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In Silico Analysis of Centella asiatica Phytochemicals Targeting the KEAP1–NRF2 Pathway as Potential Radioprotective Agents

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Abstract

Ionising radiation induces excessive oxidative stress and cellular damage, necessitating the discovery of effective radioprotective agents. The KEAP1–NRF2 pathway plays a central role in antioxidant defence, making KEAP1 inhibition a promising strategy for enhancing NRF2 activation. Centella asiatica contains diverse bioactive compounds with reported antioxidant and cytoprotective properties; yet their potential as direct KEAP1 inhibitors remains underexplored. This study aimed to evaluate the molecular interactions of Centella asiatica phytochemicals with KEAP1 using in silico approaches, in order to identify potential natural radioprotective candidates. Thirty-six bioactive compounds from Centella asiatica were subjected to molecular docking against the KEAP1 Kelch domain (PDB ID: 4L7B) using AutoDockTools 1.5.7. Ligand–protein interactions were visualised using LigPlot+ and PyMOL. Pharmacokinetic and toxicity profiles were predicted using DeepPK and admetSAR, including assessments of drug-likeness, intestinal absorption, CYP inhibition, and toxicity endpoints. Three compounds demonstrated strong binding affinities below –8 kcal/mol: acetylursolic acid (–8.88 kcal/mol), campesterol (–8.55 kcal/mol), and ursolic acid (–8.15 kcal/mol). All three interacted with the key KEAP1 residue Arg415, with additional interactions involving Ser363 (acetylursolic acid and ursolic acid) and Ser508 (campesterol). ADME–Tox analysis indicated favourable pharmacokinetic profiles, good intestinal absorption, non-mutagenic and non-carcinogenic predictions, and overall compliance with Lipinski's Rule of Five, notwithstanding a single LogP violation. Acetylursolic acid, campesterol, and ursolic acid exhibit strong binding to critical KEAP1 residues and demonstrate favourable pharmacokinetic and safety profiles, suggesting their potential as natural radioprotective agents through modulation of the KEAP1–NRF2 pathway. Further in vitro and in vivo studies are warranted to validate their radioprotective efficacy.

INTRODUCTION

Here is the proofread passage with corrections applied and technical terms italicised where appropriate, with paragraph form retained:

Ionising radiation is a form of high-energy radiation capable of removing electrons from atoms or molecules, leading to ion formation. Its sources include natural emitters such as cosmic rays and radon, as well as artificial sources such as X-rays, gamma rays, and radioactive particles (Abu Bakar et al., 2019; International Atomic Energy Agency, 2010). Ionising radiation provides wide-ranging benefits across medicine, industry, agriculture, and scientific research (Zakariya & Kahn, 2014). However, despite its utility, exposure to ionising radiation — whether at high doses or over prolonged periods — can exert detrimental effects on

biological tissues. The ionisation of biomolecules results in the excessive production of reactive oxygen species (ROS), which subsequently induces oxidative stress, DNA damage, mutations, impaired cell proliferation, and apoptosis (Donya et al., 2014; Jain, 2021; Yang et al., 2022).

Developing effective strategies to protect against the harmful biological effects of ionising radiation is therefore essential, particularly for individuals routinely exposed to radiation, such as radiotherapy patients, healthcare workers, nuclear industry personnel, and populations living in high-radiation environments. One promising approach is the use of radioprotective agents — substances capable of reducing radiation-induced tissue injury resulting from intended or unintended exposure (Mishra & Alsbeih, 2017).

The KEAP1/NRF2 signalling pathway is a critical cellular defence mechanism against oxidative stress. NRF2 (nuclear factor erythroid 2-related factor 2) is a master transcription factor that regulates the expression of detoxification and antioxidant enzymes. Under basal physiological conditions, NRF2 is sequestered in the cytoplasm through its binding to KEAP1 (Kelch-like ECH-associated protein 1), which functions as an adaptor for the E3 ubiquitin ligase complex, targeting NRF2 for ubiquitination and proteasomal degradation (Lee & Hu, 2020).

