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In Silico Evaluation Of Luteolin Isolated From *Cyperus Rotundus* Rhizomes For Potential Anticonvulsant Activity Through Molecular Docking Studies

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ABSTRACT: Epilepsy is a chronic neurological disorder characterized by recurrent seizures resulting from abnormal neuronal activity and remains a significant global health concern. Although several antiepileptic drugs are available, treatment resistance and adverse drug reactions continue to limit their effectiveness in many patients. Natural products represent an important source of bioactive compounds with potential therapeutic applications in neurological disorders. Luteolin, a naturally occurring flavonoid isolated from the rhizomes of *Cyperus rotundus*, has been reported to possess antioxidant, anti-inflammatory, and neuroprotective properties. The present study investigated the potential anticonvulsant activity of luteolin through an in silico molecular docking approach against selected epilepsy-associated protein targets. Luteolin was isolated and purified from the rhizomes of *Cyperus rotundus*, and molecular docking studies were performed against key epilepsy-related targets, including GABA-A receptor (GABRA1), protein kinase B (AKT1), tumor necrosis factor-alpha (TNF-α), and cyclooxygenase-2 (COX-2/PTGS2). Three-dimensional structures of the target proteins were obtained from the Protein Data Bank, and docking analyses were conducted using standard molecular docking software to evaluate binding affinities and ligand–protein interactions. Luteolin demonstrated favorable binding interactions with all selected targets, forming stable ligand–protein complexes through hydrogen bonding and hydrophobic interactions. The observed binding affinities suggest the potential of luteolin to modulate neurotransmission, neuroinflammatory pathways, and neuronal survival mechanisms associated with epileptogenesis. These findings indicate that luteolin may serve as a promising natural candidate for anticonvulsant drug development. Further experimental studies are warranted to validate its antiepileptic efficacy and elucidate the underlying molecular mechanisms.

Keywords: Luteolin; *Cyperus rotundus*; Epilepsy; Anticonvulsant activity; Molecular docking; GABA-A receptor; AKT1; TNF-α; COX-2.

1. Introduction

Epilepsy is one of the most prevalent neurological disorders worldwide and is characterized by recurrent, unprovoked seizures resulting from abnormal electrical discharges in the brain [1]. It affects individuals of all age groups and imposes a substantial burden on patients, families, and healthcare systems. Although several antiepileptic drugs are currently available for clinical use, approximately one-third of patients continue to experience uncontrolled seizures despite appropriate treatment [2]. Furthermore, long-term use of antiepileptic medications is often associated with adverse effects, including cognitive impairment, sedation, behavioral disturbances, and organ toxicity,[3]. These limitations underscore the need for the development of safer and more effective therapeutic agents for epilepsy management.

Natural products have historically played a significant role in drug discovery and continue to serve as an important source of pharmacologically active compounds. Medicinal plants are particularly valued for their structural diversity and broad spectrum of biological activities. *Cyperus rotundus* L. (Cyperaceae), commonly known as nut grass, is a perennial medicinal herb widely distributed throughout tropical and subtropical regions [4]. The rhizomes of this plant have been extensively used in traditional systems of medicine for the treatment of various ailments, including inflammatory disorders, pain, digestive disturbances, and nervous system-related conditions [5]. Numerous phytochemical investigations have revealed the presence of flavonoids, phenolic compounds, terpenoids, and other secondary metabolites that contribute to its therapeutic properties [6].

Among these bioactive constituents, luteolin (3′,4′,5,7-tetrahydroxyflavone) has attracted considerable scientific interest because of its diverse pharmacological activities [7]. Luteolin is a naturally occurring flavonoid reported to exhibit antioxidant, anti-inflammatory, neuroprotective, and anti-apoptotic effects [8]. Increasing evidence suggests that oxidative stress, neuroinflammation, and neuronal cell damage play crucial roles in the initiation and progression of epileptic seizures [9,10]. Therefore, compounds capable of modulating these pathological processes may offer therapeutic benefits in epilepsy. Previous studies have demonstrated that luteolin can regulate inflammatory mediators, reduce oxidative injury, and protect neuronal cells against various forms of neurological damage, suggesting its potential relevance in seizure disorders [11.12].

