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HUMAN GLUTATHIONE S-TRANSFERASE A1-1 BINDING WITH NATURALLY OCCURRING LIGANDS: ASSESSMENT BY DOCKING SIMULATIONS

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ABSTRACT: Glutathione S-transferases are phase-II enzymes associated with detoxification and resistance to drugs and xenobiotics. The majority of human tumors and human tumor cell lines express significant amounts of alpha class Glutathione S-Transferase A1-1. Present study aimed to examine hGSTA1-1 interaction with some naturally occurring ligands using docking simulations. Docking simulation using Glutathione S-transferases A1-1 monomer without Glutathione conjugate was receptor against Glutathione, Ellagic acid, Lycopene, α-Tocopherol acetate, Quercetin, Ethacrynic acid, Caffeic acid, Porphyrin, Ferulic acid, Curcumin, Dithiothreitol, Cinnamic acid, Iodoacetamide, α-Tocopherol, Beta-mercaptoethanol showed that the majority ligands tested bound at sites bordering the enzyme subunit-subunit interface. Docking results showed that all the selected ligands docked satisfactorily to the hGSTA1-1 enzyme. Lycopene has a strong binding affinity (Binding energy:-10.68 kcal/mol; docking energy: -15.96 kcal/mol) with hGSTA1-1 amongst selected ligands and predicted as a strong inhibitor against hGSTA1-1. In contrast, investigations using hGSTA1-1 monomer revealed there are additional sites for Ethacrynic acid, Betamercaptoethanol and Glutathione binding rather than H-site as expected from X-ray crystallographic data. In conclusion, the docking simulations suggest that the enzyme subunit interface may be important for hGSTA1-1 interactions with ligands. These findings may provide valuable insights for further research to identify naturally occurring therapeutic agents.

INTRODUCTION: Glutathione S-transferases (GSTs) constitute a family of phase II detoxification enzymes that catalyze the conjugation of glutathione with a number of hydrophobic compounds to yield water-soluble derivatives that are excreted in urine or bile [1, 2]. The human GST superfamily comprises at least 6 classes of isozymes: alpha, mu, pi, omega, theta, and zeta. [3, 4]

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Class alpha, mu, and pi GST isoenzymes are overexpressed in rat hepatic preneoplastic nodules and the increased levels of these enzymes are believed to contribute to the multidrug-resistant phenotype observed in these lesions. The majority of human tumors and human tumor cell lines express significant amounts of class alpha, pi, and mu GST.

In recent years, specific GST isoforms have been implicated in the clearance of drugs and environmental toxicants, such as carcinogens and pesticides, as well as in the metabolism of endogenously produced compounds such as lipid peroxidation by-products [4, 5, 6, 7, 8, 9, 10]. Many polymorphisms in the genes encoding GSTs have been identified and associated with altered enzyme

expression and activity [1, 2]. For instance, the GSTM1 gene is deleted in ∼42%–55% in Asians population [11]. Therefore, significant inter-individual variation in clearance may exist for any toxicant found to be a substrate of GST.

Furthermore, GSTs have been implicated as one of the causes for drug resistance, especially in cancer, and thus represent potential therapeutic targets [12, 13]. For these reasons, a fast and robust method for screening large compound collections against GST isozymes would provide an invaluable tool for identifying compounds liable to interfere with this class of detoxification enzymes.

Human GST A1-1 is a homodimer that belongs to the Alpha class, and each monomer contains 222 amino acids. Several crystal structures of human GST A1-1 have been reported, both of the apo form and various ligand complexes [16, 17]. The residues involved in GSH binding at the G site are Tyr9, Arg15, Arg45, Val55, Gln67 and Thr68 from one of the subunits and Asp101 and Arg131 from the other subunit. Deprotonation of GSH contributes significantly to the catalytic activity of GST A1-1 (Ibarra et al., 2003). However, it is not entirely clear why the binding of GSH to the active site lowers the pKa value of the thiol group from 9.2 in solution [15] to 6.7 when bound [18]. The conserved residue Tyr9 is positioned within hydrogen-bonding distance of the thiolate group of GSH, and this residue has been shown to be important for the catalytic activity of the enzyme [19]. Arg15 is another conserved residue in the Alpha class enzyme that has been shown to stabilize the thiolate ion [20].

Although the complexes with hGST have yet to be studied, there is growing interest in naturally occurring compounds such as tocopherol [21], quercetin [22], ellagic acid and curcumin [23] which inhibit GST. Docking simulations have been successfully applied to model the interaction of GST from filaria [24, 25, 26] and insects [27, 28].

