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In-silico Inhibitory Potential of Triphala Constituents Against Cytochrome P450 2E1 for the Prevention of Thioacetamide-induced Hepatotoxicity

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Triphala, which is a combination of fruits of *Terminalia chebula, Terminalia bellerica* and *Embilica officinalis* generally recommended as herbal drug formulation in the Indian traditional medicine system.
Study Design: To study the *in-silico* inhibitory potential of Triphala constituents against cytochrome P450 2E1 (CYP2E1) for the prevention of Thioacetamide-induced Hepatotoxicity
Place and Duration of Study: The work has been performed at MUP's College of Pharmacy (B Pharm), Degaon, Risod, Washim, Maharashtra, India in between February 2021 to May 2021.
Methodology: We have studied the inhibitory potential of Triphala on CYP2E1 by applying molecular docking tools. The major chemical constituents of Triphala i.e. gallic acid, chebulic acid, ellagic acid, epicatechin, syringic acid, and ascorbic acid were docked on CYP2E1.

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Results: Docking results revealed the very good inhibitory potential of Triphala in terms of binding affinity towards CYP2E1. All the chemical constituents have formed at least 2 and at most 6 hydrogen bonds with the crystal structure of CYP2E1. The binding energies (kcal/mol) of gallic acid, chebulic acid, ellagic acid, epicatechin, syringic acid, and ascorbic acid are -6.1, -7.1, -9.1, -8.3, -6.3, and -5.7, respectively. Ellagic acid has formed strong hydrogen bonds with Thr-303 and Thr-304 with bond length of 1.98 A^0 and 2.26 A^0 which confirms the excellent inhibition of CYP2E1.
Conclusion: These findings can be used to control the CYP2E1-facilitated biotransformation and drug interactions in the development of new chemical entities. In future, these phytoconstituents can be used as lead molecules to overcome the cancer associated with oxidative stress resulting from the hyperactivity of CYP2E1.

Keywords: Triphala; thioacetamide; CYP2E1; ellagic acid; gallic acid; chebulic acid.

ABBREVIATIONS

TAA : Thioacetamide
CYP2E1 : Cytochrome P450 2E1
TASO : Thioacetamide-S-oxide
$TASO_2$: Thioacetamide sulphdioxide
UFF : Universal Force Field

1. INTRODUCTION

Triphala, which is a mixture of fruits of *Terminalia chebula, Terminalia bellerica* and *Embilica officinalis* generally recommended as herbal drug formulation in the Indian traditional medicine system [1]. Recipe for this traditional herbal supplement has been described in the texts, 'The *Charak* and *Susruta Samhitas'* dating back to 1500 B.C [2] which governs the biological energies of human life on three doshas like Vata-Pitta- Kapha. It is also reported to have antiasthmatic [3], antiobesity [4], immunostimulatory [5], antibacterial [6], anti-cataract [7], antimutagenic [8] and wound healing properties [9].

