Molecular Docking and ADMET Profiling of Natural Compounds Targeting SIRT1/SIRT3 for Anti-Aging Intervention

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ABSTRACT

Background: Sirtuin 1 (SIRT1) and sirtuin 3 (SIRT3) are NAD^+-dependent deacylases that play critical roles in metabolic regulation, oxidative stress control, and aging. Natural products have emerged as promising sources of sirtuin-interacting molecules, yet systematic evaluation of *Hyptis verticillata* phytochemicals against these targets remains limited.

Methods: Selected phytochemicals from *Hyptis verticillata* were subjected to molecular docking against SIRT1 (PDB ID: 4I5I) and SIRT3 (PDB ID: 3GLS) using AutoDock Vina. Binding affinities and interaction patterns were analyzed, followed by in silico pharmacokinetic and toxicity (ADMET) profiling using SwissADME and admetSAR to assess drug-likeness and safety.

Results: Docking analysis revealed binding energies ranging from −5.0 to −9.5 kcal/mol across both targets. Squalene exhibited the strongest predicted affinity for SIRT1 (−9.5 kcal/mol), while oleanolic acid showed the highest affinity for SIRT3 (−8.5 kcal/mol). Several other compounds demonstrated moderate binding to both sirtuins. Interaction analysis indicated predominantly hydrophobic stabilization within the binding pockets. ADMET profiling suggested that while highly lipophilic compounds may face bioavailability limitations, oleanolic acid displayed a comparatively balanced pharmacokinetic and safety profile.

Conclusion: The findings indicate that selected H. verticillata phytochemicals exhibit structural compatibility with SIRT1 and SIRT3, supporting their consideration as preliminary sirtuin-interacting candidates. However, the results represent structure-based predictions rather than functional evidence. Further molecular dynamics simulations and experimental validation are required to elucidate binding stability and biological activity.

Keywords: Hyptis verticillata; SIRT1; SIRT3; molecular docking; ADMET profiling; aging

INTRODUCTION

Aging is a multifaceted biological process encompassing gradual functional decline at cellular, tissue, and organismal levels. Hallmarks of aging include increased oxidative stress, mitochondrial dysfunction, DNA damage accumulation, and metabolic dysregulation (Arrazati, 2023; *It takes two to tango*, 2017). Central to the molecular regulation of aging are the **sirtuins**, a family of nicotinamide adenine dinucleotide (NAD^+) - dependent deacylases that influence key cellular processes such as DNA repair, mitochondrial biogenesis, and metabolic homeostasis (*It takes two to tango*, 2017; Arrazati, 2023). Among them, **SIRT1** (predominantly nuclear) and **SIRT3** (mitochondrial) are especially implicated in longevity and the preservation of cellular function.

SIRT1 modulates critical transcriptional regulators, including PGC-1α, FOXO family members, and p53, thereby enhancing stress resistance, improving metabolic flexibility, and facilitating DNA repair mechanisms that counteract age-associated genomic instability (Arrazati, 2023; *It takes two to tango*, 2017). Declining intracellular NAD^+ levels with advancing age limit sirtuin activity, exacerbating mitochondrial dysfunction,

oxidative damage, and inflammatory responses—key contributors to the aging phenotype (Arrazati, 2023). Concurrently, **SIRT3**, a principal mitochondrial sirtuin, deacetylates metabolic and antioxidant enzymes such as superoxide dismutase 2 (SOD2) and isocitrate dehydrogenase, promoting mitochondrial integrity, reducing oxidative stress, and safeguarding energy metabolism during aging (*It takes two to tango*, 2017; Roles of SIRT3…, 2023). Given their central role in aging pathways, SIRT1 and SIRT3 have emerged as promising therapeutic targets for anti-aging interventions. Natural products, particularly phytochemicals, have attracted considerable interest due to their structural diversity, bioactivity, and potential to modulate key aging pathways with favorable safety profiles (Sirtuins and NAD… 2025). Computational molecular docking and **in silico** pharmacokinetic (ADMET) profiling serve as powerful tools for preliminary screening of such natural compounds, enabling prediction of target binding affinities and drug-like properties before empirical evaluation (Sirtuins and NAD… 2025). *Hyptis verticillata* Jacq. (Lamiaceae) is a medicinal plant traditionally used for its anti-inflammatory, antimicrobial, and antioxidant effects. Phytochemical investigations have identified a wide spectrum of bioactive compounds, including lignans, terpenes, flavonoids, and polyphenols, many of which exhibit notable antioxidant and modulatory activities (*Hyptis verticillata* Jacq…, 2013). These properties suggest potential interactions with aging-related signaling pathways, including sirtuin activation, though systematic evaluation against sirtuin targets remains unexplored.

