RESEARCH PAPER

Systems Toxicology Profiling of Roots of Semecarpus anacardium L. Phytoconstituents: Disruption of IGF1R and KDR Signaling Networks

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ABSTRACT
Semecarpus anacardium L. is a traditional medicinal plant known for its diverse therapeutic properties, including anti-inflammatory, antimicrobial, and neuroprotective effects. However, its unprocessed forms can cause severe toxicity, largely due to phytochemicals such as bhilawanol A and cardol. This study was designed to assess the toxicity profile of these compounds using comprehensive in silico approaches. Computational tools were employed to evaluate drug-likeness, predict toxicity, estimate LD_{50} values, and assess blood-brain barrier permeability. SwissTargetPrediction and GeneCards were used to identify potential toxicity-related targets, followed by Gene Ontology and pathway enrichment analysis to explore the underlying biological mechanisms. Molecular docking and molecular dynamics simulations were performed to evaluate the binding affinity and stability of interactions between the phytochemicals and key toxicity-associated targets. The analysis revealed that both bhilawanol A and cardol exhibit high predicted toxicity, with strong associations to cardiotoxicity and hepatotoxicity. Network pharmacology highlighted IGF1R and KDR as central toxicity-related genes. Molecular docking showed that bhilawanol A binds strongly to IGF1R (-7.5 kcal/mol) and KDR (-7.3 kcal/mol). Molecular dynamics simulations revealed stable binding interactions between Bhilawanol A and the 2P2I and 3I81 targets, indicating a potential modulatory effect on IGF1R-related pathways. Since IGF1R signaling is implicated in various toxicological outcomes such as neurotoxicity, hepatotoxicity, dermal toxicity, nephrotoxicity, and cardiotoxicity. Overall, this study provides a mechanistic understanding of the toxicological risks associated with Semecarpus anacardium phytoconstituents and underscores the importance of detoxification strategies to ensure its safe medicinal application.

Keywords: *Cardiotoxicity; Hepatotoxicity; Molecular Docking; Molecular Dynamics; Bhilawanol A*
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INTRODUCTION

Herbal medicines have long played a vital role in primary healthcare, largely due to their diverse therapeutic compounds, widespread availability, and affordability (Singh, V. K., 2011; Shaito, A., et al., 2020). In recent decades, the field of phyto-preparations has expanded significantly, leading to a broad array of products used in complementary and alternative medicine, and offering substantial potential for integrative healthcare approaches. However, the growing consumer demand underscores the urgent need to rigorously assess the efficacy and safety of phytoconstituents (Krishnaswamy, S., 2024). Comprehensive toxicological evaluations are essential to identify potential safety risks and to develop strategies for

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minimizing adverse effects. Given the toxicity associated with certain potent traditional remedies, the Drugs and Cosmetics Act of 1948, under Schedule E1, has classified 14 medicinal plants including *Semecarpus anacardium* L. as substances of toxicological concern (Resmi, R., and Sooraj, S., 2023).

In traditional system of medicine, *S. anacardium* is often known as Marking Nut Tree and it belongs to the family Anacardiaceae, commonly known as the “making nut" and referred to in vernacular terms as "Ballataka" or "Bhilwa," is widely distributed across the sub-Himalayan region, as well as in tropical and central parts of India. It holds significant importance in traditional Indian medicine, particularly in the Ayurvedic and Siddha systems, due to its broad therapeutic applications (Rasoanaivo, P., et al., 2011; Chopra, R., 1933). In traditional Chinese medicine, *S. anacardium*’s formulations, like Dichroa febrifuga, was often used cautiously and typically in combination with other herbs such as *Glycyrrhiza glabra*, *Ziziphus jujuba*, and *Zingiber officinale* to enhance therapeutic efficacy and mitigate potential toxicity (Khare, C. P., 2004). Extensive chemical and phytochemical investigations of the nut have revealed a rich profile of bioactive constituents, including biflavonoids, phenolic compounds, bhilawanols, minerals, vitamins, and amino acids. Various extracts derived from the nut have demonstrated efficacy in the treatment of a range of conditions such as arthritis, tumors, and infections. However, further research involving the isolation of active constituents and elucidation of their structure–function relationships is essential to fully understand the mechanisms underlying its pharmacological effects (Semalty, M., et al. 2010).

S. anacardium fruits contain bioactive compounds with therapeutic and toxic properties. Bhilawanol, a mixture of ursuhenol isomers, exhibits antimicrobial, anti-inflammatory, and neuroprotective effects by reducing oxidative stress, calcium influx, and apoptosis in neuronal cells (Al Mughairbi, F., et al., 2021; Patel, D., et al., 2020). Anacardic acid, a phenolic lipid (3-n-pentadecylcatechol), demonstrates anticancer, antioxidant, and acetylcholinesterase-inhibiting activities, potentially aiding in neurodegenerative disease management (Al Mughairbi, F., et al., 2021; U, U. T., et al., 2024). Cardol, a dihydroxy phenol, contributes to cytotoxic effects but also causes skin irritation and blisters due to urushiols (Semalty, M., et al. 2010; Patel, D., et al., 2020)[10]. Biflavonoids like semecarpetin and phenolic compounds add antioxidant, anti-inflammatory, and hypoglycemic benefits (Kumar, M. S., et al., 2017).

However, unprocessed fruits are toxic, causing dermatitis, ocular lesions, and systemic issues like acute renal failure due to allergenic oils and reactive compounds. Traditional purification (Shodhana) methods mitigate toxicity while preserving therapeutic efficacy. Proper dosing and processing are crucial to harness their medicinal value safely (Kumar, M. S., et al., 2017; Darwatkar, P., et al., 2024).

S. anacardium exhibits significant toxicity due to compounds like anacardic acid, cardol,

and bhilawanols in its fruit pericarp, which cause severe irritant reactions (Patel, D., et al., 2020). Topical exposure leads to painful blisters, eczematous eruptions, and contact dermatitis, as reported in cases where skin application caused suppurative lymphadenitis requiring surgical intervention (K, S. K. R., et al., 2018). Oral ingestion of unprocessed nuts or extracts induces gastrointestinal inflammation, vomiting, bloody diarrhoea, oliguria, and systemic effects like hypotension, delirium, coma, and death in high doses (K, V. K., and Gothoskar, S., 1979).

With the growing emphasis on therapeutic research and drug development, it is imperative to understand the mechanisms underlying the toxicological effects of medicinal plants to ensure their safe and effective use. A thorough assessment of both risks and benefits is fundamental for their rational application. In the context of herbal medicine, an in-depth understanding of the specific mechanisms of action of individual phytocompounds is particularly important. In this regard, the present study aims to explore the toxicity profile and potential mechanisms of *Semecarpus anacardium* using open-source systems biology tools, thereby contributing to safer and more evidence-based utilization of this traditional medicinal plant.

Materials and Methods

The overall in silico workflow employed for toxicity profiling of *S. anacardium* root extract is illustrated in Fig. 1

Retrieval of *S. anacardium* root phytocompounds

Reported phytocompounds from roots of *S. anacardium* were collated from Database of IMPPAT (Mohanraj, K., et al., 2018), and public repositories. Each compound information was retrieved from PubChem and the data sheet was built (Kim, S., et al., 2021).