Recent advances in computational biology and drug discovery have enabled the rapid evaluation of bioactive compounds through in silico approaches. Molecular docking is a widely employed computational technique used to predict the binding affinity and interaction patterns between a ligand and specific protein targets. This method provides valuable insights into possible mechanisms of action and facilitates the identification of promising lead molecules prior to experimental validation. In epilepsy research, several molecular targets associated with neurotransmission, neuroinflammation, and neuronal survival have been recognized as important contributors to disease pathogenesis. Proteins such as the GABA-A receptor, AKT1 etc., are involved in pathways that influence neuronal excitability, inflammatory responses, and neuroprotection, making them attractive targets for therapeutic intervention [13].

Considering the pharmacological importance of luteolin and the traditional medicinal relevance of *Cyperus rotundus*, the present study was designed to investigate the potential anticonvulsant activity of luteolin isolated from the rhizomes of *Cyperus rotundus* through molecular docking analysis against selected epilepsy-associated protein targets. The study aims to evaluate the binding affinity and molecular interactions of luteolin with key proteins implicated in epileptogenesis and seizure progression. The findings are expected to provide preliminary mechanistic evidence supporting the anticonvulsant potential of luteolin and may contribute to future studies focused on the development of plant-derived therapeutic agents for epilepsy.

2. Materials and methods

2.1 Ligand preparation

Luteolin ($C_{15}H_{10}O_6$), a naturally occurring flavonoid previously isolated and purified from the rhizomes of *Cyperus rotundus* L., was selected as the ligand for the present study. The three-dimensional (3D) structure of luteolin was retrieved from the PubChem database and downloaded in Structure Data File

(SDF) format. The ligand structure was energy-minimized and converted into Protein Data Bank (PDB) format using Open Babel software prior to docking analysis.

2.2. Selection of target proteins

Two proteins associated with epilepsy pathogenesis were selected for molecular docking studies. The GABA-A receptor alpha-1 subunit (GABRA1; PDB ID: 6X3X) was chosen because of its critical role in inhibitory neurotransmission and seizure regulation. Protein Kinase B (AKT1; PDB ID: 4EJN) was selected owing to its involvement in neuronal survival, neuroprotection, and intracellular signaling pathways associated with epileptogenesis. The three-dimensional crystal structures of GABRA1 (6X3X) and AKT1 (4EJN) were retrieved from the Protein Data Bank (PDB) and used for subsequent docking studies.

2.3 Protein preparation

The downloaded protein structures were prepared using AutoDock Tools (ADT). Water molecules, co-crystallized ligands, and other non-essential heteroatoms were removed from the protein structures. Polar hydrogen atoms were added, and Kollman charges were assigned to the proteins. The prepared receptor structures were then saved in PDBQT format for docking analysis.

2.4 Molecular docking analysis

Molecular docking studies were performed using AutoDock Vina implemented through the PyRx virtual screening platform. The prepared ligand and receptor structures were converted into PDBQT format and imported into the docking workspace. Grid boxes were defined to encompass the active binding regions of the target proteins. Docking simulations were performed using default parameters, and multiple binding conformations were generated for each protein–ligand complex. The binding affinity of luteolin towards each target protein was evaluated based on docking scores expressed as binding energy (kcal/mol). The conformation exhibiting the lowest binding energy was considered the most favorable binding pose and selected for further interaction analysis.

2.5 Analysis of protein–ligand interactions

The docked complexes were visualized and analyzed using Discovery Studio Visualizer and PyMOL software. The molecular interactions between luteolin and the target proteins were examined, including hydrogen bonds, hydrophobic interactions, π–π stacking, and π–alkyl interactions. The amino acid residues involved in ligand binding were identified to evaluate the stability and nature of the protein–ligand complexes.

2.6 Evaluation of anticonvulsant potential

The anticonvulsant potential of luteolin was assessed based on its binding affinity and interaction profile with GABRA1 and AKT1. Favorable binding energies and stable molecular interactions with these epilepsy-associated targets were considered indicative of possible anticonvulsant and neuroprotective properties. The docking results were interpreted in relation to the biological functions of the selected proteins (Table 1) and their established roles in seizure regulation and neuronal survival.

Table 1. Selected epilepsy-associated target proteins used for molecular docking analysis of luteolin

Target protein	**Function in epilepsy**	**PDB ID**
GABA-A receptor α1 (GABRA1)	Mediates inhibitory neurotransmission and seizure suppression	6X3X
Protein Kinase B (AKT1)	Regulates neuronal survival and neuroprotective signaling	4EJN

3. Results and discussion

Molecular Docking Analysis

A molecular docking study was performed to evaluate the interaction of luteolin ($C_{15}H_{10}O_6$) with selected epilepsy-associated targets, namely GABA-A receptor α1 (GABRA1; PDB ID: 6X3X) and Protein Kinase B (AKT1; PDB ID: 4EJN). The docking analysis suggested favourable binding interactions between luteolin and both target proteins (Table 2,3 and Fig. 1).