The current study aims to address this gap by performing *in silico* molecular docking of selected *Hyptis verticillata* phytochemicals against SIRT1 and SIRT3 catalytic sites, complemented by comprehensive ADMET profiling. By integrating structural interaction analysis with pharmacokinetic and toxicity predictions, this research seeks to identify promising natural modulators of sirtuin activity as candidate compounds for anti-aging interventions and provide a rational basis for subsequent biochemical and experimental studies.

METHODOLOGY

Preparation of Ligands

The phytochemical constituents of *Hyptis verticillata* were compiled from literature sources (*Hyptis verticillata* Jacq…, 2013) and chemical databases such as PubChem. A total of 15 major bioactive compounds, including terpenoids, flavonoids, and polyphenols, were selected for docking studies. The 3D structures of these ligands were downloaded in SDF format from PubChem and converted to PDBQT format using OpenBabel v3.1.1 for compatibility with AutoDock Vina. Ligands were energy-minimized using the MMFF94 force field to obtain stable conformations prior to docking.

Table 1: Library of phytocompounds derived from *hyptis verticillata*

S/N	Compound Name
1	Aromadendr-1(10)-en-9-one
2	Cadina-4,10(15)-dien-3-one
3	Dehydropodophyllotoxin
4	Oleanolic Acid
5	Thymol
6	3a.4,5,6,7,7a-hexahydro-4,7-methanoindene
7	4,7- methanon-1H-indene
8	R-R,R-E- trans-Phytol
9	Squalene
10	9,12,15-octadecatrien-1-ol