During oxidative stress or exposure to electrophilic agents, conformational changes occur in KEAP1 due to modifications at its critical cysteine residues. These alterations disrupt NRF2 ubiquitination, allowing NRF2 to dissociate from KEAP1 and translocate into the nucleus (Abed et al., 2015). In the nucleus, NRF2 binds to antioxidant response elements (AREs) within target gene promoters, activating the transcription of cytoprotective genes. These genes encode various antioxidant and phase II detoxifying enzymes, including heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and glutamate-cysteine ligase catalytic subunit (GCLC) (Johnson & Johnson, 2015; Tonelli et al., 2018; Zhang et al., 2021). Given its central role in maintaining redox homeostasis, modulation of the KEAP1–NRF2 axis has become a strategic target in radioprotective agent development.

Two main mechanisms underlie the inhibition of KEAP1–NRF2 binding: indirect and direct inhibition. Indirect inhibition typically involves electrophilic compounds — or compounds metabolised into electrophiles — that react with cysteine residues on KEAP1 through oxidation or alkylation. This mechanism mirrors natural NRF2 activation under oxidative stress but may be characterised by low specificity and off-target effects. In contrast, direct inhibition occurs when compounds interact with the KEAP1 binding domain, competitively preventing KEAP1–NRF2 complex formation. Direct inhibitors occupy the same or adjacent binding sites as NRF2 on KEAP1, offering greater selectivity and potentially fewer adverse effects.

Centella asiatica is a medicinal plant traditionally used in Chinese and Indian herbal medicine systems (Kwak et al., 2021). Extensive in vitro and in vivo studies have demonstrated its pharmacological activities, including neuroprotective, memory-enhancing, antioxidant, anti-inflammatory, anticancer, cardioprotective, and wound-healing effects (Bansal et al., 2024). These activities are associated with its diverse bioactive constituents, including triterpenoids, carotenoids, glycosides, flavonoids, alkaloids, essential oils, and essential fatty acids (Wiciński et al., 2024).

Park et al. (2021) reported that administration of a 50% ethanol extract of Centella asiatica at 200 mg/kg significantly increased NRF2 and HO-1 protein expression in a mouse model of age-related macular degeneration (Park et al., 2021). Similarly, Matthews et al. (2019) demonstrated that oral administration of an aqueous Centella asiatica extract (1,000 mg/kg/day) significantly upregulated NRF2 mRNA and its downstream target genes — including HO-1, NQO1, and GCLC — in the hippocampus of an Alzheimer's disease mouse model (Matthews et al., 2019).

However, the precise mechanism by which Centella asiatica activates the KEAP1–NRF2 pathway remains unclear. One plausible mechanism is direct inhibition of the KEAP1–NRF2 interaction. Computational approaches such as molecular docking provide an efficient method for predicting which phytochemicals from Centella asiatica may bind strongly to KEAP1 and act as direct inhibitors, potentially contributing to NRF2 activation and radioprotective effects. This study aims to evaluate the interaction potential of Centella asiatica bioactive compounds with KEAP1 using molecular docking as an initial step in exploring this medicinal plant as a natural radioprotective agent. The theoretical benefits of this study include enriching the scientific literature on natural radioprotective agents — particularly through the in silico exploration of the KEAP1–NRF2 pathway — and offering a computational screening approach that can accelerate the discovery of bioactive compounds from Centella asiatica. The practical benefits include providing preliminary data and recommendations for further in vitro and in vivo validation studies, as well as contributing to the development of plant-based radioprotective formulations that could serve as safer and more accessible alternatives for reducing radiation-induced oxidative stress in clinical and occupational settings.

RESEARCH METHOD

This in silico study was conducted to evaluate the potential of Centella asiatica bioactive compounds in activating the KEAP1–NRF2 pathway, a key mechanism in cellular defense against oxidative stress induced by ionizing radiation. The workflow included ligand and protein preparation, molecular docking, interaction visualization, and ADME-toxicity prediction using various bioinformatics tools and databases.

