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In-Silico Studies On Astilbin As A Potential Antioxidant Agent: A Multi-Faceted Computational Approach

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Abstract
Astilbin, a prominent flavonoid derived from the rhizomes of Smilax glabra, exhibits significant antioxidant properties. This study employs a comprehensive in-silico approach, encompassing Swiss Similarity studies, ADME and toxicity predictions, Cytoscape network analysis, and molecular docking studies, to elucidate the potential of astilbin as an effective antioxidant agent. Swiss Similarity analysis identified structurally similar compounds, facilitating the selection of promising candidates. ADME and toxicity predictions confirmed favourable pharmacokinetic properties and low toxicity. Cytoscape network analysis highlighted key protein interactions, and molecular docking studies demonstrated strong binding affinities of astilbin to antioxidant-related enzymes, with comparative analysis against the standard antioxidant ascorbic acid. These findings underscore the potential of astilbin in antioxidant therapy, warranting further experimental validation.

Keywords: Astilbin**,** Molecular Docking**,** Swiss Similarity, ADME, Toxicity Predictions.

Introduction

Natural compounds have been extensively studied for their potential therapeutic properties, particularly as antioxidants. Antioxidants are crucial in mitigating oxidative stress, which is implicated in various chronic diseases, including cancer, cardiovascular diseases, and neurodegenerative disorders. Among these natural compounds, astilbin, a flavonoid extracted from the rhizomes of Smilax glabra, has shown promising antioxidant activity.

Astilbin has been traditionally used in Chinese medicine for its anti-inflammatory, hepatoprotective, and immunomodulatory effects. Recent studies have suggested that astilbin's antioxidant properties could be attributed to its ability to scavenge free radicals and upregulate endogenous antioxidant defenses. This study aims to explore the antioxidant potential of astilbin using in-silico methods, providing a detailed analysis of its pharmacokinetic properties, toxicity, protein interactions, and binding affinities.

Materials and Methods

Swiss Similarity Studies

The Swiss Similarity platform (http://www.swisssimilarity.ch) was utilized to identify compounds structurally similar to astilbin. This tool integrates data from major chemical databases such as PubChem, ChemSpider, and ZINC, allowing for comprehensive molecular similarity searches and virtual screening. The identification of similar compounds aids in predicting potential bioactivity and discovering new therapeutic candidates.

ADME and Toxicity Predictions

ADME (Absorption, Distribution, Metabolism, and Excretion) and toxicity properties of astilbin were predicted using ADMET LAB 3.0 (http://admetlab.org). This tool evaluates critical pharmacokinetic parameters, including bioavailability, half-life, clearance rates, and tissue distribution, as well as toxicity profiles to ensure the compound's safety and efficacy.

Cytoscape Network Analysis

Cytoscape (http://www.cytoscape.org) was employed for visualizing protein-protein interactions and pathway analysis. Data from STRING (http://string-db.org) and KEGG (http://www.genome.jp/kegg) databases were integrated to create detailed interaction maps, highlighting pathways involved in oxidative stress and antioxidant activity. This analysis identified potential drug targets and elucidated the molecular mechanisms underlying astilbin's antioxidant effects.

Molecular Docking Studies

Molecular docking studies were conducted using Molsoft’s ICM PRO

(https://www.molsoft.com/icm_pro.html). Proteins selected for docking studies were identified through Cytoscape network analysis, focusing on key antioxidant enzymes such as Human Erythrocyte Catalase (PDB ID: 1DGF) and Human Peroxiredoxin 3 (PDB ID: 5UCX). The binding affinities and interaction mechanisms of astilbin were compared against the standard antioxidant ascorbic acid to evaluate its relative efficacy.

Results

Swiss Similarity Studies

The Swiss Similarity analysis identified several compounds with significant structural similarity to astilbin. These compounds were further analyzed to assess their potential antioxidant activity. The top-ranked compounds showed high similarity scores, indicating a strong likelihood of shared biological activity.

