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Mechanistic insights into the anti-aging potential of *Centella asiatica* via network pharmacology and molecular docking

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ABSTRACT

Network pharmacology is utilized to leverage computational power and big data to elucidate molecular function and biological processes, describing the potential mechanism of medicinal plants in certain diseases. In this study, a network pharmacology approach was used to analyze unbiased potential mechanisms of *Centella asiatica* in aging. From the analysis, 28 core protein targets were predicted, showing potential mechanisms of action in the cellular senescence pathway. Key protein targets associated with aging biological processes include PTEN, TP53, MAPK3, AKT1, MYC, IL6, and SIRT1. These proteins contribute to aging modulation by regulating cell proliferation, survival, and repair mechanisms; MYC, AKT1, and MAPK3 promote controlled cell growth; PTEN and TP53 prevent abnormal proliferation and ensure damaged cells undergo repair or apoptosis; while SIRT1 activation supports longevity through DNA repair, and IL-6 inhibition helps reduce inflammation. These interconnected activities suggest that *C. asiatica* has broad targets and the ability to integrate various biological pathways, making it an ideal anti-aging candidate. Bioactive compounds of *C. asiatica*, including Quercetin, Apigenin, Rutin, and Ursolic Acid, show high binding activity toward associated protein targets. Molecular docking with cavity-based blind docking indicates binding affinity lower than −5, suggesting strong potential for these compounds to exert their anti-aging effects *in vivo*.

INTRODUCTION

Aging is marked by a decline in tissue and organ repair, leading to reduced physiological reserves and the development of age-related diseases [1]. Research on aging focuses on understanding its physiological origin, biological responses, and potential interventions to delay aging [2,3]. The UN World Social Report predicts that by 2050, the global population aged 65 and above will reach 1.6 billion, highlighting the need for interventions to promote successful aging [4]. Lifestyle choices, such as a healthy diet and regular exercise, are essential in enhancing longevity, while herbal supplements with antioxidant and anti-inflammatory properties show promise in delaying aging [5–8]. *Centella asiatica*, known for its antioxidant polyphenols, has been studied for its anti-aging effects, including telomere preservation and enhanced survival in *Drosophila melanogaster*, although its bioactive compounds and mechanisms remain unclear [9–11].

Nowadays, drug discovery uses more computational approaches to better understand the underlying interactions between various drugs and their targets. This marks a shift from traditional methods, focusing only on one drug/one target/one therapeutic effect, to a more modern method. Among the modern methods is network pharmacology, which employs computational power to systematically map the molecular interactions of drug molecules within the biological system, followed by molecular docking, which predicts potential *in vivo* interactions. Its application extends beyond drug discovery to include drug repurposing, where known compounds are evaluated for new therapeutic use through unbiased analysis

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of all potential targets [12]. Thus, to confirm the previous research on *C. asiatica*'s potency as an anti-aging agent and to further identify the bioactive compounds and their mechanism of action contributing to those effects, network pharmacology and molecular docking analysis were conducted to explore the mechanism underlying its therapeutic potential as an anti-aging agent.

MATERIALS AND METHODS

The network pharmacology and molecular docking analysis were conducted using various databases/software, as listed in Table 1. The research workflow is illustrated in Figure 1.

Bioactive compounds data collection

The bioactive compounds associated with *C. asiatica* were collected from two databases, which are TCMSP (https://old.tcmsp-e.com/tcmsp.php) and BATMAN-TCM 2.0 (http://bionet.ncpsb.org.cn/batman-tcm/) [13,14]. The keyword used in both databases was "*Centella asiatica*". The bioactive compounds were then selected based on their oral bioavailability and Lipinski's rules of five characteristics, which were assessed using data from the SwissADME database. The criteria for oral bioavailability were set at a minimum of 30%, while drug-likeness shows not more than one violation of Lipinski's rules of five [15,16]. Some bioactive compounds, mostly high molecular weight compounds, cannot be analyzed using this tool; however, these compounds were included in the analysis if there is any published *in vitro* or *in vivo* data that shows their anti-aging properties [17].

Bioactive compounds-related protein targets data collection

Protein targets associated with bioactive compounds were predicted using several databases, including STP (http://www.swisstargetprediction.ch/), PharmMapper (https://www.lilab-ecust.cn/pharmmapper/), and HIT (https://hit2.badd-cao.net/) [18–22]. In STP, protein target prediction utilized the canonical SMILES of each bioactive compound. The species was restricted to *Homo sapiens*. For PharmMapper, the predictions were based on the 2D structures of the compounds in sdf format. Maximum generated conformations and Number of Reserved Matched Targets were set to 1,000, and targets set were set to "Human Protein Targets Only". While in HIT, only protein targets from compounds with a similarity value of 1.0 to the input canonical SMILES were included in the analysis. These protein targets were then supplemented with their UniProt ID and gene names from UniProt (https://www.uniprot.org/) for further identification and analysis purposes [23].

Aging-related protein targets data collection

Protein targets associated with aging were collected from GeneCards (https://www.genecards.org/) using the "cellular aging" keyword, to capture genes and proteins involved in cellular-level aging mechanisms and avoid the overly broad scope of aging. Additional protein targets were sourced from a publication on the aging interactome, which presents an interactome-based approach to aging by identifying protein–protein interaction networks associated with aging processes and complements the GeneCards-derived targets by adding interaction-based biological context [24,25]. These protein targets were then supplemented with their UniProt ID and gene names from UniProt (https://www.uniprot.org/) for further identification and analysis purposes [23].

Protein–protein interaction network construction

The protein–protein interaction network was constructed using the STRING version 2.1.1 (https://apps.cytoscape.org/apps/stringapp) plugin in Cytoscape version 3.10 [26]. The network was built by intersecting the aging-related protein target network with the bioactive compound-related protein target network [17]. To ensure the reliability of the interactions included, only those with a combined STRING score greater than 0.7 were retained, reflecting a high-confidence

Table 1. Database and software used in study.

No.	Database/Software	Function
1	BATMAN-TCM	Collection of bioactive compound related to *Centella asiatica*.
2	CB Dock	Prediction of protein binding sites and performing flexible docking of ligands.
3	CluGO	Integration of GO terms to generate functionally grouped networks.
4	CytoNCA	Identification of key proteins (nodes) based on centrality measures.
5	Cytoscape	Biological network visualization and analysis platform.
6	DAVID	Identification of functional annotation and enrichment analysis of gene/protein list.
7	Discovery Studio	Preparation of the protein structure before molecular docking studies.
8	Enrichr	Identification of gene set enrichment analysis.
9	GeneCards	Collection of protein targets related to aging.
10	HIT	Collection of protein targets related to bioactive compound.
11	KEGG	Collection of biochemical pathway.
12	KEGG Mapper	Identification of associated protein targets in biochemical pathway.
13	MCODE	Identification of highly interconnected regions (clusters) in PPI networks.
14	PDB	Collection of protein 3D structures.
15	PubChem	Collection of cannonical SMILES and 2D structures of bioactive compounds.
16	PharmMapper	Collection of protein targets related to bioactive compound.
17	STRING	Construction of protein–protein interaction (PPI) networks based on known and predicted interactions.
18	STP	Collection of protein targets related to bioactive compound.
19	SwissADME	Collection of Oral Bioavailability and Drug Likeness properties of bioactive compound.
20	TCMSP	Collection of bioactive compound related to *Centella asiatica*.