Drug-Likeness, Toxicity Prediction, LD50 Prediction and BBB Penetration Analysis

Drug-likeness character of the listed compounds was predicted using Molsoft online server (K, J., et al., 2019) by querying their canonical SMILES and noted molecular weight, the number of hydrogen bond acceptors and donors, and the water/lipid coefficient i.e. lipophilicity (LogP). Further, toxicity was predicted using PreADMET online server (Japti, V. P., et al., 2025)

ProTox-3.0 was employed to predict LD50 (median lethal dose) by loading chemical structures. The predicted LD50 values indicate the dose at which 50% of test subjects are expected to experience lethality following acute exposure to the compounds. The ProTox-3.0 tool (Banerjee, P., et al., 2024) provided insights into the potential toxicity of the compounds. Additionally, the Blood-brain barrier penetration was predicted using the PkCSM server (Pires, D. E. V., et al., 2015.

Toxicity Target Prediction

Swiss Target was utilized to predict the biological targets of each phytocompound (Gfeller, D., et al., 2014). Similarly, Genecards database (Mallapur, S. P., et al., 2025) was employed to retrieve the various toxicity-related genes using the keywords "cardiotoxicity, hepatotoxicity, neurotoxicity, nephrotoxicity, gastrointestinal toxicity, hematotoxicity, ototoxicity, pulmonary, and reproductive toxicity". Further, common genes among the compounds and toxicity were sorted for further enrichment analysis.

Gene Ontology (GO) and Pathway Enrichment and Network Construction

The common genes were queried to STRING 11.0 database to predict protein-protein interactions and GO enrichment analysis. The pathway enrichment analysis was carried out through the KEGG database. To intricate and visualize the inter-connections between phytoconstituents, targets, pathways, and relevant toxicity, a network was created utilizing Cytoscape version 3.9.1. (Shamnewadi, A., et al., 2025). Edge count was employed within the network to analyse the core genes participation in the major biological activity.

Docking studies

To study the interactions between compounds and hub genes within the network, virtual screening was performed. Based on network analysis, IGF1R and KDR were prioritized for docking. The x-ray crystallographic structures of IGF1R and KDR with PDB IDs 3I81 and 2P2I respectively, were retrieved from the RCSB PDB database (Berman, H. M., et al., 2000). Molecular docking was performed using PyRx ver. 0.8 to analyse the interactions between the compounds and targets. The default exhaustiveness value of 8 was set, resulting in the generation of nine conformations. The conformation with the lowest RMSD, and binding energy (BE) was generated, and interactions visualization was performed using Discovery studio visualizer version 2021(Biradar, P., et al., 2020; Patil, S. A., et al., 2023).

Molecular dynamics (MD)

MD simulations were conducted to assess the stability and interactions between the ligand and the protein molecule using Schrödinger's desmond software (Bowers, K. J., et al., 2007). The ligand-protein complex was first solvated, neutralized, and balanced for net charge with Na+ and Cl- ions whichever applicable. An energy minimization step followed, considering the number of atoms and maintaining a temperature of 310 K to relax the system. The simulation ran for 100 nanoseconds. Long-range interactions between the ligand and protein were calculated using the Particle Mesh Ewald method, with Lennard-Jones interactions having a cut-off of 10 Å (Patil, V. S., et al., 2021).

Toxicity Prediction Using ProTox-3.0

The toxicity profile of the test compound was predicted using the ProTox-3.0 webserver (https://tox.charite.de), which evaluates endpoints such as hepatotoxicity, neurotoxicity, and cytotoxicity. The compound's SMILES format was submitted, and the platform predicted organ-specific toxicities and molecular target interactions. A radar plot was generated to visualize the compound's profile against average toxicity trends. This computational assessment provided preliminary safety insights (Banerjee, P., et al., 2024.

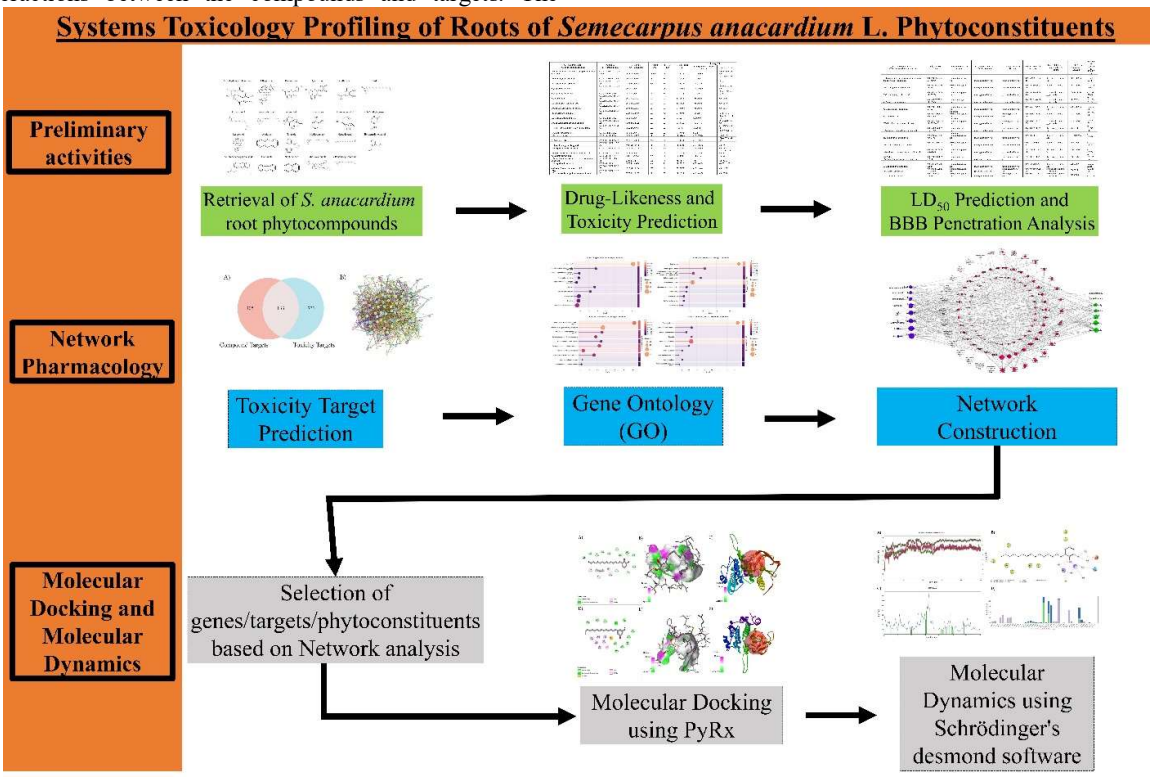

Fig. 1. Schematic representation of the overall *in silico* workflow for toxicity profiling of *S. anacardium* root extract.

RESULTS

Drug-Likeness, Toxicity and LD_{50} Prediction and BBB Penetration Analysis

A total of 23 phytocompounds were obtained from the IMPPAT database (Fig. 2). Their drug-likeness properties were evaluated using the Molsoft online platform (Table 1). Among these, 16 compounds were predicted to have mutagenic potential, whereas 7—namely Cardol, Bhilawanol A, Sclareolide, Hydroginkgol, Heptadecenal, Oboflavanone B, and 5-Pentadecylresorcinol—were found to be non-mutagenic. In terms of carcinogenicity, 9 compounds showed positive results in rat models and 4 in mice, while the rest were predicted to be non-carcinogenic. For cardiotoxicity assessed through hERG inhibition, 8 compounds posed a medium risk, while the remaining 15 were categorized as low risk (Table 2).

