Contribution ID: **15** Type: **not specified**

Mechanisms of Complex Formation Between Diphtheria Anatoxin CRM197 and Curcumin

The development of efficient drug delivery systems is an important direction in modern biomedical research. Protein carriers are widely investigated as platforms capable of improving the stability, solubility, and targeted delivery of biologically active compounds. One such protein is CRM197, a non-toxic mutant of diphtheria toxin that retains receptor-binding ability while lacking enzymatic toxicity. Due to its structural stability and biocompatibility, CRM197 is widely used as a carrier protein in conjugate vaccines and is considered a promising candidate for drug delivery applications.

Curcumin is a natural polyphenolic compound extracted from Curcuma longa, known for its antioxidant, anti-inflammatory, and anticancer properties. However, its therapeutic application is limited by poor water solubility, low stability, and limited bioavailability. Complex formation with protein carriers may significantly enhance its physicochemical stability and pharmacological efficiency.

In this work, the mechanisms of interaction between diphtheria anatoxin CRM197 and curcumin were investigated using fluorescence spectroscopy and computational modeling. Fluorescence quenching analysis revealed a static quenching mechanism, indicating the formation of a stable CRM197–curcumin complex. Binding parameters obtained using the Hill model suggest the presence of approximately one binding site for curcumin on the CRM197 molecule. Thermodynamic analysis based on the Van't Hoff approach showed that the binding process is spontaneous and predominantly driven by hydrophobic interactions.

The Förster resonance energy transfer (FRET) method estimated the donor–acceptor distance between tryptophan residues of CRM197 and curcumin to be approximately 1.52 nm, confirming close spatial proximity between the interacting molecules.

Computational studies included molecular docking using AutoDock 4.2 and molecular dynamics simulations in Desmond software packages to analyze possible binding configurations and structural stability of the complex. The results revealed several energetically favorable binding modes of curcumin near exposed tryptophan residues (Trp50, Trp153, Trp398), with binding energies in the range of −7.7 to −5.5 kcal/mol. The interaction is mainly stabilized by hydrophobic and van der Waals forces.

Overall, the results demonstrate that CRM197 can form stable complexes with curcumin, supporting its potential use as a protein carrier for hydrophobic therapeutic compounds.

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