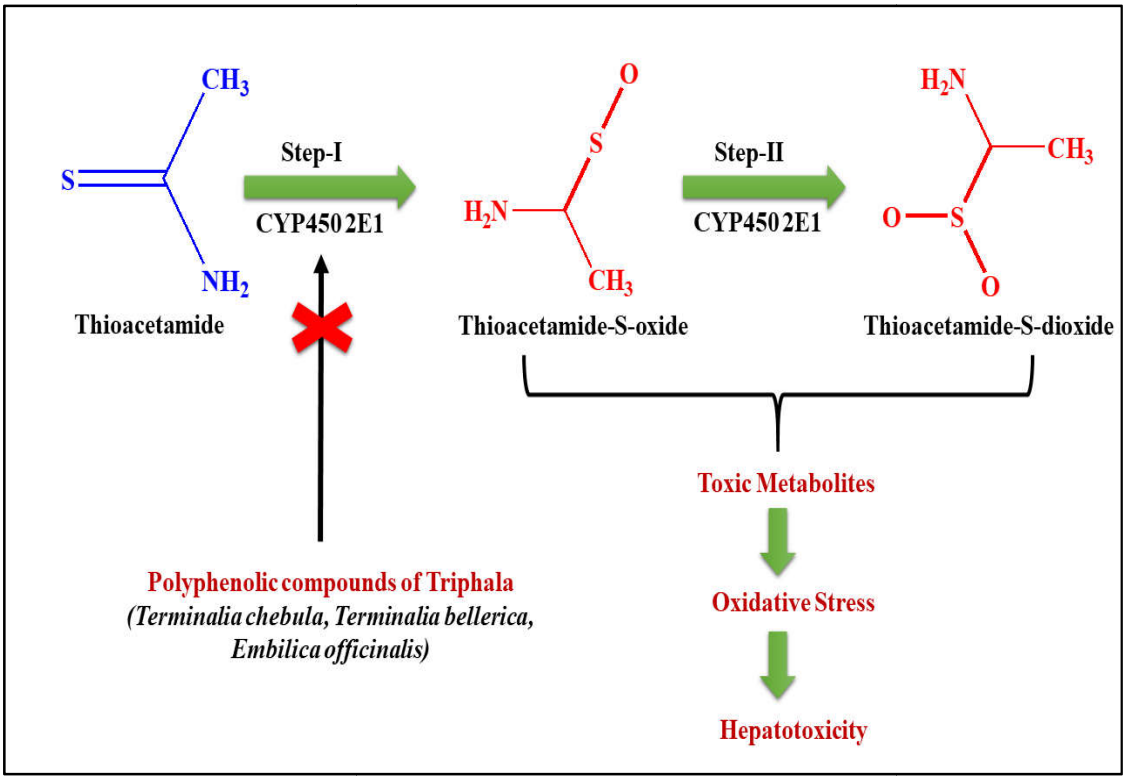


Fig. 1. The proposed mechanism of hepatotoxicity caused due to TAA

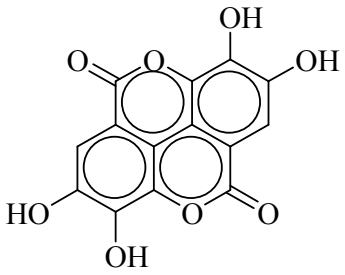
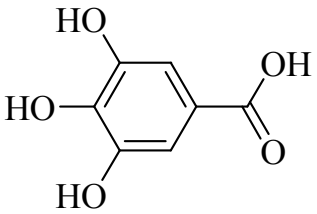
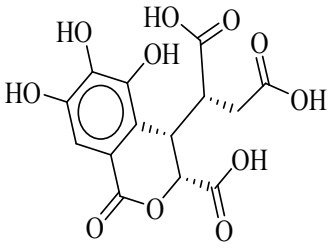
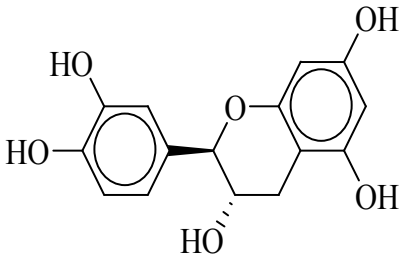
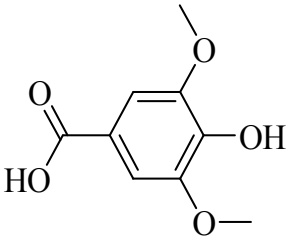
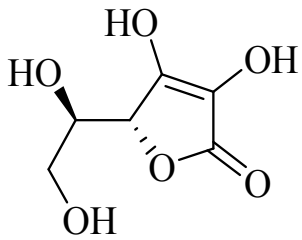
Thioacetamide (TAA), due to its toxic bio transforming substances, acetamide and thioacetamide-S-oxide (TASO) damages the liver and associated with carcinogenic activity due to depletion of reduced glutathione that causes oxidative stress [10,11]. Cancer cells associated with chromosomal abnormalities due to genetic alterations which lead to mutation which further progresses to tumor progression and metastasis [12]. TAA leads to cirrhosis, fibrosis and hepatic necrosis which results in hepatocellular carcinoma, cholangiocarcinoma and papillary adenocarcinoma. It is also used as standard hepatotoxin due to the reactive metabolite thioacetamide-S-oxide (TASO) and thioacetamide-S-dioxide ($TASO_2$) [13] which causes oxidative stress and deplete reduced glutathione content [14]. Natural substances owing to a variety of phytoconstituents such as polyphenols, flavonoids, tannins, or their derivatives, possess anti-mutagenic properties [15,16].