This study aimed to examine hGSTA1-1 interaction with some naturally occurring ligands using docking simulations. To allow for possible receptor-site steric hindrance in the design of this study, we selected single GST subunit for docking simulations. The results are considered regarding binding site motifs and their possible interrelationships with GST activity and structure. This research may provide valuable insights into the effect of naturally occurring compounds on GST and the role of such compounds as chemotherapeutic agents.

MATERIALS AND METHODS: The 3D coordinates of glutathione transferase A1-1 complexed with an ethacrynic acid glutathione conjugate (PDB ID: 1GSE) in Homo sapiens were retrieved from Protein Databank (http://www.rcsb.org/). PROCHECK [32] tool was used to assess the stereochemical properties of the polypeptide structure. The 3D structures for ligands **Table 1** were downloaded from the PubChem compound database in SDF format and converted in PDB format with the help of Open Babel [33] tool. All the ligands were subjected to energy minimization and molecular dynamics using the Hyper Chem software [31]. Energy calculations were carried out using the AMBER force field. Molecular structure optimization of ligands was carried out using conjugate gradient method Polak-Ribiere until the maximum energy derivative was lower than 0.1kcal/Å mol to obtain a correct geometry.

Docking simulations employed AutoDock v3.0.5 [29, 30]. Gasteiger charges were added to the ligand, and maximum 6 number of active torsion are given to the lead compound using Auto Dock Tool (http://autodock.scripps.edu/resources/adt).

Kollaman charges and solvation term were added to the protein structure using Auto Dock Tool. The Grid for docking calculation was adjusted to cover entire protein. During the docking procedure, a Lamarckian Genetic Algorithm (LGA) were used for flexible ligand rigid protein docking calculation. Docking parameters were as follows: 30 docking trials, the population size of 150, the maximum number of energy evaluation ranges of 25,0000, the maximum number of generations is 27,000, the mutation rate of 0.02, cross-over rate of 0.8, Other docking parameters were set to the software's default values.

Modeling operations were performed using a 2GB-64-bit computer to facilitate large 3D rotational grids. The structure for either hGSTA1-1 monomer was loaded to AutoDock keeping default parameters. Shape, electrostatics and potential distributions were used for docking control. Simulations were conducted in the full rotation

mode where the ligand is flexible, but the receptor is rigid. Docked poses were analyzed based on the minimum values for the interaction energy. Structures with low values for docking energies were selected, and amino acid residues within 3.5 Å of the ligand were noted as possible binding sites.

TABLE 1: LIST OF LIGANDS

S. no.	Ligand	CID no.	MWT (g/mol)	Molecular formula	X Log P	HBD	HBA
1	Glutathione	124886	307.32348	$C_{10}H_{17}N_3O_6S$	-4.5	6	8
2	Ellagic acid	5281855	302.19264	$C_{14}H_6O_8$	1.1	4	8
3	Lycopene	446925	536.87264	$C_{40}H_{56}$	15.6	0	0
4	α-Tocopherol acetate	2117	472.74278	$C_{31}H_{52}O_3$	10.8	0	3
5	Quercetin	5280343	302.2357	$C_{15}H_{10}O_7$	1.5	5	7
6	Ethacrynic acid	3278	303.13798	$C_{13}H_{12}C_{l2}O_4$	3.8	1	4
7	Caffeic acid	689043	180.15742	$C_9H_8O_4$	1.2	3	4
8	Porphyrin	5481276	678.7334	$C_{44}H_{30}N_4O_4$	5.3	6	5
9	Ferulic acid	445858	194.184	$C_{10}H_{10}O_4$	1.5	2	4
10	Curcumin	969516	368.3799	$C_{21}H_{20}O_6$	3.2	2	6
11	Dithiothreitol	19001	154.251	$C_4H_{10}O_2S_2$	-0.4	4	4
12	Cinnamic acid	444539	148.15862	$C_9H_8O_2$	2.1	1	2
13	Iodoacetamide	3727	184.96373	C_2H_4INO	-0.2	1	1
14	α-Tocopherol	14985	430.7061	$C_{29}H_{50}O_2$	10.7	1	2
15	Betamercaptoethanol	1567	78.13344	C_2H_6OS	-0.2	2	2

RESULTS AND DISCUSSION: Glutathione transferases (GSTs) help to protect the cell from potentially toxic alkylating agents that carry electrophilic functional groups, by catalyzing their conjugation with the tripeptide glutathione. The active form of hGSTA1-1 consists of two subunits (Cameron et al., 1995). Each subunit contains two domains: an N-terminal α/β-domain, with βαβαββα topology, and a C-terminal α-helical domain. There are two distinct subsites: a glutathione-binding site (G-site) and a pocket in which the hydrophobic substrates bind (H-site).

