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Topic of research: Interaction study of antimalarials with serum albumins using biophysical and computational approaches

Findings

Overview

The study investigates the binding mechanisms of various antimalarial compounds with serum albumins, specifically human serum albumin (HSA) and bovine serum albumin (BSA). Employing a combination of biophysical and computational techniques, the research assesses how these interactions influence the pharmacokinetic and pharmacodynamic properties of the drugs. The goal is to enhance understanding of drug efficacy and stability through detailed interaction mechanisms.

Techniques Used

A comprehensive array of techniques was utilized to study these interactions:

- Spectroscopic Methods: UV-VIS, steady-state, synchronous, 3D fluorescence, and circular dichroism spectroscopy.
- Computational Approaches: Molecular docking studies and molecular dynamics (MD) simulations.
- Other Analytical Methods: Time-resolved fluorescence and isothermal titration calorimetry (ITC).

Binding Studies and Findings

1. Drug HCQ, synthetic compounds, including JMI-346, and natural compounds gartanin and friedelin demonstrated distinct binding mechanisms to distinct domains involving static quenching.
2. The thermodynamic favourability and binding constants of these compounds exhibited stable and influential interactions emphasizing their potential for targeted drug delivery and metabolism modulation.
3. On the other hand, JMI-105, PC-5 and PC-11 involved dynamic quenching, JMI-105, PC-11 showcasing distorting effects on the protein's structure at higher concentrations.
4. The experimental findings collectively contribute to our insights into compound-protein interactions, binding mechanisms, and structural changes, providing valuable knowledge for advancing drug design and dosage, and development in the field of pharmacology.
5. The computational analysis provided dynamic insights into the long-term behavior of the ligand-protein complex complementing the experimental analysis.

Abstract:

Chapter 1:

This review focuses on recent trends in binding study of various antimalarial agents with serum albumins in detail. Serum albumin has a significant role in the transport of drugs and endogenous ligands. The nature and magnitude of serum albumin and drug interactions have a tremendous impact on the pharmacological behavior and toxicity of that drug. Binding of drug to serum albumin not only controls its free and active concentration, but also provides a reservoir for a long duration of action. This ultimately affects drug absorption, distribution, metabolism, and excretion. Such interaction determines the actual drug efficacy as the drug action can be correlated with the amount of unbound drug. With the advancement in spectroscopic techniques and simulation studies, binding studies play an increasingly important role in biophysical and biomedical science, especially in the field of drug delivery and development. This review assesses the insight we have gained so far to improve drug delivery and discovery of antimalarials on the basis of plethora of drug-serum protein interaction studies done so far.

Chapter 2:

A brief discussion about the comprehensive array of multi-spectroscopic techniques, including UV-VIS, steady state, synchronous, 3D fluorescence and circular dichroism spectroscopy, docking studies and molecular dynamics (MD) simulations, are presented which were used to probe the intricate details of the interaction between the antimalarial compounds and serum albumins-HSA and BSA.

Chapter 3:

Hydroxychloroquine (HCQ), a quinoline based drug is commonly used to treat malaria and autoimmune diseases such as rheumatoid arthritis. Hydroxychloroquine (HCQ), a quinoline based medicine is commonly used to treat malaria and autoimmune diseases such as rheumatoid arthritis. Also, human serum albumin (HSA) serves as excipient for vaccines or therapeutic protein drugs. Hence, it is important to understand the effect of HCQ on the structural stability of HSA. In this study, the binding mechanism of HCQ and their effect on stability of HSA have been studied using various spectroscopic techniques and molecular dynamic simulation. The UV-VIS results confirmed the strong binding of HCQ with HSA. The calculated thermodynamics parameters confirmed that binding is spontaneous in nature and van der Waals forces and hydrogen bonding are involved in the binding system which is also confirmed by molecular docking results. The steady-state fluorescence confirms the static quenching mechanism in the interaction system, which was further validated by time-resolved fluorescence. The synchronous fluorescence confirmed the more abrupt binding of HCQ with tryptophan residue of HSA compared to Tyr residue of HSA. Isothermal titration calorimetry (ITC) was done to validate the thermodynamics parameters of HSA-HCQ complex in one experiment, supporting the values obtained from the spectroscopic techniques. The circular dichroism (CD) demonstrated that the HCQ affected the secondary structure of HSA protein by reducing their α-helical content. The docking and molecular dynamic simulation results further helped in understanding the effect of HCQ on conformational changes of HSA.

Chapter 4:

Comparative investigation was done to explore the interaction mechanisms between two potential antimalarial compounds, JMI 346 and JMI 105, and HSA. A comprehensive array of multi-spectroscopic techniques, including UV-VIS, steady state, synchronous, 3D fluorescence and CD spectroscopy, docking studies and molecular dynamics (MD) simulations, were performed to probe the intricate details of the interaction between the compounds and HSA. Our results revealed that both JMI 346 and JMI 105 displayed promising pharmacological effectiveness within the context of malaria therapy. However, JMI 346 was found to exhibit a significantly higher affinity and only minor altered impact towards HSA, suggesting a more favorable interaction with the protein on the dynamic behavior and overall stability of the protein in comparison to JMI 105.

Chapter 5:

Plant derived compounds have great potential in the medicinal and pharmaceutical fields. The binding of natural compounds with serum albumins could give deep insight into the important information necessary for designing novel agents with greater efficacy. The present study uses multi-spectroscopic and computational approaches to describe the interaction mechanism of two plant derived potential antimalarial compounds gartanin and friedelin, with bovine serum albumin (BSA). The conformational changes in the protein due to binding of gartanin and friedelin have been monitored through various spectroscopic techniques, molecular docking and MD simulation. Both the plant products bound with BSA through static quenching with moderate binding affinity. Overall, the results showed that complex systems of the protein and the plant products were stable, not much affecting the protein's conformation.

Chapter 6:

Interaction mechanisms of two potent synthetic antimalarial compounds were investigated. The study revealed that all three compounds bind strongly with HSA and show 1:1 binding pattern; PC-5 relatively binds to HSA with greater affinity than PC-11. It was found that dynamic quenching occurred in PCs, which was further confirmed by time-resolved fluorescence spectroscopy results. Both compounds were found to be located in subdomain IIA of Sudlow's site I. Binding of these compounds to HSA induced some microenvironmental and conformational changes in the protein. At higher concentration of the compounds, disruption in α-helix of protein was noted, but disruption due to PC-11 was more significant which resulted in the appearance of β-sheets and random coils. Overall, HSA maintained stability with both PCs throughout the simulation time; PC-5 being relatively more stable. This study can be applicable in dose designing and enhancing the pharmacodynamic and pharmacokinetic properties of these compounds, when used as a drug.