Bio-activation of TAA is induced by cytochrome P450 (CYP) 2E1 which forms thioacetamide-S-oxide (TASO) in the first step and second step thioacetamide-S-dioxide (TASO2), a reactive metabolite [17–19]. Many studies have reported the role of CYP2E1 in TAA-mediated hepatotoxicity through increased oxidative stress [11,20-21]. The proposed mechanism of hepatotoxicity caused due to TAA is represented in (Fig. 1.) Ponnusankar S. *et al.* published a study on Triphala's Cytochrome P450 inhibitory potential [22]. Concerning the above literature, we have studied the inhibitory potential of Triphala on CYP2E1 by applying molecular docking tools. The major chemical constituents of Triphala [2,23–25] i.e. gallic acid, chebulic acid, ellagic acid, epicatechin, syringic acid, and ascorbic acid were docked on CYP2E1.

2. MATERIALS AND METHODS

The autodock vina 1.1.2 in PyRx-Virtual Screening Tool 0.8 were used to perform the molecular docking studies [26]. The receptor-ligand interactions after docking were studied by using BIOVIA Discovery Studio Visualizer (version-19.1.0.18287) [27]. The Structures of major chemical constituents of Triphala (gallic acid, chebulic acid, ellagic acid, epicatechin, syringic acid, and ascorbic acid) (SDF File) were downloaded from the official website of the U.S. National Library of Medicine PubChem. Energy minimization (optimization) was performed by Universal Force Field (UFF) [28]. Table 1 represents the structures of the major chemical constituents of Triphala used for molecular docking.

Table 1. The structures of the major chemical constituents of Triphala used for molecular docking