The predicted LD_{50} values (mg/kg) allowed classification of the phytoconstituents into high, moderate, and low acute toxicity categories. Compounds such as quercetin and benzenediol demonstrated high toxicity, with LD_{50} values below 500 mg/kg, indicating potential harm even at low doses. Constituents like ellagic acid and hexahydroxydiphenic acid were moderately toxic, with LD_{50} values between 1000 and 2000 mg/kg, warranting careful consideration in therapeutic contexts. In contrast, compounds such as kaempferol and sclareolide showed low toxicity, with LD_{50} values above 3000 mg/kg, suggesting a relatively safe profile. Interestingly, naturally occurring phenolic lipids like bhilawanol and cardol were also categorized as moderately toxic (Table 2).

Predicted blood-brain barrier (BBB) permeability indicates that the phytoconstituents vary in their ability to enter the central nervous system (CNS). Compounds with log BB values lower than -1.0, such as hexahydroxydiphenic acid and quercetin, are predicted to have poor BBB penetration, limiting their CNS availability. Conversely, compounds like hydroginkgol and acridine display strong BBB permeability, while bhilawanol A and cardol show moderate potential, highlighting their possible relevance for neurological use (Table 2).

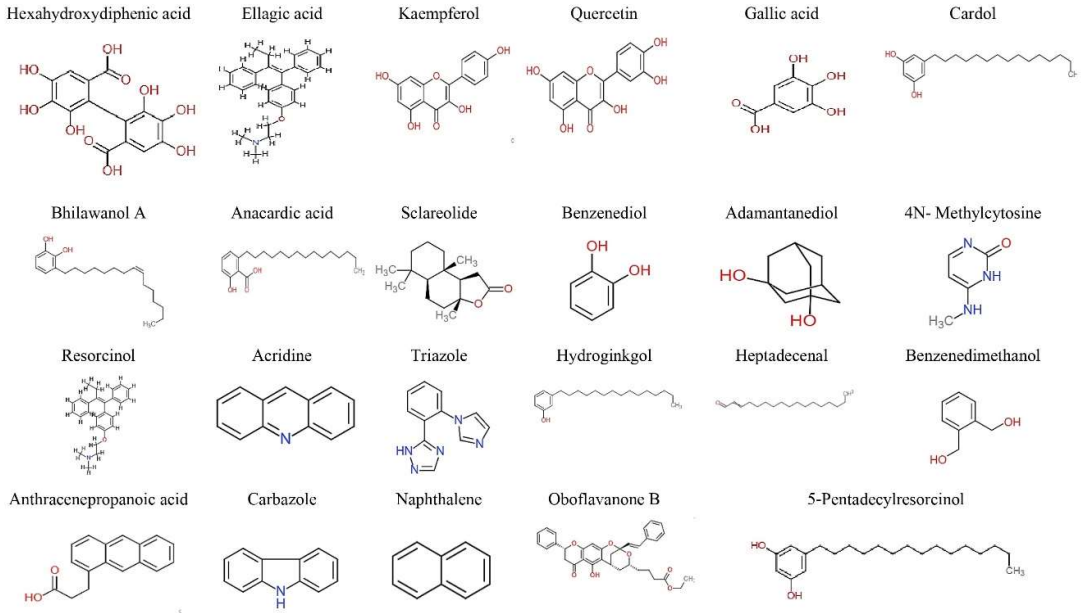

Fig. 2. Chemical structures of the selected Phytocompounds

Table 1. Drug-likeliness characteristics of the phytoconstituents.

Chemical Constituents	Mol. Formula	Mol. Weight	HBA	HBD	MLogP	MlogS	
						Log(moles/L)	mg/L
Hexahydroxydiphenic acid	C14H10O10	338.03	10	8	1.61	-1.69	6959.56
Ellagic acid	C14H6O8	302.01	8	4	1.53	-1.62	7265.67
Kaempferol	C15H10O6	286.05	6	4	1.61	-2.21	1744.17
Quercetin	C15H10O7	302.04	7	5	1.19	-2.19	1952.89
Gallic acid	C7H6O5	170.02	5	4	0.78	-1.1	13467.71
Cardol	C21H36O6	320.27	2	2	8.51	-6.05	0.28
Bhilawanol A	C21H34O2	318.26	2	2	8.13	-6.08	0.27
Anacardic acid	C22H36O3	348.27	3	2	9.09	-6.08	0.29

Sclareolide	C16H26O2	250.19	2	0	3.66	-3.54	71.99
Benzenediol	C6H6O2	110.04	2	2	1.2	0.09	136441.9
Adamantanediol	C10H16O2	168.12	2	2	0.82	-0.47	57218.9
4N- Methylcytosine	C15H7N3O	125.06	2	2	-0.84	1.51	3897.31
Resorcinol	C6H6O2	110.04	2	2	1.01	0.14	150243.9
Acridine	C13H9N	179.07	1	0	3.46	-3.74	32.26
Triazole	C11H9N5	211.09	3	1	1.01	-1.59	5473.42
Hydroginkgol	C21H36O6	304.28	1	1	9.07	-6.18	0.2
Heptadecenal	C17H32O	252.25	1	0	7.54	-5.99	0.26
Benzenedimethanol	C8H10O2	138.07	2	2	0.53	-0.51	42343.65
Carbazole	C12H9N	167.07	0	1	3.58	-4.43	6.21
Anthracenepropanoic acid	C17H14O2	250.1	2	1	4.14	-5	2.52
Naphthalene	C10H8	128.06	0	0	3.25	-3.43	47.62
oboflavanone B	C34H34O7	554.23	7	1	7.22	-5.94	0.63
5-Pentadecylresorcinol	C21H36O2	320.27	2	2	8.51	-6.05	0.28

Mol.: Molecular, HBA: Hydrogen bond acceptor, HBD: Hydrogen bond donor

Table 2. Toxicity and LD_{50} Prediction and BBB Penetration Analysis of the phytoconstituents.

