

**Determination of the role of Syringic acid
in diet-induced obesity-associated mouse
model for memory improvement**

**Thesis Submitted to Vidyasagar University
for the Award of the degree of
Doctor of Philosophy (Science)**

**Submitted by
Amina Khatun
Reg. No. 977/Ph.D. (Sc.)**

**Midnapore City College
Biodiversity and Environmental Studies Research Centre
Affiliated to Vidyasagar University
Kuturiya, Bhadutala, Midnapore-721129
West Bengal, India
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MIDNAPORE CITY COLLEGE

Certificate

This is to certify that the thesis entitled "*Determination of the role of Syringic acid in diet-induced obesity-associated mouse model for memory improvement*" submitted by Ms. Amina Khatun, Registration No.977/Ph.D. (Sc.) w.e.f. 09.12.2022, a research fellow of the Biodiversity and Environmental Studies Research Centre of Vidyasagar University at Midnapore City College, is based on her own research work under my supervision.

The contribution of others in terms of intellectual support or collaborative research, wherever applicable, has been indicated clearly.

The original thesis work has not been submitted elsewhere for any other degree/diploma in India or abroad. I endorse the work and hereby believe that his thesis fulfils the requirements for the award of the degree of Doctor of Philosophy and makes conceptual advances in the field.

 03/09/25

Sudipta Chakrabarti, Ph.D.

Principal, Midnapore City College,

Kuturiya, Bhadutala, Midnapore-721129

West Bengal, India.

Date:01/09/2025

Dr. Sudipta Chakrabarti
Principal
MIDNAPORE CITY COLLEGE
Kuturiya Bhadutala, Paschim Medinipur
Pin-721129 West Bengal



Abstract

Obesity, a global health concern, is increasingly linked not only to metabolic disorders but also to cognitive impairments, including deficits in memory, learning, and executive function. Diet-induced obesity (DIO) has been shown to adversely affect hippocampal plasticity through mechanisms involving oxidative stress, neuroinflammation, and impaired neuronal signaling. As the hippocampus is essential for acquiring knowledge and retaining special information, therapeutic strategies targeting hippocampal dysfunction are essential for addressing obesity-associated cognitive decline.

Recent attention has shifted toward plant-derived phenolic compounds for their multi-targeted neuroprotective effects and favorable safety profiles. In this context, the naturally occurring phenolic component syringic acid (SA), which is found in various fruits, vegetables, and medicinal plants, has been shown to possess neuroprotective, anti-inflammatory, and antioxidative properties. The purpose of this study was to investigate how SA can enhance memory and learning in a diet-induced obesity-associated mouse model, with a focus on its impact on neuronal plasticity and behavior. We hypothesized that SA would enhance spatial memory and cognitive flexibility in diet-induced obese mice by upregulating synaptic markers such as PSD95 and NR2A, as well as plasticity-related proteins and transcription factors involved in memory formation, including cAMP response element-binding protein (CREB).

The study was conducted in both *in vitro* and *in vivo* systems. For the *in vitro* study, N2a neuronal cells were treated with different concentrations of SA (100, 200, 300, and 500 μ M), and the status of calcium influx, memory consolidation, and plasticity-related molecules was then observed. In cultured N2a neuronal cells, SA upregulated the expression of plasticity-associated proteins, including NR2A, and PSD95, and facilitated calcium influx through NMDA and AMPA receptors. Mechanistic investigations revealed that SA activates CREB via a PKA-dependent pathway, leading to the enhanced expression of synaptic plasticity markers. The *in vitro* study demonstrated CREB activation and upregulation of plasticity-related proteins, which were significantly restored following SA treatment. Furthermore, PPAR α was identified as a critical factor in reducing inflammation, as well as an upstream regulator of CREB activation. These findings highlight the potential of SA to promote synaptic plasticity and improve cognitive function through the PPAR α -PKA-CREB signaling axis, offering

promising insights into novel therapeutic strategies for cognitive impairments via the upliftment of neuronal plasticity.