According to crystallographic data, 28 interface residues from chain A and 29 interface residues from chain B form the inter-subunit contact (Cameron et al., 1995). The existences of multiple isoforms of GST, together with the relatively non-specific binding of the substrate, meaning that a wide variety of compounds, including certain anti-cancer drugs, can be conjugated to glutathione. Ethacrynic acid (EAA) has been administered to cancer patients in attempts to increase the efficacy of alkylating cytostatic drugs. The rationale is that EAA would serve as GST inhibitors and overcome the resistance caused by GST-dependent inactivation of the cytostatic drug.

Docking simulation using Glutathione S-transferases A1-1 monomer as receptor against natural ligands showed that the majority ligands tested bound at sites bordering the enzyme subunit-subunit interface. Docking results showed that all the selected ligands docked satisfactorily to the hGSTA1-1 enzyme with good docking energies **Table 2**. Lycopene has a strong binding affinity (Binding energy:-10.68 kcal/mol; docking energy: -15.96 kcal/mol) with hGSTA1-1 amongst selected ligands.

It can be a strong inhibitor against hGSTA1-1. Docked complexes of Glutathione, Ellagic acid, Lycopene, α-Tocopherol acetate, Quercetin, Ethacrynic acid, Caffeic acid, Porphyrin, Ferulic acid, Curcumin, Dithiothreitol, Cinnamic acid, Iodoacetamide, α-Tocopherol, Beta-mercapto-ethanol with hGSTA1-1 were shown in **Fig. 2-8**.

TABLE 2: ENERGY VALUES OF LIGAND BINDING WITH GLUTATHIONE S-TRANSFERASES MONOMER

S. no.	Ligand	Binding Energy (Kcal/mol)	Docking Energy (Kcal/mol)	Intermol Energy (Kcal/mol)	Torsional Energy (Kcal/mol)	Internal Energy (Kcal/mol)
1	Ellagic acid	-7.87	-7.85	-7.87	0.0	0.02
2	Betamercaptoethanol	-3.21	-3.57	-3.52	0.31	-0.05
3	Glutathione	-1.46	-5.07	-4.88	3.42	-0.19
4	Lycopene	-10.68	-15.96	-15.66	4.98	-0.29

5	α-Tocopherol acetate	-3.59	-8.0	-7.95	4.36	-0.04
6	Quercetin	-8.05	-7.35	-8.4	0.31	1.06
7	Ethacrynic acid	-5.78	-7.81	-7.65	1.87	-0.17
8	Caffeic acid	-5.31	-5.95	-5.93	0.62	-0.02
9	Porphyrin	-7.16	-9.84	-8.41	1.25	-1.43
10	Ferulic acid	-5.46	-6.23	-6.4	0.93	0.17
11	Curcumin	-7.72	-7.33	-10.21	2.49	2.88
12	Dithiothreitol	-3.99	-5.06	-4.93	0.93	-0.13
13	Cinnamic acid	-5.28	-5.85	-5.9	0.62	0.06
14	Iodoacetamide	-4.01	-4.34	-4.32	0.31	-0.02
15	α-Tocopherol	-4.62	-9.1	-8.36	3.74	-0.74

The docking studies using a single hGSTA1-1 subunit as template showed a variety of binding sites **Table 3**.