Chemical Constituents	**algae_at**	**Ames_test**	**Carcino_ Mouse**	**Carcino _Rat**	**daphnia _at**	**hERG_ inhibition**	**LD_{50} (mg/kg)**	**BB B (log BB)**
Hexahydroxydiphenic acid	0.0150349	mutagen	negative	positive	0.22305	low_risk	1700	-1.801
Ellagic acid	0.043818	mutagen	negative	positive	0.15038	low_risk	1190	-1.054
Kaempferol	0.0483223	mutagen	negative	positive	0.19688	medium_risk	3919	-0.886
Quercetin	0.0378136	mutagen	negative	positive	0.21435	medium_risk	159	-1.065
Gallic acid	0.0780307	mutagen	negative	positive	0.68964	low_risk	2000	-0.93
Cardol	0.0007096 1	non-mutagen	negative	negative	0.00183	low_risk	2100	0.04
Bhilawanol A	0.0010223 6	non-mutagen	negative	negative	0.00223	medium_risk	4000	0.067
Anacardic acid	0.0007309 8	mutagen	negative	negative	0.00172	low_risk	481	-174
Sclareolide	0.0248096	non-mutagen	negative	positive	0.13714	low_risk	4400	0.179
Benzenediol	0.105721	mutagen	negative	positive	0.72694	low_risk	100	-0.225
Adamantanediol	0.0787646	mutagen	negative	positive	2.34461	low_risk	5000	-0.163
4N-Methylcytosine	0.318324	mutagen	positive	negative	5.11165	low_risk	584	-0.29
Resorcinol	0.106625	mutagen	negative	positive	0.72694	low_risk	200	-0.225

Acridine	0.0826729	mutagen	positive	negative	0.08923	medium_risk	331	0.527
Triazole	0.243153	mutagen	negative	negative	0.61202	medium_risk	720	-0.008
Hydroginkgol	0.00089137	non-mutagen	negative	negative	0.00169	low_risk	2100	0.862
Heptadecenal	0.00318918	non-mutagen	negative	negative	0.00854	low_risk	5000	0.936
Benzenedimethanol	0.125558	mutagen	negative	negative	1.83884	low_risk	1400	-0.146
Carbazole	0.0627517	mutagen	positive	negative	0.08436	medium_risk	360	0.463
Anthracenepropanoic acid	0.0558606	mutagen	negative	negative	0.05566	medium_risk	2300	0.3
Naphthalene	0.102469	mutagen	positive	negative	0.24615	medium_risk	316	0.575
oboflavanone B	0.00122831	non-mutagen	negative	negative	0.00228	low_risk	2300	-0.728
5-Pentadecylresorcinol	0.00070961	non-mutagen	negative	negative	0.00183	low_risk	2100	0.04

BBB: Blood brain barrier

Toxicity Target Prediction

A total of 438 potential protein targets for the 23 phytocompounds were predicted using the Swiss Target Prediction tool. Additionally, toxicity-associated gene targets related to cardiotoxicity, hepatotoxicity, neurotoxicity, nephrotoxicity, gastrointestinal toxicity, hematotoxicity, ototoxicity, pulmonary toxicity, and reproductive toxicity were obtained from the GeneCards database, resulting in 866 targets. A comparison of targets from both sources revealed 133 overlapping targets (Fig. 3A).

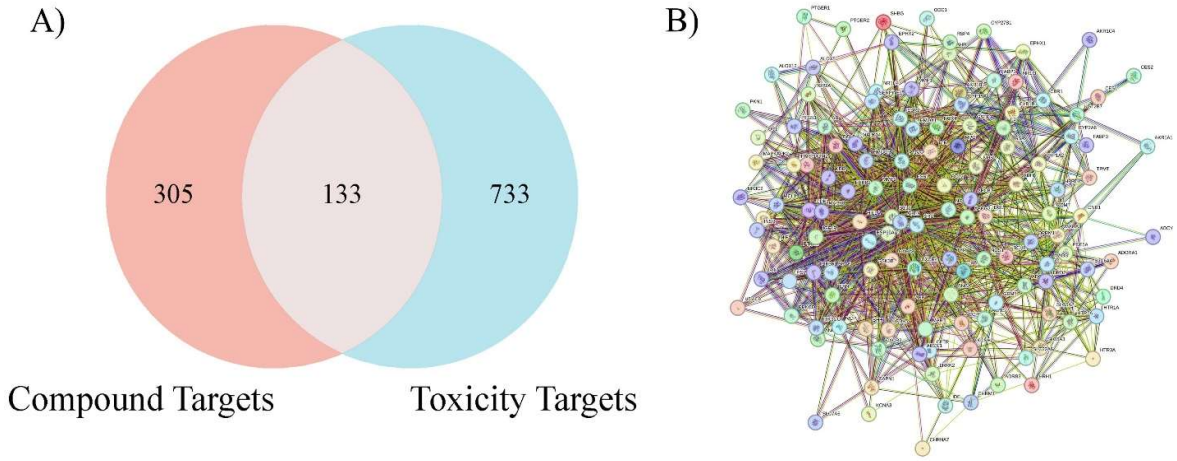

Fig. 3. (A) Venn diagram represents the common number of genes between the *S. anacardium* phytocompounds modulated probable targets and genes associated with multiple toxicities. (B) Protein-protein interaction association network of common genes (N=133).

GO enrichment, Prediction of Toxic Pathways and Network Construction

The GO and pathway enrichment analysis for 133 targets were carried out using STRING and the KEGG pathway database (Fig. 4 and Fig. 3B). GO and disease-gene association analyses reveal that the identified genes are primarily involved in neuronal structures such as membrane rafts and synaptic membranes, with functions related to oxidoreductase activity, neurotransmitter receptor binding, and hormone interaction. Biologically, they are enriched in responses to oxidative stress and various organic compounds, indicating roles in cellular defense and signaling. Disease association data show strong links to neurological and psychiatric conditions

including cognitive disorders, dementia, depression, and substance dependence, suggesting the gene set's potential involvement in CNS-related pathologies.

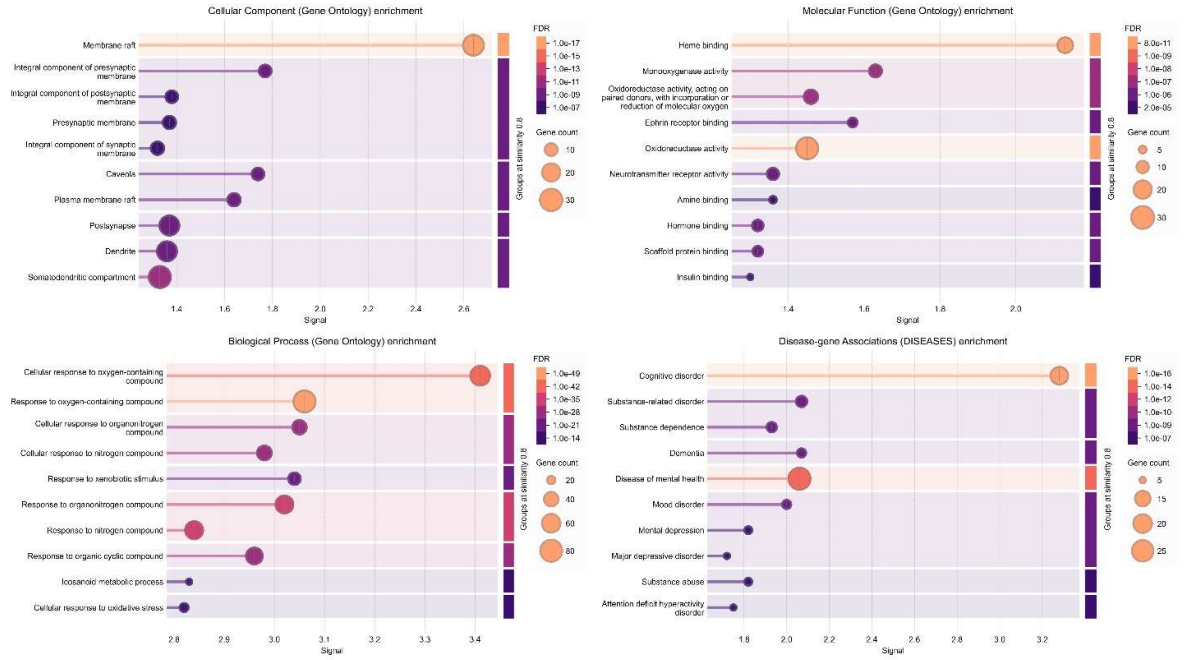

Fig. 4. Gene-Ontology enrichment analysis using STRING data base.