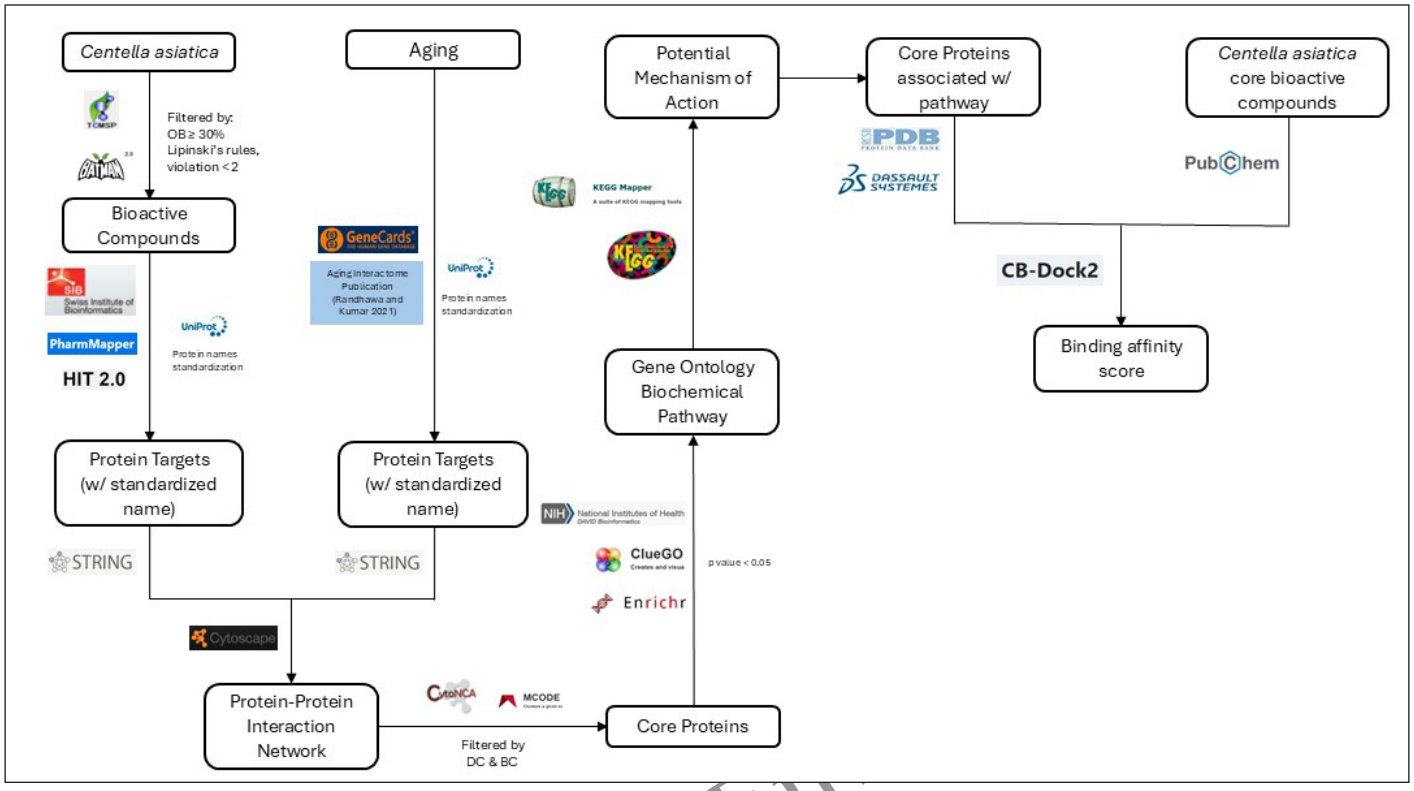


Figure 1. Research workflow.

threshold commonly applied in PPI network analyses. Further analysis was conducted in Cytoscape for visualization and interpretation of the interaction.

Protein–protein interaction network analysis

The protein–protein interaction network was analyzed using CytoNCA version 2.1.6 (https://apps.cytoscape.org/apps/cytonca) plugin in Cytoscape version 3.10 for its degree centrality (DC) and betweenness centrality (BC) calculation, which were used to further determine the core protein within the protein–protein interaction network [27]. To cluster the network into cluster(s) with highly interconnected regions, the network was analyzed using the MCODE version 2.0.3 (https://apps.cytoscape.org/apps/mcode) plugin in Cytoscape version 3.10 [28].

Gene ontology and pathway enrichment

The gene ontology and pathway of the core proteins were identified using the Enrichr (https://maayanlab.cloud/Enrichr/) database [29–31]. The pathway with a *p*-value of less than 0.05 is considered to be potentially relevant for those core proteins. Multiple testing correction was performed using the Benjamini–Hochberg procedure to control the false discovery rate, and the adjusted *p*-values are reported accordingly. The pathway was obtained from the KEGG database (https://www.kegg.jp/kegg/pathway.html), and the KEGG mapper database (https://www.genome.jp/kegg/mapper/) was used to pinpoint the core protein targets in the selected pathway [32–34].

A two-step ClueGO analysis was conducted to understand the molecular functions and biological processes associated with the selected pathway. The first analysis only focused on the molecular functions of the core protein targets. This was done to gain a general understanding of how the core proteins might work *in vivo*. The second analysis was conducted using pathway-relevant protein targets, exploring both molecular functions and biological processes of those proteins. This was done further to predict their specific contribution within the selected pathway. Both analyses were done using the ClueGO version 2.5.10 plugin (https://apps.cytoscape.org/apps/cluego) in Cytoscape version 3.10 [35]. The visualization of the results was done on the same platform. ClueGO groups proteins based on their shared functions or interactions to show the interconnectedness of the proteins, influencing the whole process. Therefore, it gives insight into the most relevant hallmarks of aging influenced by these proteins and how they might be targeted to slow the aging process or to treat age-related diseases.

Molecular docking analysis

Molecular docking analysis used *C. asiatica* core bioactive compounds and reference compound Resveratrol as ligands, and aging-associated core protein targets as proteins. The core bioactive compounds have the most relevant number of core protein targets within the pathway, whereas the core protein targets are the core proteins that contribute to the pathway. The 3D structures of the protein were collected from PDB (https://www.rcsb.org/), whereas the 2D structures of

the ligands were collected from PubChem (https://pubchem.ncbi.nlm.nih.gov/) [15,36,37]. Initially, each protein structure was prepared using Discovery Studio before being used in the molecular docking analysis. The molecular docking analysis was done using the CB Dock (https://cadd.labshare.cn/) website with an auto-blind docking feature [38,39]. Due to the exploratory nature of the work and the complexity of defining suitable control compounds for broadly characterized aging-related protein targets, this study does not include validation using negative controls. Therefore, blind docking and binding affinity analysis were employed as an initial validation step for identifying potential binding regions and scores.

RESULTS

Data collection

The number of bioactive compounds data collected from TCMSP and BATMAN are 141. After removing some duplicates, the final set of bioactive compounds associated with *C. asiatica* was further evaluated for its oral bioavailability, and Lipinski's rule of five violations was 134 bioactive compounds. Among these, some high molecular weight compounds, such as madecassoside and asiaticoside, could not be analyzed using SwissADME. However, based on the literature review, these compounds have shown anti-aging potential and were included in the analysis [11,17]. Following this screening, a total of 73 compounds fulfill the oral bioavailability and Lipinski's rules of five violation requirements. These compounds were selected to be further analyzed in this network pharmacology study.

Protein targets associated with the selected bioactive compounds were obtained from STP, PharmMapper, and HIT databases, resulting in 19,053 protein targets in total. From the initial dataset of 19,053 targets, identical entries were removed based on UniProt ID, resulting in 1,361 unique targets, regarded as *C. asiatica*-related protein targets. As for protein targets related to aging, 224 protein targets were collected from GeneCard using "cellular aging" keywords. Another 483 were collected from Randhawa and Kumar [25] aging interactome publication. After removing duplicates, the aging-related protein target used in the analysis was 634 protein targets.

Protein–protein interaction network construction

Each category of protein targets, aging-related and *C. asiatica*-related, was constructed using the STRING database into two different networks, resulting in an aging-related network and a *C. asiatica*-related network. Protein–protein interaction networks were then constructed by intersecting these two networks using Cytoscape, resulting in *C. asiatica* and an aging network with 240 nodes and 7,493 edges, as visualized using Cytoscape, shown in Figure 2. In this network, nodes represent protein targets, while edges represent the interaction between protein targets.