TABLE 3: LIGAND BINDING SITE IDENTIFIED USING HUMAN GLUTATHIONE S-TRANSFERASE A1-1 MONOMER AS DOCKING TEMPLATE

S. no.	Ligand	Amino acid residues
1	Ellagic acid	GLU104, HIS159, LEU163, GLU162, GLY103, LEU107, LYS15, TYR166
2	Beta-mercaptoethanol	GLY201, SER202, ARG204, PRO200, GLN199, LEU198
3	Glutathione	GLY14, ARG13, LEU107, SER18, LEU72, ALA100, GLY103, ILE106, GLU162, TYR166, ARG155, HIS159, LEU163, ILE96, ILE99
4	Quercetin	GLU17, TYR166, GLY14, MET16, SER18, GLU162, ARG15, HIS159, LEU72, ARG155, GLU104, ALA100, ILE96, ARG69, GLU97
5	Curcumin	ALA100, ILE99, HIS159, GLY103, ILE106, TYR166, GLU17, ARG13, GLY14, GLU169, LEU170
6	Ferulic acid	GLY14, MET208, ARG13, LEU107, GLY103, ILE106
7	Caffeic acid	ARG15, SER18, HIS159, LEU107, GLU162, LEU163, GLU104
8	Cinnamic acid	PRO207, PRO206, ARG13, ARG204, SER202, GLY201, GLN199, LYS205
9	Lycopene	GLN54, VAL55, GLN67, THR68, ARG15, ARG69, LEU107, GLY103, ARG13, PRO207, GLU169, LEU170, SER172
10	α-Tocopherol acetate	ARG45, GLN54, GLN67, ARG15, TYR9, PHE220, VAL55
11	Ethacrynic acid	PHE30, VAL28, GLY27, ALA24, SER202, GLY201, LYS196, PRO200
12	Iodoacetamide	SER202, ARG204, PHE197, GLN199, LEU198
13	α-Tocopherol	ASP209, MET208, PRO110, ARG13, PRO207, LEU109, TYR166, ILE106, GLU169, LEU170
14	Dithiothreitol	GLY14, GLU17, ARG13, SER18, LEU107, GLU162, TYR166
15	Porphyrin	PHE30, VAL28, LEU23, ALA24, LYS196, PRO203, GLY201, PRO200, GLN199, GLU32

Residues within a 3.5Å radius of the binding site for the Ethacrynic acid with subunit A of hGSTA1-1 included PHE30, VAL28, GLY27, ALA24, SER202, GLY201, LYS196, PRO200 **Fig. 2a** rather than H-site (MET208, ARG13, LYS15, GLY14, LEU107, TYR9, PHE222) as expected from X-ray data shown in **Fig. 1a**.

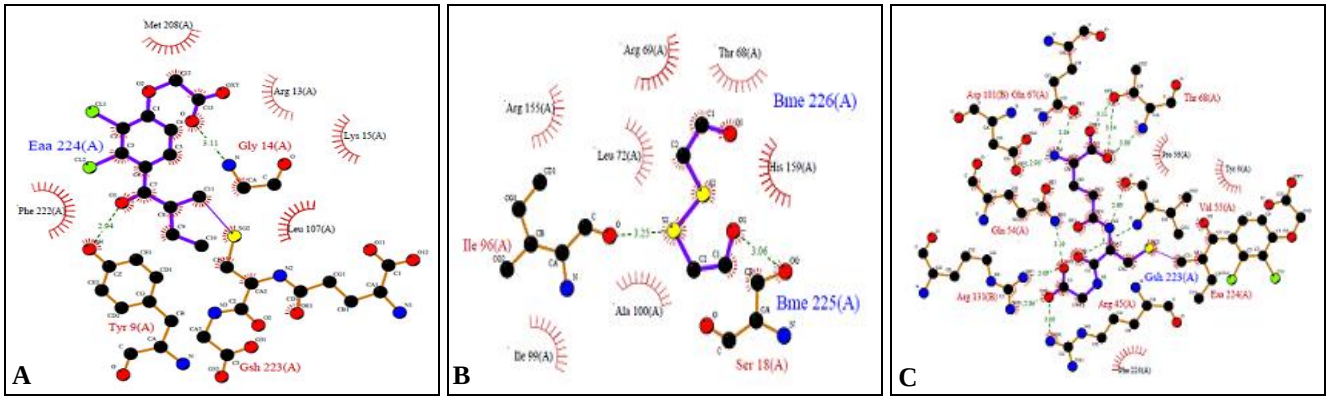

FIG. 1(A-B-C): (A): SCHEMATIC ILLUSTRATING THE RESIDUES CONTACTING ETHACRYNIC ACID (EAA). (B): RESIDUES CONTACTING BETA-MERCAPTOETHANOL (BME). (C): RESIDUES CONTACTING GLUTATHIONE (GSH). THESE FIGURES WERE TAKEN FROM PDBSUM ENTRY OF 1GSE

Binding site residues within a 3.5Å radius of Beta-mercaptoethanol with subunit A of hGSTA1-1 included GLY201, SER202, ARG204, PRO200, GLN199, LEU198 **Fig. 2b** rather than H-site (ARG155, ARG69, THR68, LEU72, HIS159, ILE96, ALA100, SER18) as expected from X-ray data shown in **Fig. 1b**.

