MOLECULAR DYNAMICS SIMULATION AND FREE ENERGY PROFILING OF GLYCYRRHIZIN ACID IN AQUEOUS SOLUTION

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Annotatsiya. Glitsirizin kislotasi, shirinmiya ildizidan olingan bioaktiv birikma, o‘zining yallig‘lanishga qarshi va virusga qarshi xususiyatlari tufayli muhim terapevtik salohiyatni namoyon etadi. Ushbu tadqiqotda glitsirizin kislotasining suvli eritmalardagi tuzilish barqarorligi, solvatatsiya dinamikasi va termodinamik xatti-harakatlari molekulyar dinamika (MD) simulyatsiyalari yordamida o‘rganildi. Natijalar glitsirizin kislotasining yuqori eruvchanligi, barqaror tuzilishi va qulay termodinamik xususiyatlarini (ΔG = -404.67 ± 11.57 kJ/mol) ta’kidlaydi, bu uning farmatsevtik salohiyatini yanada mustahkamlaydi.

Kalit so‘zlar: Glitsirizin kislotasi, Molekulyar dinamika simulyatsiyalari, Termodinamik barqarorlik, Erkin energiya profillanishi, Suvli eritmalar, Eruvchanlik tahlili, Farmatsevtik qo‘llanmalar, Bioaktiv birikmalar, Gidratatsiya qobig‘i dinamikasi, Tuzilish barqarorligi

Аннотация. Глицирризиновая кислота, биоактивное соединение, получаемое из корня солодки, продемонстрировала значительный терапевтический потенциал благодаря своим противовоспалительным и противовирусным свойствам. В данном исследовании с помощью моделирования молекулярной динамики (МД) изучается структурная стабильность, динамика сольватации и термодинамическое поведение глицирризиновой кислоты в водных растворах. Результаты свидетельствуют о высокой растворимости глицирризиновой кислоты, стабильной структуре и благоприятных термодинамических свойствах (ΔG = -404,67 ± 11,57 кДж/моль), что усиливает ее фармацевтический потенциал.

Ключевые слова: Глицирризиновая кислота, моделирование молекулярной динамики, термодинамическая стабильность, профилирование свободной энергии, водные растворы, анализ растворимости, фармацевтические приложения, биологически активные соединения, динамика гидратационной оболочки, структурная стабильность

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Abstract. Glycyrrhizin acid, a bioactive compound derived from licorice root, has demonstrated significant therapeutic potential due to its anti-inflammatory and antiviral properties. This study investigates the structural stability, solvation dynamics, and thermodynamic behavior of glycyrrhizin acid in aqueous solutions using molecular dynamics (MD) simulations. Results highlight glycyrrhizin acid's high solubility, stable structure, and favorable thermodynamic properties ($\Delta G = -404.67 \pm 11.57$ kJ/mol), reinforcing its pharmaceutical potential.

Keywords: Glycyrrhizin acid, Molecular dynamics simulations, Thermodynamic stability, Free energy profiling, Aqueous solutions, Solubility analysis, Pharmaceutical applications, Bioactive compounds, Hydration shell dynamics, Structural stability

Introduction

Glycyrrhizin acid, a triterpenoid saponin from licorice root, has gained considerable attention in pharmaceuticals for its anti-inflammatory, antiviral, and hepatoprotective properties[1]. These attributes make it a valuable candidate for drug development against chronic and infectious diseases.

However, despite its therapeutic potential, the molecular mechanisms governing glycyrrhizin acid's behavior in aqueous environments remain insufficiently studied. Key factors, such as solubility, structural stability, and interactions with water, are crucial for optimizing its pharmaceutical formulations and improving its bioavailability[2].

This research addresses the critical gap of why glycyrrhizin acid's molecular behavior in water has not been fully characterized. By focusing on its solvation dynamics and thermodynamic properties through molecular dynamics simulations, this study provides valuable insights to support its effective use in drug formulations[3].

Materials and Methods

The molecular model of glycyrrhizin acid was prepared using custom parameterizations defined in the TO8.itp file, designed to align with the CHARMM36 [4]force field. The system was solvated in a cubic box containing TIP3P water molecules, ensuring a minimum distance of 1.2 nm from the glycyrrhizin molecule to the box edges. Sodium and chloride ions were added to neutralize the system and achieve a physiological salt concentration of 0.15 M.