Protein–Protein Interaction Network analysis

To identify core proteins in the network—meaning the proteins that are crucial to the network—a CytoNCA centrality analysis was used. These core proteins are regarded as important because of their position in the topological structure of the

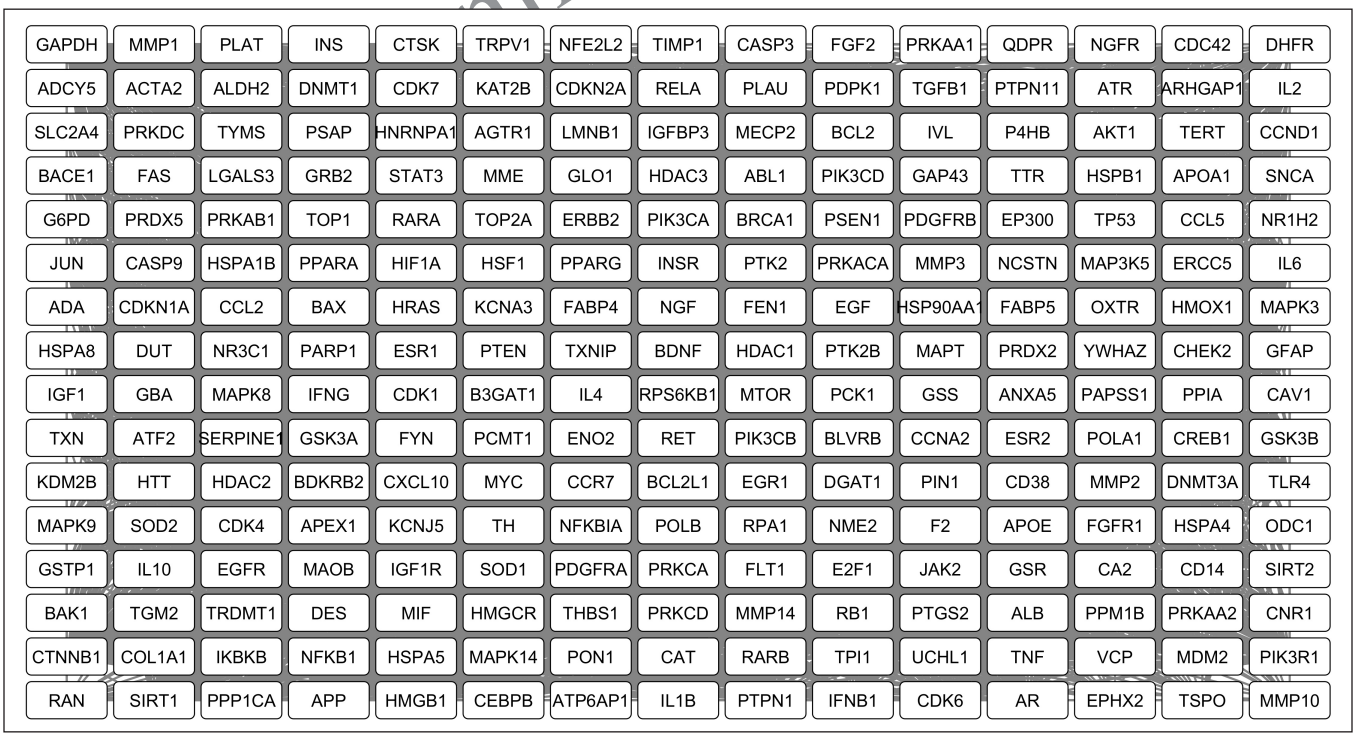


Figure 2. Protein–protein interaction (PPI) network of intersecting protein targets between *Centella asiatica*-related targets and aging-related targets, highlighting shared key proteins that may contribute to its potential anti-aging mechanisms. The network consists of 240 nodes and 7,493 edges. Nodes in square shape represent protein targets, while edges represent interactions between these proteins.

network. Metrics such as DC and BC were used to determine the importance of each protein. These metrics were calculated and applied to filter the proteins. Ideally, core proteins are highly connected within the network; therefore, they hold a key role in the overall mechanism. In this study, a protein is considered a core protein if it has a DC value that is more than twice the median of the DC and twice the median of the BC. A total of 28 protein targets met the requirements and were therefore classified as core proteins of the network, as outlined in Table 2.

In research related to aging, DC and BC values are regarded as more relevant parameters because DC shows the number of direct interactions of a protein with another protein in a network. DC value directly describes how important a protein is in a network because a protein with a high DC value tends to influence more biological pathways. On the other hand, in the aging process, many pathways are related interdependently. In this condition, a high BC value becomes important to identify proteins that are critical in connecting various biological processes. Proteins with high BC value are hubs between different pathways and help protect complex biological mechanism integration.

Table 2. Core protein targets.

No.	Gene	DC	BC
1	GAPDH	194	2,781.692
2	TP53	183	2,122.807
3	AKT1	182	1,917.274
4	INS	163	1,475.949
5	ALB	160	1,214.544
6	TNF	160	958.3428
7	JUN	159	1,077.336
8	IL6	159	958.5557
9	MYC	158	1,103.816
10	BCL2	156	806.6445
11	CTNNB1	153	642.2092
12	STAT3	152	707.8372
13	EGFR	151	799.5482
14	CASP3	151	779.927
15	IL1B	144	684.0333
16	HSP90AA1	142	750.1618
17	ESR1	141	672.7091
18	HIF1A	139	440.0974
19	MAPK3	137	628.4423
20	PTEN	134	445.4079
21	PPARG	129	644.4901
22	SIRT1	125	564.0872
23	PTGS2	121	430.3908
24	HSPA4	119	439.9843
25	EP300	115	688.4621
26	APOE	96	479.5161
27	PRKACA	85	660.2856
28	HSPA8	79	483.8716

These core proteins were then mapped into a core protein network, as shown in Figure 3. To identify whether the network consists of several clusters, the network was analyzed using MCODE. The result from MCODE analysis shows that the network belongs only to one cluster, which consists of 28 protein targets.

Gene ontology and pathway enrichment

Enrichment analysis was done on these 28 protein targets to identify the most relevant cellular components, molecular function, biological process, and biological pathway in a broader biological context. Statistically, a significant result is marked with an adjusted *p*-value at a maximum of 0.05. The top 10 cellular components, molecular function, and biological process results are outlined in Table 3.

For the biological pathway, the enrichment analysis shows that the most significant pathway is related to cancer, with a *p*-value of 2.73E-15 (FDR-adjusted). This result aligns with the understanding that aging and cancer share a lot of common biological pathways, such as cellular senescence, inflammation, apoptosis, and DNA damage. This finding reinforces the interconnectedness of aging and tumorigenesis. However, in the context of this study, the cellular senescence pathway is emphasized because it directly describes the mechanism of aging and connects widely to the hallmarks of aging. This pathway is also a highly significant pathway with a *p*-value of 4.89E-06 (FDR-adjusted).

ClueGO grouped the molecular function of the core protein targets into eight groups. The top three groups, namely Group 5, 7, and 6, with *p* values of 9.09E-12, 2.12E-10, and

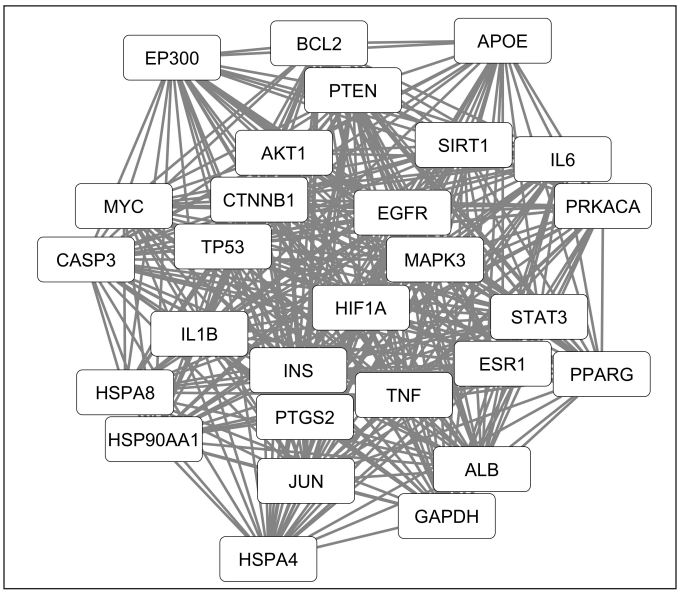


Figure 3. Core protein–protein interaction (PPI) network representing key protein targets associated with *Centella asiatica* and aging. Nodes represent proteins, while edges represent interactions between them. The core network consists of highly interconnected proteins that may play central roles in mediating the biological effects of *Centella asiatica* in aging-related pathways.

Table 3. Top 10 enriched GO terms in the cellular components (CC), molecular function (MF), and biological process (BP) categories for the core proteins.