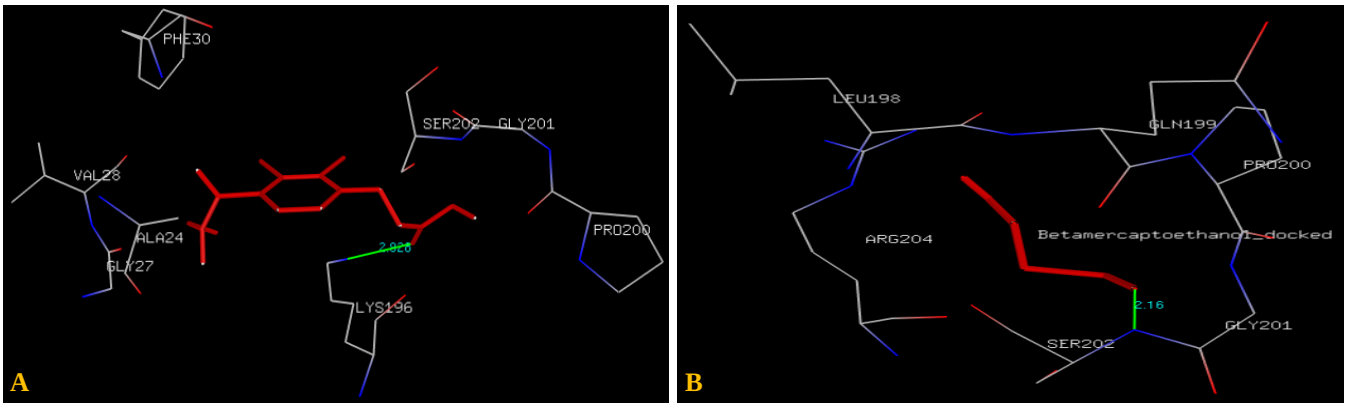

FIG. 2(A-B): (A): THE ETHACRYNIC ACID BINDING SITE RESIDUES. (B): THE BETA-MERCAPTOETHANOL BINDING SITE RESIDUES. THESE RESIDUES ARE IDENTIFIED USING GLUTATHIONE S-TRANSFERASE A1-1 (PDB ID: 1GSE) MONOMER AS DOCKING TEMPLATE. LIGANDS ETHACRYNIC ACID AND BETA-MERCAPTOETHANOL SHOW IN STICK & BALL REPRESENTATION AND IS COLORED WITH RED USING PYTHON MOLECULAR VIEWER. AMINO ACID RESIDUES ARE A REPRESENTATION AS LINES. A HYDROGEN BOND IS REPRESENTED BY THE GREEN LINE

Residues within a 3.5Å radius of the binding site for the Glutathione with subunit A of hGSTA1-1 included GLY14, ARG13, LEU107, SER18, LEU72, ALA100, GLY103, ILE106, GLU162, TYR166, ARG155, HIS159, LEU163, ILE96, ILE99 **Fig. 3a** rather than H-site (ASP101, GLN67, THR68, PRO56, TYR9, GLN54, VAL55, ARG131, ARG45, PHE220) as expected from X-ray data shown in **Fig. 1c**.

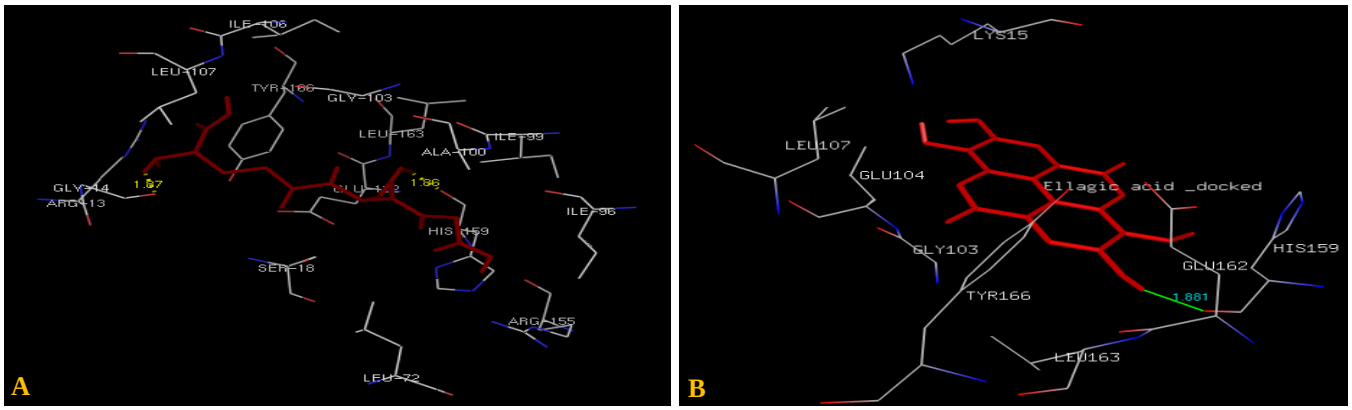

FIG. 3(A-B): (A): THE GLUTATHIONE BINDING SITE RESIDUES.(B): THE ELLAGIC ACID BINDING SITE RESIDUES. THESE RESIDUES ARE IDENTIFIED USING GLUTATHIONE S-TRANSFERASE A1-1 (PDB ID: 1GSE) MONOMER AS DOCKING TEMPLATE. LIGANDS GLUTATHIONE AND ELLAGIC ACID ARE SHOWN IN THE STICKS AND IS COLORED WITH RED. AMINO ACID RESIDUES ARE A REPRESENTATION AS LINES. A HYDROGEN BOND IS REPRESENTED BY A DOTTED YELLOW LINE AND BY THE GREEN LINE