11	1-octadecyne
12	1-fluorodecane

Preparation of Protein Targets

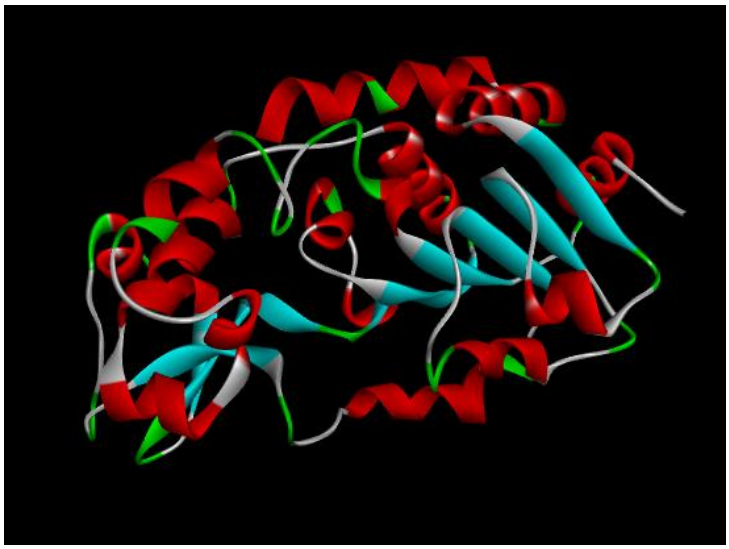

Figure 1: 3D structure of 3GLS protein

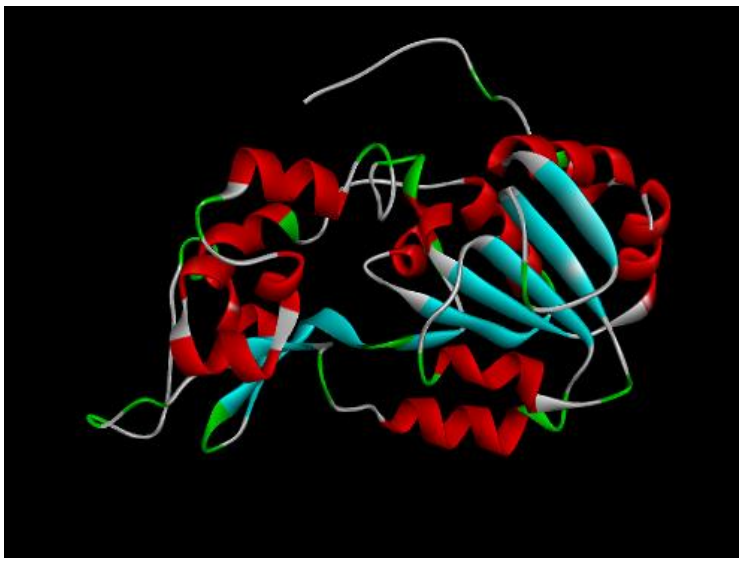

Figure 2: 3D structure of 4I5L protein

The crystal structures of SIRT1 (PDB ID: 4I5I) and SIRT3 (PDB ID: 3GLS) were retrieved from the Protein Data Bank (PDB). Proteins were prepared using AutoDock Tools v1.5.7 by performing the following steps: removal of water molecules, addition of polar hydrogens, and assignment of Kollman charges. The active site residues were identified based on co-crystallized ligands and literature reports (Arrazati, 2023).

Table 2: Protein Targets and Their PDB Information

Protein Target	**PDB ID**	**Chain(s) Used**
SIRT1	**4I5I**	**A**
SIRT3	3GLS	A

Molecular Docking

Molecular docking was conducted using AutoDock Vina v1.2.0 to predict the binding affinities and interaction modes of *H. verticillata* phytochemicals with SIRT1 and SIRT3. The grid box was centered on the catalytic domain of each protein, covering the known binding pockets with dimensions optimized to accommodate the largest ligand. Docking parameters were set to default exhaustiveness (8), and each ligand was docked five times to ensure reproducibility. The best binding pose for each ligand was selected based on the lowest binding energy (kcal/mol) and analyzed for hydrogen bonding, hydrophobic, and π–π interactions using Discovery Studio Visualizer 2021.

ADMET Profiling

Pharmacokinetic and toxicity properties of the selected ligands were predicted using SwissADME and admetSAR v2.0. Parameters evaluated included:

Absorption: Human intestinal absorption (HIA), Caco-2 permeability, and P-glycoprotein substrate prediction.

Distribution: Blood-brain barrier penetration and volume of distribution.

Metabolism: Cytochrome P450 (CYP) inhibition and substrate prediction.

Excretion: Predicted half-life and clearance.

Toxicity: AMES mutagenicity, hepatotoxicity, and LD50 values.

Compounds that satisfied Lipinski's rule of five and displayed favorable ADMET profiles were considered potential candidates for further experimental validation (Sirtuins and NAD+, 2018).

Data Analysis and Visualization

Docking results were tabulated with ligand names, binding energies, and key interacting residues. Molecular interactions were visualized in Discovery Studio Visualizer 2021 to generate 2D and 3D interaction diagrams. ADMET parameters were summarized in tables to facilitate comparison of pharmacokinetic and safety profiles.

RESULTS

Molecular docking results

The results of molecular docking against the selected receptor are shown below as represented by the docking scores. The docking scores of the compounds range from -5.0 to – 9.2.