Table 1: Top Structurally Similar Compounds Identified in Swiss Similarity Analysis

SR.NO.	MOLECULAR FORMULA	NAME	SMILES
1.	$C_{15}H_{12}O_7$	2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-2,3-dihydro-4H-chromen-4-one	c1cc(c(cc1C2C(C(=O)c3c(cc(cc3O2)O)O)O)O)O
2.	$C_{15}H_{12}O_7$	(2R,3R)-2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-2,3-dihydro-4H-chromen- 4-one	c1cc(c(cc1[C@@H]2[C@H](C(=O)c3c(cc(cc3O2)O)O)O)O)O
3.	$C_{16}H_{14}O_7$	(2S,3S)-2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-6-methyl-2,3-dihydro-4H-chromen-4-one	Cc1c(cc2c(c1O)C(=O)[C@H]([C@@H](O2)c3ccc(c(c3)O)O)O)O
4.	$C_{16}H_{14}O_7$	(2R,3R)-2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-6-methyl-2,3-dihydro-4H-chromen-4-one	Cc1c(cc2c(c1O)C(=O)[C@@H]([C@H](O2)c3ccc(c(c3)O)O)O)O
5.	$C_{15}H_{12}O_8$	(2R,3S)-3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphenyl)-2,3-dihydro-4H-chromen-4-one	c1c(cc(c(c1O)O)O)[C@@H]2[C@@H](C(=O)c3c(cc(cc3O2)O)O)O
6.	$C_{15}H_{12}O_8$	(2R,3R)-3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphenyl)-2,3-dihydro-4H-chromen-4-one	c1c(cc(c(c1O)O)O)[C@@H]2[C@H](C(=O)c3c(cc(cc3O2)O)O)O
7.	$C_{15}H_{14}O_6$	(2R,3S)-2-(3,4-Dihydroxyphenyl)-3,5,7-chromanetriol	c1cc(c(cc1[C@@H]2[C@H](Cc3c(cc(cc3O2)O)O)O)O)O
8.	$C_{15}H_{14}O_6$	(2S,3R)-2-(3,4-Dihydroxyphenyl)-3,5,7-chromanetriol	c1cc(c(cc1[C@H]2[C@@H](Cc3c(cc(cc3O2)O)O)O)O)O
9.	$C_{15}H_{14}O_6$	(2S,3S)-2-(3,4-Dihydroxyphenyl)-3,5,7-chromanetriol	c1cc(c(cc1[C@H]2[C@H](Cc3c(cc(cc3O2)O)O)O)O)O
10.	$C_{15}H_{14}O_6$	(2R,3R)-2-(3,4-Dihydroxyphenyl)-3,5,7-chromanetriol	c1cc(c(cc1[C@@H]2[C@@H](Cc3c(cc(cc3O2)O)O)O)O)O

ADME and Toxicity Predictions

The ADME analysis revealed that astilbin's similar compounds have high gastrointestinal absorption rate and moderate solubility. Toxicity predictions indicated a low risk of hepatotoxicity, cardiotoxicity, and mutagenicity, supporting its potential as a safe therapeutic agent.

For instance amoung the 10 top structurally similar compounds only one compound with the lowest toxicity was selected for the further study and who's ADMET data is presented below

Table 2: ADME and Toxicity Profile of the least toxic molecule from top similar compounds
Compound No. 2. $C_{15}H_{12}O_7$
(2R,3R)-2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-2,3-dihydro-4H-chromen-4-one

PHYSICOCHEMICAL PROPERTY

Molecular Weight (MW)	304.06
Volume	285.403
Density	1.065
nHA	7.0
nHD	5.0
nRot	1.0

nRing	3.0
MaxRing	10.0
nHet	7.0
fChar	0.0
nRig	18.0
Flexibility	0.056
Stereo Centers	2.0
TPSA	127.45
logS	-3.331
logP	0.932
logD7.4	1.224
pka (Acid)	7.266
pka (Base)	3.56
Melting point	248.755
Boiling point	352.509

