RESEARCH ARTICLE

Catechins as Catalase Modulators: A Comprehensive *In-silico* Analysis Unveiling their Potential Antioxidant Effects

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ABSTRACT

This research explores the potential of carefully selected catechins as catalase modulators, leveraging their documented antioxidant effects. The catalase protein's structural quality was rigorously evaluated, revealing an overall high-quality 3D structure. Ligand-based virtual screening identified ten novel catechin hits with promising interactions, presenting candidates designed for new validation. Molecular docking simulations demonstrated robust binding empathies between selected catechins and catalase, with CHEMBL223855 exhibiting the highest affinity. ADMET analysis highlighted CHEMBL223855 as a promising candidate for drug development, boasting favorable properties, including high gastrointestinal absorption and absence of blood-brain barrier permeation. Despite medicinal chemistry alerts and lead likeness violations, this comprehensive analysis guides future experimental validation efforts, supporting the potential of these catechins as effective catalase modulators.

Keywords: Catechins, Catalase modulators, *In-silico* analysis, Antioxidant effects, Computational insights, Bioactive compounds, Drug development, Oxidative stress.

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INTRODUCTION

In the landscape of contemporary health challenges, combating oxidative stress and its implications has become a focal point for innovative therapeutic strategies.[1] Oxidative stress, rising after a difference among reactive oxygen species (ROS) and cellular antioxidant defense mechanisms, plays a pivotal role in various pathological conditions, including cancer, neurodegenerative diseases, and cardiovascular disorders.[2-5] Catalase, a crucial antioxidant enzyme, serves as a frontline defense against oxidative stress by catalyzing the breakdown of H_2O_2 into H_2O and O_2.[6]

Catechins, a class of polyphenolic compounds abundantly found in green tea and other plant sources, have gathered consideration for their prospective role in modulating catalase activity. The interplay between catechins and catalase is of particular interest due to its implications for antioxidant defenses within cells. Recent advancements in computational biology offer a promising avenue to explore and understand the complex interactions between bioactive compounds and target enzymes.[7,8]

This paper embarks on a comprehensive *in-silico* analysis to unravel the potential antioxidant effects of catechins through their modulation of catalase. As we delve into ligand-based virtual screening, molecular docking, and ADMET analysis, we aim to shed light on the intricate binding interactions between catechins and catalase. Through this multi-faceted approach, we strive to provide insights into the molecular mechanisms underlying the antioxidant properties of catechins and their potential as modulators of catalase activity.

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By elucidating the role of catechins in catalase modulation through advanced computational methodologies, this study contributes to the expanding knowledge base in antioxidant research. The findings presented herein aim to pave the way for further experimental validations and, ultimately, the expansion of innovative therapeutic approaches harnessing the antioxidant potential of catechins.

MATERIALS AND METHODS

Catechin Selection

A thorough review of relevant literature and comprehensive database searches were conducted in an effort to find possible catechins for this study. Compounds with established antioxidant qualities and those thought to be easily obtainable for further experimental verification were given precedence. In order to guarantee a thorough and inclusive review, the selection method also took structural diversity within the catechin class into account.

Preparing the Catalase Protein Structure and Thorough Assessment

Catalase's three-dimensional structure was obtained from a dependable source, the Protein Data Bank (PDB). To get everything ready, we followed a strict routine that involved getting rid of water, adding hydrogen, and using less power. The quality of the painstakingly created protein structure was evaluated by applying SAVES and ProSAweb servers.[9-11]

Ligand Preparation

Catechins selected for this research were obtained from chemical databases and underwent careful preparation in order to be used in the next steps of the molecular docking process. Energy minimization was done after ligand structural integrity was improved to remove anomalies. Topology files were carefully prepared and ligands were partially charged utilizing force fields consistent with protein production.

Ligand-based Virtual Screening

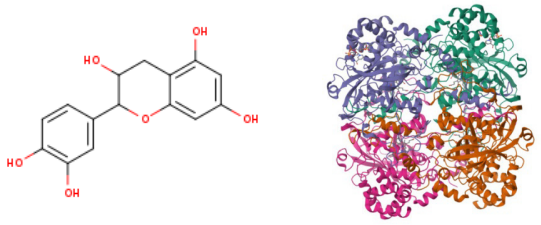
This method was implemented through Swiss Similarity online tool (http://www.swisssimilarity.ch). The query for screening was a SMILES formatted catechin molecule. The vast screening database contained a variety of chemicals, such as licensed medications, bioactive materials, and an extra 200 million virtual compounds. The bioactive chemical class was highlighted, and ChEMBL database (version 29) was exploited for screening progression.[12,13]

Molecular Docking

Potential catalase binding sites were explored via molecular docking simulations utilizing a blind docking method. Cavity detection, docking centre and box size calculation, molecular docking simulations, and binding pose evaluation established on docking scores to detect best binding conformations were all part of procedural workflow.[14]

ADMET Analysis

ADMET characteristics linked to the chosen catechins were evaluated using *in-silico* tools, most notably SwissADME.