Table 3: Docking score of phytochemicals from *Hyptis Verticillata* with receptor

Ligand	**4I5L**	**3GLS**
1-fluorodecane	-5.4	-5
1-octadecyne	-6.7	-4.7
3a,4,5,6,7,7a-hexahydro-4,7-methanoindene	-6.7	-5.8
4,7,methanon-1H-indene	-7.2	-6
9,12,15-octadecatrien-1-ol,	-7.3	-6.6
Aromadendr-1(10)-en-9-one	-8.1	-7.2
Cadina-4,10(15)-dien-3-one	-8.8	-7

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Dehydropodophyllotoxin	-8	-7.6
Oleanolic_Acid	-7.3	-8.5
R-R-R-E-trans-Phytol	-8.2	-6.6
Squalene	-9.5	-7.1
Thymol	-7	-6.1

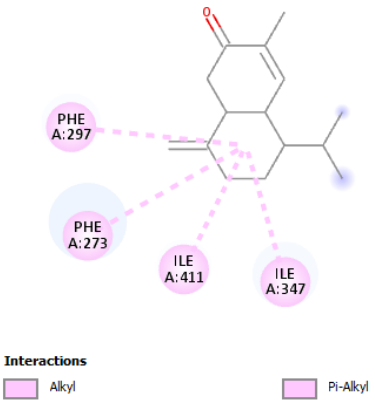
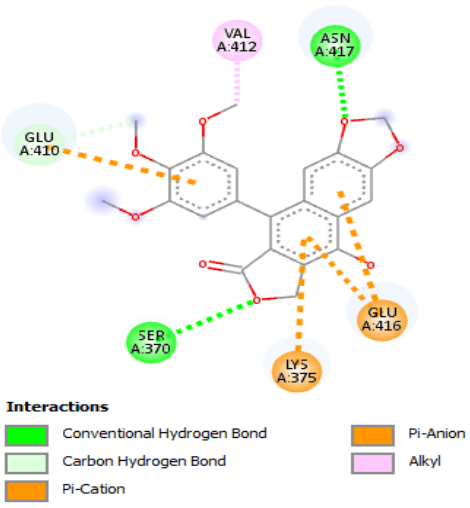


Figure 3: 2D and 3D interactions of Cadina-4,10(15)-dien-3-one with 4I5L protein



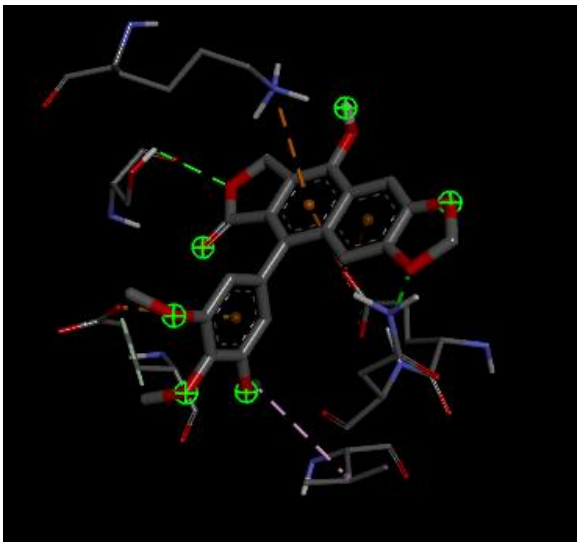
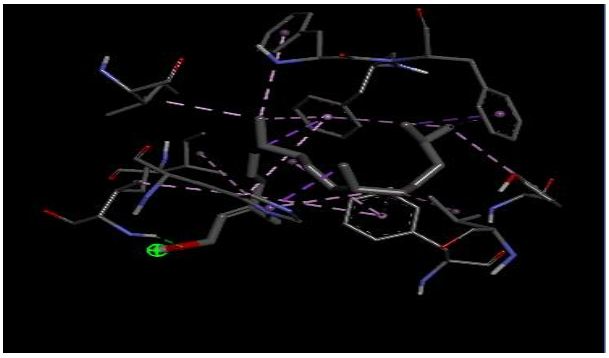


Figure 4: 2D and 3D interactions of Dehydropodophyllotoxin with 4I5L protein



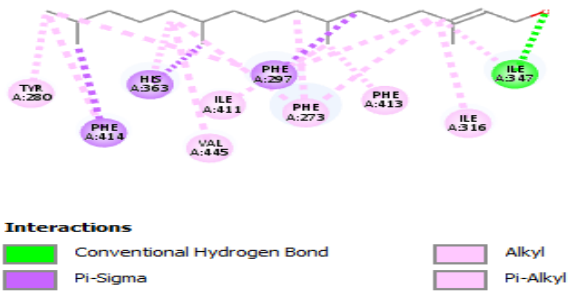


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Figure 5: 2D and 3D interactions of Phytol with 4I5L protein