MEDICINAL CHEMISTRY

QED	0.501
SAscore	Easy
GASA	Easy
Fsp^3	0.133
MCE-18	61.471
NPscore	2.298
Lipinski Rule	Accepted
Pfizer Rule	Accepted
GSK Rule	Accepted
GoldenTriangle	Accepted
PAINS	1
Alarm_NMR Rule	3
BMS Rule	1
Chelating Rule	1
Colloidal aggregators	0.649
FLuc inhibitors	0.535
Blue fluorescence	0.18
Green fluorescence	0.153
Reactive compounds	0.583
Promiscuous compounds	0.316

ABSPORPTION

Caco-2 Permeability	-6.151
MDCK Permeability	-4.921
PAMPA	+
Pgp inhibitor	---
Pgp substrate	--
HIA	---

F20%	++
F30%	+++
F50%	+++

DISTRIBUTION

PPB	95.1%
VDss	-0.352
BBB	---
Fu	4.4%
OATP1B1 inhibitor	+++
OATP1B3 inhibitor	+++
BCRP inhibitor	++
MRP1 inhibitor	++
BSEP inhibitor	---

METABOLISM

CYP1A2 inhibitor	---
CYP1A2 substrate	+++
CYP2C19 inhibitor	---
CYP2C19 substrate	---
CYP2C9 inhibitor	---
CYP2C9 substrate	---
CYP2D6 inhibitor	---
CYP2D6 substrate	---
CYP3A4 inhibitor	+++
CYP3A4 substrate	---
CYP2B6 inhibitor	--
CYP2B6 substrate	---
CYP2C8 inhibitor	+++
HLM Stability	---

EXCRETION

CL_{plasma}	13.376
T1/2	2.089

TOXICOPHORE RULES

Acute Aquatic Toxicity Rule	2
Genotoxic Carcinogenicity Mutagenicity Rule	0
NonGenotoxic Carcinogenicity Rule	0
Skin Sensitization Rule	10
Aquatic Toxicity Rule	0
NonBiodegradable	1
SureChEMBL Rule	0
FAF-Drugs4 Rule	2

TOXICITY

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hERG Blockers	0.061
hERG Blockers (10um)	0.538
DILI	0.472
AMES Toxicity	0.653
Rat Oral Acute Toxicity	0.3
FDAMDD	0.632
Skin Sensitization	0.986
Carcinogenicity	0.241
Eye Corrosion	0.017
Eye Irritation	0.984
Respiratory	0.671
Human Hepatotoxicity	0.499
Drug-induced Nephrotoxicity	0.126
Drug-induced Neurotoxicity	0.037
Ototoxicity	0.675
Hematotoxicity	0.078
Genotoxicity	0.992
RPMI-8226 Immunitoxicity	0.05
A549 Cytotoxicity	0.769
Hek293 Cytotoxicity	0.582
BCF	0.998
IGC50	3.582
LC50DM	4.604
LC50FM	4.064

TOX21 PATHWAY

NR-AhR	++
NR-AR	---
NR-AR-LBD	--
NR-Aromatase	--
NR-ER	--
NR-ER-LBD	+
NR-PPAR-gamma	---
SR-ARE	+
SR-ATAD5	---
SR-HSE	+
SR-MMP	++
SR-p53	---

Cytoscape Network Analysis

The Cytoscape network analysis identified key proteins and pathways involved in oxidative stress and antioxidant defense mechanisms. Significant interactions were observed with enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx).