1. Ligand and Protein Preparation and Molecular Docking

A total of 36 Centella asiatica compounds were selected based on published literature and the PubChem database (Budiman et al., 2025; Chonsut et al., 2024; Lili et al., 2020). These compounds included acetylursolic acid (CID: 6475119), campesterol (CID: 173183), ursolic acid (CID: 64945), pomolic acid (CID: 382831), centellasapogenol A (CID: 73196815), 3-epimaslinic acid (CID: 25564831), asiatic acid (CID: 119034), madasiatic acid (CID: 23132225), 2-alpha-hydroxyursolic acid (CID: 6918774), astragalin (CID: 5282102), β-caryophyllene (CID: 5281515), quercetin (CID: 5280343), kaempferol (CID: 5280863), centellasaponin B (CID: 85411973), isothankunic acid (CID: 12302703), α-caryophyllene (CID: 5281520), madecassic acid (CID: 73412), neochlorogenic acid (CID: 5280633), labiatenic acid (CID: 5281792), isoquercetin (CID: 5280804), myricetin (CID: 5281672), chlorogenic acid (CID: 1794427), centellin (CID: 163184102), 1-cyclohexyl-11-heneicosanone (CID: 129882177), catechin (CID: 9064), rutin (CID: 5280805), epicatechin (CID: 72276), centellasaponin C (CID: 85348461), asiaticoside E (CID: 102212085), centellasaponin D (CID: 101103168), asiaticoside C (CID: 101103169), asiaticoside (CID:

11954171), centellicin (CID: 163183805), asiaticoside D (CID: 102212084), asiaticoside B (CID: 91618002), and madecassoside (CID: 24825675).

Structures were downloaded from PubChem in .sdf format, converted and optimized to 3D structures using MarvinSketch v25.1.3, and saved as .pdb files.

The target protein KEAP1 (PDB ID: 4L7B) was retrieved from the Protein Data Bank. Protein preparation was performed using AutoDockTools v1.5.7 by removing water molecules and native ligands, adding polar hydrogens, and assigning Gasteiger charges. The prepared protein was saved in .pdbqt format. Grid box size validation was performed with three configurations: 40 × 40 × 40, 50 × 50 × 50, and 60 × 60 × 60. Docking was conducted using the Lamarckian Genetic Algorithm (LGA) integrated in AutoDockTools v1.5.7. Each compound was docked individually to KEAP1 to evaluate its potential binding affinity.

2. Ligand–Protein Interaction Visualization

Docking results were analyzed based on binding affinity values (kcal/mol). Ligand–protein interactions, particularly hydrogen bonds and hydrophobic contacts within the active site, were visualized using LigPlot+ v2.2.4 for 2D diagrams and PyMOL for 3D structural visualization. These analyses were used to identify compounds with biologically relevant interactions with KEAP1.

3. ADME–Toxicity Predictions

Compounds with the most favorable binding affinities were further evaluated for pharmacokinetic and toxicity profiles using DeepPK (https://biosig.lab.uq.edu.au/deeppk/) and admetSAR (http://lmmd.ecust.edu.cn/admetsar1/predict/). The evaluated parameters included P-gp substrate probability, human intestinal absorption (HIA), inhibition of cytochrome P450 enzymes (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4), AMES toxicity, carcinogenic potential, and acute oral toxicity (AOT). These data were then used to select the most suitable candidates for future experimental studies.

RESULTS AND DISCUSSION

Validation of Docking Procedure

The KEAP1 protein used in this study (PDB ID: 4L7B) is co-crystallized with (S,R,S)-1a, a cysteine-independent NRF2 activator known to function as a direct inhibitor of KEAP1–NRF2 complex formation (Jnoff et al., 2014). (S,R,S)-1a was used as the reference ligand for redocking to validate the docking protocol for Centella asiatica compounds. The primary validation parameter was the root mean square deviation (RMSD), with RMSD $\leq$ 2 Å considered acceptable, indicating successful reproduction of the native ligand pose (Muttaqin, 2019). Docking results were assessed based on binding free energy values, which reflect the strength and stability of ligand–protein interactions; lower energy values indicate more stable interactions (Meiyanto, 2012).