GO category	ID	Term	Adjusted *p* Value	Genes
CC	GO:0005634	Nucleus	2.86E-09	HSPA8; JUN; HSP90AA1; HSPA4; STAT3; PTEN; HIF1A; ESR1; SIRT1; EGFR; MYC; CASP3; ALB; BCL2; AKT1; EP300; CTNNB1; PPARG; APOE; PRKACA; GAPDH; TP53; MAPK3
CC	GO:0043231	Intracellular membrane-bounded organelle	3.09E-08	HSPA8; JUN; HSP90AA1; HSPA4; STAT3; PTEN; HIF1A; ESR1; SIRT1; EGFR; MYC; CASP3; ALB; BCL2; AKT1; EP300; CTNNB1; PPARG; APOE; PRKACA; GAPDH; TP53; MAPK3
CC	GO:0000791	Euchromatin	1.15E-05	JUN; CTNNB1; ESR1; SIRT1
CC	GO:0070013	Intracellular organelle lumen	3.29E-05	HSPA8; HSP90AA1; IL6; ALB; APOE; PTGS2; EGFR; INS; MAPK3
CC	GO:0005788	Endoplasmic reticulum lumen	3.87E-05	IL6; ALB; APOE; PTGS2; INS; MAPK3
CC	GO:0030665	Clathrin-coated vesicle membrane	0.003276	HSPA8; APOE; EGFR
CC	GO:0031965	Nuclear membrane	0.003276	BCL2; PTGS2; SIRT1; GAPDH
CC	GO:0031982	Vesicle	0.003276	AKT1; APOE; GAPDH; EGFR
CC	GO:0071682	Endocytic vesicle lumen	0.003731	HSP90AA1; APOE
CC	GO:0060205	Cytoplasmic vesicle lumen	0.004698	HSPA8; HSP90AA1; INS
MF	GO:0140297	DNA-binding transcription factor binding	9.76E-12	JUN; MYC; STAT3; BCL2; EP300; CTNNB1; PPARG; HIF1A; SIRT1; TP53; MAPK3
MF	GO:0031625	Ubiquitin protein ligase binding	5.80E-09	HSPA8; JUN; HSP90AA1; BCL2; CTNNB1; PRKACA; HIF1A; TP53; EGFR
MF	GO:0044389	Ubiquitin-like protein ligase binding	6.85E-09	HSPA8; JUN; HSP90AA1; BCL2; CTNNB1; PRKACA; HIF1A; TP53; EGFR
MF	GO:0061629	RNA Polymerase II-specific DNA-binding transcription factor binding	2.51E-08	JUN; STAT3; EP300; CTNNB1; PPARG; HIF1A; SIRT1; TP53
MF	GO:0001221	Transcription Coregulator binding	1.36E-07	MYC; EP300; CTNNB1; PPARG; HIF1A; ESR1
MF	GO:0003677	DNA binding	2.96E-06	JUN; MYC; STAT3; ALB; BCL2; EP300; PPARG; HIF1A; TP53; EGFR
MF	GO:0016922	Nuclear receptor binding	1.13E-05	EP300; CTNNB1; HIF1A; ESR1; SIRT1
MF	GO:0002020	Protease binding	1.50E-05	PTEN; BCL2; TNF; TP53; INS
MF	GO:0000976	Transcription Cis-regulatory region binding	5.36E-05	JUN; MYC; STAT3; PPARG; TNF; HIF1A; TP53
MF	GO:0097718	Disordered domain specific binding	6.66E-05	HSP90AA1; GAPDH; TP53
BP	GO:1902893	Regulation Of miRNA Transcription	7.33E-14	JUN;MYC;STAT3;PPARG;TNF;HIF1A;ESR1;TP53;EGFR
BP	GO:1903508	Positive Regulation Of Nucleic Acid-Templated Transcription	7.33E-14	JUN;STAT3;TNF;HIF1A;ESR1;EGFR;IL6;MYC;IL1B;AKT1;EP300;CTNNB1;PPARG;APOE;TP53
BP	GO:1902895	Positive regulation Of miRNA transcription	3.21E-13	JUN;MYC;STAT3;PPARG;TNF;HIF1A;TP53;EGFR
BP	GO:2000630	Positive Regulation Of miRNA Metabolic Process	7.46E-13	JUN;MYC;STAT3;PPARG;TNF;HIF1A;TP53;EGFR
BP	GO:0050999	Regulation of nitric-oxide synthase activity	1.52E-12	IL1B;AKT1;APOE;HIF1A;TNF;EGFR;INS
BP	GO:0051091	Positive regulation of DNA-binding transcription factor activity	3.25E-12	IL6;IL1B;STAT3;PTEN;AKT1;EP300;CTNNB1;PPARG;TNF;ESR1;INS
BP	GO:0031328	Positive regulation Of cellular biosynthetic process	4.39E-12	HSP90AA1;IL6;IL1B;AKT1;CTNNB1;PTGS2;TNF;HIF1A;SIRT1;INS
BP	GO:0045893	Positive regulation Of DNA-templated transcription	5.41E-12	JUN;STAT3;TNF;HIF1A;ESR1;SIRT1;EGFR;IL6;MYC;IL1B;AKT1;EP300;CTNNB1;PPARG;APOE;TP53;MAPK3
BP	GO:0010628	Positive regulation Of Gene expression	1.06E-10	IL6;MYC;IL1B;STAT3;AKT1;EP300;PPARG;TNF;HIF1A;GAPDH;TP53;INS
BP	GO:0032770	Positive regulation Of monooxygenase activity	1.34E-10	IL1B;AKT1;APOE;HIF1A;TNF;INS

Table 4. Top 3 ClueGO analysis results for the core protein groups in the molecular function category.

Groups	Groups Adjusted *p* value	ID	Term	Term Adjusted *p* value	Associated Genes
5	9.09E-12	GO:0003720	Telomerase activity	7.00E-11	[CTNNB1, HSP90AA1, MAPK3, MYC, PPARG, PTEN, TP53]
5	9.09E-12	GO:0003964	RNA-directed DNA polymerase activity	1.82E-10	[CTNNB1, HSP90AA1, MAPK3, MYC, PPARG, PTEN, TP53]
5	9.09E-12	GO:0051972	Regulation of telomerase activity	4.03E-09	[CTNNB1, HSP90AA1, MAPK3, MYC, PPARG, TP53]
5	9.09E-12	GO:0034061	DNA polymerase activity	4.19E-09	[CTNNB1, HSP90AA1, MAPK3, MYC, PPARG, PTEN, TP53]
5	9.09E-12	GO:0019903	Protein phosphatase binding	4.77E-08	[BCL2, CTNNB1, EGFR, HSP90AA1, PPARG, STAT3, TP53]
5	9.09E-12	GO:0051973	positive regulation of Telomerase activity	2.38E-06	[CTNNB1, HSP90AA1, MAPK3, MYC]
5	9.09E-12	GO:0097718	Disordered domain specific binding	2.73E-06	[CTNNB1, GAPDH, HSP90AA1, TP53]
5	9.09E-12	GO:0001046	Core promoter sequence-specific DNA binding	3.12E-04	[CTNNB1, MYC, TP53]
7	2.12E-10	GO:0004517	Nitric-oxide synthase activity	1.09E-15	[AKT1, APOE, EGFR, ESR1, HIF1A, HSP90AA1, IL1B, INS, TNF]
7	2.12E-10	GO:0016709	Oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, NAD(P)H as one donor, and incorporation of one atom of oxygen	3.57E-13	[AKT1, APOE, EGFR, ESR1, HIF1A, HSP90AA1, IL1B, INS, TNF]
7	2.12E-10	GO:0050999	Regulation of nitric-oxide synthase activity	7.24E-12	[AKT1, APOE, EGFR, HIF1A, IL1B, INS, TNF]
7	2.12E-10	GO:0032768	Regulation of monooxygenase activity	6.41E-11	[AKT1, APOE, EGFR, HIF1A, IL1B, INS, TNF]
7	2.12E-10	GO:0004497	Monooxygenase activity	6.84E-11	[AKT1, APOE, EGFR, ESR1, HIF1A, HSP90AA1, IL1B, INS, TNF]
7	2.12E-10	GO:0032770	Positive regulation of monooxygenase activity	3.02E-10	[AKT1, APOE, HIF1A, IL1B, INS, TNF]
7	2.12E-10	GO:0030235	Nitric-oxide synthase regulator activity	3.28E-09	[AKT1, EGFR, ESR1, HSP90AA1]
7	2.12E-10	GO:0051000	Positive regulation of nitric-oxide synthase activity	4.41E-09	[AKT1, APOE, HIF1A, INS, TNF]
7	2.12E-10	GO:0051341	Regulation of oxidoreductase activity	4.58E-09	[AKT1, APOE, EGFR, HIF1A, IL1B, INS, TNF]
7	2.12E-10	GO:0051353	Positive regulation of oxidoreductase activity	1.04E-08	[AKT1, APOE, HIF1A, IL1B, INS, TNF]
6	1.78E-09	GO:0001221	Transcription coregulator binding	3.50E-07	[CTNNB1, EP300, ESR1, HIF1A, MYC, PPARG]
6	1.78E-09	GO:0016922	Nuclear receptor binding	8.77E-07	[CTNNB1, EP300, ESR1, HIF1A, PPARG, SIRT1]
6	1.78E-09	GO:0002039	p53 binding	9.45E-07	[EP300, HIF1A, PTEN, SIRT1, TP53]
6	1.78E-09	GO:0098531	Ligand-activated transcription factor activity	1.18E-04	[ESR1, PPARG, STAT3]
6	1.78E-09	GO:0004879	Nuclear receptor activity	1.18E-04	[ESR1, PPARG, STAT3]
6	1.78E-09	GO:0043388	Positive regulation of DNA binding	2.14E-04	[CTNNB1, EP300, PPARG]
6	1.78E-09	GO:0030331	Nuclear estrogen receptor binding	2.58E-04	[CTNNB1, ESR1, PPARG]
6	1.78E-09	GO:0070888	E-box binding	2.65E-04	[HIF1A, MYC, PPARG]
6	1.78E-09	GO:0001223	Transcription coactivator binding	3.64E-04	[EP300, ESR1, HIF1A]