C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O

Figure 1: Standard Catechin 2 D structure, SMILES and 1DGB protein structure

The safety profiles, bioavailability, and drug-likeness of the identified compounds were all profoundly revealed by this analytical method.[13,15]

RESULTS

Selection of Catechins

Catechins were meticulously selected for their potential as catalase modulators through an extensive literature review and database searches. The compounds chosen demonstrated documented antioxidant effects, and their availability for experimental validation was a key consideration. This selection process aimed to ensure a thorough evaluation of catechins for their role as catalase modulators.

Protein Structure Quality Assessment

Assessment of Protein Structure Quality

Using a variety of online analysis tools, the catalase protein's quality metrics, as displayed in Figure 1, were carefully assessed. The remarkable quality and dependability of the 3D structure are confirmed by the Ramachandran plot (85.5%) in Figures 2a and 2b, the ERRAT score (95.03) in Figure 3, the high verify3d Score in Figure 4, and the ProSAweb Z-Score closer to zero in Figure 5. These findings bolster its applicability for additional *in-silico* research.

According to Table 1 and Figures 2a and 2b, a high-quality model should include more than 90% of the residues in the most preferred areas [A, B, and L]. This is based on data from 118 structures having a resolution of at least 2.0 Angstroms and an R-factor of no more than 20%. But the questioned model has 85.3% of its residues in these areas, suggesting that it is marginally below the anticipated cutoff. Positively, it's important to note that the model has a comparatively low percentage of residues in the prohibited regions (0.3%).

A score of 95.50% suggests that the model has a high degree of agreement between the calculated non-bonded interactions and those expected from a high-quality protein structure.

A VERIFY3D chart provided a detailed view of the model's agreement with experimental data along the protein sequence. High scores across the majority of the sequence are desirable for a reliable protein model.

A ProSA chart provided an overall assessment of the model's quality in terms of its energy compared to

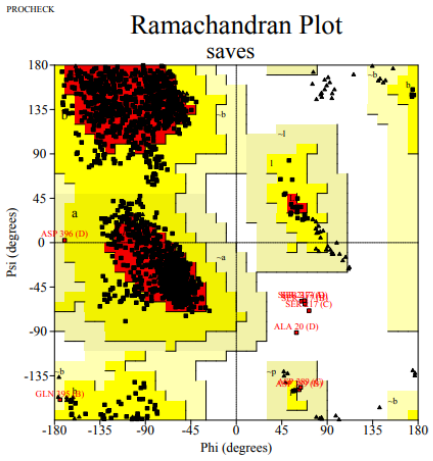


Figure 2a: Ramachandran plot

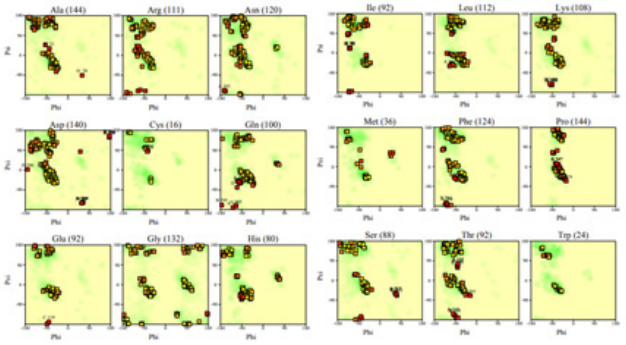


Figure 2b: Ramachandran plot of all residues

experimental structures. A model has a ProSA Z-score close to zero, indicating that its energy is within the range expected for native protein structures.

Ligand-based Virtual Screening

Pharmacophore models and two-dimensional (2D) fingerprints were used in the ligand-based virtual screening procedure to identify a group of catechins with potential interactions. Ten novel hits from the virtual compounds library stood out among the screened compounds, indicating possible directions for experimental and synthesis confirmation. High-potential prospects are recorded in Table 1 (Figures 6 and 7).

Molecular Docking

Robust binding affinities between the chosen catechins and the catalase protein were found using molecular docking simulations. The range of binding energies was -8.2 to -10.0, with the maximum binding affinity being shown by CHEMBL223855. Key results are summarised in Table 2.