The CHARMM36 force field described the interactions between glycyrrhizin acid, water molecules, and ions. Custom parameterizations were validated using TO8.itp for glycyrrhizin acid to ensure accurate molecular interactions, while the TIP3.itp file defined water model parameters. All files were preprocessed using GROMACS 2024.1 [5]to confirm compatibility and consistency.

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Energy minimization was conducted using the steepest descent algorithm to remove steric clashes and relax the system. The equilibrated system was subjected to:

1. **NVT Ensemble:** A 100 ps simulation at 300 K to stabilize the temperature.
2. **NPT Ensemble:** A 100 ps simulation at 1 bar pressure to equilibrate the density.
3. **Production MD:** A 1 ns molecular dynamics simulation with a 2 fs timestep was performed in the NPT ensemble. Long-range electrostatics were calculated using the Particle Mesh Ewald (PME) method, and periodic boundary conditions were applied in all directions.

The system was solvated in a cubic box containing TIP3P water molecules, ensuring a minimum distance of 1.2 nm from the glycyrrhizin molecule to the box edges (Figure 1).

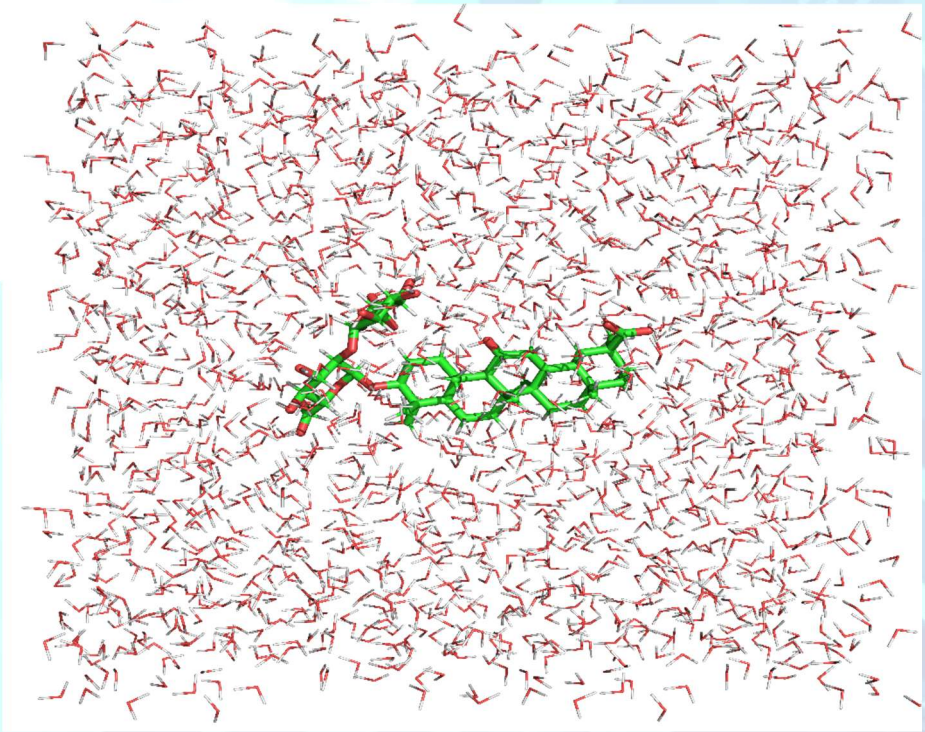


Figure 1: A snapshot from the molecular dynamics simulation showing the glycyrrhizin acid molecule (center, with carbon in green, oxygen in red, and hydrogen in white) solvated in a cubic water box containing 1829 TIP3P water molecules (oxygen in red, hydrogen in white). The system was prepared with a minimum distance of 1.2 nm between the glycyrrhizin molecule and the box edges, as described in the methodology.

Results and Discussion

The free energy calculations provide critical insights into the thermodynamic stability of glycyrrhizin acid in aqueous solutions.

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The **free energy integral plot** (Figure 2) illustrates the cumulative free energy changes (\Delta G) across the lambda windows, highlighting the molecule's transition between states. The profile shows a consistent thermodynamic favorability with a total free energy change of approximately -404.67 ± 11.57 kJ/mol. This result underscores the strong solvation dynamics and stability of glycyrrhizin acid in water.

The **free energy differences plot** (Figure 3) further breaks down these changes, depicting localized stability and transitions across different lambda values. Error bars indicate the reliability of the data, confirming the robustness of the simulations.