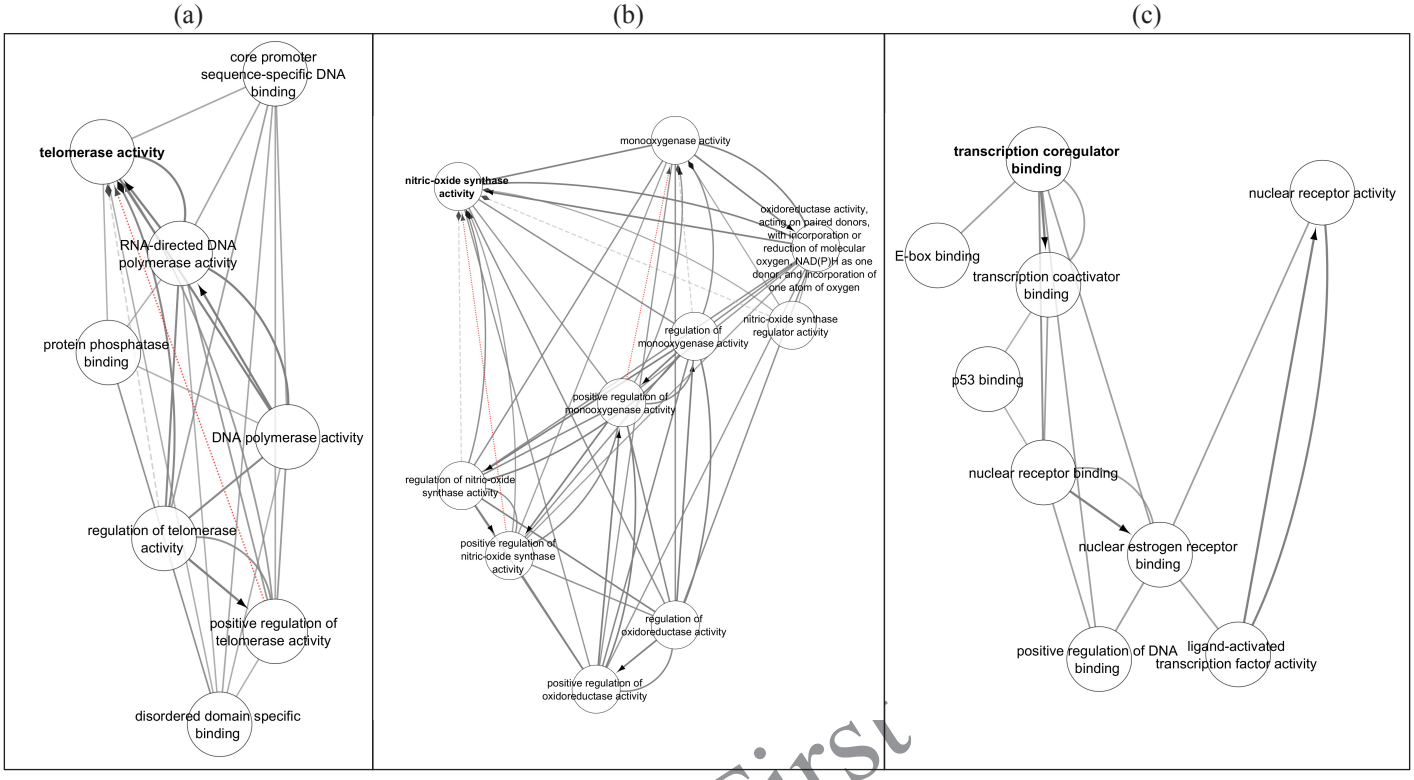


Figure 4. Top three ClueGO analysis results for the core protein groups in the molecular function category categorizing proteins based on their key biological roles in aging related mechanisms. The results highlight: (a) Group related to telomerase activity; (b) Group related to nitric-oxide synthase activity; and (c) Group related to Transcription coregulator binding. Bold labels indicate the most relevant functioins within each group. The network layout is structured to emphasize functional relationships, with proteins involved in similar biological processes positioned in closed proximity.

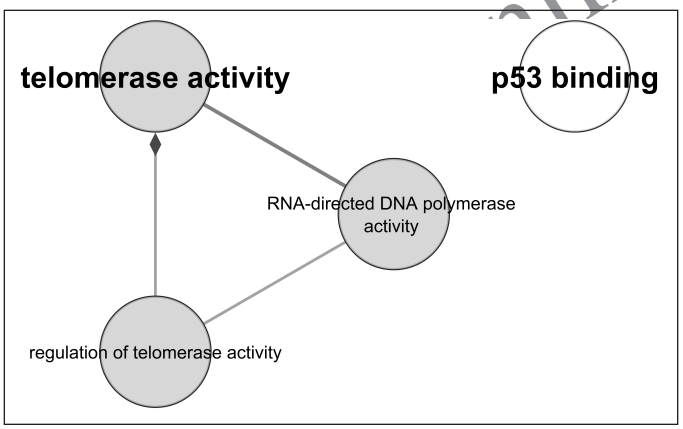


Figure 5. ClueGO analysis results for the cellular senescence pathway-associated protein groups in the molecular function category. The network layout enhances the visualization of functional relationships, grouping related molecular functions to highlight key biological process involved in cellular senescence. Bold labels indicate the most relevant functional terms.

1.78E-09, are related to telomerase activity, nitric oxide synthase activity, and transcription coregulator binding, respectively. The result of this analysis is outlined in Table 4 and visualized in Figure 4.

A second analysis using ClueGO was conducted to study the molecular function and biological process of seven protein targets associated with said cellular senescence pathway.

Table 5. ClueGO analysis results for the cellular senescence pathway-associated protein groups in the molecular function category.

Groups	ID	Term	Adjusted *p* value	Associated Genes
0	GO:0003720	Telomerase activity	1.32E-08	[MAPK3, MYC, PTEN, TP53]
0	GO:0003964	RNA-directed DNA polymerase activity	1.77E-08	[MAPK3, MYC, PTEN, TP53]
0	GO:0051972	Regulation of telomerase activity	1.75E-06	[MAPK3, MYC, TP53]
1	GO:0002039	p53 binding	1.98E-06	[PTEN, SIRT1, TP53]

This analysis helps identify which aging-related mechanisms these proteins influence, specifically related to the cellular senescence hallmark. The results of the analysis are visualized in Figure 5 and outlined in Table 5 for molecular function groups, and Figure 6 and Table 6 for biological process.

The biological processes are grouped into two groups, the white group (Group 0) with a *p*-value of 8.71E-13 and the grey group (Group 1) with a p-value of 5.07E-08. Both groups share overlapping functions, wherein the most significant function in both groups is the “leukocyte apoptotic process”, with the lowest *p*-value of 4.2E-09. Bold edges between the nodes show a strong relationship between biological functions.

