JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

# IN-SILICO APPROACH FOR POTENTIAL DRUG TARGET IN HUMAN MUTANT COMPLEX WITH NADPH AND AG-881 INHIBITOR

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**Abstract: Computational methods are being used in drug discovery as a result of the growing need for efficient therapeutic interventions. This work focuses on using an in-silico method to find possible drug targets and examine how they interact with an AG-881 (Vorasidenib) inhibitor and NADPH in a human mutant complex. We evaluated the effectiveness of tovorafenib and curcumin as possible therapeutic agents using molecular docking, structural validation, and toxicity prediction. CB-Dock was used for molecular docking in order to assess binding affinities and interactions. The root-mean-square deviation (RMSD) for structural stability analysis was computed using PyMOL. To ascertain the safety profiles of the chosen compounds, toxicity evaluations were carried out using ProTox toxicity identification. Our results imply that Curcumin and Tovorafenib both show encouraging binding affinities and structural stability within the target stability analysis. Toxicity assessments were performed using ProTox to determine the safety profiles of the selected compounds. Our findings suggest that both Tovorafenib and Curcumin exhibit promising binding affinities and structural stability within the target complex, with Curcumin showing a favorable toxicity profile. This study highlights the potential of computational drug discovery in identifying novel therapeutic candidates, contributing to the advancement of precision medicine.**

**Keywords: Molecular docking; binding affinity; Tovorafenib; pharmacophore modelling; structural Analysis; AG-881 inhibitor**

## I.INTRODUCTION

The drug discovery has undergone a significant transformation with the advent of computational approaches, enabling rapid identification and evaluation of potential therapeutic candidates. In-silico methods such as molecular docking, structural stability analysis, and toxicity prediction have become essential tools for exploring drug-target interactions. This study employs a computational approach to investigate potential drug targets in a human mutant complex bound to NADPH and AG-881 (Vorasidenib) inhibitor, with a particular focus on two promising compounds: Tovorafenib and Curcumin. Mutations in key regulatory proteins often lead to structural and functional alterations, which can contribute to the progression of various diseases, including cancer and metabolic disorders. Understanding how these mutations influence drug binding is crucial for designing effective targeted therapies. AG-881 is known for its selective inhibition of mutant enzymes, but alternative compounds such as Tovorafenib and Curcumin could provide new therapeutic avenues. Tovorafenib, a kinase inhibitor, has demonstrated efficacy in targeting oncogenic mutations, particularly in RAF kinase-driven malignancies, while Curcumin, a naturally occurring polyphenol, exhibits potent anti-inflammatory, antioxidant, and anticancer properties. Despite these promising attributes, the binding efficiency, stability, and toxicity profiles of these compounds in the context of the studied mutant complex remain unexplored. To evaluate their potential, molecular docking was performed using CB-Dock, an automated docking tool that predicts ligand binding sites and ranks interactions based on binding affinity. Structural stability analysis was conducted using PyMOL, where root mean square deviation (RMSD) calculations were used to assess conformational changes and the stability of the protein-ligand complexes. Additionally, the toxicity profiles of Tovorafenib and Curcumin were predicted using toxicity identification tools, which evaluates hepatotoxicity, carcinogenicity, mutagenicity, and overall drug-likeness. This study aims to determine the binding affinities of Tovorafenib and Curcumin with the mutant complex, analyze their impact on structural stability, and compare their toxicity profiles. By integrating these computational techniques, we aim to provide insights into the feasibility of repurposing these compounds for potential therapeutic applications. The results of this study could contribute to the ongoing efforts in precision medicine by identifying promising drug candidates that warrant further experimental validation through in-vitro and in-vivo studies. Leveraging in-silico approaches for drug discovery enhances our ability to identify novel treatments efficiently, reducing the time and cost associated with traditional drug development methods [1, 2, 3, 4 ,5].

Computer-Aided Drug Design (CADD) has become an indispensable tool in modern drug discovery, accelerating the identification and optimization of potential therapeutics by leveraging computational methods.