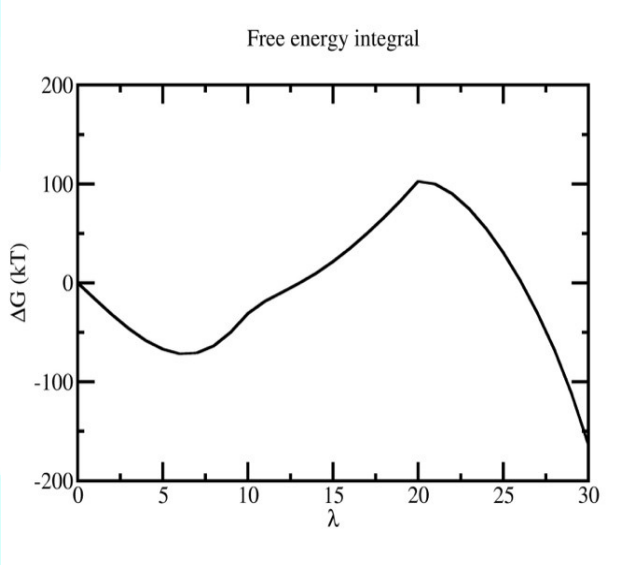


Figure 2: Free energy integral plot showingthe cumulative change in Delta G for glycyrrhizin acid in aqueous solutions

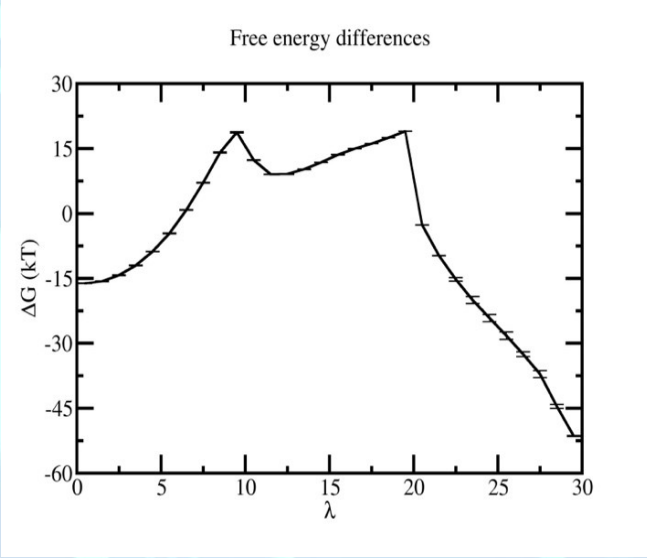


Figure 3: Free energy differences plot illustrating localized stability transitions and error analysis for glycyrrhizin acid in aqueous solutions.

Implications and Conclusion The results of the molecular dynamics simulations validate the solvation and thermodynamic stability of glycyrrhizin acid in aqueous conditions. Its strong interaction with water molecules ensures solubility and stability, making it a viable candidate for pharmaceutical applications. Future studies could extend these simulations to include interactions with biological membranes or other solvents to further elucidate its pharmacokinetics and pharmacodynamics.

REFERENCES

1. Matsuoka, K., Miyajima, R., Ishida, Y., Karasawa, S., & Yoshimura, T. (2016). Aggregate formation of glycyrrhizic acid. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 500, 112–117. https://doi.org/10.1016/j.colsurfa.2016.04.032

ISSN 3030-3907

2. Matsuoka, K., Miyajima, R., Ishida, Y., Karasawa, S., & Yoshimura, T. (2021). Micelle formation of monoammonium glycyrrhizinate. *Journal of Oleo Science*, 70(7), 911–918. https://doi.org/10.5650/jos.ess21046

3. You, G., Feng, T., Zhang, G., & Zhang, D. (2021). Preparation, optimization, characterization and in vitro release of baicalein-solubilizing glycyrrhizic acid nano-micelles. *International Journal of Pharmaceutics*,601,120546. https://doi.org/10.1016/j.ijpharm.2021.120546

4. Huang, J., & MacKerell, A. (2013). CHARMM36 all-atom additive protein force field: Validation based on comparison to NMR data. *Journal of Computational Chemistry, 34*(24), 2135–2145. https://doi.org/10.1002/jcc.23354

5. Vieira, I. H. P., Botelho, E. B., de Souza Gomes, T. J., Kist, R., Caceres, R. A., & Zanchi, F. (2023). Visual dynamics: A WEB application for molecular dynamics simulation using GROMACS. *BMC Bioinformatics, 24*. https://doi.org/10.1186/s12859-023-05304-3

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