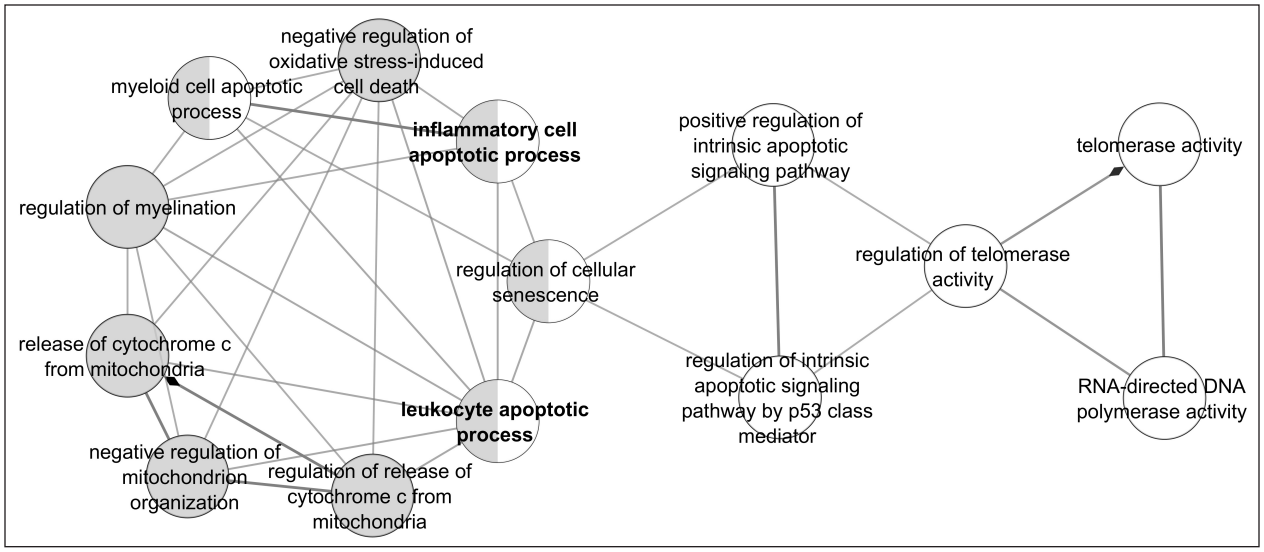


Figure 6. ClueGO analysis results for the cellular senescence pathway-associated protein groups in the Biological Process category. The network represents biological process enriched in the identified protein targets, proving insight into their potential roles in cellular senescence. Bold labels indicate the most relevant biological process.

Table 6. ClueGO analysis results for the cellular senescence pathway-associated protein groups in the biological process category.

Groups	Groups adjusted *p* value	ID	Term	Adjusted *p* value	Associated genes
0	8.71E-13	GO:0071887	Leukocyte apoptotic process	4.23E-09	[AKT1, IL6, PTEN, SIRT1, TP53]
0	8.71E-13	GO:0003720	Telomerase activity	4.61E-08	[MAPK3, MYC, PTEN, TP53]
0	8.71E-13	GO:0003964	RNA-directed DNA polymerase activity	7.61E-08	[MAPK3, MYC, PTEN, TP53]
0	8.71E-13	GO:0006925	Inflammatory cell apoptotic process	8.95E-07	[IL6, PTEN, SIRT1]
0	8.71E-13	GO:2001244	Positive regulation of intrinsic apoptotic signaling pathway	2.53E-06	[MYC, SIRT1, TP53]
0	8.71E-13	GO:1902253	Regulation of intrinsic apoptotic signaling pathway by p53 class mediator	3.23E-06	[MYC, SIRT1, TP53]
0	8.71E-13	GO:0051972	Regulation of telomerase activity	4.62E-06	[MAPK3, MYC, TP53]
0	8.71E-13	GO:0033028	Myeloid cell apoptotic process	5.14E-06	[IL6, PTEN, SIRT1]
0	8.71E-13	GO:2000772	Regulation of cellular senescence	5.52E-06	[PTEN, SIRT1, TP53]
1	5.07E-08	GO:0071887	Leukocyte apoptotic process	4.23E-09	[AKT1, IL6, PTEN, SIRT1, TP53]
1	5.07E-08	GO:0006925	Inflammatory cell apoptotic process	8.95E-07	[IL6, PTEN, SIRT1]
1	5.07E-08	GO:0001836	Release of cytochrome c from mitochondria	1.46E-06	[AKT1, IL6, TP53]
1	5.07E-08	GO:0010823	Negative regulation of mitochondrion organization	3.26E-06	[AKT1, IL6, TP53]
1	5.07E-08	GO:1903202	Negative regulation of oxidative stress-induced cell death	3.90E-06	[AKT1, IL6, SIRT1]
1	5.07E-08	GO:0090199	Regulation of release of cytochrome c from mitochondria	4.95E-06	[AKT1, IL6, TP53]
1	5.07E-08	GO:0031641	Regulation of myelination	5.14E-06	[AKT1, IL6, PTEN]
1	5.07E-08	GO:0033028	Myeloid cell apoptotic process	5.14E-06	[IL6, PTEN, SIRT1]
1	5.07E-08	GO:2000772	Regulation of cellular senescence	5.52E-06	[PTEN, SIRT1, TP53]

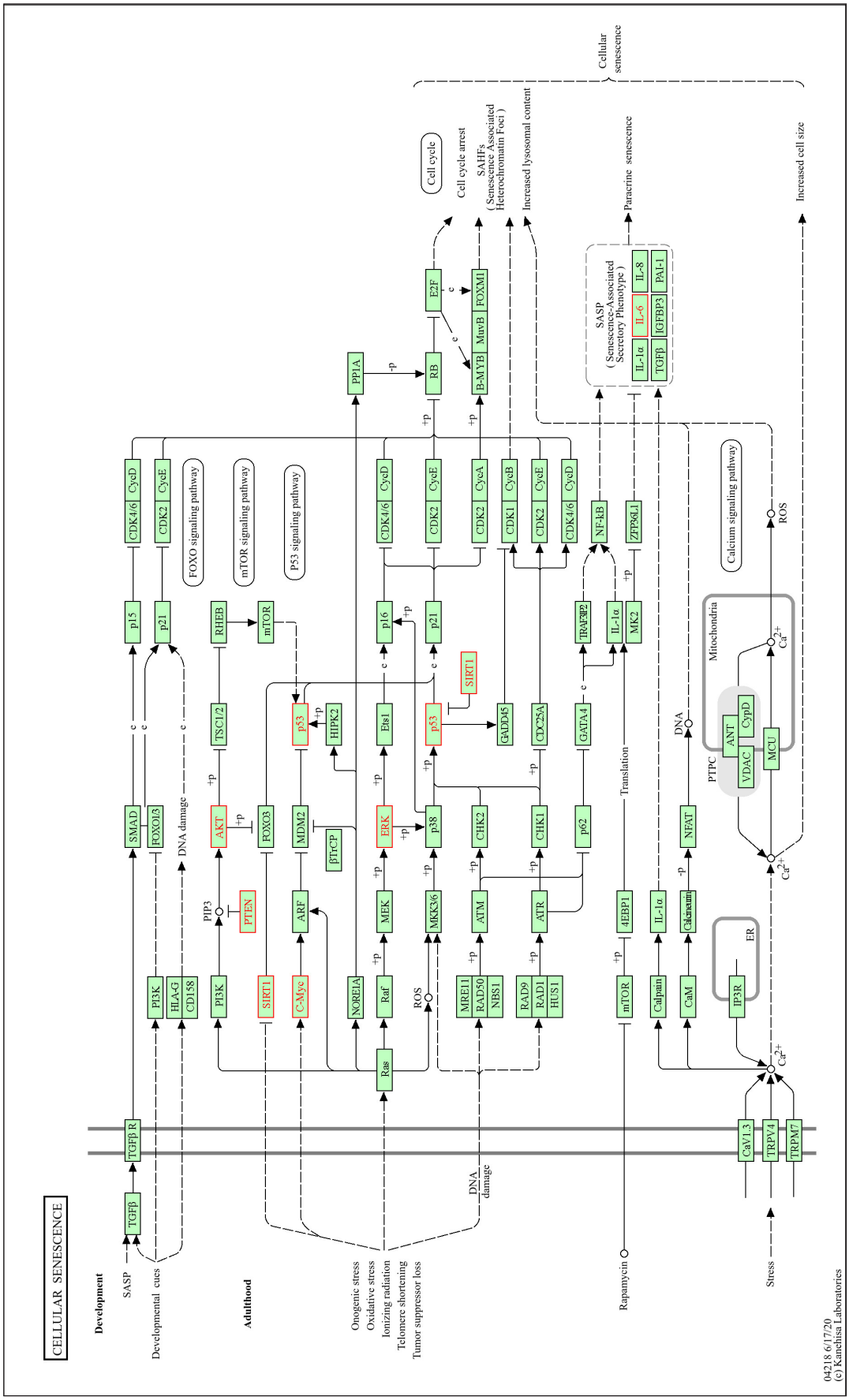


Figure 7. Putative targets of *Centella asiatica* in the cellular senescence pathway. This figure shows the KEGG cellular senescence pathway with core protein targets identified through network pharmacology and KEGG pathway enrichment analysis using DAVID Bioinformatics. Protein highlighted in red represents predicted targets of *Centella asiatica* bioactive compounds, mapped onto the generic KEGG pathway for visualization purposes.