A possible explanation for this result is that using the enzyme monomer without Glutathione conjugate as docking template leads to unreliable energy minima. As support of this view, in the structure of the complex with EAA, Beta-mercaptoethanol and Glutathione substrate are revealed as binding in a non-productive mode, suggesting that the substrate will only form an active complex when glutathione is already bound. This is biologically sensible as the intracellular levels of glutathione are much higher than the dissociation constant of its complex with GST Al-1. Glutathione is, therefore, probably involved in the molecular recognition of the electrophilic substrate and should be considered when designing drugs to inhibit GST.

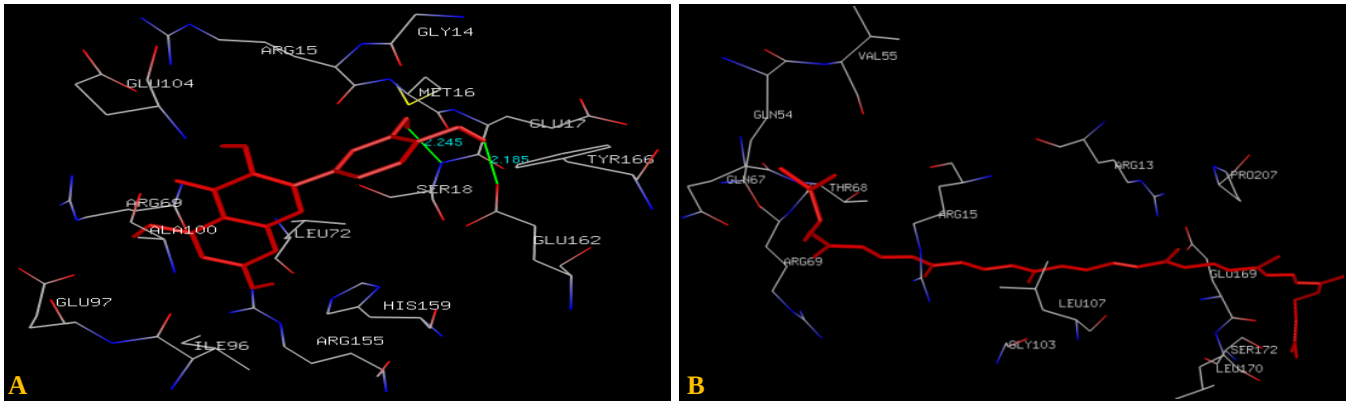

FIG. 4(A-B): (A): THE QUERCETIN BINDING SITE RESIDUES. (B): LYCOPENE BINDING SITE RESIDUES. THESE RESIDUES ARE IDENTIFIED USING GLUTATHIONE S-TRANSFERASE A1-1 (PDB ID: 1GSE) MONOMER AS DOCKING TEMPLATE. LIGAND QUERCETIN AND LYCOPENE ARE SHOWN IN STICKS REPRESENTATION AND IS COLORED WITH RED USING PYTHON MOLECULAR VIEWER. AMINO ACID RESIDUES ARE A REPRESENTATION AS LINES. A HYDROGEN BOND IS REPRESENTED BY THE GREEN LINE