ADMET Analysis

ADMET investigation provided insights into drug-likeness and safety silhouettes of particular catechins. CHEMBL223855, the compound of interest, exhibited favorable properties for drug development, as outlined below. The molecular entity under investigation possesses a chemical formula of C25H30O6, with a calculated molecular weight of 426.50 g/mol. Comprising 31 heavy atoms, including 12 aromatic

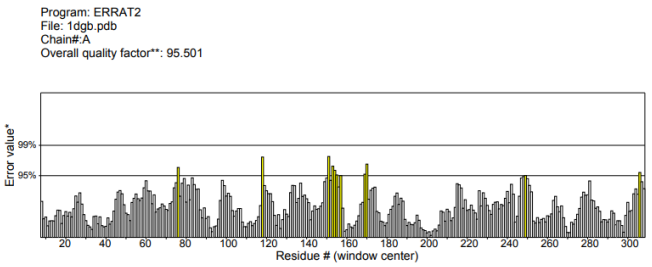


Figure 3: ERRAT Chart

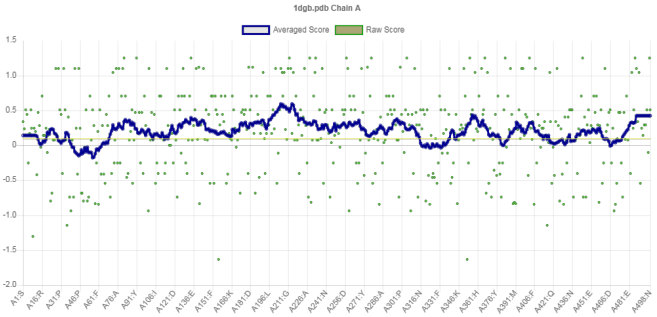


Figure 4: VERIFY3D Chart

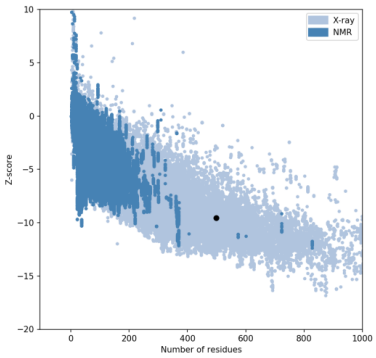
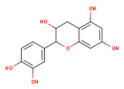
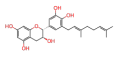
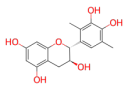
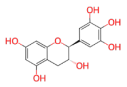
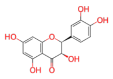
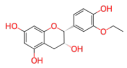
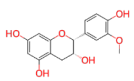
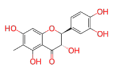
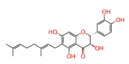
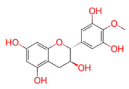
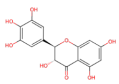


Figure 5: ProSA Chart

heavy atoms, the compound exhibits a fractional Csp3 value of 0.36. Notably, it features 6 H-bond acceptors, 6 rotatable bonds, and 5 H-bond donors. The molar refractivity stands at 121.61, accompanied by a total polar surface area (TPSA) of 110.38 Å². In terms of lipophilicity, the compound demonstrates a consent Log Po/w of 3.70, representing a modest level of lipophilicity. Moving to water solubility, Log S (ESOL) registers at -4.98, corresponding to a moderately soluble classification. An alternative measurement, Log S (Ali), reveals a less favorable solubility profile, categorized as poorly soluble. SILICOS-IT analysis yields a Log S value of -4.60, aligning with a moderately soluble classification. Regarding pharmacokinetics, the compound shows extraordinary GI absorption but not a blood-brain barrier permeant. It is identified as a P-glycoprotein substrate. Notably, it does not inhibit CYP1A2, CYP2C19, CYP2C9, CYP2D6, or CYP3A4. The compound's skin permeation potential, as indicated by Log Kp, is -5.96 cm/s. Assessing drug-likeness, the compound meets the norms given to Ghose, Egan, Lipinski, Veber, and

Table 1: Result of virtual screening by Swiss-similarity server

CHEMBL ID, Catching Score, SMILES	*2D Structure*	*Cb-Dock Score*
CHEMBL583912. 1.000, C1C(C(OC2=CC(=CC(=C21)O)O)C3=CC(=C(C=C3)O)O)O		-9.2
CHEMBL223855, 0.977, CC(C)=CCC/C(C)=C/Cc1cc([C@H]2Oc3cc(O)cc(O)c3C[C@@H]2O)cc(O)c1O		-10.0
CHEMBL3260914, 0.941, Cc1cc([C@H]2Oc3cc(O)cc(O)c3C[C@@H]2O)c(C)c(O)c1O		-9.2
CHEMBL264167, 0.939, Oc1cc(O)c2c(c1)OC@@HC@HC2		-9.1
CHEMBL9249, 0.892, O=C1c2c(O)cc(O)cc2OC@@H[C@H]1O		-9.3
CHEMBL2408678, 0.877, CCOc1cc([C@H]2Oc3cc(O)cc(O)c3C[C@H]2O)ccc1O		-8.7
CHEMBL2297044, 0.877, COc1cc([C@H]2Oc3cc(O)cc(O)c3C[C@H]2O)ccc1O		-8.7
CHEMBL4577306, 0.854, Cc1c(O)cc2c(c1O)C(=O)C@@HC@HO2		-9.8
CHEMBL411385, 0.854, CC(C)=CCC/C(C)=C/Cc1c(O)cc2c(c1O)C(=O)C@HC@@HO2		-9.8
CHEMBL1651274, 0.846, COc1c(O)cc([C@H]2Oc3cc(O)cc(O)c3C[C@@H]2O)cc1O		-8.3
CHEMBL3348861, 0.842 O=C1c2c(O)cc(O)cc2OC@@H[C@H]1O		-9.0