Binding Energy Analysis

Docking of the 36 Centella asiatica compounds produced binding free energy values ranging from –2.92 to –8.88 kcal/mol (Table 1). Three compounds exhibited binding energies lower than –8 kcal/mol: acetylursolic acid (–8.88 kcal/mol), campesterol (–8.55 kcal/mol), and ursolic acid (–8.15 kcal/mol). Acetylursolic acid and ursolic acid belong to the triterpenoid class, while campesterol is a phytosterol.

Tabel 1. Docking 36 compunds from Centella asiatica with KEAP1

No.	Compounds	Binding Energy (kcal / mol)	No.	Compounds	Binding Energy (kcal / mol)
1	**Native Ligand**	**-8.68**	20	Labiatenic Acid	-5,98
2	**Acetylursolic Acid**	**-8,88**	21	Isoquercetin	-5,94
3	**Campesterol**	**-8,55**	22	Myricetin	-5,91
4	**Ursolic Acid**	**-8,15**	23	Chlorogenic Acid	-5,56
5	Pomolic acid	-7,42	24	Centellin	-5,54
6	Centellasapogenol A	-7,15	25	1-Cyclohexyl-11-heneicosanone	-5,43
7	3-Epimaslinic acid	-7,08	26	Catechin	-5,36
8	asiatic acid	-7,03	27	Rutin	-5,12
9	madasiatic acid	-6,95	28	Epicatechin	-5,02
10	2-alpha-Hydroxyursolic acid	-6,85	29	Centellasaponin C	-4,88
11	Astragalin	-6,79	30	Asiaticoside E	-4,58
12	Beta-Caryophyllene	-6,73	31	Centellasaponin D	-4,57
13	Quercetin	-6,68	32	Asiaticoside C	-4,44
14	Kaempferol	-6,64	33	Asiaticoside	-4,08
15	Centellasaponin B	-6,62	34	Centellicin	-3,72
16	Isothankunic acid	-6,28	35	Asiaticoside D	-3,52
17	alpha-Caryophyllene	-6,25	36	Asiaticoside B	-3,08
18	Madecassic acid	-6,17	37	Madecassoside	-2,92
19	Neochlorogenic acid	-6,04			

Source: Molecular docking results using AutoDockTools 1.5.7, processed by the author, 2025

Notably, acetylursolic acid displayed a lower binding energy than the native ligand (S,R,S)-1a (–8.68 kcal/mol), suggesting that it may form a more stable interaction with KEAP1 and could serve as a potent KEAP1 inhibitor. These top-scoring compounds were selected for further analysis, including identification of amino acid interactions, drug-likeness evaluation based on Lipinski's Rule of Five, and ADMET profiling.

Visualization and Analysis of Amino Acid Interactions

In addition to evaluating binding energy, analyzing interactions with amino acid residues is essential for identifying specific binding positions that contribute to the stabilization of the ligand–protein complex. The interaction between a ligand and a protein is influenced by the functional groups present on the ligand as well as the chemical characteristics of the amino acid residues within the protein. These features synergistically give rise to various types of non-covalent forces, including hydrogen bonds (donor and acceptor), electrostatic interactions, van der Waals forces, and hydrophobic interactions (Candraningrum et al., 2023). Using LigPlot+, hydrophobic interactions and hydrogen bonds formed between the three top-binding compounds and the amino acid residues of KEAP1 were visualized. These results are summarized in Table 2.

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analysis, including identification of amino acid interactions, drug-likeness evaluation based on Lipinski's Rule of Five, and ADMET profiling.