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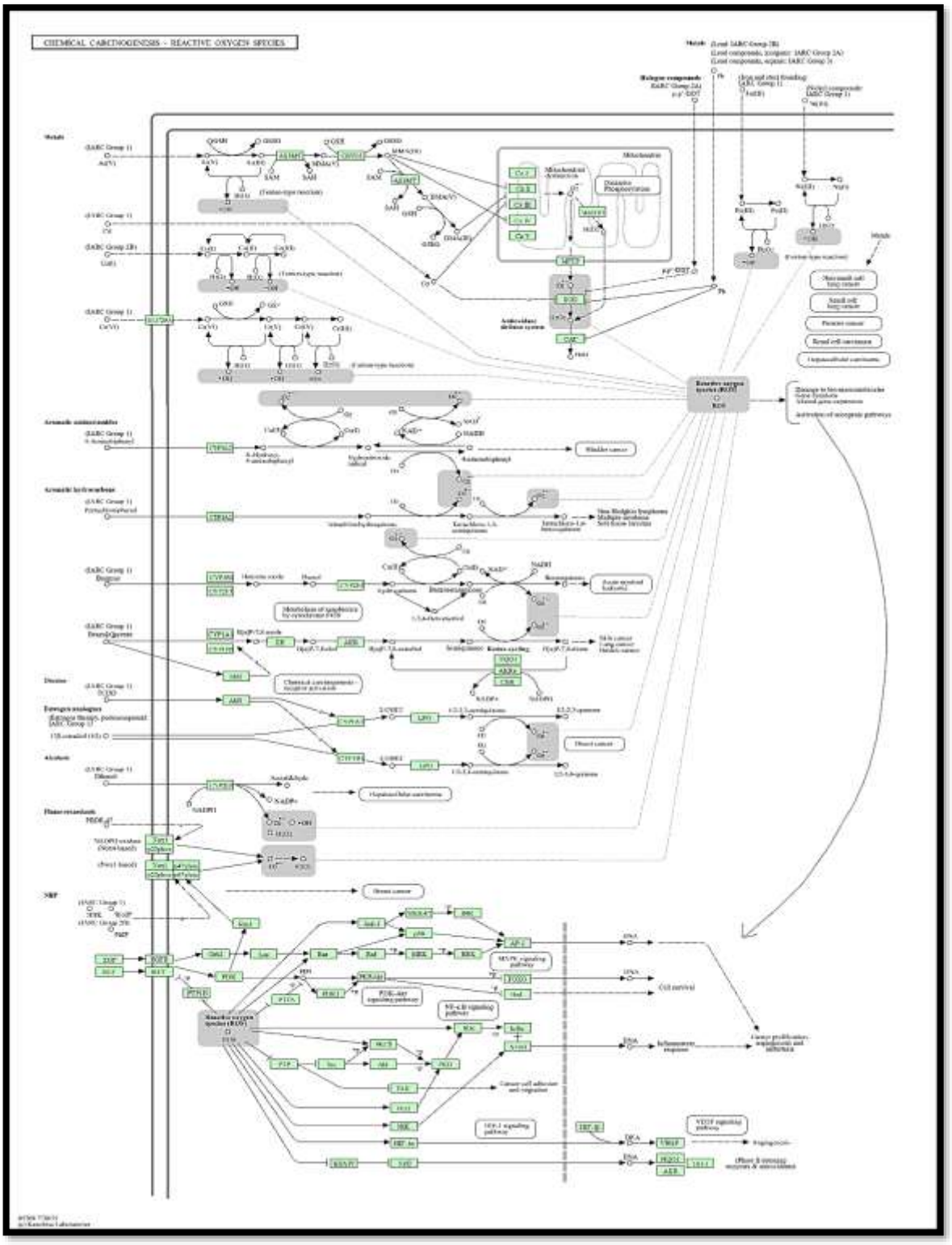

Figure 1: Cytoscape Network Analysis of Protein-Protein Interactions for antioxidant activity

Molecular Docking Studies

Molecular docking studies demonstrated that the compound $C_{15}H_{12}O_7$ has strong binding affinities to key antioxidant enzymes. For Human Erythrocyte Catalase (PDB ID: 1DGF), the compound $C_{15}H_{12}O_7$ exhibited a docking score of -28.20624, while ascorbic acid had a docking score of -22.32259. For Human Peroxiredoxin 3 (PDB ID: 5UCX), $C_{15}H_{12}O_7$ had a docking score of 21.29366 compared to -12.70578 for ascorbic acid.

