटोकॉल में एक अनुक्रमिक विलायक ध्रुवीयता-ढाल निष्कर्षण विधि का पालन किया गया था, जिसके बाद ढाल सिलिका-जेल कॉलम क्रोमैटोग्राफी की गई थी। बेकोसाइड ए सामग्री को एचपीटीएलसी द्वारा मात्राबद्ध किया गया था, और 93% शुद्धता के साथ कच्चे ब्राह्मी अर्क के प्रति ग्राम 34.6 मिलीग्राम बेकोसाइड ए की उपज प्राप्त की गई थी। इसके बाद बाध्यकारी माउस मॉडल (p. T8I-VGLUT3) में इन विवो प्रयोग किए गए, जिसे अल्जाइमर रोग में देखी गई कोलीनर्जिक शिथिलता की नकल करने के लिए डिज़ाइन किया गया था। इसका उद्देश्य एसिटाइलकोलिनेस्टरेज़ अवरोधक के रूप में बैकोसाइड ए की भूमिका और बाध्यकारी व्यवहार को कम करने में इसकी चिकित्सीय क्षमता को मान्य करना था। परिणामों ने यौगिक की प्रभावकारिता और सुरक्षा की पुष्टि की, जिससे एक व्यवहार्य चिकित्सीय एजेंट के रूप में इसकी उम्मीदवारी मजबूत हुई।

खराब जैवउपलब्धता और पर्यावरणीय अस्थिरता की सीमाओं को दूर करने के लिए, नैनो-प्रौद्योगिकी-आधारित वितरण प्रणाली विकसित की गई। एनकैप्सुलेशन दक्षता को बढ़ाने और जठरांत्र द्रव में निरंतर रिलीज को प्राप्त करने के लिए पतली-फिल्म हाइड्रेशन विधि का उपयोग करके नैनो-लिपोसोम को संश्लेषित किया गया था। कोलेस्ट्रॉल का उपयोग लिपोसोम को स्थिर करने और कम पीएच पर बैकोसाइड ए और विथेनोलाइड ए की रिहाई को सीमित करने के लिए किया गया था। इस दृष्टिकोण को जैवसक्रिय यौगिकों के फार्माकोकाइनेटिक्स में सुधार करने की आवश्यकता के कारण तर्कसंगत बनाया गया था, जिससे रक्त-मस्तिष्क बाधा के पार प्रभावी वितरण सुनिश्चित हो सके। लिपोसोमल फॉर्मूलेशन ने सभी तापमानों (-20 से 55 डिग्री सेल्सियस) पर बेहतर अल्पकालिक भंडारण स्थिरता और 4 डिग्री सेल्सियस पर

दीर्घकालिक भंडारण स्थिरता प्रदर्शित की। लिपोसोम ने SH-SY5Y सेल लाइन पर कोई साइटोटॉक्सिसिटी नहीं दिखाई, जैसा कि MTT परख और लाइव सेल-इमेजिंग द्वारा संकेत दिया गया था।

निष्कर्ष में, यह कार्य कम्प्यूटेशनल, प्रायोगिक और नैनोटेक्नोलॉजिकल दृष्टिकोणों को एकीकृत करता है ताकि अल्जाइमर रोग के उपचार में फाइटोकेमिकल्स के उपयोग के लिए एक व्यापक रूपरेखा प्रदान की जा सके। रोग विकृति विज्ञान के कई पहलुओं को संबोधित करके, निष्कर्ष प्रभावी और टिकाऊ चिकित्सीय रणनीतियों को विकसित करने में महत्वपूर्ण अंतर्दृष्टि प्रदान करते हैं।

TABLE OF CONTENT

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide	MTT
2,2-Diphenyl-1-Picrylhydrazyl	DPPH
4′,6-Diamidino-2-Phenylindole	DAPI
5,5'-Dithiol-Bis-(2-Nitrobenzoic Acid)	DTNB
50 % Inhibitory Concentration	IC_{50}
Absorption, Distribution, Metabolism, Elimination & Toxicity	ADMET
Acetone Extract	AE
Acetylcholine	ACH
Acetylcholinesterase	AChE
Alanine	ALA
Ammonium Hydroxide	NH_4OH
Amyloid Precursor Protein	APP
Amyloid β protein, 40 Residues	$A\beta_{40}$
Amyloid β protein, 42 Residues	$A\beta_{42}$
Amyloid-Beta	Aβ
Angiotensin Converting Enzyme	ACE
Apo-Lipoprotein E	APOE E4
Arbitrary Unit	A.U.
Bacoside A	BA