Ellagic acid	Gallic acid	Chebulic acid
		
Epicatechin	**Syringic acid**	**Ascorbic acid**
		

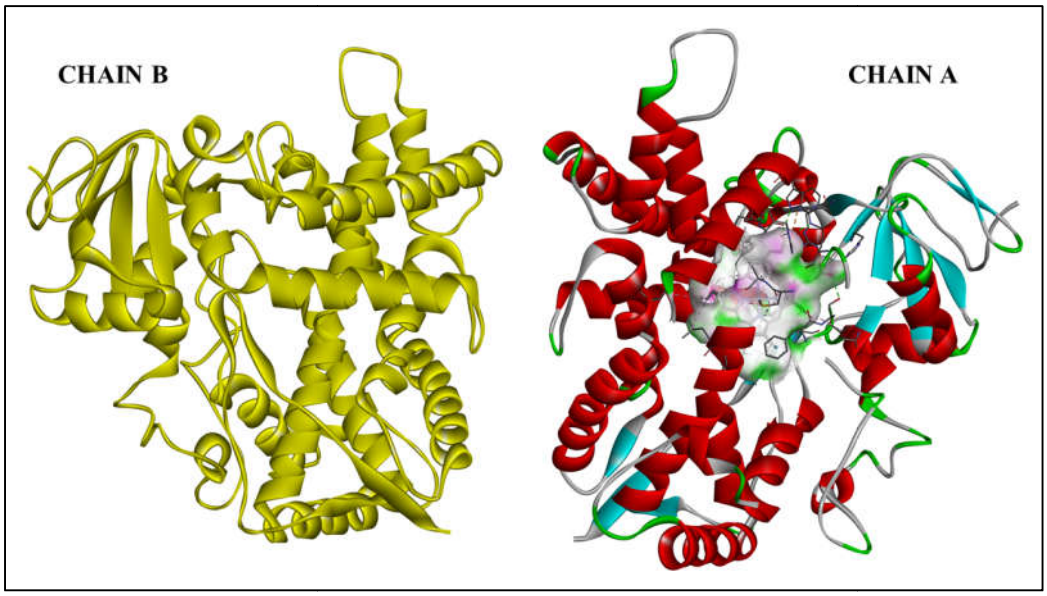


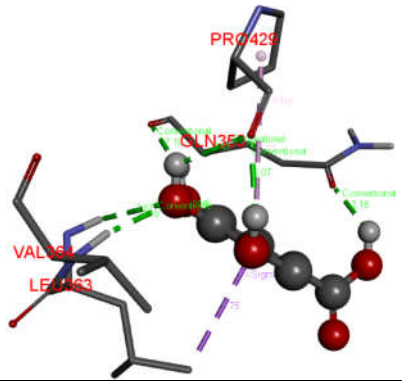
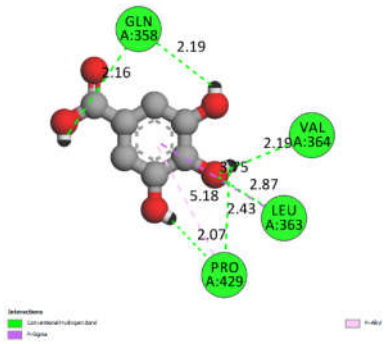
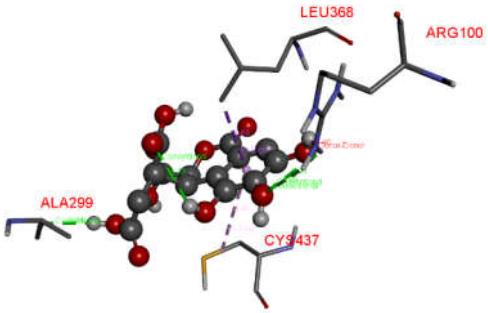
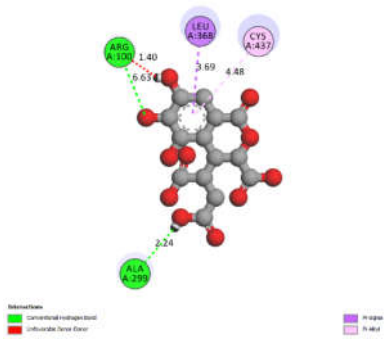
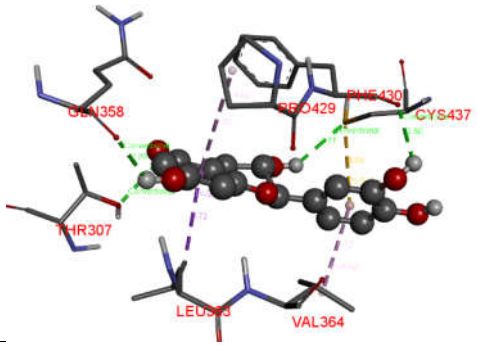
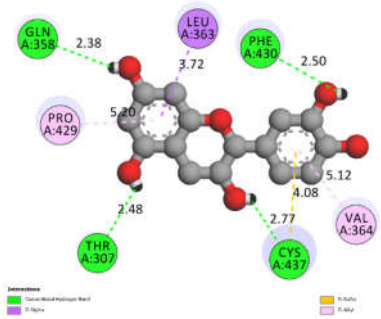
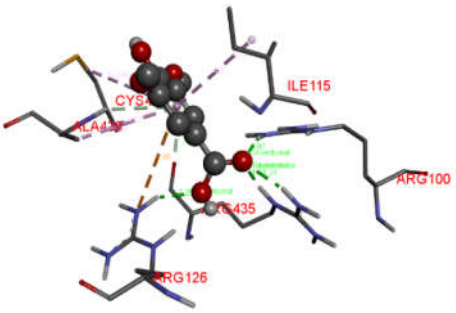
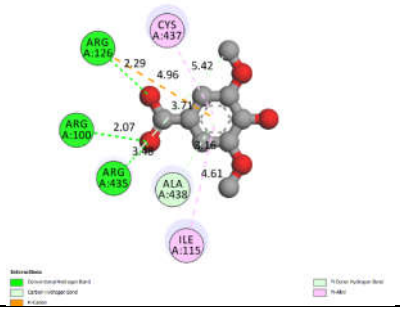
Fig. 2. The structure of Cytochrome P450 2E1 (PDB ID: 3LC4); Chain-B: In Yellow colour and Chain-A with Co-crystallized Ligand in Active Cavity

The elucidated crystal Human Cytochrome P450 2E1 in Complex with Omega-Imidazolyl-Dodecanoic Acid was obtained from the RCSB Protein Data Bank (PDB ID: 3LC4) which was released on 12 May 2010 (https://www.rcsb.org/structure/3LC4) [29]. There were two chains (Chain A & B) in the crystal structure of Cytochrome P450 2E1 (PDB ID: 3LC4). Chain A was selected to perform the molecular docking. The complete molecular docking was performed as per the procedure described by *Chaudhari R. N* and *et. al.* [30,31,31–34]. The structure of Cytochrome P450 2E1 (PDB ID: 3LC4); Chain-B: In Yellow color and Chain-A with Co-crystallized Ligand in Active Cavity represented in (Fig. 2) which was obtained from Discovery Studio.

