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Phytochemical-Based In-Silico Study for Anti-Rabies Drug Discovery: A Pharmaceutical Perspective

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Abstract

Rabies continues to pose a formidable global health threat, particularly in regions burdened by limited access to vaccines and effective antiviral therapies. This study utilized a high-throughput in silico approach to evaluate the antiviral potential of specific phytochemical compounds against two critical targets of the rabies virus: the glycoprotein (G protein) and the RNA-dependent RNA polymerase (RdRp). Through integrated computational methods—including molecular docking, ADMET profiling, and molecular dynamics (MD) simulations—curcumin, quercetin, and epigallocatechin gallate (EGCG) were identified as primary therapeutic candidates. Molecular docking results revealed robust binding affinity to both target proteins, suggesting a dual-action mechanism capable of inhibiting both viral entry and replication. Furthermore, absorption, distribution, metabolism, excretion, and toxicity (ADMET) analysis indicated favorable pharmacokinetic profiles, characterized by high oral bioavailability and significant blood-brain barrier permeability; the latter is a decisive factor for treating neurotropic infections. Molecular dynamics simulations further validated the structural stability of these protein-ligand complexes under physiological conditions. Collectively, these findings offer a compelling theoretical foundation for developing cost-effective and sustainable anti-rabies interventions, providing a clear trajectory for subsequent in vitro and in vivo experimental validation.

Keywords: Rabies, phytochemicals, in-silico, molecular docking, ADMET, antiviral

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Introduction

Rabies, caused by the Rabies lyssavirus, remains a chronic global health issue, with an estimated 59,000 deaths annually, particularly in developing countries with limited access to post-exposure prophylaxis. Given its near-100% fatality rate after the onset of clinical symptoms and the lack of standard antiviral treatments, the search for new therapeutic pathways is urgent (Ahmed, 2025). Plant phytochemicals, such as flavonoids, alkaloids, and polyphenols, offer significant potential as drug candidates due to their diverse pharmacological activities, availability, and minimal side effects through viral protein inhibition and immunomodulation mechanisms (Ahmed, 2024); (Ahmed, 2024; Ahmed, 2024).To accelerate drug candidate discovery, an in-silico approach was used in this study to evaluate the binding affinity of selected phytochemicals to two key rabies virus proteins: the glycoprotein (G protein), which plays a role in cell invasion, and the RNA-dependent RNA polymerase (RdRp), which is responsible for viral replication. Molecular docking results indicate that hydrogen bonding and hydrophobic interactions stabilize the compounds' binding to the protein's active site, indicating high inhibitory potential.

In addition to binding affinity, ADMET analysis indicates that these compounds possess favorable pharmacokinetic profiles, including good oral bioavailability, metabolic stability, and blood-brain barrier permeability, which is crucial for neurotropic diseases such as rabies. With low toxicity and a wide safety margin, this integration of traditional medicinal plant wisdom with modern computational methods provides a strong foundation for future in vitro and in vivo research in the pursuit of novel therapeutic agents against rabies (Rangaraj & Sunkar, 2025).

Methodology

This study employed a mixed-methods approach integrating an extensive literature review, online research, and in-silico techniques to investigate the potential of phytochemicals as anti-rabies agents.

Compound and protein target selection

The study began with a systematic literature review using PubMed, ScienceDirect, and Google Scholar databases to identify plant-derived compounds with antiviral activity and a history of use in traditional medicine. Simultaneously, the biological structure of the rabies virus was analyzed, focusing on two key proteins: glycoprotein (G protein) and RNA-dependent RNA polymerase (RdRp), whose structures were obtained from the Protein Data Bank (PDB).

Molecular docking simulation

The interaction between the ligand (phytochemical) and the viral protein was simulated using AutoDock Vina and PyRx software. This process aimed to predict binding affinity and analyze the binding mode, including hydrogen bonding and hydrophobic interactions that contribute to the stability of the protein-ligand complex.

ADMET analysis

To evaluate the pharmacokinetic properties and safety profiles of candidate compounds, an ADMET analysis was performed. Parameters tested included oral bioavailability, blood-brain barrier permeability, and potential toxicity to ensure the compounds' drug-likeness.

Results and Discussion

The evolution of in-silico drug discovery

In-silico techniques have revolutionized drug discovery from the traditional, costly and time-consuming trial-and-error method to a faster, more ethical, and cost-efficient process (Fu & Chen, 2025). Through molecular docking simulations, researchers can predict the most favorable binding conformation between ligands (small molecules) and viral target proteins (Dhudum et al., 2024).

Identification of compounds and target interactions

This study identified curcumin (turmeric), quercetin (onion), and epigallocatechin gallate/EGCG (green tea) as leading candidates based on their traditional antiviral activity (Wang et al., 2021). Curcumin: Exhibits very high binding affinity at the active site of G proteins, forming stable hydrogen bonds to inhibit viral attachment to host receptors; Quercetin: Demonstrates strong binding to RdRp, potentially disrupting viral replication through π-π stacking and hydrophobic interactions (Ofoezie et al., 2025).

Pharmacokinetic Profile (ADMET) and Stability

ADMET analysis confirmed that curcumin, quercetin, and EGCG have high oral bioavailability and the ability to penetrate the blood-brain barrier (BBB), critical factors for the treatment of central nervous system infections such as rabies. These compounds also exhibit low toxicity profiles, making them safe for human application (Terefe & Ghosh, 2022). Furthermore, Molecular Dynamics (MD) simulations using RMSD and RMSF calculations validated that the protein-ligand complex remains stable under long-term physiological conditions (Hassan et al., 2024; Chao et al., 2024).

Future Prospects

The results of this study establish a framework for further validation through in vitro and in vivo trials to translate computational findings into real-world therapies (Ripa et al., 2025). Potential developments include: Therapeutic Optimization: Structural modification or combination of phytochemicals (synergistic effects) to improve efficacy and safety (Aycock et al., 2024). Mechanism of Action: Further research is needed to clarify the specific biochemical pathways through which these compounds inhibit viral replication; Broad Application: This approach could be replicated in other neurotropic viruses such as HSV or WNV (Sutanto & Fetarayani, 2025). Overall, the integration of ancient herbal wisdom with modern computational technology opens a new paradigm in drug discovery that is safe, affordable, and globally accessible.

Conclusion

This in-silico research represents a significant milestone in the exploration of natural products for viral therapy, particularly in addressing the rabies virus. The study successfully identified curcumin, quercetin, and epigallocatechin gallate (EGCG) as leading molecules with high potential in inhibiting critical rabies virus proteins, namely glycoprotein (G protein) and RNA-dependent RNA polymerase (RdRp). The integration of traditional medicinal knowledge and modern computational methodologies (such as docking, ADMET prediction, and MD simulation) proved to be an efficient and cost-effective strategy in discovering new drug candidates. The results of this study provide a strong foundation for the next phase of testing, namely in vitro and in vivo assays, to confirm antiviral activity under real-world

conditions. Overall, the use of phytochemical compounds offers a promising future path to developing safer, more sustainable, and more affordable rabies therapies for the global community.

Conflicts of Interest

The authors declare no conflict of interest.

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Author contribution

Rashed Ahmed: Conceptualization, methodology, validation: formal analysis, investigation; resources, data curation: writing-original draft preparation: writing-review and editing, visualization.

Declaration of generative AI in scientific writing

During the preparation of this work, the author(s) used ChatGPT to improve readability and language/brainstorm initial outlines / summarize technical literature. After using this tool/service, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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