A total of 133 targets were mapped to 162 unique biological pathways. Upon expert analysis, 20 of these pathways were identified as directly associated with various forms of toxicity. Among the 133 targets, IGF1R and KDR showed the highest level of interaction with the phytocompounds (Fig. 5). IGF1R is involved in multiple signaling pathways, including PI3K-Akt, MAPK, FoxO, and mTOR, while KDR is primarily linked to the PI3K-Akt and MAPK pathways. Both genes are implicated in several toxicity types, including neurotoxicity, hepatotoxicity, dermal toxicity, nephrotoxicity, and cardiotoxicity.

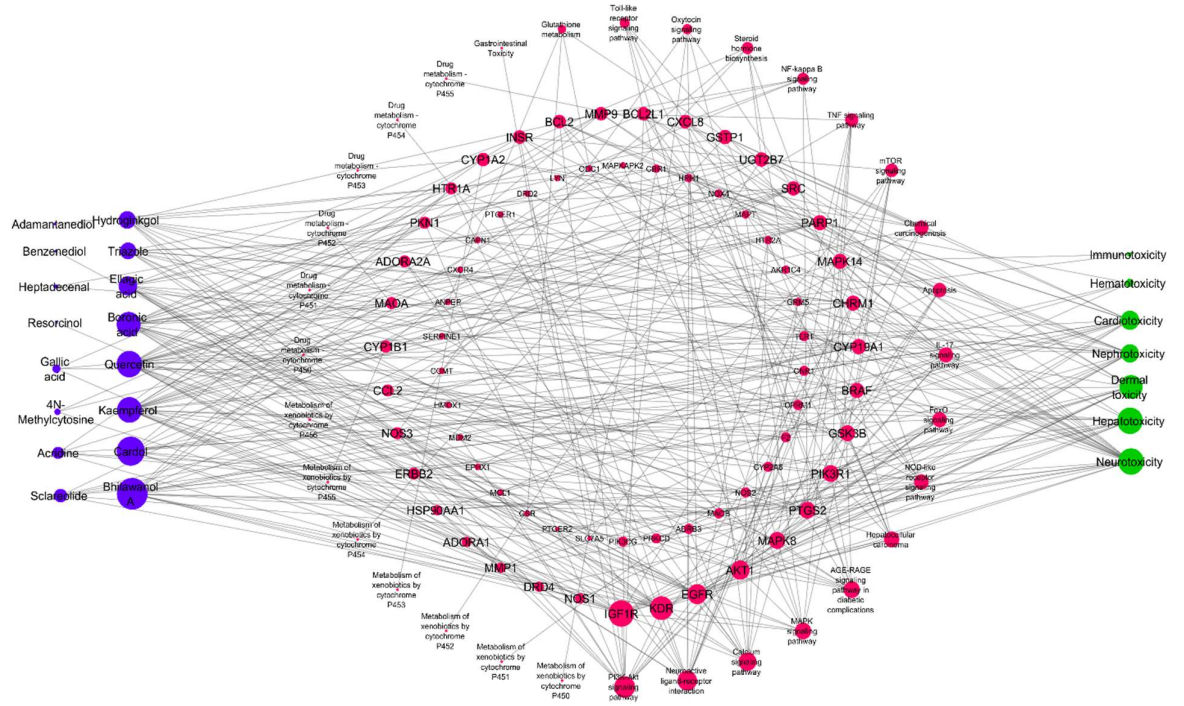

Fig. 5. Interaction of phytoconstituents of *S. anacardium* with their targets and regulated pathways.

Docking studies

The molecular docking analysis revealed that Bhilawanol A exhibited the strongest binding affinity (-7.5 kcal/mol) with IGF1R, forming a hydrogen bond with Arg1128 and total 13 number of interactions. Cardol formed hydrogen bonds with Asp1123 and formed 13 interactions. Kaempferol interacting Gly1125 and formed 6 interactions. Quercetin interacting through hydrogen bonds with Arg1128, and Asp1129 and formed 7 interactions. Overall, Bhilawanol A demonstrated the highest binding efficiency and interactions, indicating its potential as a strong inhibitor (Table 3 and Fig. 6).

Table 3. Docking results of the *S. anacardium* Phytoconstituents with IGF1R

Ligand Name	Score (kcal/mol)	HBI	NHBI	Total No. Interactions	Active sites
Bhilawanol A	-7.5	Arg1128	Met1112(4), Leu975, Ala1001(2), Met1049, Met1052, Met1126, Val1033(2)	13	13
Cardol	-7.3	Asp1123	Val1033(2), Ala1001(3), Met1112(2), Leu975, Met1049, Met1052, Met1126(2)	13	13
Kaempferol	-6.2	Gly1125	Leu1143, Tyr1135, Arg1104, Asp1105(2)	6	2
Quercetin	-5.7	Arg1128, Asp1129	Met1112(2), Leu975, Ala1001(2)	7	6

HBI: Hydrogen bond interaction, NHBI: Non-hydrogen bond interaction

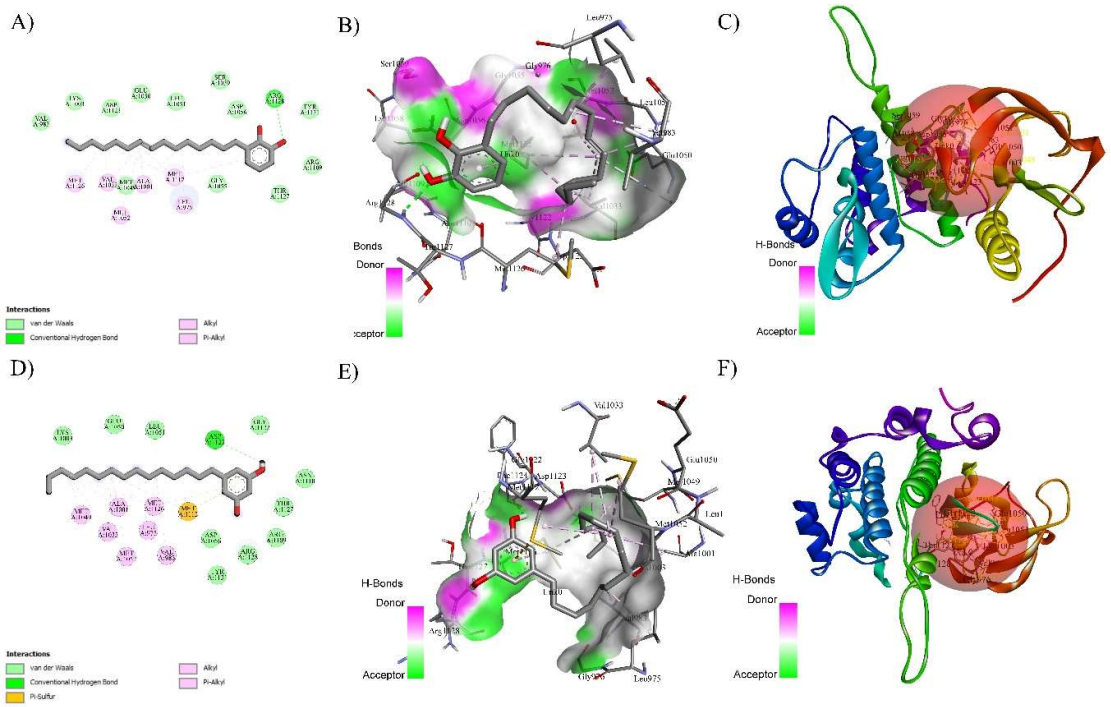

Fig. 6. Interaction of Bhilawanol A and Cardol with IGF1R. A,D) 2D representation of interaction of Bhilawanol A and Cardol. B,E) 3D representation of interaction of Bhilawanol A and Cardol with residues. C,F) 3D representation of interaction of Bhilawanol A and Cardol within binding pocket.