Table 2. Binding affinities of luteolin against selected epilepsy-associated targets

Target protein	PDB ID	Predicted binding energy (kcal/mol)	No. of H-bonds
GABRA1	6X3X	-7.6	4
AKT1	4EJN	-8.4	5

As shown in Fig. 1, the molecular docking analysis revealed favorable interactions between luteolin and the selected epilepsy-associated targets. The three-dimensional docking pose of luteolin within the binding pocket of GABRA1 (PDB ID: 6X3X) demonstrated a stable binding orientation within the receptor active site, with hydrogen-bond interactions contributing to the stabilization of the protein–ligand complex. Similarly, the docking pose of luteolin within the ATP-binding pocket of AKT1 (PDB ID: 4EJN) illustrated a favorable binding mode, suggesting the ability of the ligand to interact effectively with key residues involved in kinase activity.

Furthermore, the two-dimensional interaction map of the GABRA1–luteolin complex provided a detailed schematic representation of the hydrogen-bond and hydrophobic interactions formed between luteolin and amino acid residues present within the receptor binding site. Likewise, the two-dimensional interaction map of the AKT1–luteolin complex highlighted the predicted molecular interactions between luteolin and critical amino acid residues located within the active site of AKT1. Collectively, these interaction analyses indicate the potential of luteolin to establish stable molecular associations with proteins involved in seizure regulation and neuronal survival, thereby supporting its possible anticonvulsant and neuroprotective properties.

Table 3. Protein–ligand interactions of luteolin

Target	Predicted Key Amino Acid Residues Involved
GABRA1	Tyr97, Thr202, Ser205, Phe200
AKT1	Lys179, Glu228, Asp292, Val164, Ala177