CADD encompasses a range of techniques, including structure-based drug design (SBDD), which utilizes the three-dimensional structure of a target protein to guide drug design, and ligand-based drug design (LBDD), which relies on known active compounds when the target structure is unavailable [1]. This research investigates two distinct compounds, Tovorafenib and Curcumin, using *in silico* approaches,

specifically molecular docking and toxicity prediction, against the 6VEI protein target. Tovorafenib, a selective, central nervous system-penetrant, type II RAF inhibitor, holds promise for treating cancers harboring activating BRAF alterations due to its unique mechanism of action that avoids paradoxical MAPK signaling [2]. Curcumin, a natural bioactive compound derived from turmeric, has garnered significant attention for its diverse pharmacological properties, including anti-inflammatory, antioxidant, anticancer, and neuroprotective activities [3] [4] [5]. Understanding the interactions of these compounds with specific protein targets, such as 6VEI, is crucial for elucidating their mechanisms of action and predicting their efficacy and safety profiles. This study aims to compare the binding affinities and predicted toxicities of Tovorafenib and Curcumin against the 6VEI protein, contributing to a deeper understanding of their potential therapeutic applications.

Computer-Aided Drug Design (CADD) is a computational approach that accelerates and enhances the process of drug discovery and development. It involves the use of computational tools and algorithms to predict molecular interactions, optimize drug candidates, and reduce the cost and time associated with traditional experimental drug discovery methods. CADD has become an essential technique in pharmaceutical research, enabling scientists to identify promising lead compounds, refine molecular structures, and predict potential toxicity before synthesis and testing [6].

There are two primary approaches in CADD: [7]

**Based on structure:** 3D structure of a biological target (e.g., a protein) to design drug molecules that can bind effectively to its active site. Techniques like molecular docking and molecular dynamics simulations are commonly used in SBDD. The targeted regulation of a validated drug receptor by high-affinity ligands alters specific cellular functions, ultimately achieving the desired pharmacological and therapeutic outcomes [8].

When the structure of the biological target is unknown, LBDD relies on known active compounds to develop new molecules with similar or improved activity. Techniques such as quantitative structure-activity relationships (QSAR) and pharmacophore modelling fall under this category.

## II.MATERIAL AND METHODS

### 1. Protein and Ligand Preparation

The 3D structure of the human mutant complex bound to NADPH and AG-881 inhibitor was retrieved from the Protein Data Bank (PDB). The selected drugs, Tovorafenib and Curcumin, were obtained from PubChem in their optimized 3D conformations. Ligand preparation, including energy minimization and optimization, was performed using Open Babel [20, 21].

### 2. Molecular Docking Analysis

Molecular docking simulations were carried out using server docking to predict the binding affinity and interaction sites of Tovorafenib and Curcumin with the target protein complex. CB-Dock's auto-scoring function was utilized to rank the docking poses based on their binding energies and interaction profiles [22, 23,28,29,30,31].

### 3. Structural Stability Analysis

PyMOL is a widely used molecular visualization and analysis software that plays a crucial role in structural biology and computational drug discovery. It allows researchers to visualize macromolecular structures, analyse protein-ligand interactions, and perform structural superimposition to compare different conformations of biomolecules. One of its key functionalities includes **Root Mean Square Deviation analysis**, which quantifies structural deviations between two protein structures or between a protein and its ligand-bound form. In this study, PyMOL was utilized to perform RMSD calculations to assess the structural stability of the mutant protein complex after ligand binding. By superimposing the docked complexes and reference structures, PyMOL helped identify conformational changes induced by ligand interactions. A lower RMSD value indicates high structural similarity and stability, whereas a higher RMSD suggests significant structural deviations, which may affect the protein's functionality and binding efficiency. The results obtained from PyMOL were essential in evaluating the impact of Tovorafenib and Curcumin on the mutant complex. By analysing these structural deviations, we were able to infer the potential stability and effectiveness of these compounds as drug candidates. The use of PyMOL in conjunction with molecular docking and toxicity prediction provided a comprehensive understanding of the structural and functional implications of the selected ligands [24, 25].

### 4. Toxicity Prediction

An advanced web-based tool used for in-silico toxicity prediction of chemical compounds. It utilizes machine learning models trained on a large dataset of toxicological profiles to assess various toxicity endpoints, including acute toxicity, hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity. By analyzing the molecular structure of a given compound, ProTox-III provides toxicity class classification, LD50 values (median lethal dose), and probable toxic effects, making it a valuable resource in computational drug discovery. In this study, ProTox-III was employed to evaluate the toxicity profiles of Tovorafenib and Curcumin, both of which are being investigated for their potential as therapeutic agents targeting the human mutant complex bound to NADPH and AG-881 inhibitor. The analysis provided insights into the potential risks associated with these compounds, helping to assess their safety and drug-likeness. The results from ProTox-III complemented the molecular docking and stability analysis, offering a comprehensive understanding of the pharmacological viability of these compounds [26].