3. RESULTS AND DISCUSSION

The chemical constituents of Triphala showed very good binding affinity towards CYP2E1. The 2D- and 3D-docking poses of the molecules represented in Table 2. Ellagic acid has -9.1 kcal/mol binding affinity which formed 3 hydrogen bonds with CYP2E1. The active amino acid residues with bond lengths are Ala-A: 443 (4.66A^0), Gly-A:300 (3.43A^0), Leu-A:442 (5.28A^0), Glu-A:446 (2.45A^0), Thr-A:304 (2.26A^0), Thr-A:303 (1.98A^0), Cys-A:437 (3.82A^0, 4.93A^0), Ala-A:299 (3.41A^0, 3.98A^0), Ala-A:438 (4.67A^0). Gallic acid has low binding affinity i.e. -6.1 kcal/mol comparing to Ellagic acid but it has formed 6 hydrogen bonds that are good enough to inhibit the activity of the enzyme. Gallic acid interacted with Gln-A:358 (2.19A^0, 2.16A^0), Val-A:364 (2.19A^0), Leu-A:363 (2.87A^0, 3.75A^0), Pro-A:429 (2.07A^0, 2.43A^0, 5.18A^0). Chebulic acid has a docking score of -7.2 kcal/mol with the formation of 2 hydrogen bonds. The active amino acid residues involved in the interactions were Arg-A:100 (1.40A^0, 6.63A^0), Leu-A:368 (3.69A^0), Cys-A:437 (4.48A^0), Ala-A:299 (2.24A^0). Epicatechin interacted with Thr-A:307 (2.48A^0), Pro-A:429 (5.20A^0), Gln-A:358 (2.38A^0), Leu-A:363 (3.72A^0), Phe-A:430 (2.50A^0), Val-A:364 (5.12A^0), Cys-A:437 (2.77A^0, 4.08A^0) and binding affinity was -8.3 kcal/mol with the formation of 4 hydrogen bonds. The binding affinity of Syringic acid was -6.3 kcal/mol which has formed 3 hydrogen bonds with CYP2E1 and interacted with Cys-A:437 (5.42A^0), Arg-A:126 (2.29A^0, 4.96A^0), Arg-A:100 (2.07A^0), Arg-A:435 (3.48A^0, 3.71A^0), Ala-A:438 (3.16A^0), Ile-A:115 (4.61A^0). Ascorbic acid found to have -5.7 kcal/mol binding energy and formed 5 hydrogen bonds with CYP2E1 and reacted with Ala-A:438 (1.97A^0), Ile-A:115 (2.89A^0, 2.34A^0), Arg-A:435 (3.62A^0), Arg-A:100 (3.01A^0), Arg-A:126 (2.20A^0, 1.07A^0). Table 3 represents the name of molecules, docking score (kcal/mol), no. of hydrogen bonds formed and active amino acid residues with bond length (A^0).

Table 2. The 2D- and 3D-docking poses of the molecules with CYP2E1 (PDB ID: 3LC4)

Name of Compound	3D-Docking Pose	2D-Docking Pose
Gallic acid		
Chebulic acid		
Epicatechin		
Syringic acid		

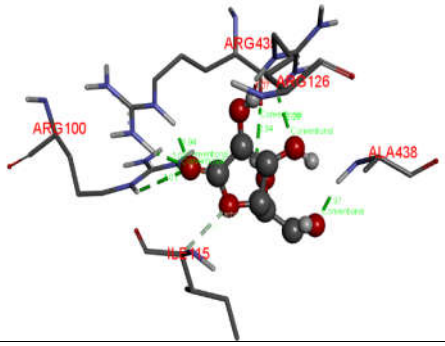
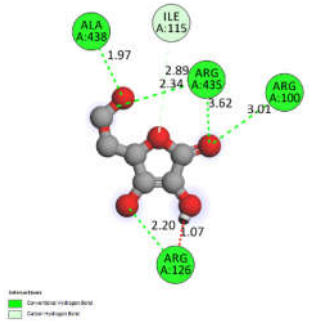
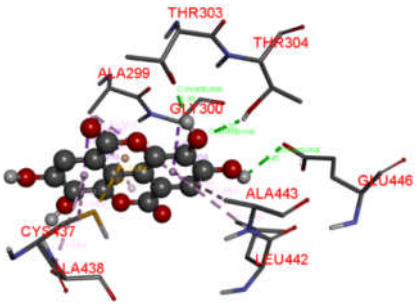
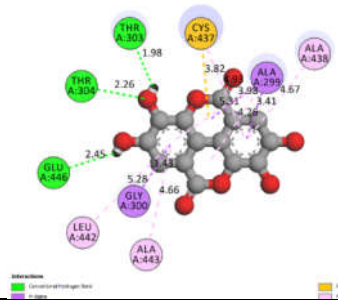
Name of Compound	3D-Docking Pose	2D-Docking Pose
Ascorbic acid		
Ellagic acid		