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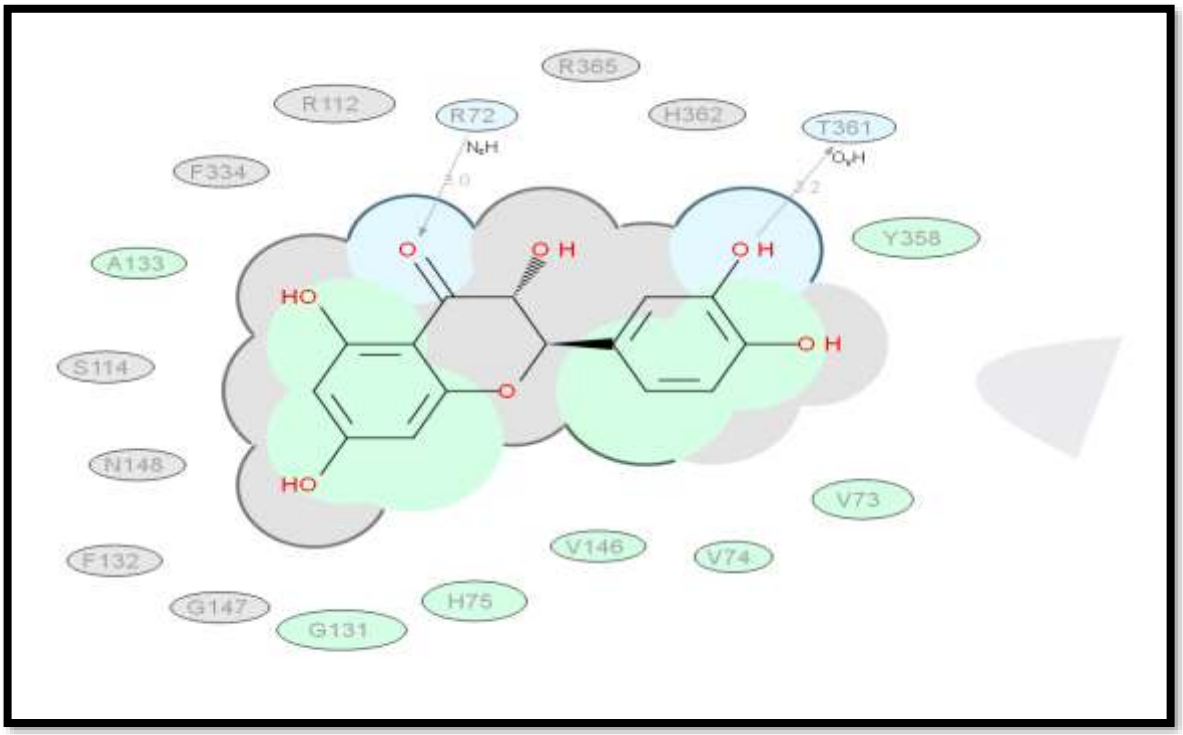
Table 3: Docking Scores of Compound No. 2 $C_{15}H_{12}O_7$ and Ascorbic Acid.

Enzyme	Compound	Docking Score
Human Erythrocyte CAT	$C_{15}H_{12}O_7$	-28.20624
Human Erythrocyte CAT	Ascorbic Acid	-22.32259
Human Peroxiredoxin 3	$C_{15}H_{12}O_7$	-21.29366
Human Peroxiredoxin 3	Ascorbic Acid	-12.70578

Figure 2: 2D Molecular Docking Interaction diagram of Compound No. 2. $C_{15}H_{12}O_7$