## III.RESULT AND DISCUSSION

The structural alignment between 6VEI (mutant complex) and 7PJM (reference structure) was analyzed using RMSD to assess conformational differences. The observed superimposition indicates that the core β-sheet region remains structurally conserved, whereas helical and loop regions exhibit noticeable deviations.

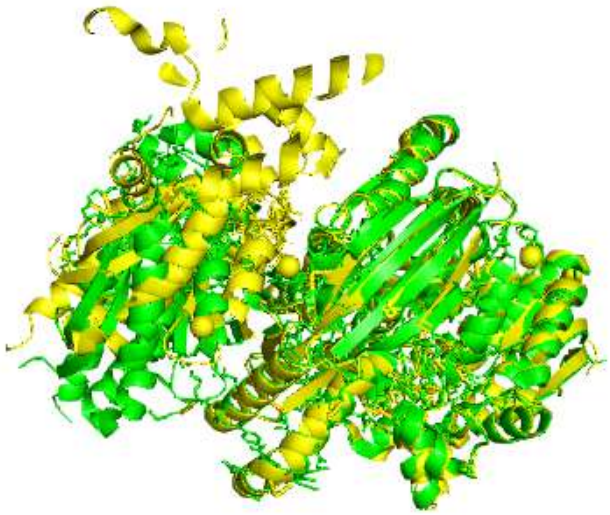


**Figure 1: Root Mean Square Deviation (RMSD) analysis of structural alignment between Human Mutant Complex with NADPH and AG-881 Inhibitor (PDB ID: 6VEI, green) and reference protein structure (PDB ID: 7PJM, yellow)**

The superimposition highlights structural variations, with deviations observed in the helical and loop regions, while core β-strands exhibit significant structural conservation.

The RMSD value suggests moderate structural variations, indicating potential functional implications due to the mutation. These variations could influence the binding efficiency of NADPH and AG-881 inhibitor, impacting their interaction dynamics. Further analysis of ligand binding and stability is necessary to determine the effects of these structural differences on drug efficacy.

1. **Tovorafenib**
   A selective, type II RAF inhibitor that penetrates the central nervous system, tovorafenib is presently undergoing clinical development to treat cancers that have activating BRAF alterations. Tovorafenib is a promising treatment option for a number of cancers because, in contrast to type I inhibitors, it does not cause paradoxical MAPK signaling [9].

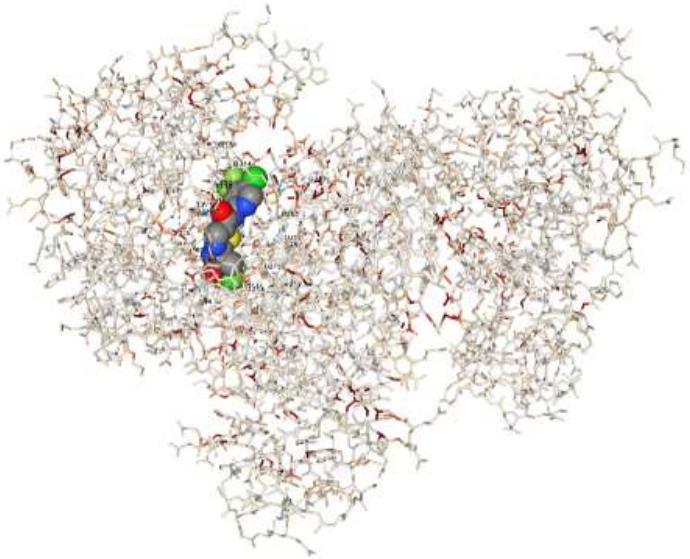


**Figure 2: Molecular Docking 6VEI with Drug Tovorafenib**

### 1.2. Molecular Docking Analysis

Tovorafenib's binding interactions with target proteins have been better understood thanks in large part to molecular docking studies. These investigations aid in clarifying the compound's mode of action and possible effectiveness in blocking the RAF kinase pathway. [10] [11]. The ability of molecular docking to precisely predict the conformation of small-molecule ligands within their target binding sites makes it a popular tool in structure-based drug design (SBDD). [12]