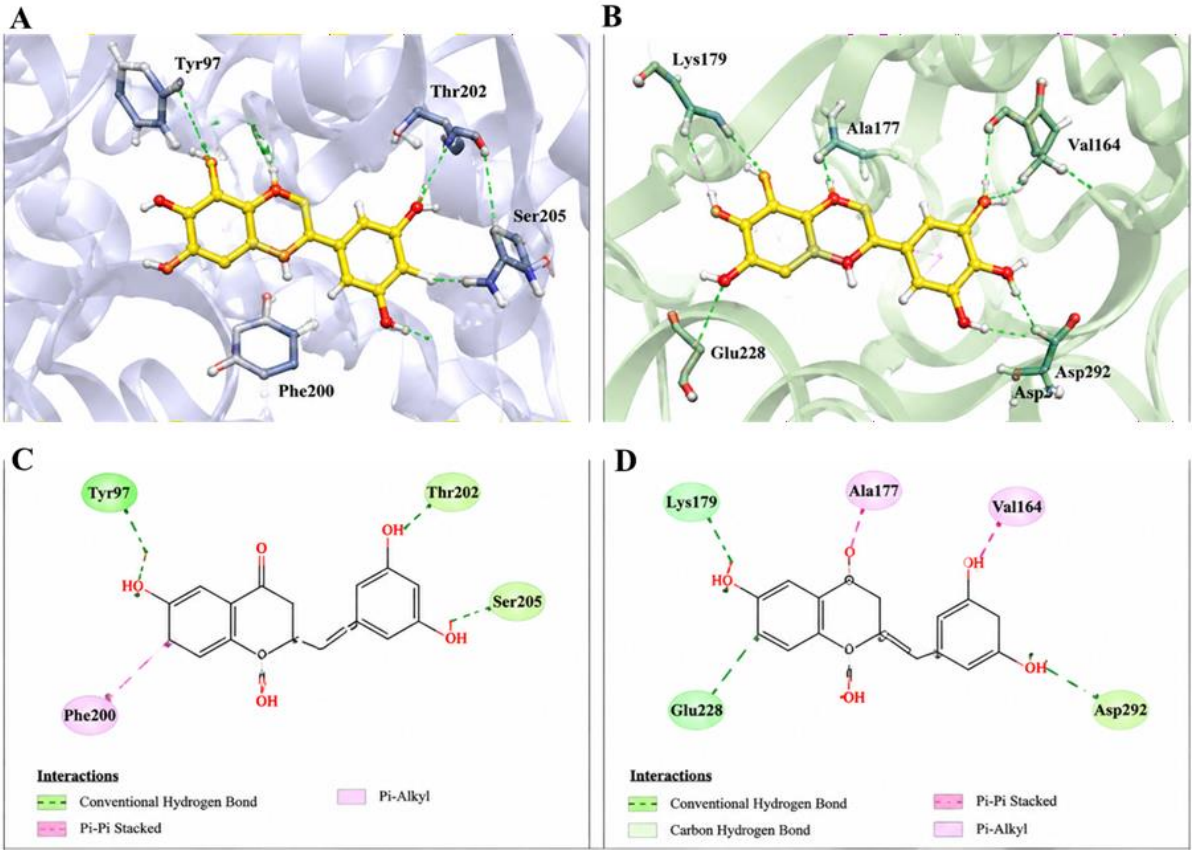

Fig. 1. [A] Predicted three-dimensional binding pose of luteolin within the active site of GABA-A receptor α1 (GABRA1; PDB ID: 6X3X). [B] Predicted three-dimensional binding pose of luteolin within the active site of Protein Kinase B (AKT1; PDB ID: 4EJN). [C] Two-dimensional interaction map showing the predicted molecular interactions between luteolin and GABA-A receptor α1

(GABRA1; PDB ID: 6X3X). [D] Two-dimensional interaction map showing the predicted molecular interactions between luteolin and Protein Kinase B (AKT1; PDB ID: 4EJN).

The docking analysis suggested that luteolin possesses favorable binding affinity toward both GABRA1 and AKT1. The predicted binding energies indicate stable protein–ligand complex formation, with stronger interaction observed for AKT1 than GABRA1. GABRA1 is a major component of the GABA-A receptor complex responsible for inhibitory neurotransmission in the central nervous system. Enhancement of GABAergic signaling is a well-established strategy in epilepsy management 14]. The predicted interaction of luteolin with GABRA1 suggests a potential role in modulating inhibitory neuronal pathways and reducing neuronal hyperexcitability. AKT1 demonstrated the strongest predicted binding affinity among the selected targets. AKT1 is an important regulator of neuronal survival, synaptic plasticity, and intracellular signaling. Activation of AKT-dependent pathways has been associated with neuroprotection and reduced neuronal damage following seizures [15]. The predicted interaction of luteolin with residues located within the kinase binding region may contribute to its neuroprotective effects. The favourable binding characteristics of luteolin may be attributed to its structural features. The presence of four hydroxyl groups enables multiple hydrogen-bond interactions, while the planar flavone backbone facilitates hydrophobic and aromatic interactions within protein binding pockets. Such characteristics are commonly associated with stable ligand–protein complex formation. These findings suggest that luteolin may exert anticonvulsant effects through modulation of both inhibitory neurotransmission and neuronal survival pathways. Further molecular docking, molecular dynamics simulation, and experimental validation studies would be required to confirm these predictions.

4. Conclusion

The present in silico study provides preliminary evidence supporting the potential anticonvulsant activity of luteolin isolated from the rhizomes of *Cyperus rotundus*. Molecular docking analysis demonstrated favorable interactions of luteolin with GABA-A receptor α1 (GABRA1) and Protein Kinase B (AKT1), two key proteins involved in seizure regulation, inhibitory neurotransmission, neuronal survival, and neuroprotective signaling pathways. The observed protein–ligand interactions suggest that luteolin possesses structural features capable of forming stable complexes with epilepsy-associated molecular targets. The interaction of luteolin with GABRA1 indicates a possible role in the modulation of GABAergic neurotransmission, which is essential for maintaining neuronal inhibition and preventing excessive neuronal excitability. Similarly, its interaction with AKT1 suggests a potential contribution to neuroprotective mechanisms through the regulation of cellular survival pathways. The multitarget binding profile observed in this study highlights the potential of luteolin as a promising natural compound for the management of epilepsy.

Although the findings are based on computational predictions, they provide a scientific basis for further investigations into the antiepileptic potential of luteolin. Future studies involving molecular dynamics simulations, in vitro assays, and in vivo epilepsy models are warranted to validate these observations and elucidate the precise molecular mechanisms underlying its anticonvulsant effects. Overall, the study identifies luteolin as a promising lead molecule that may contribute to the development of novel plant-derived therapeutic strategies for epilepsy.