Table 7. Molecular docking results for protein-ligand complexes.

Protein Ligand	Vina Score						
	PTEN	TP53	MAPK3	AKT1	MYC	SIRT1	IL6
Quercetin	−6.7	−7.7	−8.7	−9.5	−6.9	−9.2	−7.1
Apigenin	−6.5	−7.5	−8.5	−9.0	−6.8	−9.0	−6.7
Rutin	−8.5	−9.7	−9.7	−11.4	−6.9	−8.5	−7.0
Ursolic Acid	−7.1	−9.0	−8.4	−8.7	−6.6	−9.1	−6.9
Resveratrol (Reference)	−6.1	−6.8	−8.2	−8.2	−6.1	−8.3	−6.1

Molecular docking analysis

The result of molecular docking analysis of Quercetin, Apigenin, Rutin, and Ursolic Acid toward PTEN, TP53, MAPK3, AKT1, MYC, SIRT1, and IL6, shows negative values, preferably less than −5, indicating that the high binding capacity of these bioactive compounds allows them to bind to these proteins readily. Among these proteins, Ursolic Acid more often shows different binding sites than the other three bioactive compounds. Additionally, the vina score of these four *C. asiatica* bioactive compounds indicates more negative binding scores compared to Resveratrol, which was used as a reference. The molecular docking result is shown in Table 7. The visualization of molecular docking of the protein and ligand complexes is shown in Table 8.

DISCUSSION

The network pharmacology approach was employed to explore the molecular mechanisms underlying the anti-aging potential of *C. asiatica* [40]. Bioactive compounds from *C. asiatica* were screened and mapped to their predicted protein targets, which were then intersected with known aging-related targets. This intersection yielded 28 core proteins, identified through centrality analysis using degree and betweenness metrics. To gain insights into the biological relevance of these proteins, subsequent enrichment analysis revealed a strong association between these targets and key aging-related pathway, notably cellular senescence, apoptosis, and telomere maintenance. Functional clustering using ClueGO highlighted pathways related to transcriptional regulation, nitric oxide synthase activity, and telomerase regulation.

Seven of the 28 core proteins—TP53, PTEN, MAPK3, AKT1, MYC, IL6, and SIRT1—were mapped directly to the cellular senescence pathway (Fig. 7), suggesting their central role in meditating the anti-aging effects of *C. asiatica*. This is particularly important because cellular senescence represents a key hallmark of aging, wherein cells permanently exit the cell cycle in response to various stressors, including DNA damage, oxidative stress, and telomere attrition. While senescence serves as a protective mechanism to prevent malignant transformation, the accumulation of senescent cells over time contributes to age-related tissue dysfunction [41]. These cells adopt a pro-inflammatory secretory profile—known as the senescence-associated secretory phenotype—which promotes chronic inflammation and disrupts tissue regeneration [42].

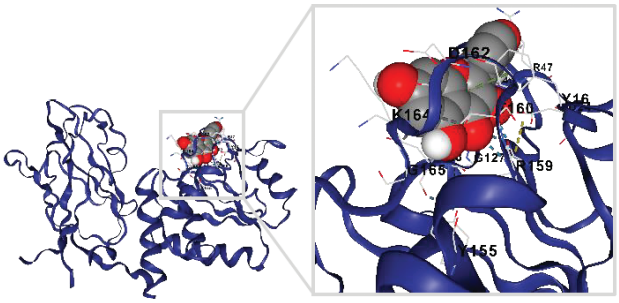
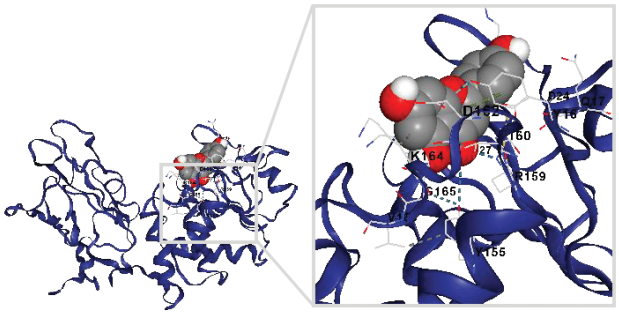
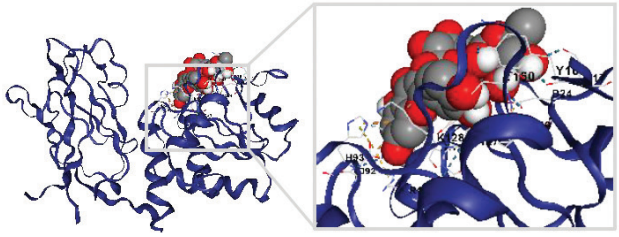
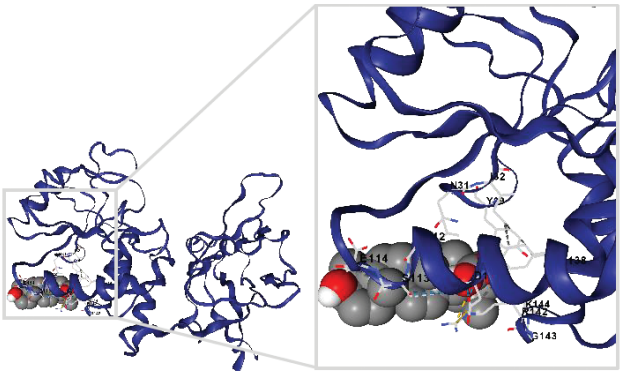
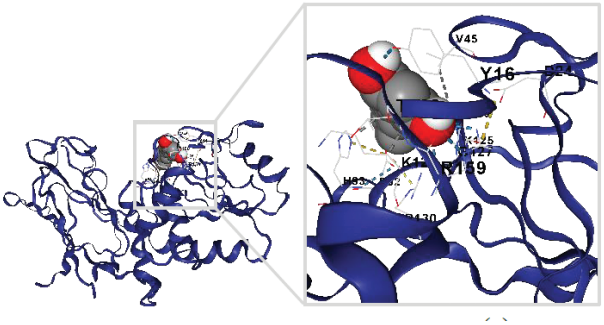
Notably, among the senescence regulating proteins identified, MYC modulation has been previously observed *in vitro* studies involving *C. asiatica*, highlighting its potential to influence transcriptional networks related to cellular proliferation and stress response. Meanwhile, PTEN and p53 act as major gatekeepers of genomic integrity, regulating PI3K/AKT pathway and cell cycle arrest, respectively [43–45]. *Centella asiatica* appears to balance proliferative signals via AKT1 and MAPK3 with protective checkpoints such as PTEN and p53, ensuring growth only in healthy cells [11].

In addition to these findings, enrichment analysis revealed leukocyte apoptosis as one of the most significantly associated biological processes. Proper regulation of immune cell turnover is vital during aging, as impaired apoptosis can lead to persistence of dysfunctional leukocytes, which may evade death, become senescent, and contribute to a chronic inflammatory environment (inflammaging) [46]. By potentially modulating these apoptosis-related pathways, *C. asiatica* could help restore immune balance, mitigate excessive inflammation, and thereby slow the aging process at the systemic level.