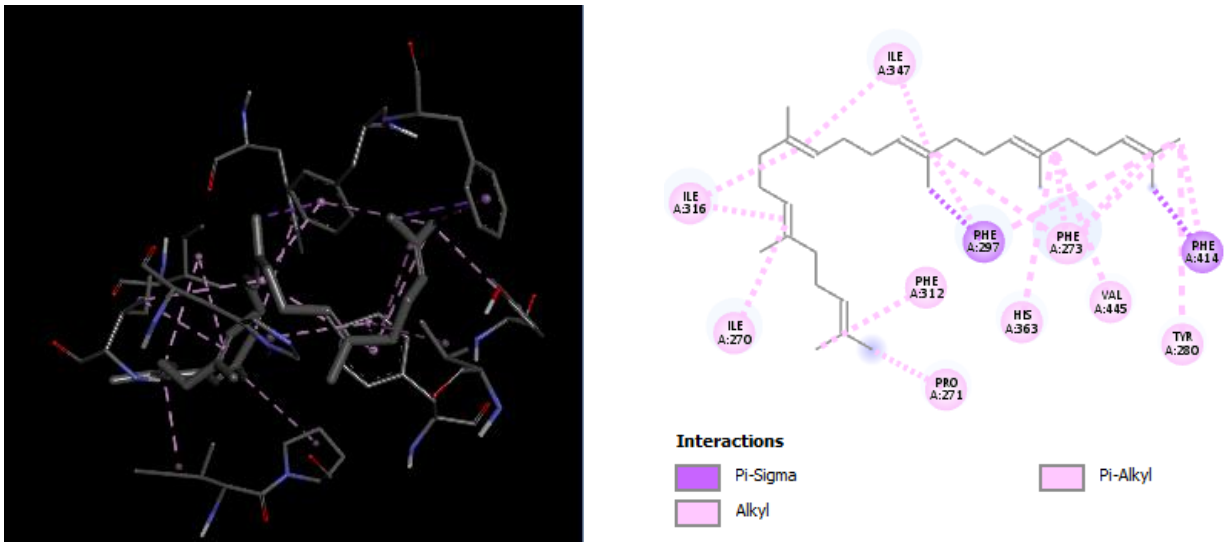

Figure 6: 2D and 3D interactions of Squalene with 4I5L protein

3gls Protein Result

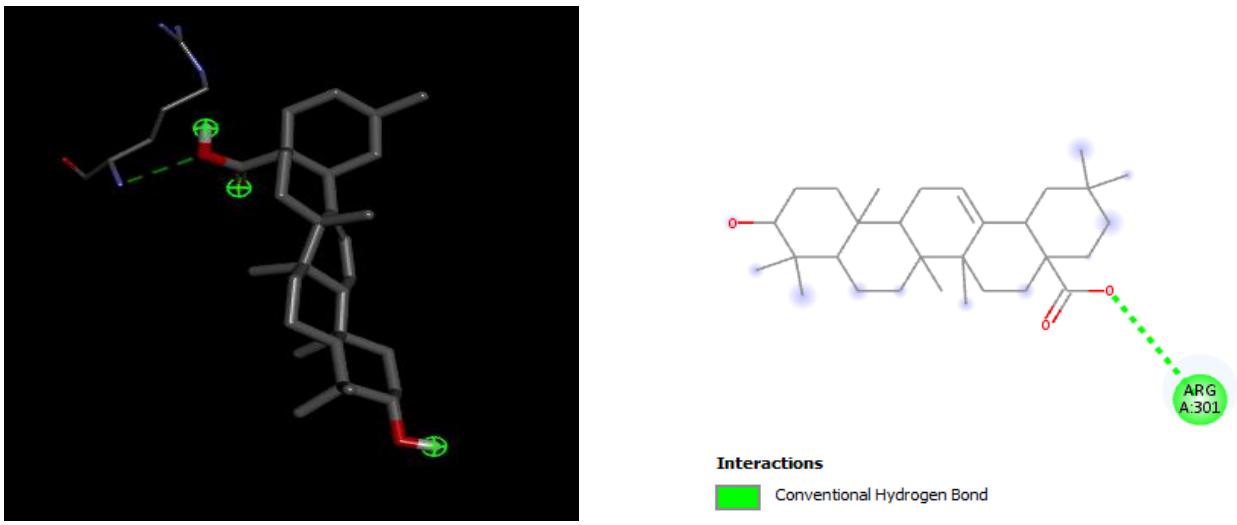

Figure 7: 2D and 3D interactions of Oleanoic Acid with 3gls protein

Admet results of high binding compounds

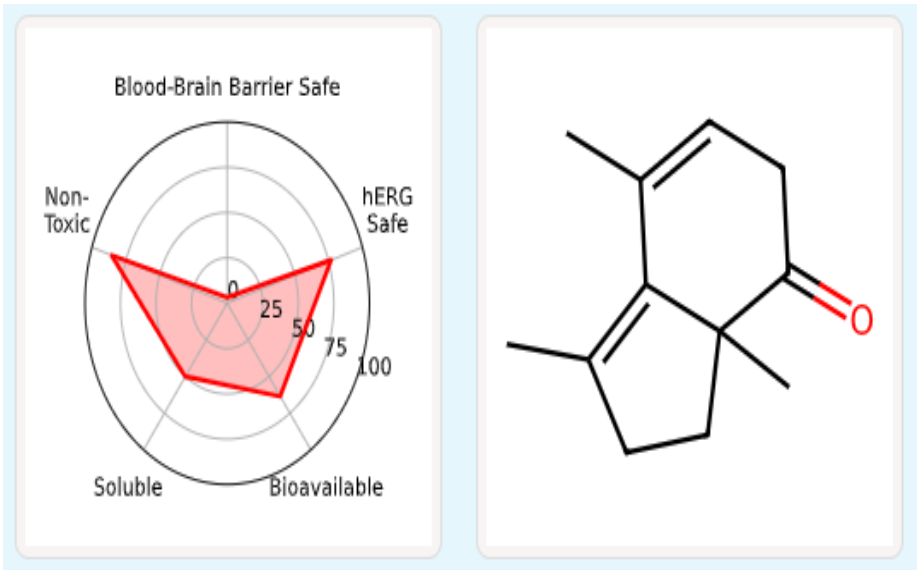

Figure 8: Admet result of Cadina-4,10(15)-dien-3-one

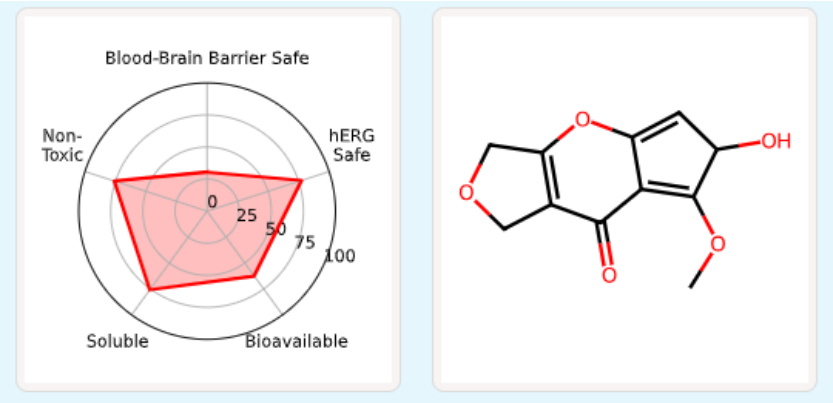

Figure 9: Admet result of Dehydropodophyllotoxin

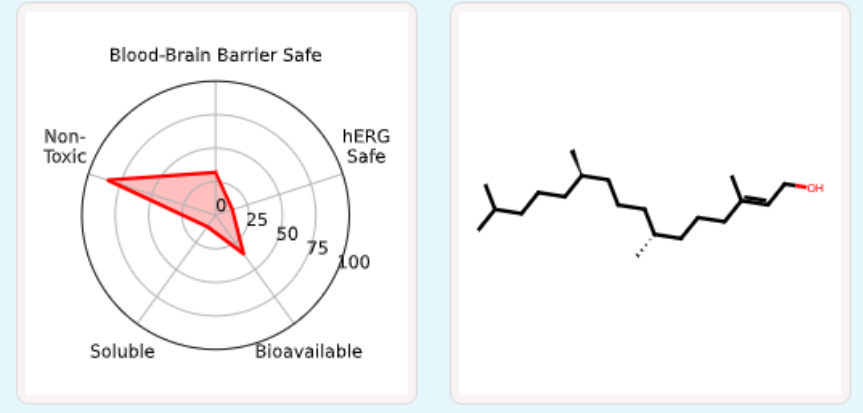

Figure 10: Admet result of **Phytol**

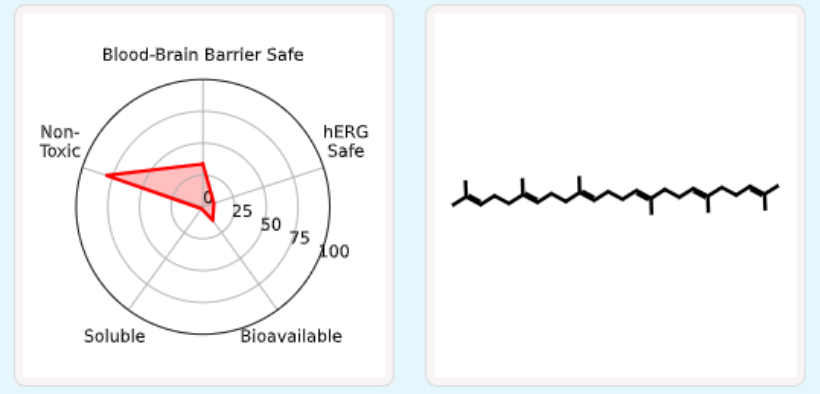

Figure 11: Admet result of Squalene

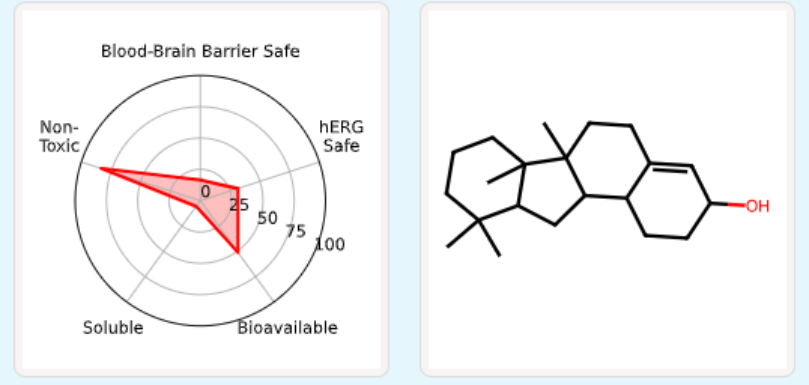

Figure 12: Admet result of Oleanoic Acid

DISCUSSION

This study applied molecular docking and in silico ADMET profiling to explore the interaction potential of selected *Hyptis verticillata* phytochemicals with SIRT1 and SIRT3, two NAD^+-dependent deacylases centrally involved in metabolic regulation, oxidative stress control, and aging biology. The results provide preliminary structural evidence that several constituents of *H. verticillata* can occupy sirtuin binding pockets with energetically favorable conformations, supporting their prioritization for further experimental investigation.

Comparative Docking Performance and Target Preference

Docking simulations revealed binding energies ranging from −5.0 to −9.5 kcal/mol across both targets, consistent with values reported for small-molecule ligands interacting with sirtuin catalytic or regulatory regions. Among the screened compounds, squalene exhibited the strongest predicted affinity for SIRT1 (−9.5 kcal/mol), whereas oleanolic acid showed the highest affinity toward SIRT3 (−8.5 kcal/mol). Several compounds, including cadina-4,10(15)-dien-3-one, aromadendr-1(10)-en-9-one, phytol, and dehydropodophyllotoxin, demonstrated moderate to strong binding across both targets, suggesting limited but discernible cross-target compatibility.