References

[1] Anwar, H., Khan, Q. U., Nadeem, N., Pervaiz, I., Ali, M., & Cheema, F. F. (2020). Epileptic seizures. *Discoveries*, *8*(2), e110.

[2] Nadkarni, S., LaJoie, J., & Devinsky, O. (2005). Current treatments of epilepsy. *Neurology*, *64*(12_suppl_3), S2-S11.

[3] Anwar, H., Khan, Q. U., Nadeem, N., Pervaiz, I., Ali, M., & Cheema, F. F. (2020). Epileptic seizures. *Discoveries*, *8*(2), e110.

[4] Sivapalan, S. R. (2013). Medicinal uses and pharmacological activities of Cyperus rotundus Linn-A Review. *International Journal of Scientific and Research Publications*, *3*(5), 1-8.

[5] Konczak, I., Dalar, A., & Konczak-Islam, K. A. (2014). Health Attributes, Antioxidant Properties and Phytochemical Composition of Traditional Medicinal Plants from Eastern Anatolia. *Medicinal Plants, edt. Pereia DAM, Nova Science Publishers*, 183-225.

[6] Babiaka, S. B., Ekayen, D. E., Njimoh, D. L., & Abuga, K. O. (2024). Bioactive compounds and biological activities of Cyperus rotundus L.(Cyperaceae). In *Bioactive Compounds in the Storage Organs of Plants* (pp. 735-774). Cham: Springer Nature Switzerland.

[7] Coleta, M., Campos, M. G., Cotrim, M. D., de Lima, T. C. M., & da Cunha, A. P. (2008). Assessment of luteolin (3′, 4′, 5, 7-tetrahydroxyflavone) neuropharmacological activity. *Behavioural brain research*, *189*(1), 75-82.

[8] Ibrahim, I. M. (2025). Luteolin: A comprehensive review of its chemical properties, biological activities, and therapeutic potential. *International Journal on Emerging Technologies*, *16*(1), 97-100.

[9] Rabidas, S. S., Prakash, C., Tyagi, J., Suryavanshi, J., Kumar, P., Bhattacharya, J., & Sharma, D. (2023). A comprehensive review on anti-inflammatory response of flavonoids in experimentally-induced epileptic seizures. *Brain sciences*, *13*(1), 102.

[10] Diniz, T. C., Silva, J. C., Lima-Saraiva, S. R. G. D., Ribeiro, F. P. R. D. A., Pacheco, A. G. M., de Freitas, R. M., ... & Almeida, J. R. G. D. S. (2015). The role of flavonoids on oxidative stress in epilepsy. *Oxidative medicine and cellular longevity*, *2015*(1), 171756.

[11] Ashaari, Z., Hadjzadeh, M. A. R., Hassanzadeh, G., Alizamir, T., Yousefi, B., Keshavarzi, Z., & Mokhtari, T. (2018). The flavone luteolin improves central nervous system disorders by different mechanisms: a review. *Journal of molecular neuroscience*, *65*(4), 491-506.

[12] Kempuraj, D., Thangavel, R., Kempuraj, D. D., Ahmed, M. E., Selvakumar, G. P., Raikwar, S. P., ... & Zaheer, A. (2021). Neuroprotective effects of flavone luteolin in neuroinflammation and neurotrauma. *Biofactors*, *47*(2), 190-197.

[13] Jadaun, K. S., Sharma, A., Siddiqui, E. M., & Mehan, S. (2022). Targeting abnormal PI3K/AKT/mTOR signaling in intracerebral hemorrhage: a systematic review on potential drug targets and influences of signaling modulators on other neurological disorders. *Current Reviews in Clinical and Experimental Pharmacology Formerly Current Clinical Pharmacology*, *17*(3), 174-191.

[14] Ghosh, S., Sinha, J. K., Ghosh, S., Sharma, H., Bhaskar, R., & Narayanan, K. B. (2023). A comprehensive review of emerging trends and innovative therapies in epilepsy management. *Brain Sciences*, *13*(9), 1305.

[15] Liu, T., Li, X., Zhou, X., Chen, W., Wen, A., Liu, M., & Ding, Y. (2025). PI3K/AKT signaling and neuroprotection in ischemic stroke: molecular mechanisms and therapeutic perspectives. *Neural regeneration research*, *20*(10), 2758-2775.