Muegge rules. The bioavailability score is calculated at 0.55. In the realm of medicinal chemistry, potential concerns arise

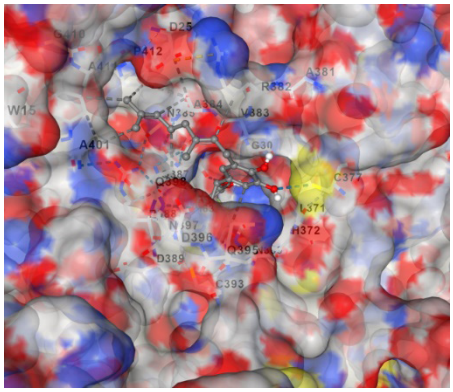


Figure 6: Ligand with protein obtained from cb-dock server

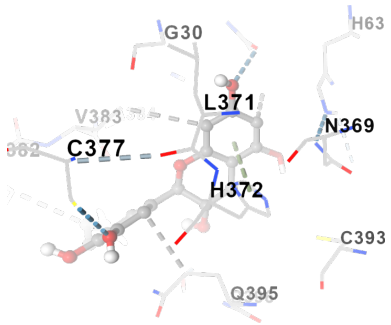


Figure 7: Ligand with Amino acids obtained from cb-dock server

Table 2: Results of molecular docking of highest auto dock vina score

Vina score	*Cavity size*	*Center*			*Size*		
		x	*y*	*z*	*x*	*y*	*z*
-10	5977	47	32	48	30	35	23
-9.8	5790	21	20	73	33	31	23
-9.7	5518	25	32	11	23	35	23
-9	5453	24	0	33	31	35	23
-7	5640	20	53	45	31	32	23

with 1 PAINS alert (catechol_A) and 2 Brenk alerts (catechol, isolated_alkene). Notably, the compound does not adhere to leadlikeness criteria due to two violations: molecular weight (MW) exceeding 350 and XLOGP3 surpassing 3.5. Synthetic accessibility is computed at 4.67, reflecting a moderate level of ease in synthesis.

The molecule, with a molecular weight of 426.50 g/mol and 31 heavy atoms, demonstrates favorable physicochemical properties such as moderate flexibility with 6 rotatable bonds and a sp3 hybridization fraction of 0.36. Lipophilicity measurements vary, indicating potential differences in solubility, and the molecule is predicted to have high gastrointestinal absorption but not to permeate the blood-brain barrier. It serves as a substrate for P-glycoprotein and is not expected to inhibit key cytochrome P450 enzymes. Although it conforms to Lipinski's Rule of Five and has a relatively high bioavailability score (0.55), it should be used with caution due to medicinal chemistry alerts for catechol_A and isolated_alkene. Leadlikeness violations indicate deviations from

typical lead compounds. Experimental validation is crucial to confirm these predictions and guide further development.

CONCLUSION

In conclusion, our research focused on the meticulous selection of catechins for their potential as catalase modulators, considering documented antioxidant effects and experimental feasibility. The catalase protein's structural quality was rigorously assessed, revealing an overall high-quality 3D structure, as evidenced by favorable metrics in the Ramachandran plot (85.5%), ERRAT score (95.50), high verify3d score and ProSAweb Z-score close to zero. While the model slightly falls below the expected threshold in the most favored regions, its low percentage in disallowed regions (0.3%) is a positive aspect. Ten new catechin hits with promising interactions were found through ligand-based virtual screening, offering prospective candidates for additional experimental validation. Strong binding affinities between a few chosen catechins and catalase were shown by molecular docking simulations; CHEMBL223855 showed the highest binding affinity. The safety profiles and drug-likeness of the chosen catechins were emphasized by ADMET analysis, with CHEMBL223855 exhibiting qualities that are advantageous for drug development, such as high gastrointestinal absorption and lack of blood-brain barrier permeation. Despite medicinal chemistry alerts and lead likeness violations, the comprehensive analysis provides valuable insights for guiding future experimental validation and optimization efforts, supporting the potential of these catechins as catalase modulators.

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