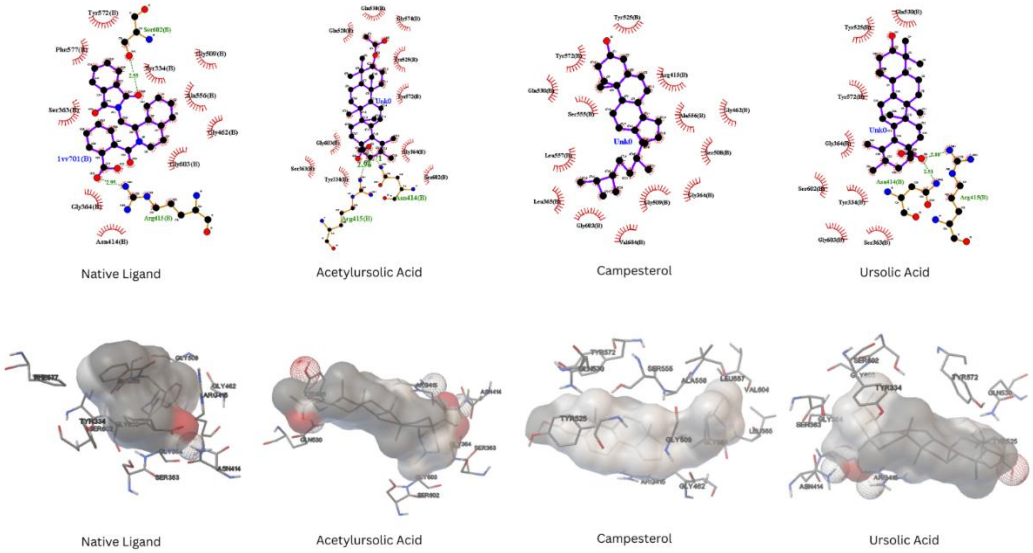

Figure 1. Specific interactions of selected ligands with amino acid residues of the KEAP1 protein.
Source: 3D visualization using PyMOL, processed by the author, 2025

Based on the interaction analysis, the three test compounds and the native ligand were found to bind to residues Tyr572, Gly364, and Arg415. At residue Arg415, the native ligand, acetylursolic acid, and ursolic acid formed hydrogen bonds with distances of 2.95 Å, 2.96 Å, and 2.88 Å, respectively, whereas campesterol interacted through hydrophobic contact. In addition, acetylursolic acid and ursolic acid formed additional hydrogen bonds with Asn414.

The similarity in amino acid residue interactions between the test ligands and the native ligand is an important factor in evaluating the validity of the docking procedure for identifying potential ligand candidates. Such similarity indicates that the test ligands may bind to the same active site as the native ligand, thereby potentially exhibiting similar biological activity (Amrulloh et al., 2023).

Table 2. Specific ligand–amino acid residue interactions.

Residu	Native IVV (Kontrol Pos.)	Acetylursolic Acid	Campesterol	Ursolic Acid
Tyr572	✓	✓	✓	✓
Phe577	✓	-	-	-
Ser602	2,55	✓	-	✓
Tyr334	✓	✓	-	✓
Gly509	✓	-	✓	-
Ala556	✓	-	✓	-
Ser363	✓	✓	-	✓
Gly462	✓	-	✓	-
Gly603	✓	✓	✓	✓
Gly364	✓	✓	✓	✓

Residu	Native IVV (Kontrol Pos.)	Acetylursolic Acid	Campesterol	Ursolic Acid
Arg415	2,95	2,96	✓	2,88
Asn414	✓	2,71	-	2,91
Gln530	-	✓	✓	✓
Gly574	-	✓	-	-
Gln528	-	✓	-	-
Tyr525	-	✓	✓	✓
Ser555	-	-	✓	-
Ser508	-	-	✓	-
Leu557	-	-	✓	-
Leu365	-	-	✓	-
Val604	-	-	✓	-

Source: Ligand–protein interaction analysis using LigPlot+ v2.2.4, processed by the author, 2025

Note: ✓ hydrophobic interaction; - no interaction

The total number of interactions formed was 12 for acetylursolic acid, 14 for ursolic acid, and 10 for campesterol. Acetylursolic acid and ursolic acid interacted with eight residues identical to those of the native ligand, whereas campesterol shared seven residues.