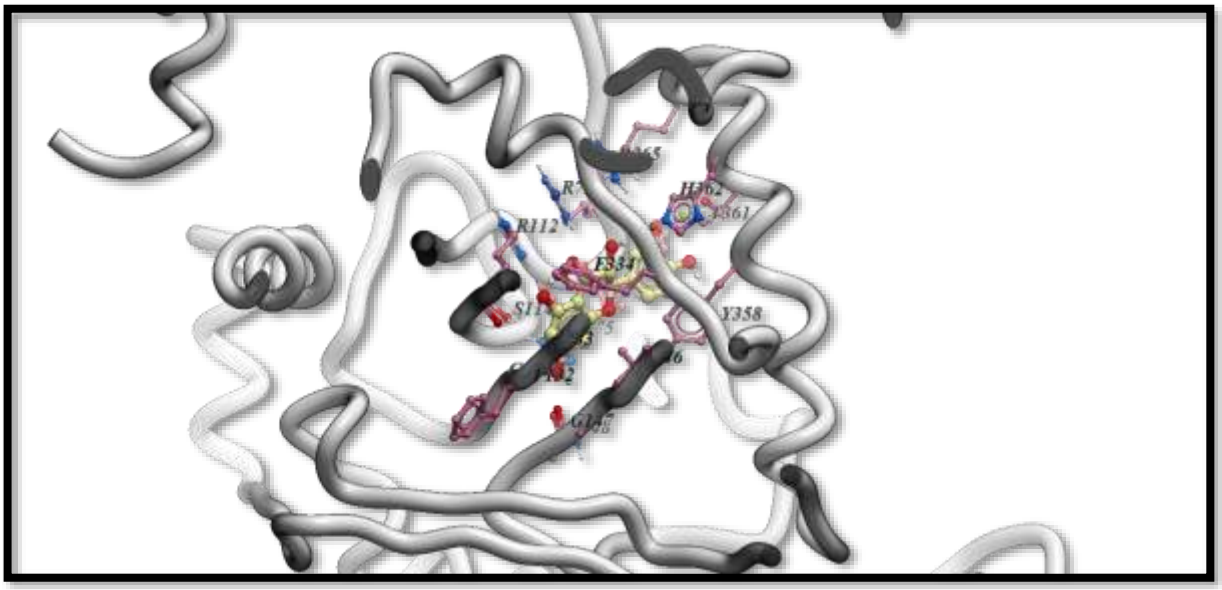


Figure 3: 2D Molecular Docking Interaction diagram of Compound No. 2. $C_{15}H_{12}O_7$ with Human Erythrocyte protein.

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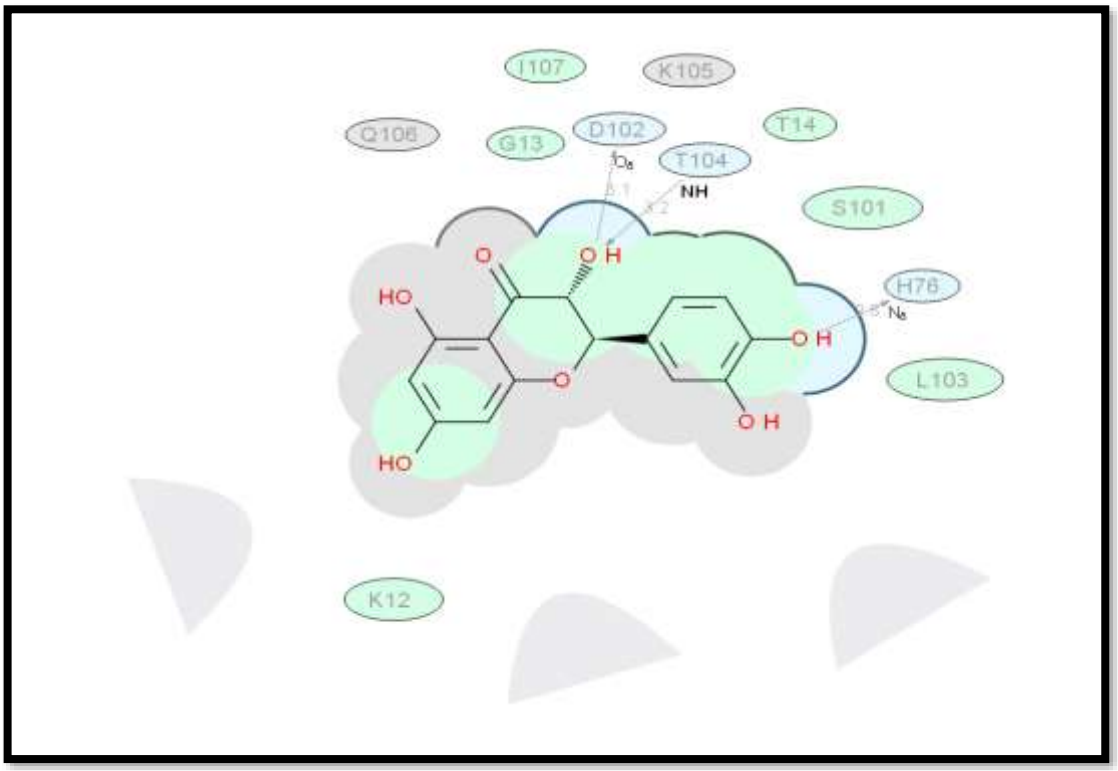

Figure 4: 2D Molecular Docking Interaction diagram of Compound No. 2. $C_{15}H_{12}O_7$ with Human Peroxidin 3 protein.

