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The molecular mechanism for DDT detoxification in *Anopheles gambiae*: a molecular docking study

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ABSTRACT

The epsilon class glutathione-*S*-transferase of *Anopheles gambiae*, agGSTe2, is capable of metabolizing DDT. A molecular docking analysis of DDT with agGSTe2 support an E2 elimination mechanism wherein the glutathione sulfur serves as the base to convert DDT to DDE.

Keywords: Malaria; DDT; *Anopheles gambiae*; Glutathione *S*-Transferase; Docking

1. INTRODUCTION

Malaria continues to be a devastating disease worldwide with an estimated 1 billion cases and more than 2 million deaths annually [1] with an estimated 800,000 deaths among sub-Saharan African children [2]. House spraying with DDT [1,1,1-trichloro-2,2-*bis*(*p*-chlorophenyl)ethane] was the primary method of *Anopheles gambiae* vector control of malaria in the 1950s and 1960s [3], but the advent of DDT-resistant strains of the mosquito resulted in failure of this eradication campaign [4].

Glutathione *S*-transferases (GSTs) are a major family of detoxification enzymes found in most organisms [5]. The GSTs of *A. gambiae* are of particular interest because of their involvement in DDT resistance [6,7]. The epsilon class GST of *A. gambiae*, agGSTe2, is known to be capable of metabolizing DDT, and the X-ray crystal structure has been recently determined [8]. This report presents a molecular docking study of DDT with agGSTe2.

2. METHODOLOGY

Protein-ligand docking studies were carried out using the crystal structure of agGSTe2 with bound glutathione (PDB: 2imi). All water molecules were removed from the structure. Molecular docking calculations for DDT and DDE with agGSTe2 were carried out using Molegro Virtual Docker 3.2.1 [9,10], with a 15-Å sphere centered on the cavity containing the glutathione. The glutathione was treated as a cofactor. Different orientations of the DDT ligand were searched and ranked based on their energy scores. The RMSD threshold for multiple cluster poses was set at <1.00Å. The docking algorithm was set at maximum iterations of 1500 with a simplex evolution population size of 50 and a minimum of 30 runs.

Table 1. Molegro docking energies (kJ/mol) for DDT and DDE with agGSTe2 (PDB: 2imi).

Ligand	Site A	Site B
DDT	–102.1	–104.2
DDE	–97.6	–97.8

3. RESULTS AND DISCUSSION

The lowest-energy docked poses (**Table 1**) for DDT with agGSTe2 oriented the DDT molecule adjacent to the glutathione such that the proton on C(2) of DDT was in contact with the sulfur atom of glutathione (**Figure 1**). This orientation allows for facile E2 elimination of HCl from DDT leading to DDE (**Figure 1**). In addition to favorable interactions of DDT with the glutathione, important interactions of docked DDT are with Arg 112, Phe 120, Leu 36, and Glu 116, which form a hydrophobic pocket embracing the DDT. Interestingly, the docking energies of DDE are about 4.5-6.4 kJ/mol less than the docking energies of DDT. These docking results support the hypothesis [8] that overexpression of agGSTe2 provides DDT resistance to *Anopheles gambiae* by readily decomposing DDT to DDE via an E2 elimination mechanism.

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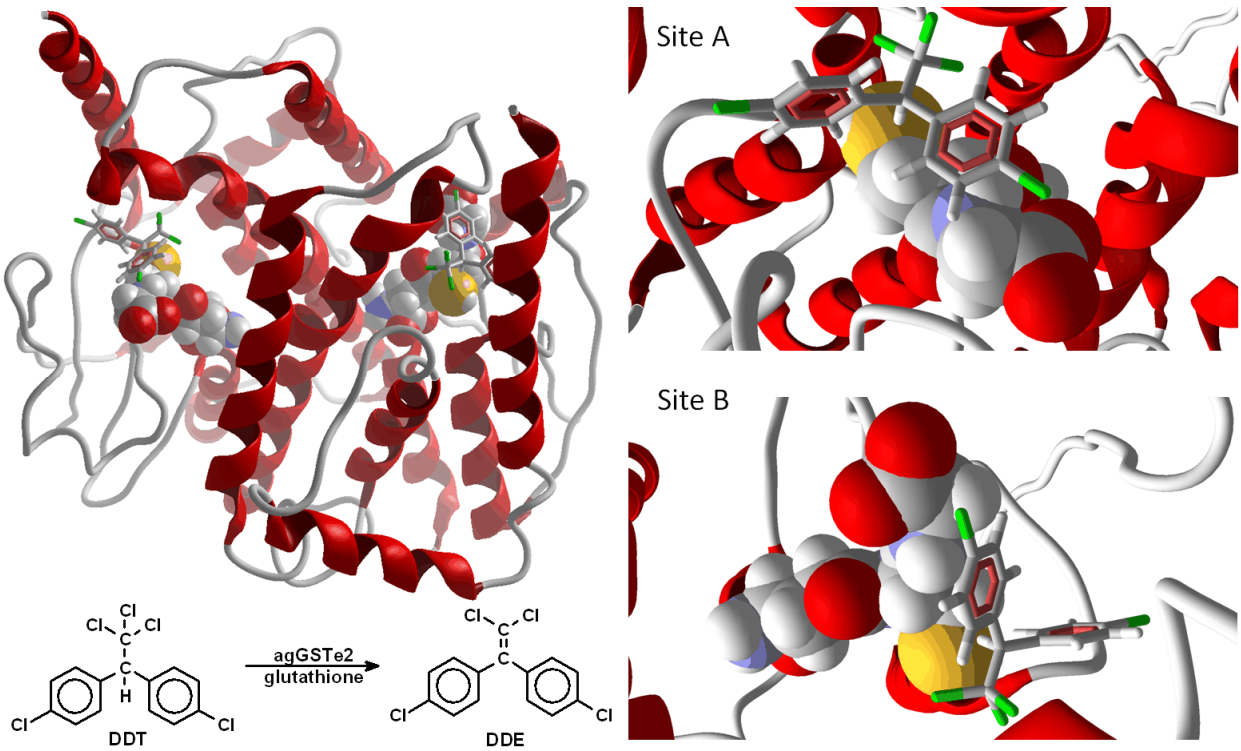

Figure 1. Molegro docking poses of DDT into the epsilon class glutathione *S*-transferase of *Anopheles gambiae*, agGSTe2 (PDB: 2imi). Note that the proton on C(2) of the DDT is in contact with the sulfur atom of glutathione.