Bacoside-Rich Extract	BRE
Beta-Site App Cleaving Enzyme	BACE1
Blood-Brain Barrier	BBB
Butylated Hydroxytoluene	BHT
Butyrylcholinesterase	BChE
Calcium	Ca^{2+}
Carbon dioxide	CO_2
Catalase	CAT
Cell Division Cycle	CDC
Centimeter	CM
Central Nervous System	CNS
Circular Dichroism	CD
C-Jun N-Terminal Kinase	JNK
Coenzyme A	CoA
Cyclin-Dependent Kinase 5	CdK
Cyclooxygenase-1	COX-1
Cyclooxygenase-2	COX-2
Database Of Secondary Structure Assignments	DSSP
Dimethyl Sulfoxide	DMSO
Direct Extract	DE
Dorsomedial Striatum	DMS

Dulbecco's Phosphate-Buffered Saline	DPBS
Dynamic Light Scattering	DLS
Emmision Wavelength	λ_{EM}
Encapsulation Efficiency	EE
Epigallocatechin-3-Gallate	EGCG
Equation	Eq.
Excitation Wavelength	λ_{EX}
Fetal Bovine Serum	FBS
Field Emission Scanning Electron Microscope	FESEM
Fourier-Transform Infra-Red	FT-IR
Gastrointestinal	GI
Genome-Wide Association Studies	GWAS
Glutamine	GLN
Glutathione	GSH
Glycine	GLY
Glycogen Synthase Kinase	GSK
Gram	g
Hexafluoroisopropanol	HFIP
Hexane Extract	HE
High-Performance Liquid Chromatography	HPLC
High-Performance Thin Layer Chromatography	HPTLC

High-Resolution Electron Spray Ionization Mass Spectroscopy	ESI-Q-TOF-MS
High-Resolution Electrospray Ionization Mass Spectrometry	HR-ESI-MS
Histidine	HIS
Hour	H
Hydrochloric Acid	HCl
Inducible Nitric Oxide Synthase	INOS
Inositol 1,4,5-Trisphosphate Receptors	INSP3R
Interleukin 1β	IL-1β
Intraperitoneal	IP
Isoleucine	ILE
Leucine	LEU
Loading Capacity	LC
Lysine	LYS
Malondialdehyde	MDA
Maximum Reaction Velocity	V_{MAX}
Methanolic Extract	ME
Michaelis-Menten Constant (Substrate Concentration At Half Vmax)	K_M
Microgram	µg
Microliter	µL
Micrometer	µM
Micromolar	µM

Micro RNA	miRNA
Mili Volt	mV
Milligram	mg
Milliliter	mL
Millimolar	mm
Minute	min
Molecular Dynamic	MD
Molecular Mechanics Poisson–Boltzmann Surface Area	MM-PBSA
Molecular Weight	MW
Multi-Target Directed Ligand	MTDL
Na^{+}/Ca^{2+} Exchanger	NCX
Nanometer	nm
National Centre for Cell Science	NCCS
Neural Stem Cells	NSC
Neurofibrillary Tangles	NFT
Nitric Oxide Synthase	NOS
N-Methyl D-Aspartate	NMDA
Nuclear Factor (Erythroid-Derived 2)-Like 2	NRF2
Number Of Hydrogen Bond Acceptors	NOH
Number Of Hydrogen Bond Donors	NOHNH
Obsessive-Compulsive Disorder	OCD

Paraformaldehyde	PFA
Particle Mesh Ewald	PME
Partition Coefficient	Log P
Periodic Boundary Conditions	PBC
Phenylalanine	PHE
Phosphate Buffer Saline	PBS
Phosphodiesterase-5	PD-5
Picosecond	ps
Plasma Membrane Ca^{2+} ATPase	PMCA
Polydispersity Index	PDI
Polyethylene Glycol	PEG
Protein Data Bank	PDB
Radius Of Gyration	Rg
Reactive Nitrogen Species	RNS
Reactive Oxygen Species	ROS
Relative Fluorescence Intensity	RFI
Retention Coefficient	Rc
Root-Mean-Square Deviation	RMSD
Root-Mean-Square Fluctuation	RMSF
Rotation Per Minute	RPM
Ryanodine Receptors	RYR

Sarco/Endoplasmic Reticulum ATPase	SERCA
Second	sec
Secondary Structure Content	SSC
Serine	SER
Serotonin Reuptake Inhibitor	SSRI
Sodium Hydroxide	NaOH
Sodium Hydroxide	NaCl
Solvent Accessible Surface Area	SASA
Standard Deviation	SD
Store-Operated Ca^{2+} Entry	SOCE
Structure Data File	sdf
Structure-Based Drug Discovery	SBDD
Superoxide Dismutase	SOD
Tar DNA-Binding Protein 43	TDP-43
Thioflavin-T	ThT
Three Dimensional	3D
Transmission Electron Microscope	TEM
Tumor Necrosis Factor α	TNF-α
Two Dimensional	2D
Valine	VAL
Vesicular Acetylcholine Transporter	VAChT

Vesicular Glutamate Transporter 3	VGLUT3
White Blood Cells	WBC
Wild Type	WT
Withanolide A	WA