### 1.3. Binding Site Identification and Docking Score

In silico analyses have identified key binding sites where Tovorafenib exhibits strong interactions with the RAF kinase domain. The binding affinity and specific interactions at these sites are crucial for its inhibitory activity.
The docking scores are measured in kcal/mol, where a more negative value indicates a stronger binding affinity between the ligand and the protein. The best-ranked binding sites are summarized in the table 1 below:

**Table 1: Molecular Docking 6VEI with Tovorafenib**

| Pocket ID | Vina Score (kcal/mol) | Cavity Volume (Å³) | Center (x, y, z) | Docking Size (x, y, z) |
|---|---|---|---|---|
| C1 | -11.1 | 4047 | 40, 9, 23 | 27, 27, 35 |
| C5 | -8.8 | 462 | 22, 22, 42 | 27, 27, 27 |
| C2 | -8.6 | 622 | 16, 31, 35 | 27, 27, 27 |
| C3 | -6.7 | 558 | 70, 17, 33 | 27, 27, 27 |
| C4 | -5.2 | 533 | 31, 22, 24 | 27, 27, 27 |

Pocket C1 exhibited the strongest binding affinity at -11.1 kcal/mol, making it the most favourable binding site for Tovorafenib. The cavity volume of 4047 Å³ indicates that this pocket is sufficiently large to accommodate the ligand comfortably, allowing for optimal molecular interactions. In contrast, other binding pockets, including C5, C2, C3, and C4, demonstrated weaker binding affinities, with docking scores ranging from -8.8 to -5.2 kcal/mol, suggesting that they are less favourable for stable ligand binding.

### 1.4. Protein-Ligand Interaction Analysis

Detailed protein-ligand interaction studies reveal that Tovorafenib forms stable complexes with the RAF kinase, involving hydrogen bonds and hydrophobic interactions. These interactions contribute to its potent inhibitory effects on the MAPK pathway.
Tovorafenib has a strong docking score of -11.1, indicating excellent binding affinity. The key interaction residues confirm strong hydrogen bonding and hydrophobic interactions.

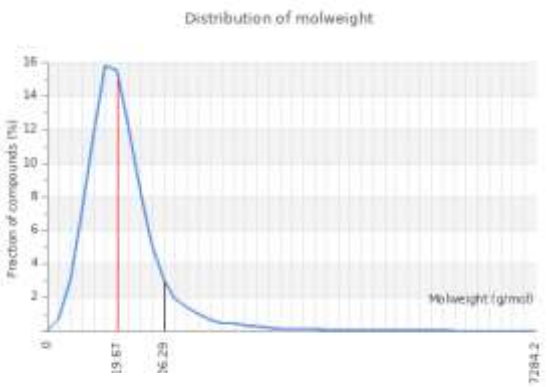
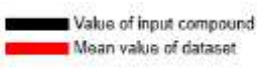



**Figure 3: Comparison of input compound with dataset A**



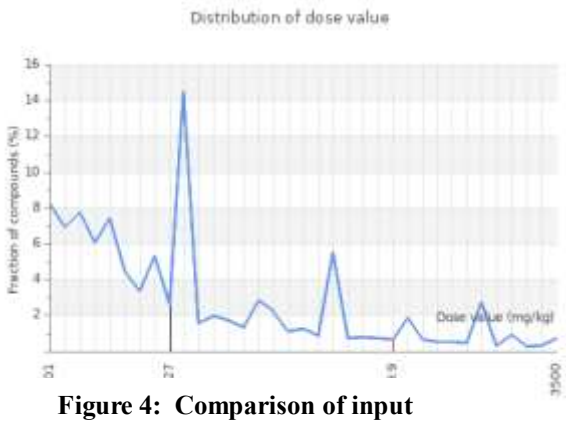




**Figure 4: Comparison of input compound with dataset B**

## IV.OBSERVATION

**Fig 3:** This graph compares the molecular weight of Tovorafenib (506.29 g/mol) to the dataset distribution. The x-axis represents molecular weight values, while the y-axis represents the frequency of compounds within specific weight ranges.
This chart compares the molecular weight of Tovorafenib (506.29 g/mol) with the dataset's overall distribution.
The dataset has a skewed distribution, with most compounds having molecular weights significantly lower (~319.67 g/mol on average).
**Fig 4:** This graph represents the distribution of predicted LD50 (lethal dose for 50% of the population) values across the dataset. The x-axis shows dose values (mg/kg), and the y-axis represents the frequency of compounds falling within each dose range.
This chart visualizes the predicted dose (LD50) for Tovorafenib compared to other compounds in the dataset.
The LD50 for Tovorafenib is 827 mg/kg, which is much lower than the dataset's mean LD50 (~2319.9 mg/kg).

