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Insights into the Interactions Between Bovine β-Lactoglobulin and Reduced Coumarins: A Computational Perspective on Solubility Enhancement

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The goal of this work is to investigate the role of bovine β-lactoglobulin (BLG) in enhancing the solubility and bioavailability of reduced coumarins using in silico methods. Molecular docking and molecular dynamics (MD) simulations were explored to understand the interactions. Further, MM-PBSA simulations were performed to get the change in free energy. The binding affinity from docking studies for 7-ethyl-4-phenylchroman-2-one (CMPD 226) with the IGXA was found to be strongest and is −8.5 kcal/mol. RMSD and RMSF graphs were extracted from the MD simulations through GROMACS and AMBER and were compared. The MM-PBSA study indicates a favourable binding interaction, with the change in enthalpy (ΔH) estimated at −28.04 kcal/mol. According to ADME studies, this molecule may improve the bioavailability and solubility of reduced coumarins. Key atomic movements using principal component analysis (PCA) of the complex were highlighted by eigenvector analysis, and flexible regions were identified as possible binding sites. The results of this study provide insightful information about the use of BLG in enhancing the solubility of CMPD226 significantly.

1. Introduction

Coumarins have gained attention for their diverse biological activities[1]. They exhibit anti-inflammatory properties and also act as potential candidates in neurological and chronic diseases due to their ability to scavenge free radicals.[2] Despite their biological potential, coumarin have poor solubility in water and so faces many challenges.[3] Coumarin in methanol with a concentration of 0.0333 mg/mL,[4] solubility mole fraction of 3.02×10^{-4} in water at room temperature.[5] Coumarin solubility in ethylene glycol (0.0169 mol kg^{-1}) and in water is 0.0179 mol kg^{-1}.[6] Studies utilizing UV–visible spectroscopy have revealed that coumarin's solubility is highest in water-DMF mixtures and lowest in water-ethylene glycol solutions. Additionally, its temperature-dependent solubility in pure water, ethanol, and aqueous–ethanolic mixtures is governed by both enthalpy and entropy driven mechanisms, depending on the solvent composition.[7]

Several coumarin derivatives exhibit poor aqueous solubility, which hampers their pharmacological applications. A study demonstrated that the solubility of coumarin could be enhanced using arginine due to its favorable interaction with aromatic structures. However, the effect was limited to approximately a two-fold increase, making arginine a suboptimal solubility enhancer for practical applications.[7] Another study investigated the inclusion complexation of 3-acetylcoumarin (3-AC) with β-cyclodextrin (β-CD) to improve aqueous solubility and bioavailability. The molecular docking and spectroscopic analyses confirmed that 3-AC forms a stable 1:2 inclusion complex with β-CD, enhancing its solubility and facilitating its transfer to a carrier protein like BSA.[8] Additionally, a recent study explored the solubility enhancement of two coumarin derivatives, 4,7-dimethyl-2H-chromen-2-one (DMC) and 7-methoxy-4-methyl-2H-chromen-2-one (MMC), through complexation with β-CD. The inclusion complex significantly improved aqueous solubility, and in vivo wound healing studies further demonstrated enhanced biological activity. The study highlighted the role of hydrogen bonding and π–π stacking interactions in stabilizing these complexes, which underscores the necessity of solubility-enhancing strategies for coumarins.[9]

To address the solubility limitations of coumarin derivatives, β-lactoglobulin (BLG), a major whey protein found in cow's milk, has emerged as a promising delivery system for hydrophobic molecules like coumarin derivatives. BLG is a member of the lipocalin family, known for its ability to bind and transport small hydrophobic molecules through non-covalent interactions.[10] The structure of BLG has been extensively studied, including its complexation with molecules such as retinol

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