In the case of KDR, Bhilawanol A had the highest binding affinity (-7.3 kcal/mol) with 13 interactions, including hydrogen bonds with Leu840. Cardol interacted mainly with Arg842 and other non-hydrogen bonds as well, forming 10 interactions. Kaempferol formed interactions with Glu885. Quercetin formed interactions with Arg946, Thr940, Lys939, Thr1001, and Arg962. Overall, Bhilawanol A showed the strongest affinity, and the most interactions (Table 4 and Fig. 7).

Table 4. Docking results of the *S. anacardium* Phytoconstituents with KDR

Ligand_Name	Score	HBI	NHBI	Total No. Interaction	Active sites
Bhilawanol_A	-7.3	Leu840	Leu840(2), Phe1047(4), Arg1032, Leu1035(2),	13	13

			Ala866, Val848, Val916		
Cardol	-6.8	Arg842	Phe1047(4), Val848, Ala866, Leu1035, Leu840(2)	10	10
Kaempferol	-7.0	Glu885	Leu889(2), Ile888, Ala1050(2)	6	6
Quercetin	-6.5	Arg946, Thr940, Lys939, Thr1001, Arg962	Lys939, Glu1003(2), Arg962, Lys949	10	0

HBI: Hydrogen bond interaction, NHBI: Non-hydrogen bond interaction

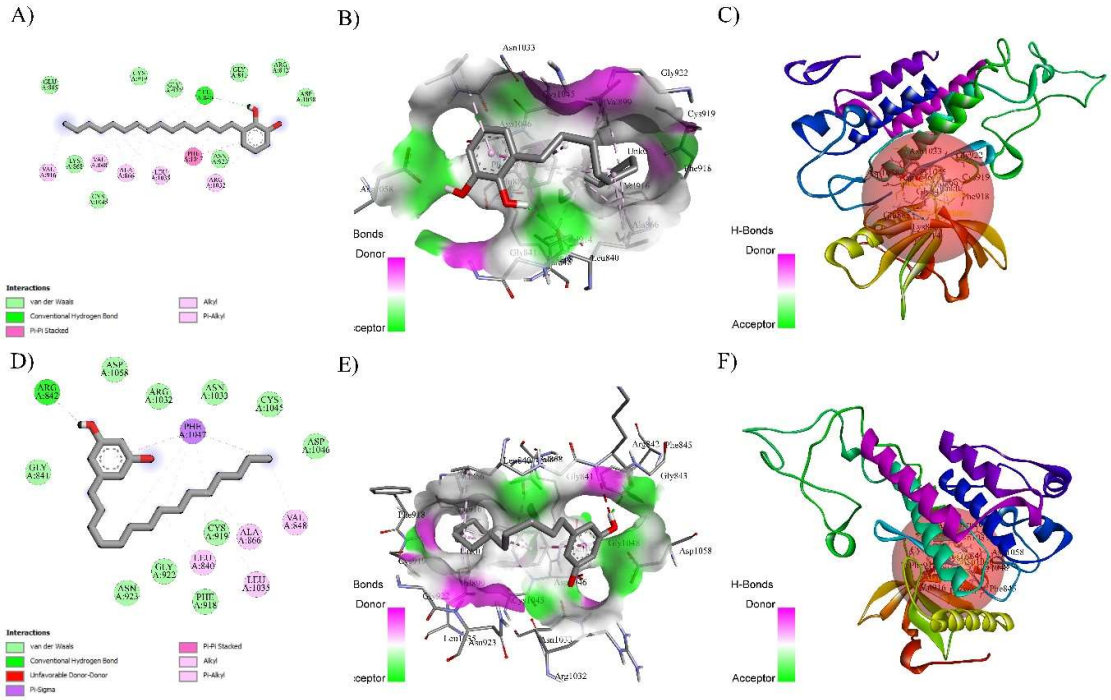

Fig. 7. Interaction of Bhilawanol A and Cardol with KDR. A,D) 2D representation of interaction of Bhilawanol A and Cardol. B,E) 3D representation of interaction of Bhilawanol A and Cardol with residues. C,F) 3D representation of interaction of Bhilawanol A and Cardol within binding pocket.

Molecular Dynamics

Molecular dynamics (MD) simulation of the Bhilawanol A–2P2I complex over 100 ns revealed a stable interaction profile, as shown in Fig. 8. The RMSD plot (Fig. 8A) indicated stable protein-ligand binding with fluctuations within acceptable ranges, while the ligand retained a consistent conformation in the binding pocket. Protein flexibility analysis (Fig. 8C) through RMSF showed minor fluctuations, mostly at loop regions, with key interacting residues maintaining stability. The interaction diagram (Fig. 8B) highlighted hydrogen bonds and hydrophobic contacts with residues such as Asp33 and Val36, supporting stable binding. Interaction frequency analysis (Fig. 8D) showed Bhilawanol A maintained frequent hydrogen bonds, hydrophobic interactions, and water bridges, reinforcing its strong affinity and stable association with 2P2I throughout the simulation.