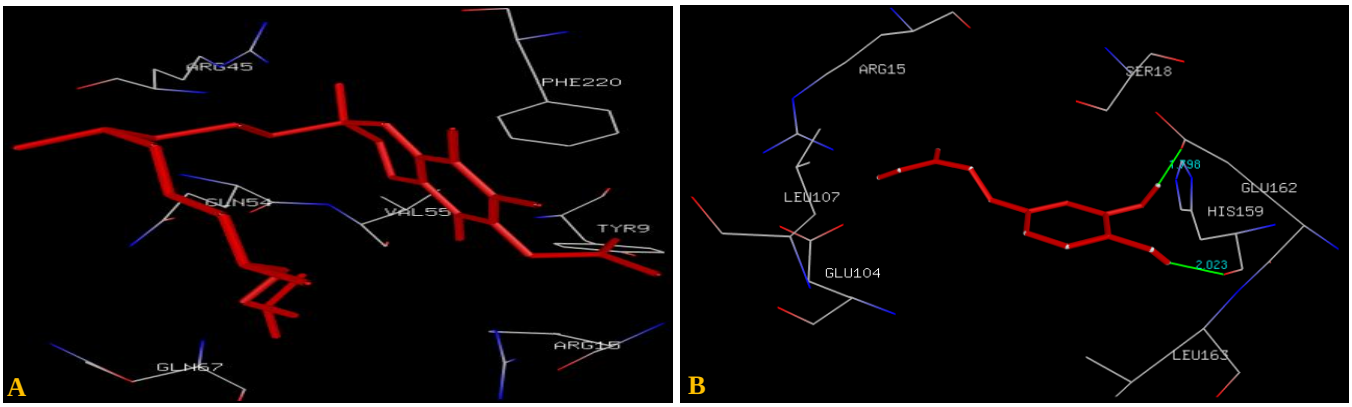

FIG. 5(A-B): (A): THE *A*-TOCOPHEROL ACETATE BINDING SITE. (B): THE CAFFEIC ACID BINDING SITE RESIDUES. THESE RESIDUES ARE IDENTIFIED USING GLUTATHIONE S-TRANSFERASE A1-1 (PDB ID: 1GSE) MONOMER AS DOCKING TEMPLATE. LIGAND *A*-TOCOPHEROL ACETATE AND CAFFEIC ACID ARE SHOWN IN STICKS AND STICKS & BALL REPRESENTATION AND IS COLORED WITH RED USING PYTHON MOLECULAR VIEWER. AMINO ACID RESIDUES ARE A REPRESENTATION AS LINES. A HYDROGEN BOND IS REPRESENTED BY THE GREEN LINE

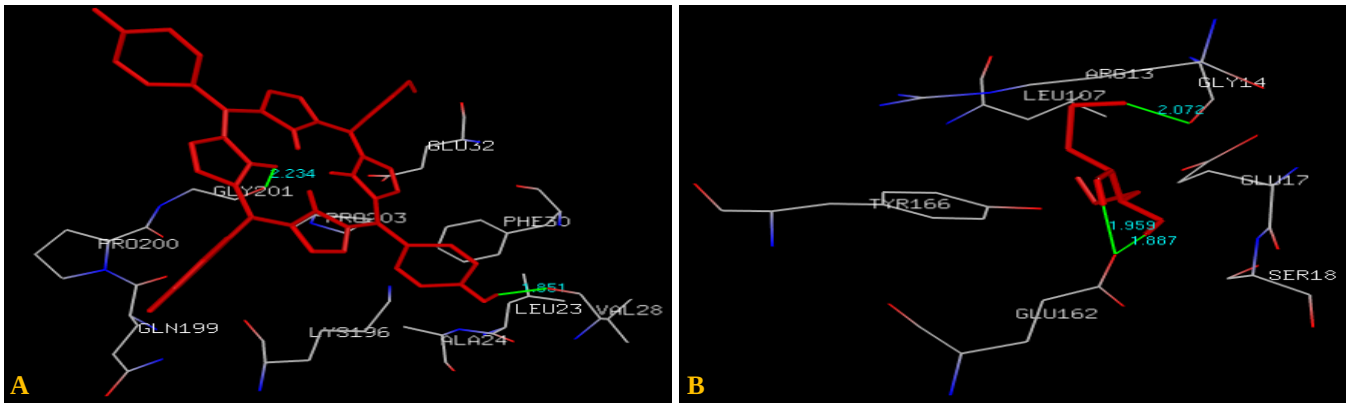

FIG. 6(A-B): (A): THE PORPHYRIN BINDING SITE RESIDUES. (B): THE DITHIOTHREITOL BINDING SITE RESIDUES. THESE RESIDUES ARE IDENTIFIED USING GLUTATHIONE S-TRANSFERASE A1-1 (PDB ID: 1GSE) MONOMER AS DOCKING TEMPLATE. LIGAND PORPHYRIN AND DITHIOTHREITOL ARE SHOWN IN STICKS REPRESENTATION AND IS COLORED WITH RED USING PYTHON MOLECULAR VIEWER. AMINO ACID RESIDUES ARE A REPRESENTATION AS LINES. A HYDROGEN BOND IS REPRESENTED BY THE GREEN LINE

