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Determination of interactions between human serum albumin and niraparib through multi-spectroscopic and computational methods

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Abstract

The interactions between 2-{4-[(3S)-piperidin-3-yl] phenyl}-2H-indazole-7-carboxamide (niraparib) and human serum albumin (HSA) were investigated through fluorescence and computational studies. Fluorescence experiments showed that the static quenching mechanism and the binding constant of the HSA–niraparib system at a single binding site was approximately 4×10^4 L mol^{-1}. Thermodynamic constants indicated that the binding of niraparib to HSA was mainly driven by electrostatic interactions. Competition experiments and molecular docking simulations revealed that niraparib bound to site III of HSA. Synchronous fluorescence and Fourier transform infrared spectroscopy (FT-IR) results suggested that interactions between niraparib and HSA could affect the conformation and microenvironment of HSA. Circular dichroism (CD) measurements revealed that the α-helix contents of HSA negligibly increased after binding with niraparib. Molecular dynamics simulations demonstrated the stability of the binary HSA–niraparib system and confirmed that electrostatic forces accounted for the dominant contribution to system energy between HSA and niraparib.

Keywords: Niraparib; Human serum albumin; Fluorescence; Molecular docking; Molecular dynamics simulation.

1. Introduction

Poly(ADP-ribose) polymerase (PARP) is an important DNA repair enzyme that participates in the base excision repair pathway, which is involved in many cellular processes, including DNA damage response and apoptosis regulation [1]. PARP inhibitors block DNA repair. This blockage, in turn, affects the function of PARP and causes the death of cells that have lost the function of homologous recombination repair [2].

PARP inhibitors are novel options for the treatment of various cancers and nonneoplastic diseases [3-5]. In 2017, the FDA approved the use of niraparib (trade name ZEJULA) as a PARP inhibitor [6]. It is the third PARP inhibitor to be approved by