Table 3. The name of molecules, docking score (kcal/mol), no. of hydrogen bonds formed and active amino acid residues with bond in length (A^0)

Names of Compound	Dock Score (kcal/mol)	No. of Hydrogen Bonds	Active Amino Acid Residues (Bond Length in A^0)
Gallic acid	-6.1	6	Gln-A:358 (2.19, 2.16), Val-A:364 (2.19), Leu-A:363 (2.87, 3.75), Pro-A:429 (2.07, 2.43, 5.18)
Chebulic acid	-7.2	2	Arg-A:100 (1.40, 6.63), Leu-A:368 (3.69), Cys-A:437 (4.48), Ala-A:299 (2.24)
Epicatechin	-8.3	4	Thr-A:307 (2.48), Pro-A:429 (5.20), Gln-A:358 (2.38), Leu-A:363 (3.72), Phe-A:430 (2.50), Val-A:364 (5.12), Cys-A:437 (2.77, 4.08)
Syringic acid	-6.3	3	Cys-A:437 (5.42), Arg-A:126 (2.29, 4.96), Arg-A:100 (2.07), Arg-A:435 (3.48, 3.71), Ala-A:438 (3.16), Ile-A:115 (4.61)
Ascorbic acid	-5.7	5	Ala-A:438 (1.97), Ile-A:115 (2.89, 2.34), Arg-A:435 (3.62), Arg-A:100 (3.01), Arg-A:126 (2.20, 1.07)
Ellagic acid	-9.1	3	Ala-A:443 (4.66), Gly-A:300 (3.43), Leu-A:442 (5.28), Glu-A:446 (2.45), Thr-A:304 (2.26), Thr-A:303 (1.98), Cys-A:437 (3.82, 4.93), Ala-A:299 (3.41, 3.98), Ala-A:438 (4.67)

4. CONCLUSION

Toxic metabolites of TAA damages the liver by causing oxidative stress and promote carcinogenic activity which is supported by the evidence that TAA decreases the phagocyte index and also disrupts the morphology of liver especially sinusoids where Kupffer cells reside. The inhibitory potential of Triphala on CYP2E1 was studied by applying the molecular docking tool. Docking results revealed the very good inhibitory potential of Triphala in terms of binding

affinity towards CYP2E1. CYP2E1 is not only generating ROS in the biological system but it also stimulates the numerous pro-carcinogen to active carcinogens. All the chemical constituents have formed at least 2 and at most 6 hydrogen bonds with the crystal structure of CYP2E1. The binding energies (kcal/mol) of gallic acid, chebulic acid, ellagic acid, epicatechin, syringic acid, and ascorbic acid are -6.1, -7.1, -9.1, -8.3, -6.3, and -5.7 respectively. Triphala is already proven to have a safe biological window and well known for its antioxidant as well as immune-modulatory properties, which ultimately helps to improve the immunity of the individuals. Although exhaustive study regarding molecular mechanisms is still needed, to explore Triphala against genoprotection. The ellagic acid (-9.1 kcal/mol) may also reveal a promising role in future research against genoprotection. The molecular docking studies provide an efficient way for the screening of potential inhibitors from the Triphala for blocking a specific biotransformation enzyme. Thioacetamide induces the toxicity due to its biotransformation into toxic metabolites (TASO and TASO2) by the enzyme CYP2E1. The results of molecular docking indicate that all the chemical constituents of Triphala have adequately negative energy for binding human CYP2E1, which recommends a decent affinity of each compound to the active site. Laura E. Martikainen *et al.* have reported the interactions of inhibitor molecules with the human CYP2E1 enzyme active site through molecular docking studies [35]. They have concluded that Electrostatic interactions nearby the Thr-303 residue showed to be a vital for inhibition of the enzyme activity. More interestingly, in our study Ellagic acid has formed strong hydrogen bonds with Thr-303 and Thr-304 with bond length of 1.98 A^0 and 2.26 A^0 which confirms the excellent inhibition of CYP2E1. These findings can be used to control the CYP2E1-facilitated biotransformation and drug interactions in the development of new chemical entities. In future, these phytoconstituents can be used as lead molecules to overcome the cancer associated with oxidative stress resulting from the hyperactivity of CYP2E1.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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