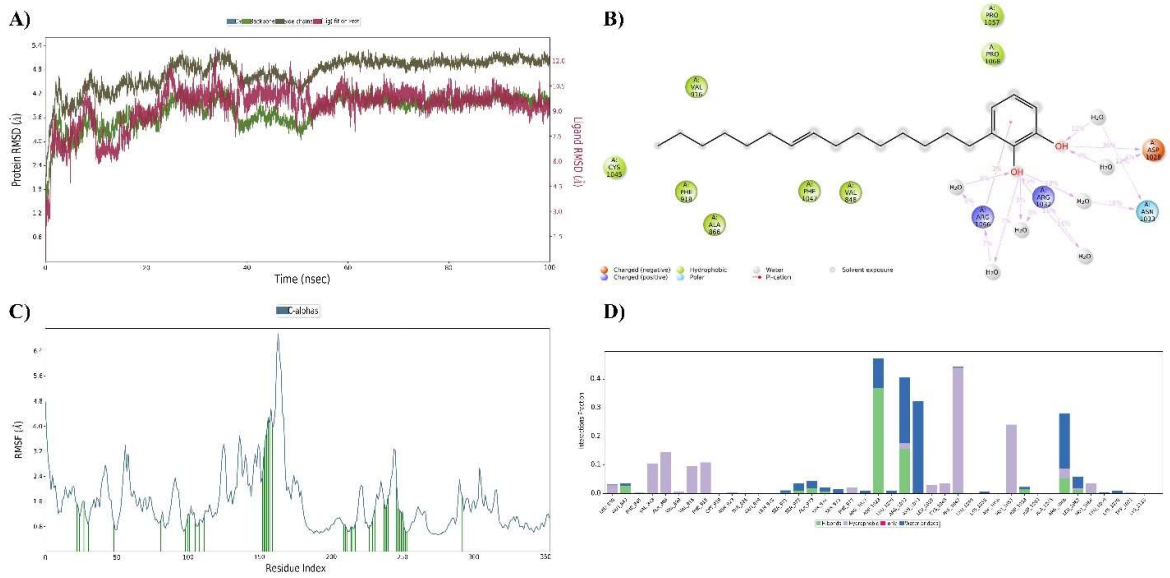

Fig. 8. Molecular dynamic simulation of Bhilawanol A – 2P2I complex at 100 ns. (A) Protein-Ligand RMSD, (B) Ligand-Protein contacts, (C) Protein RMSF (Green vertical lines-Ligand contacts), and (D) hydrogen, hydrophobic, ionic bonds, and water bridges.

Similarly, MD simulation of the Bhilawanol A–3I81 complex over 100 ns revealed stable binding interactions. As shown in Fig. 9A, RMSD plots for both protein backbone and ligand indicated minor fluctuations, confirming a stable binding conformation throughout the simulation. Fig. 9B highlights key interactions including hydrogen bonds, hydrophobic contacts, and water bridges between Bhilawanol A and residues such as PHE, VAL, ILE, SER, and ASN, supporting strong ligand affinity. RMSF analysis in Fig. 9C showed moderate flexibility in loop regions, while ligand-contacting residues remained stable. The interaction histogram in Fig. 9D further illustrates predominant hydrogen bonding and hydrophobic interactions, emphasizing the ligand's sustained and stable binding within the 3I81 active site.

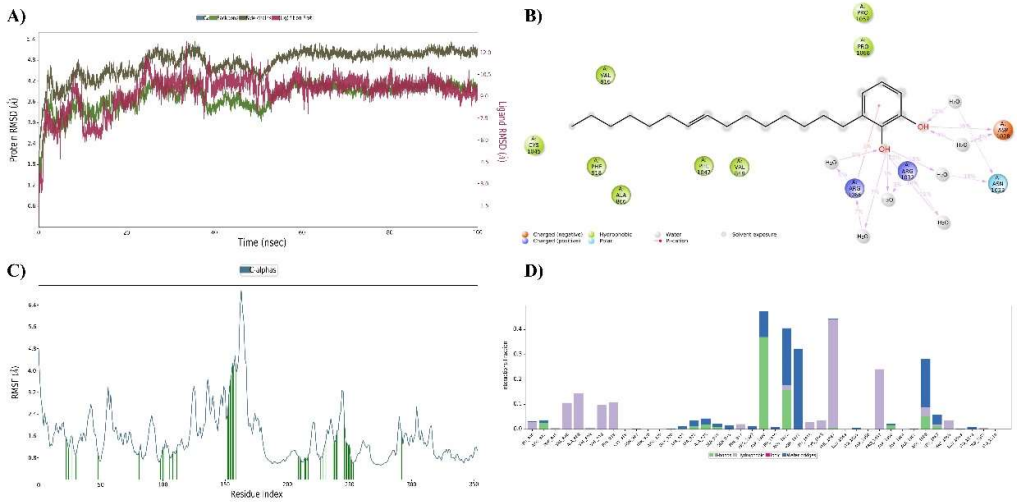

Fig. 9. Molecular dynamic simulation of Bhilawanol A – 3I81 complex at 100 ns. (A) Protein-Ligand RMSD, (B) Ligand-Protein contacts, (C) Protein RMSF (Green vertical lines-Ligand contacts), and (D) hydrogen, hydrophobic, ionic bonds, and water bridges.

Toxicity Prediction Using ProTox-3.0

The radar plot reveals that the molecule exhibits high predicted hepatotoxicity (89%) and notable neurotoxicity, along with moderate risks of nephrotoxicity, cardiotoxicity, and respiratory toxicity (Fig. 10). It also shows significant inhibition of several cytochrome P450 enzymes (CYP2E1, CYP3A4, CYP2D6), indicating a potential for drug-drug interactions. In contrast, it displays low probabilities for mutagenicity, cytotoxicity, immunotoxicity, and carcinogenicity, suggesting minimal genotoxic or carcinogenic risk. The molecule shows limited interaction with hormonal receptors (AR, ER,

AhR) and nuclear receptors (PXR, CAR), with negligible concern for BBB penetration or neuroreceptor disruptions. Overall, while the compound appears relatively safe in terms of genotoxic and endocrine effects, the high liver and CNS toxicity predictions, along with CYP inhibition, warrant further experimental validation.

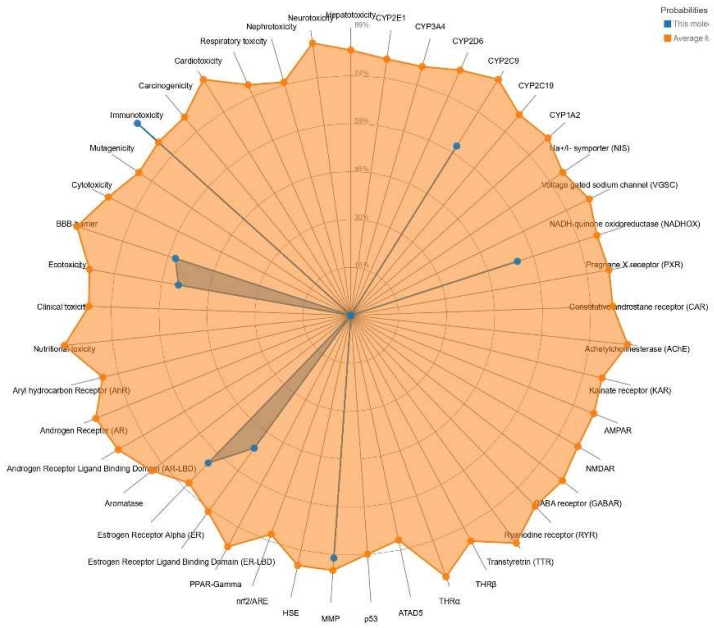

Fig. 10. Radar plot representing the *in-silico* toxicity prediction of the test compound using ProTox-3.0.

DISCUSSION

Our comprehensive analysis of *S. anacardium* phytoconstituents revealed critical insights into their toxicological profiles. The toxicity assessment of *S. anacardium* phytoconstituents, particularly bhilawanol A and cardol, reveals significant risks due to their irritant, pro-oxidant, and cytotoxic properties. Bhilawanol causes severe skin reactions, while cardol has been associated with cardiovascular toxicity. Network pharmacology and docking analyses identified IGF1R and KDR as key targets, with strong binding affinities suggesting modulation of toxicity-related pathways such as PI3K-Akt and MAPK. Molecular dynamics simulations confirmed stable interactions, indicating sustained receptor modulation that may disrupt cellular homeostasis. These findings align with literature on IGF1R/KDR-mediated toxicities, linking these interactions to neurotoxicity, hepatotoxicity, and cardiotoxicity through chronic pathway dysregulation.