Previous studies have reported six key residues within the KEAP1 Kelch domain that interact with the Neh2 domain of NRF2, namely Ser363, Asn382, Arg380, Arg415, Arg438, and Ser508. Docking results showed that acetylursolic acid and ursolic acid interacted with Arg415 and Ser363, whereas campesterol interacted with Arg415 and Ser508. The involvement of these critical residues suggests that all three tested compounds may partially occupy the Neh2 binding site on KEAP1 and play a role in modulating NRF2 activation.

ADME–Tox Analysis

The discovery of new compounds with drug development potential often encounters challenges related to efficacy and safety (Guan et al., 2019). To assess these aspects, drug-likeness evaluation based on Lipinski's Rule of Five and ADME–Tox (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction was performed using web-based tools such as Deep-PK and admetSAR.

Table 3. ADME–TOX profile of selected ligands.

Ligands			Acetylursolic Acid	Campesterol	Ursolic Acid
Drug-likeness	MW		498.74	400.68	456.70
	HBD		1	1	2
	HBA		4	1	3
	LogP		7.66	7.635	7.09
Farmakokinetik	Pgp-Substrate		-	-	-
	HIA		Absorbed	Absorbed	Absorbed
	CYP Inhibitor	CYP1A2	-	-	-
		CYP2C19	-	-	-
		CYP2C9	-	-	-
		CYP2D6	-	-	-
		CYP3A4	-	-	-
Toksisitas	AMES		-	-	-
	Carcinogenesis		-	-	-
	AOT		III	I	III

Source: ADME–Tox predictions using DeepPK and admetSAR, processed by the author, 2025

Lipinski's Rule of Five is a commonly used guideline for evaluating whether a compound with pharmacological activity is likely to be well absorbed when administered orally. A compound is predicted to have poor oral absorption if it violates two or more of the following criteria: (1) more than 5 hydrogen bond donors, (2) more than 10 hydrogen bond acceptors, (3) a molecular weight greater than 500 Da, and (4) a LogP value greater than 5 (Roskoski, 2019). Among the three compounds with the highest docking scores, drug-likeness evaluation based on Lipinski's Rule of Five showed that all compounds possessed fewer than five hydrogen bond donors, fewer than ten hydrogen bond acceptors, and molecular weights below 500 Da. However, all of them exhibited LogP values greater than 5. A high LogP indicates increased hydrophobicity, meaning the compound is more soluble in lipids (Atangcho et al., 2019). Elevated LogP values may present challenges such as low aqueous solubility or pronounced first-pass metabolism, which can complicate drug delivery. Nevertheless, since each of the three compounds violates only one Lipinski criterion, they are still predicted to have favorable absorption properties.

Regarding pharmacokinetic and toxicity predictions, all three ligands were predicted to be non-substrates of P-glycoprotein (P-gp), a transporter protein responsible for expelling drugs from cells, indicating they are unlikely to experience efflux limitations that could reduce bioavailability (Finch & Pillans, 2014). They were also predicted to exhibit good Human Intestinal Absorption (HIA), suggesting efficient uptake across the intestinal wall. Additionally, all compounds were predicted not to inhibit cytochrome P450 (CYP) enzymes—key enzymes in hepatic drug metabolism—indicating a low likelihood of interfering with the metabolism of other drugs and therefore a reduced risk of drug–drug interactions (DDIs) (Deodhar et al., 2020).