The differential affinity profiles observed between SIRT1 and SIRT3 likely reflect structural divergence between the nuclear and mitochondrial sirtuins, particularly in pocket topology and hydrophobic character. Compounds with higher lipophilicity tended to show stronger predicted interactions with SIRT1, while bulkier or more polar ligands, such as oleanolic acid, displayed preferential binding toward SIRT3. These trends are consistent with prior structural analyses of sirtuin isoforms and reinforce the relevance of ligand physicochemical properties in target selectivity.

Interaction Characteristics and Structural Implications

Interaction analysis indicated that binding stabilization was driven predominantly by hydrophobic contacts, with limited hydrogen bonding observed, particularly for highly non-polar compounds such as squalene and phytol. This interaction pattern aligns with the known architecture of sirtuin binding sites, which accommodate hydrophobic acyl substrates and NAD^+ intermediates. Compounds containing polar functional groups, notably oleanolic acid and dehydropodophyllotoxin, formed additional stabilizing interactions within the SIRT3 pocket, potentially contributing to their comparatively stronger affinity for this target.

However, the absence of explicit modeling of NAD^+ or reaction intermediates, as well as the static nature of docking simulations, constrains interpretation of these interactions in terms of catalytic modulation. Binding affinity alone cannot distinguish between potential activation, inhibition, or non-productive binding modes, particularly for multifunctional enzymes such as sirtuins.

ADMET Considerations and Translational Relevance

In silico ADMET profiling provided additional context for interpreting docking outcomes. While several high-affinity ligands exhibited favorable toxicity predictions, highly lipophilic compounds such as squalene and phytol may face limitations related to solubility, bioavailability, and systemic distribution. In contrast, oleanolic acid displayed a more balanced pharmacokinetic profile, combining strong SIRT3 affinity with acceptable predicted absorption and safety parameters, thereby emerging as a comparatively promising lead compound.

These findings underscore the importance of integrating pharmacokinetic considerations with docking metrics, as compounds with moderate binding energies but favorable ADMET properties may ultimately possess greater translational potential than those selected solely on the basis of docking scores.

Biological Interpretation and Study Limitations

The present results should be interpreted as **structure-based predictions rather than functional evidence**. Sirtuin activity is governed by complex regulatory mechanisms involving NAD^+ availability, protein dynamics, and downstream signaling pathways that are not captured by molecular docking. Consequently, the predicted interactions cannot be equated with biological activation or lifespan-modulating effects.

Moreover, the lack of molecular dynamics simulations, enzymatic assays, and cellular validation represents a key limitation. Future studies incorporating dynamic simulations and experimental evaluation will be necessary to determine binding stability, isoform selectivity, and functional outcomes.

Implications for Anti-Aging Research

Despite these limitations, the study provides a rational computational framework for identifying *H. verticillata*-derived compounds with potential relevance to aging-associated molecular targets. The identification of phytochemicals capable of engaging both SIRT1 and SIRT3 supports further investigation into their role as structural leads for modulating longevity-related pathways. Rather than advancing definitive anti-aging claims, the findings contribute to early-stage target engagement assessment and inform subsequent experimental design in the search for natural sirtuin modulators.

CONCLUSION

This study provides a preliminary in silico assessment of selected *Hyptis verticillata* phytochemicals against SIRT1 and SIRT3. Molecular docking indicated that several compounds can bind favorably within the sirtuin binding pockets, with squalene showing the strongest predicted affinity for SIRT1 and oleanolic acid for SIRT3. ADMET profiling further suggested that oleanolic acid possesses a comparatively balanced pharmacokinetic profile among the high-affinity ligands.

While these findings indicate structural compatibility between *H. verticillata* phytochemicals and key aging-related targets, they do not establish functional modulation of sirtuin activity. Overall, the study serves as an initial target-engagement screening that supports further dynamic and experimental validation of selected compounds as potential sirtuin modulators.

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