The *in vivo* study was conducted by feeding male C57BL6 mice a high-fat diet (HFD) for 12 weeks in order to induce obesity and cognitive impairment. Mice in the treatment group were given oral SA (50mg/Kg of body weight) from week 8th to week 12th. Behavioral assessments were conducted using the Barnes maze and T-maze test, a validated paradigm to evaluate spatial learning, memory consolidation, decision-making, and goal-directed navigation. The performance of SA-treated DIO mice was compared with untreated DIO controls. Our behavioral data revealed that SA-treated mice exhibited significantly enhanced memory performance. They showed reduced latency to locate the escape area, indicating faster spatial learning and improved memory retrieval. Additionally, the SA group had many fewer reference and working memory errors, which may indicate better short-term retention and longer-term memory consolidation. Analysis of decision-making strategies revealed that SA-treated mice made fewer negative turns and more accurate choices, highlighting improved cognitive flexibility and reduced perseverative behavior. These behavioral changes were accompanied by reduced trial durations and more effective utilization of spatial cues, pointing to restored hippocampal-dependent navigation. At the molecular level, SA therapy increased the expression of phosphorylated CREB (p-CREB), a transcription factor that is essential for memory consolidation. Furthermore, in the brain, SA increased the expression of important synaptic plasticity-related proteins such as NR2A and PSD-95. These proteins are central to synaptic strength, plasticity, and neurotransmission, and their restoration further supports the observed behavioral improvements.

The modulation of these plasticity-related molecules suggests that SA may enhance synaptic remodeling and neuronal connectivity, which are typically compromised in DIO mice. These findings collectively demonstrate that SA effectively reverses obesity-induced cognitive impairments by enhancing neuronal plasticity and memory-related behaviors. The combined behavioral and molecular outcomes underscore SA's potential as a natural therapeutic agent capable of restoring cognitive function in metabolic disease conditions. Unlike many phytochemicals that show efficacy only *in vitro*, SA displayed significant *in vivo* activity, highlighting its translational relevance.

In conclusion, our study establishes SA as a promising compound for mitigating obesity-associated cognitive deficits. Through its ability to improve hippocampal function, reduce

memory errors, and upregulate plasticity-associated signaling molecules, SA offers a multifaceted approach to neuroprotection. These results pave the way for future investigations into the long-term cognitive benefits of SA and its possible integration into dietary or pharmacological interventions aimed at combating metabolic and neurodegenerative disorders.

Keywords: Syringic acid, diet-induced obesity, hippocampal plasticity, memory consolidation, spatial learning, CREB, synaptic proteins, cognitive flexibility.

Declaration

I, Amina Khatun, a research fellow, registered in Ph.D. program at Vidyasagar University (Reg. No. 977/Ph.D. (Sc.) w.e.f. 09.12.2022), have completed the thesis entitle **“Determination of the role of Syringic acid in diet-induced obesity-associated mouse model for memory improvement”**, for the award of Ph.D. degree under the guidance of Dr. Sudipta Chakrabarti, Biodiversity and Environmental Studies Research Centre of Vidyasagar University at Midnapore City College.

I hereby declare that this thesis is my own work and, to the best of my knowledge, it neither contains materials previously published nor written by any other person. I have compiled this thesis, and the research work has not been submitted for any other degree of professional qualification. I have taken due copyright permissions for any material used from published works.

Amina Khatun.

Name: Amina Khatun

Registration No: 977/Ph.D. (Sc.) w.e.f. 09.12.2022

Biodiversity and Environmental Research Centre

Midnapore City College

Vidyasagar University

Date:01/09/2025

Dedication

To the cherished memory of my beloved grandparents,

Late Md. Mostak Hussain Khan, my guiding light, my hero

And,

Late Hapijun Bibi, the soul of my being, the quiet force behind my strength.

*You were the roots from which I drew courage, the voices that echoed wisdom when
I faltered, and the hearts that loved me unconditionally.*

*Dada, your strength, dignity, and unwavering belief in the power of education
inspired me to dream beyond boundaries. You taught me what it means to walk
with purpose and integrity.*

*Didi, your gentle spirit, boundless love, and quiet resilience gave me the inner
strength to endure and persevere. In your embrace, I found peace; in your prayers,
I found protection.*

*Though you are not here to see this day, I feel your presence in every page, every
word, and every moment of this journey.*

*This thesis is not just my achievement; it is a tribute to your love, sacrifices, and
the timeless power of your blessings.*

You live on in me, always.

---**---"Even in absence, the echo of love lingers in the synapses of the mind."---**---

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As I complete this thesis, I would like to extend my deepest gratitude to my family for their unwavering love, support, and encouragement throughout this journey.

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