In the toxicity category, prediction results indicated that all tested compounds were non-mutagenic in the AMES test, which is used as an indicator of mutagenic potential. Furthermore, the compounds were predicted to be non-carcinogenic, indicating relatively low risks of genotoxicity and cancer. Based on Acute Oral Toxicity (AOT) classification, acetylursolic acid and ursolic acid fell into Class III, which according to the U.S. Environmental Protection Agency (EPA) corresponds to LD_{50} values between 500–5000 mg/kg and is categorized as "slightly toxic." In contrast, campesterol was classified as Class I, with $LD_{50} < 50$ mg/kg, and is categorized as "highly toxic." (Bishop et al., 2024; Gadaleta et al., 2019)

Integrated Analysis

This in silico study demonstrated that several bioactive compounds from Centella asiatica, particularly acetylursolic acid, ursolic acid, and campesterol, exhibit strong binding affinities toward the KEAP1 Kelch domain, suggesting their potential role as direct inhibitors of the KEAP1–NRF2 interaction. Among these, acetylursolic acid and ursolic acid showed binding energies lower than that of the native ligand (S,R,S)-1a, indicating that these compounds may form highly stable ligand–protein complexes. Their interactions with key residues such as Arg415, Ser363, and Ser508—previously identified as critical for binding the Neh2 domain of NRF2—further support their ability to occupy essential pockets within the KEAP1 binding site.

The similarity in amino acid interaction patterns between the test ligands and the native ligand strengthens the reliability of the docking approach and suggests that acetylursolic acid and ursolic acid may mimic the mechanism of established KEAP1 inhibitors. By potentially

disrupting KEAP1–NRF2 complex formation, these compounds could facilitate NRF2 nuclear translocation and subsequent activation of cytoprotective genes involved in antioxidant defense, which is particularly valuable in counteracting oxidative damage induced by ionizing radiation.

ADME–Tox predictions further support the suitability of acetylursolic acid and ursolic acid as candidate radioprotective agents. Both compounds met most of Lipinski's Rule of Five criteria, indicating favorable oral absorption, and did not exhibit predicted mutagenic or carcinogenic properties. Although high LogP values may present solubility challenges, this limitation could be addressed through formulation strategies such as nanoencapsulation or complexation. Campesterol, despite showing good binding affinity, displayed higher predicted toxicity, making it a less favorable candidate for further development.

Overall, the findings suggest that acetylursolic acid and ursolic acid warrant further investigation through molecular dynamics simulations, in vitro assays, and in vivo radioprotection models. These steps are necessary to validate their potential as natural KEAP1 inhibitors and to advance Centella asiatica–derived compounds as promising radioprotective agents.

CONCLUSION

Molecular docking results identified three Centella asiatica compounds with binding free energies below –8 kcal/mol—acetylursolic acid (–8.88 kcal/mol), campesterol (–8.55 kcal/mol), and ursolic acid (–8.15 kcal/mol). All three interacted with the key KEAP1 residue Arg415, with additional interactions involving Ser363 for acetylursolic acid and ursolic acid, and Ser508 for campesterol. ADME–Tox analysis indicated that these compounds possess favorable pharmacokinetic profiles, exhibit good intestinal absorption, are non-toxic, and meet drug-likeness criteria despite violating one Lipinski parameter. Therefore, acetylursolic acid, campesterol, and ursolic acid demonstrate potential as natural radioprotective agents through modulation of the KEAP1–NRF2 pathway.

Based on these findings, it is recommended that acetylursolic acid and ursolic acid, which showed the strongest binding affinities and favorable safety profiles, be further evaluated through molecular dynamics simulations to assess complex stability under physiological conditions. Subsequent in vitro assays using cell-based models of oxidative stress and in vivo radioprotection studies in animal models are necessary to validate their efficacy and safety. For campesterol, despite its good binding affinity, its predicted high acute oral toxicity warrants caution; therefore, structural modification or formulation strategies such as nanoencapsulation should be explored before further development. Additionally, future research should consider testing combinations of these compounds to evaluate potential synergistic effects on KEAP1 inhibition and NRF2 activation.

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