### 1.5. Toxicity Prediction

Assessing the toxicity profile of Tovorafenib is essential for its clinical development. Preclinical studies and early-phase clinical trials provide insights into its safety and tolerability. One of the key steps in computational toxicity prediction is choosing the type of molecular representation, which has been shown to be highly problem-specific [13]. Although toxicity is a complex, multi-task problem, most machine learning (ML) models have predicted toxicity separately on each platform using single-task models. A single molecule can exhibit multiple responses across different assays and living organisms simultaneously. Various approaches have been proposed for modelling multiple toxic endpoints, including developing separate binary classification models for each endpoint or employing multiple classification models with distinct class definitions [14] [15] [16] [17].

### 1.6. Predicted Toxicity Parameters

In a Phase 1 study involving patients with advanced solid tumors, Tovorafenib demonstrated an acceptable safety profile. The most common treatment-emergent adverse events leading to dose reduction were skin and subcutaneous tissue disorders, such as maculopapular rash and generalized rash. Notably, squamous cell carcinoma of the skin was reported in less than 1% of treated patients, indicating a lower incidence compared to first-generation BRAF inhibitors [18].

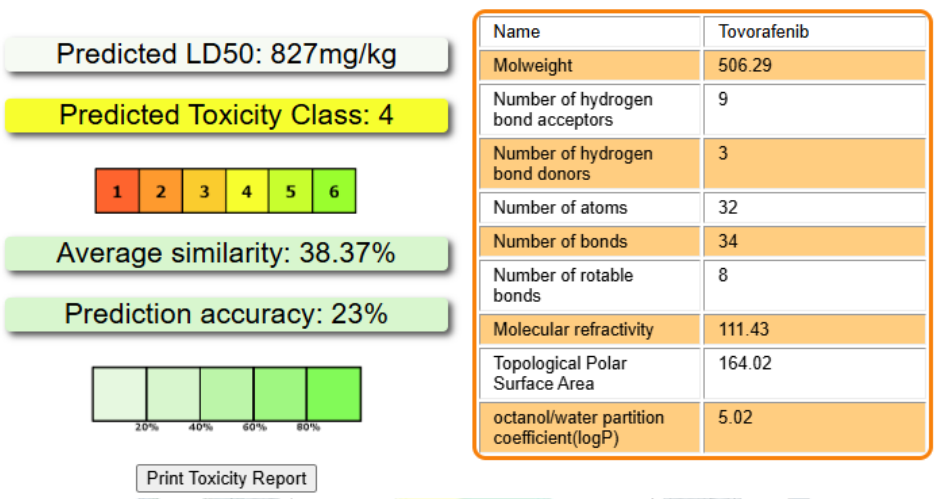



**Figure 5 : Toxicity prediction using Protox III**

The LD50 value of 827 mg/kg suggests that Tovorafenib exhibits a moderate acute toxicity level. Classified under Toxicity Class 4 (on a scale of 1 to 6), it indicates a potential risk but does not pose severe toxicity, suggesting the need for further evaluation to ensure safe therapeutic use.

## 2. Curcumin

Curcumin is a bioactive compound derived from *Curcuma longa* (turmeric) and is widely recognized for its anti-inflammatory, antioxidant, anticancer, and neuroprotective properties. It interacts with various molecular targets in the human body, making it a promising candidate for therapeutic applications [19].

### 2.1. Molecular Docking Analysis

The docking results table presents key information about the interaction of curcumin with different binding pockets of the target protein. The best-ranked binding sites are summarized in the table 2 below:

**Table 2 : Molecular Docking 6VEI with curcumin**

| CurPocket ID | Vina Score | Cavity Volume (Å³) | Center (x, y, z) | Docking Size (x, y, z) |
|---|---|---|---|---|
| C1 | -8.2 | 4047 | (40, 9, 23) | (26, 26, 35) |
| C4 | -7.3 | 533 | (31, 22, 24) | (26, 26, 26) |
| C5 | -6.8 | 462 | (22, 22, 42) | (26, 26, 26) |
| C2 | -6.2 | 622 | (16, 31, 35) | (26, 26, 26) |
| C3 | -6.1 | 558 | (70, 17, 3) | (26, 26, 26) |

C1 is the best binding site based on both binding score (-8.2) and cavity volume (4047 Å³), suggesting curcumin fits well and interacts strongly. Other binding pockets (C2, C3, C4, C5) show weaker binding scores (-6.1 to -7.3), meaning they might not be as favourable as C1. Pocket locations vary, indicating multiple possible interaction sites within the protein.