The toxicity of *S. anacardium* phytoconstituents, particularly bhilawanol A and cardol, when the skin comes into contact with bhilawanol, it often results in severe irritation, burning, and the development of painful blackish blisters containing acrid serum, frequently accompanied by intense itching and eczematous eruptions. In some cases, these skin lesions can progress to suppurative lymphadenitis, requiring surgical intervention (Patel, D., et al., 2020; Illanchezhian, R., et al., 2012). Toxicity from excessive cardol intake can lead to serious cardiovascular complications. The primary manifestations of Cardol toxicity include dizziness, light-headedness, fainting, and significant disturbances in heart rhythm, such as a very slow heart rate (bradycardia) or a fast and irregular heart rate (arrhythmia) (Anastasiou-Nana, M. I., et al., 1987).

Previous studies support LD_{50} and BBB predictions, showing quercetin's cytotoxicity and limited CNS access, while ellagic acid shows moderate risk (Barreca, D., et al., 2016; Khan, N., et al., 2013). Kaempferol is safer with low toxicity (Calderón-Montaño, J. M., et al., 2011). Acridine derivatives cross the BBB effectively, and *S. anacardium* constituents like bhilawanol show moderate BBB permeability, aligning with their potential neuroactive effects (Belmont, P., et al., 2007; Seeram, N. P., et al., 2008). As per GO, enrichment of synaptic and oxidoreductase-related genes supports prior findings linking CNS signaling, oxidative stress, and neuropsychiatric disorders, underscoring their therapeutic relevance in cognitive and mood pathologies (Usmani Rana, H. M., et al., 2024).

The network pharmacology analysis highlights IGF1R and KDR as key targets, interacting with multiple phytocompounds and central to toxicity-related pathways such as PI3K-Akt and MAPK. Previous studies confirm that dysregulation of IGF1R and KDR contributes to neurotoxicity, hepatotoxicity, nephrotoxicity, and cardiotoxicity through their roles in cell survival, angiogenesis, and stress response signaling (Riedemann, J., and Macaulay, V. M., 2006; Shibuya, M., 2003).

Recent studies show that bhilawanol can reduce cell toxicity and oxidative stress in neuronal models, higher

concentrations or chronic exposure to phenolic lipids like bhilawanol and cardol have been reported to induce cytotoxicity, inflammation, and allergic reactions, consistent with their irritant and pro-oxidant properties (Al Mughairbi, F., et al., 2021). Therefore, their interaction with IGF1R and KDR may exacerbate toxicity by amplifying downstream signaling related to cell survival and stress responses, potentially leading to organ damage, as documented in previous reports on IGF1R/KDR-mediated toxicities (Wang, Q., et al., 2020; Elmadani, M., et al., 2019; Werner, H., 2023).

The docking results showing that bhilawanol and cardol have the best binding energies with IGF1R and KDR strongly support their potential to induce toxicity through these targets. Previous literature demonstrates that compounds with high binding affinity to receptor tyrosine kinases like IGF1R and VEGFR2 (KDR) can significantly modulate downstream signaling pathways, leading to biological effects including toxicity[44-46]. For example, molecular docking studies have established that strong binding to VEGFR2 correlates with potent biological activity and, in some cases, adverse effects due to pathway modulation 46. Similarly, high-affinity binding to IGF1R has been shown to disrupt normal cellular signaling, contributing to toxicities such as neurotoxicity, hepatotoxicity, and cardiotoxicity through the PI3K-Akt and MAPK pathways (Fan, C., et al., 2012; Verma, J., and Vashisth, H., 2024). These findings correlate with the observed docking results for bhilawanol and cardol, suggesting that their strong interactions with IGF1R and KDR are mechanistically linked to their reported toxicological profiles in previous experimental and clinical studies (Fan, C., et al., 2012; Verma, J., and Vashisth, H., 2024; Paramashivam, S. K., et al., 2015).

The stable binding interactions observed between Bhilawanol A and the 2P2I and 3I81 targets, as demonstrated by molecular dynamics simulations, suggest a promising modulatory effect on IGF1R-related pathways. Insulin-like growth factor 1 receptor (IGF1R) signaling is well-documented in mediating diverse toxicological effects, including neurotoxicity (Bassil, F., et al., 2014), hepatotoxicity (Gui, R., et al., 2023), dermal toxicity (Sadagurski, M., et al., 2006), nephrotoxicity (Yang, Q., et al., 2021), and cardiotoxicity (Lee, W. S., and Kim, J., 2018). Prior studies have shown that aberrant IGF1R activation or inhibition can contribute to neuronal damage by influencing apoptotic pathways, exacerbate liver injury through altered cellular proliferation and fibrosis, and promote skin inflammation and damage by modulating keratinocyte responses. Additionally, IGF1R dysregulation impacts renal tubular cell survival and cardiac myocyte function, leading to nephrotoxic and cardiotoxic outcomes respectively. The observed stable interactions of Bhilawanol A with IGF1R structural domains may thus underlie its potential protective effects by modulating receptor activity, offering a mechanistic basis for mitigating IGF1R-associated toxicities. Further in vitro and in vivo studies are warranted to confirm these protective roles and elucidate downstream signaling impacts.

The toxicity radar analysis indicates that the compound poses significant hepatotoxic and neurotoxic risks, alongside moderate cardiotoxicity and nephrotoxicity. Its strong inhibition of key CYP enzymes suggests a potential for drug-drug interactions. Despite low genotoxic and endocrine disruption potential, the predicted toxicities necessitate further in vitro and in vivo validation.

CONCLUSION

In conclusion, this study provides a detailed toxicological assessment of select *S. anacardium* phytoconstituents, with bhilawanol A emerging as a key toxic agent. Integrating network pharmacology, molecular docking, and molecular dynamics simulations, we elucidated potential mechanisms through which bhilawanol A may exert toxicity—primarily via high-affinity interactions with IGF1R and KDR. These interactions appear to disrupt critical signaling pathways, including PI3K-Akt, MAPK, FoxO, and mTOR signalling pathways, thereby contributing to a spectrum of toxic effects such as neurotoxicity, hepatotoxicity, nephrotoxicity, dermal toxicity, and cardiotoxicity. Our findings align with existing literature and underscore the necessity for comprehensive toxicological evaluations when considering these compounds for therapeutic use. Further *in vivo* validation and mechanistic studies are essential to confirm these computational predictions and develop strategies to mitigate associated risks, thereby ensuring safer application in pharmacological contexts.

STATEMENT OF USAGE OF ARTIFICIAL INTELLIGENCE

The author declares that no help was received from artificial intelligence.

DATA AVAILABILITY

The data that support the findings of this study are available upon reasonable request.

AUTHOR CONTRIBUTIONS

VPJ: Investigation, formal analysis, data curation, writing-original draft. **MBP&BSU:** Conceptualization, data curation, methodology, resources, supervision, writing-review and editing. **SPM&AS:** Investigation, methodology, formal analysis, writing-original draft. **VSP, JD, AVD& SP:** Investigation, methodology, formal analysis, manuscript review and editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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