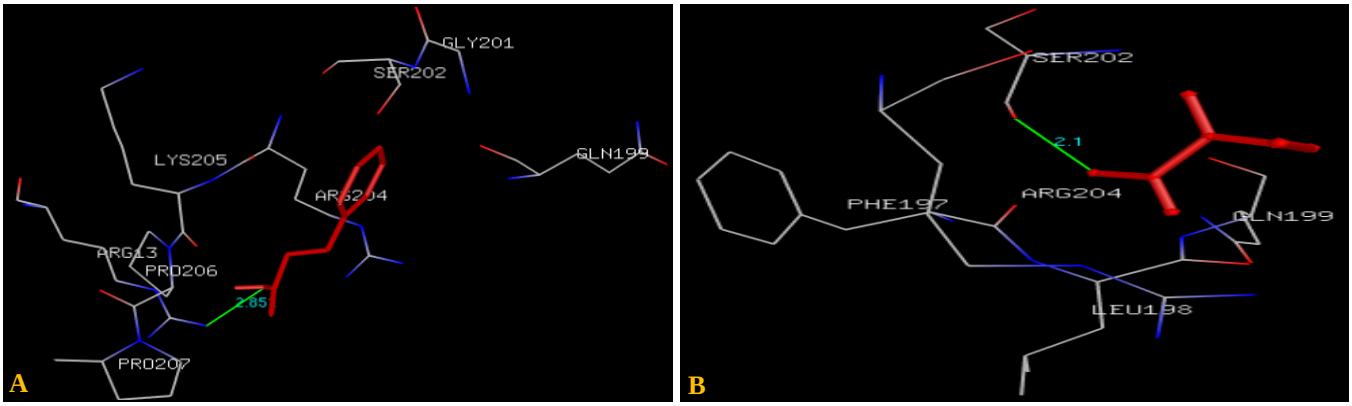

FIG. 7(A-B): (A): THE CINNAMIC ACID BINDING SITE RESIDUES. (B): THE IODOACETAMIDE BINDING SITE RESIDUES. THESE RESIDUES ARE IDENTIFIED USING GLUTATHIONE S-TRANSFERASE A1-1 (PDB ID: 1GSE) MONOMER AS DOCKING TEMPLATE. LIGAND CINNAMIC ACID AND IODOACETAMIDE ARE SHOWN IN STICKS AND STICKS & BALL REPRESENTATION AND IS COLORED WITH RED USING PYTHON MOLECULAR VIEWER. AMINO ACID RESIDUES ARE A REPRESENTATION AS LINES. A HYDROGEN BOND IS REPRESENTED BY THE GREEN LINE

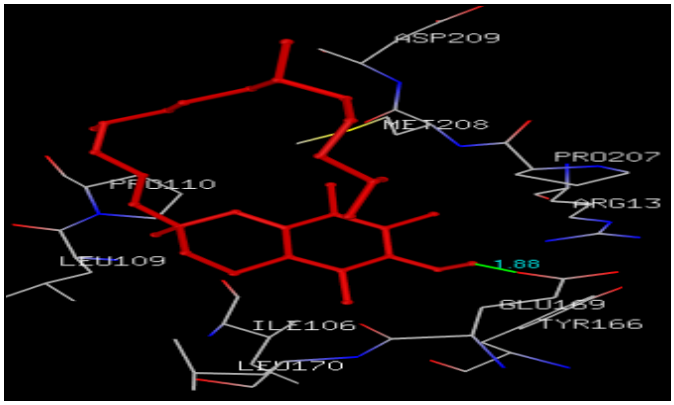

FIG. 8: THE A-TOCOPHEROL BINDING SITE RESIDUES ARE IDENTIFIED USING GLUTATHIONE S-TRANSFERASE A1-1 MONOMER AS DOCKING TEMPLATE. LIGAND A-TOCOPHEROL IS SHOWN IN STICKS REPRESENTATION AND IS COLORED WITH RED USING PYTHON MOLECULAR VIEWER. AMINO ACID RESIDUES ARE A REPRESENTATION AS LINES. A HYDROGEN BOND IS REPRESENTED BY THE GREEN LINE

CONCLUSION: Single enzyme subunit was found to provide a wider range of binding sites for naturally occurring ligands. Some inherent limitations of docking were considered perhaps explaining the low level of agreement between docking interaction energies and observed experimental values for enzyme-ligand binding. Finally, the evidence is also presented for differential ligand binding to the GST monomer which, if confirmed by direct measurements, could open the intriguing possibility that the single hGSTA1-1 subunit might be formed under some physiological conditions. More research is needed to determine whether naturally occurring ligands can disturb the structure and stability of hGSTA1-1.

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CONFLICT OF INTEREST: Nil

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