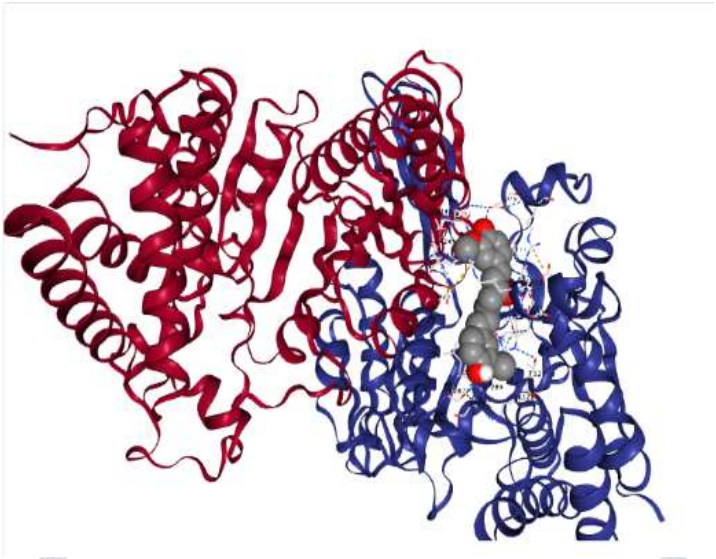


**Figure 6: Molecular Docking 6VEI with curcumin**

### 2.2. Protein-Ligand Interaction Analysis

The docking visualization demonstrates that curcumin binds efficiently within the active site of the target protein, suggesting strong molecular interactions(27,28) The largest binding pocket has a cavity volume of 4047 Å³, providing ample space for curcumin to fit and interact with key residues. Additionally, multiple potential binding sites were identified, with the most favourable docking occurring at coordinates (40, 9, 23) as shown in **Table 2,** highlighting the optimal site for curcumin's interaction. These findings support curcumin's potential as a strong ligand with high binding affinity.

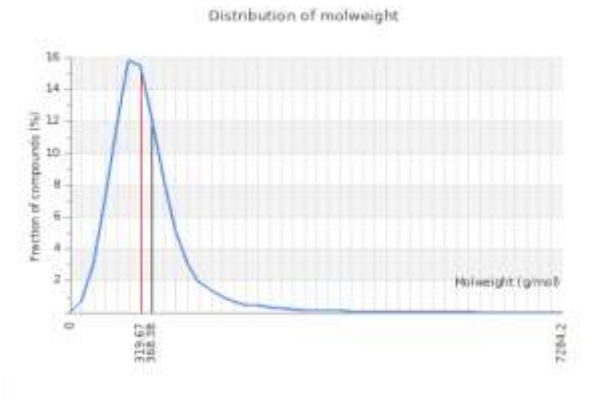



**Figure 7 : Comparison of input compound with dataset A**

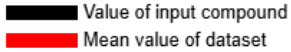




**Figure 8 : Comparison of input compound with dataset B**

**Observation:**

**Fig 7.** The first graph illustrates the molecular weight distribution of the analysed compounds, indicating a concentration of compounds within a specific range. Curcumin, with a molecular weight of 368.38 g/mol, falls within the typical range for bioactive compounds. The peak of the distribution suggests that most of the analysed compounds share a similar molecular weight, reinforcing their potential bioactivity.