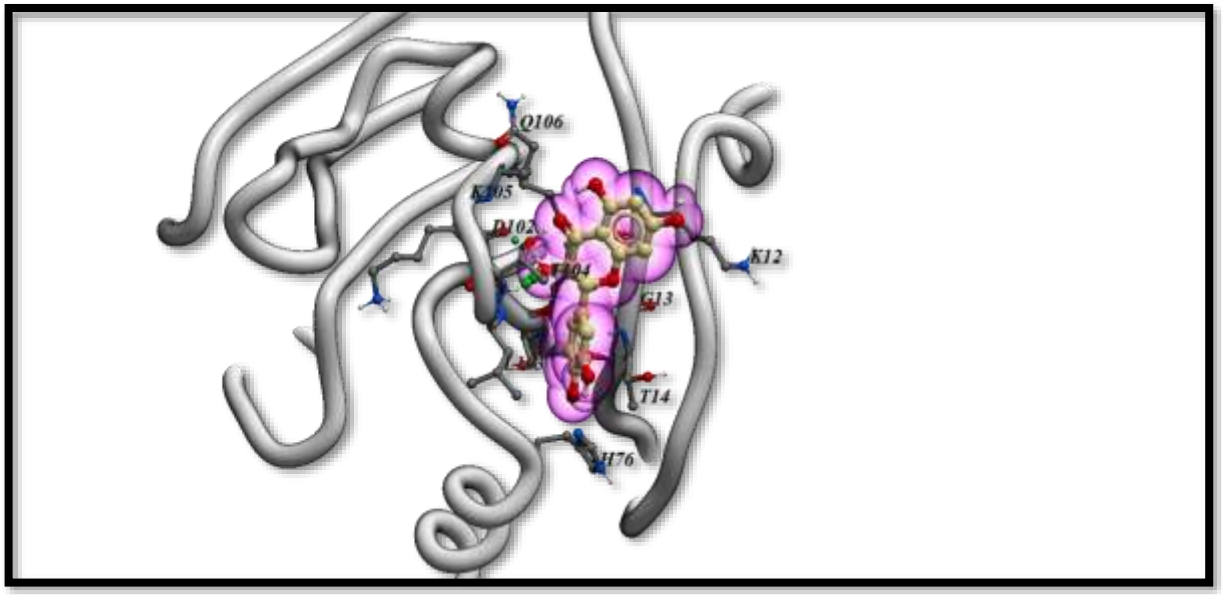

Figure 5: 3D Molecular Docking Interaction diagram of Compound No. 2. $C_{15}H_{12}O_7$ with Human Peroxidin 3 protein.

Discussion

The comprehensive in-silico analysis of astilbin related similar compounds underscores its potential as a potent antioxidant agent. The Swiss Similarity studies provided a robust framework for identifying structurally similar compounds, while ADME and toxicity predictions confirmed its favourable pharmacokinetic and safety profiles. Cytoscape network analysis elucidated the complex interactions within antioxidant pathways, and molecular docking studies validated astilbin's strong binding affinities to critical enzymes involved in oxidative stress defense. Comparative analysis with ascorbic acid further underscores astilbin's therapeutic potential.

Conclusion

Astilbin, derived from the rhizomes of Smilax glabra, exhibits promising antioxidant properties validated through comprehensive in-silico studies. The favourable ADME profile, low toxicity, and strong binding affinities to key antioxidant enzymes position astilbin as a viable candidate for further experimental validation and potential therapeutic application in antioxidant therapy.

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