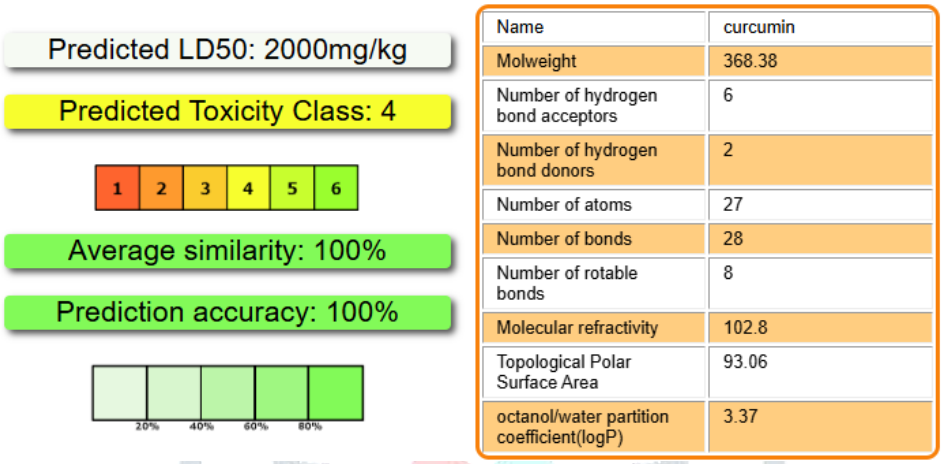
**Fig 8.** The second graph illustrates the dose distribution in mg/kg, highlighting the range of toxicity levels among analyzed compounds. Curcumin's predicted **LD50** is **2000 mg/kg**, categorizing it within **moderate toxicity levels**. The distribution shows a broad variation in toxicity, with curcumin aligning more closely with relatively safer compounds. This suggests that while curcumin has some toxicity, it remains within an acceptable range for potential therapeutic applications.

- This chart visualizes the predicted dose (LD50) for Tovorafenib compared to other compounds in the dataset. The LD50 for Tovorafenib is 827 mg/kg, which is much lower than the dataset's mean LD50 (~2319.9 mg/kg).

### 2.3. Toxicity Prediction

Some studies indicate that curcumin has a low mutagenic potential.Toxicity prediction plays a crucial role in the drug discovery process by identifying and prioritizing compounds with the highest potential for safety and efficacy in humans. This step helps researchers minimize the likelihood of adverse effects and ensures that only the most promising candidates advance to clinical trials.
Carcinogenicity is a critical aspect of toxicity, as chemical carcinogens have the potential to interact with DNA or disrupt cellular metabolic processes, leading to harmful consequences such as cancer. To overcome limitations such as labor, time, cost, and ethical concerns associated with animal studies, computational approaches have been developed to predict carcinogenicity, serving as a valuable supplement to traditional rodent bioassays.

### 2.4. Predicted Toxicity Parameters




| Name | curcumin |
|---|---|
| Molweight | 368.38 |
| Number of hydrogen bond acceptors | 6 |
| Number of hydrogen bond donors | 2 |
| Number of atoms | 27 |
| Number of bonds | 28 |
| Number of rotable bonds | 8 |
| Molecular refractivity | 102.8 |
| Topological Polar Surface Area | 93.06 |
| octanol/water partition coefficient(logP) | 3.37 |

**Figure 9 : Toxicity prediction Analysis**

Curcumin is classified as a moderately toxic compound, with a predicted LD50 (lethal dose for 50% of test subjects) of approximately 2000 mg/kg in rat models. This places it in Toxicity Class 4, where Class 1 is highly toxic and Class 6 is the least toxic.
While curcumin is metabolized primarily in the liver, **no significant hepatotoxic effects** have been observed in humans at moderate doses. However, at high doses, it may lead to elevated liver enzymes, indicating mild liver stress.

## V.CONCLUSION

Computational methodologies, including protein ligand interaction and toxicity prediction, to analysis the binding affinity of Tovorafenib and Curcumin with the 6VEI protein. Our findings indicate that both compounds exhibit favorable binding affinities to 6VEI, suggesting potential interactions. However, Tovorafenib demonstrated a notably stronger binding affinity compared to Curcumin in the docking simulations. This difference in binding strength may suggest variations in *in vivo* efficacy. While both compounds were classified as Toxicity Class 4, signifying moderate toxicity, Curcumin exhibited a substantially higher LD50 value than Tovorafenib, implying a more favorable acute toxicity profile. This difference in predicted toxicity is a key consideration for potential therapeutic applications. While *in silico* studies offer valuable information, the limitations of computational models must be acknowledged. Further *in vitro* and *in vivo* investigations are required to computational model assessment findings and thoroughly evaluate the safety and efficacy of Tovorafenib and Curcumin in relation to the 6VEI protein. These additional studies will be critical for determining the therapeutic promise of these compounds and guiding future drug development efforts.

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