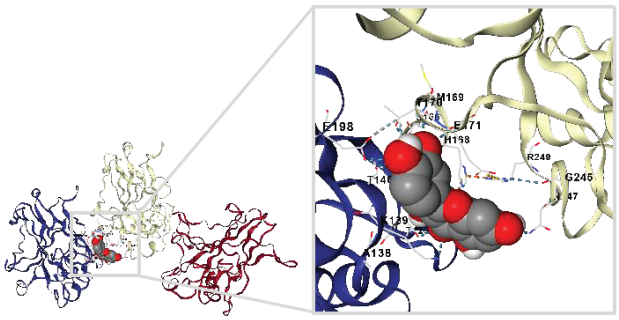
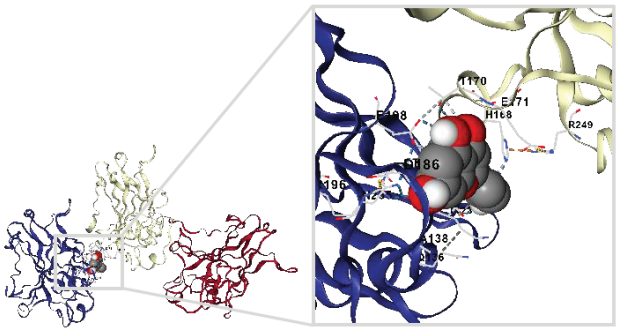
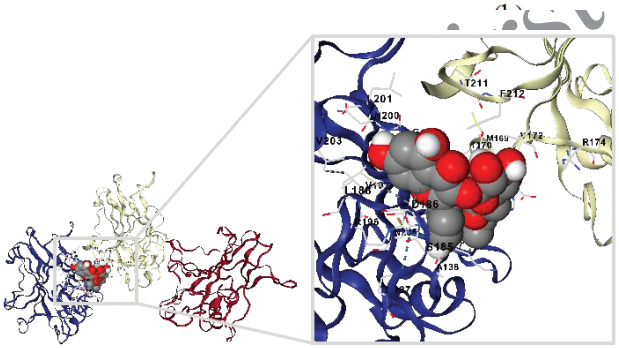
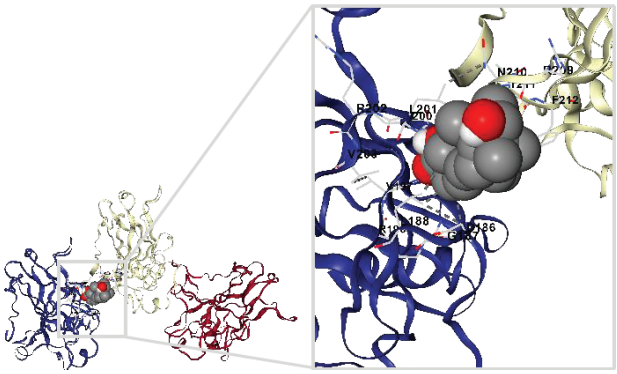
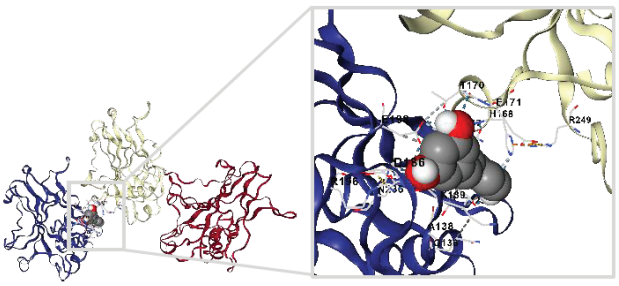
Aging is also marked by functional decline in glial cells, especially oligodendrocytes and microglia, which play critical roles in maintaining neuronal integrity. Oligodendrocytes are responsible for the formation and maintenance of the myelin sheath, essential for rapid signal conduction and metabolic support to neurons. Aging reduces the capacity of oligodendrocyte precursor cells to remyelinate damaged axons, leading to demyelination and associated cognitive deficits [47].

Moreover, chronic oxidative stress in aging promotes persistent activation of microglia. While microglia are initially protective—clearing myelin debris and supporting repair—prolonged activation can result in a senescent microglial phenotype. These senescent microglia exhibit impaired phagocytic ability and secrete pro-inflammatory cytokines such as IL-1B, TNF-a, and IL-6, perpetuating neuroinflammation and contributing to neurodegeneration [48,49]. Experimental evidence supports the neuroprotective role of *Centella asiatica*, particularly its aqueous extract, which improves learning and memory in aged mice. These effects are likely mediated by its antioxidant properties and ability to modulate glial cell function [50]. Our findings, in conjunction with previous *in vivo* results, suggest that *C. asiatica* may protect against age-related cognitive decline by supporting oligodendrocyte integrity, reducing oxidative damage, and preventing chronic glial senescence [50].

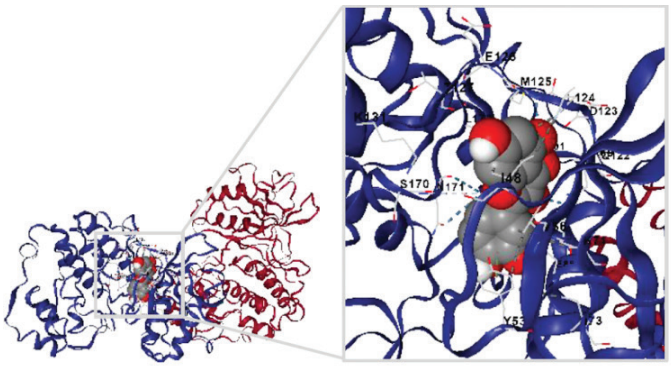
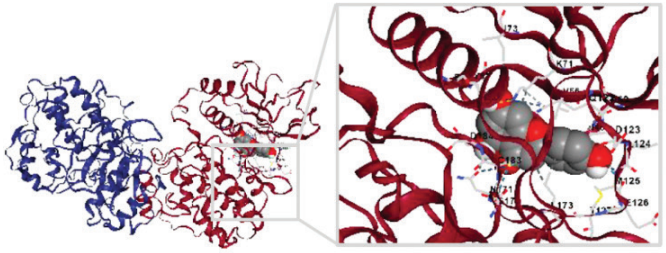
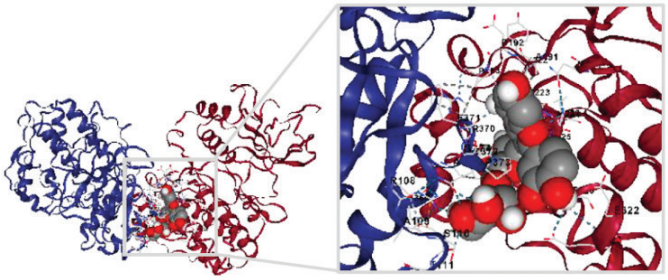
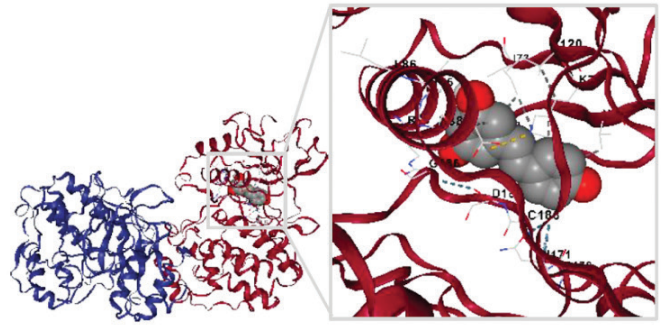
Table 8. Molecular docking results of seven core protein target associated with cellular senescence pathway, namely PTEN, TP53, MAPK3, AKT1, MYC, SIRT1, and IL6, with bioactive compounds from *Centella asiatica* and Resveratrol as reference compound, alongside with their binding sites and docking scores.

	PTEN
Quercetin	 **Pocket: C1 & Score: -6.7** **Chain A**: TYR16 GLN17 ASP22 LEU23 ASP24 VAL45 TYR46 ARG47 ASN48 ASP92 HIS93 ASN94 ALA126 GLY127 LYS128 GLY129 TYR155 ARG159 THR160 ASP162 LYS164 GLY165 THR167 ILE168 PRO169 LYS269 HIS272 ASP326 LYS327 ALA328 ASN329 LYS330
Apigenin	 **Pocket: C1 & Score: -6.5** **Chain A**: TYR16 GLN17 ASP22 LEU23 ASP24 GLY44 VAL45 TYR46 ARG47 ASN48 ASN49 ASP92 HIS93 CYS124 LYS125 ALA126 GLY127 LYS128 GLY129 ARG130 TYR155 ARG159 THR160 ASP162 LYS164 GLY165 VAL166 GLN171
Rutin	 **Pocket: C1 & Score: -8.5** **Chain A**: TYR16 GLN17 ASP22 LEU23 ASP24 LEU25 GLY44 VAL45 TYR46 ARG47 ASN48 ASN49 ASP92 HIS93 CYS124 LYS125 ALA126 GLY127 LYS128 GLY129 ARG130 TYR155 ARG159 THR160 ASP162 LYS164 GLY165 THR167 ILE168 HIS272
Ursolic Acid	 **Pocket: C5 & Score: -7.1** **Chain A**: TYR29 PRO30 ASN31 ILE32 LYS102 GLU106 ASP109 GLN110 LEU112 SER113 GLU114 HIS118 TYR138 LEU139 LEU140 HIS141 ARG142 GLY143 LYS144 PHE145 LEU146 TYR178 LEU182 LYS183 HIS185
Resveratrol	 **Pocket: C1 & Score: -6.1** **Chain A**: TYR16 GLN17 ASP22 LEU23 ASP24 GLY44 VAL45 TYR46 ARG47 ASN48 ASP92 HIS93 LYS125 ALA126 GLY127 LYS128 GLY129 ARG130 TYR155 ARG159 THR160 ASP162 LYS164 GLY165 VAL166

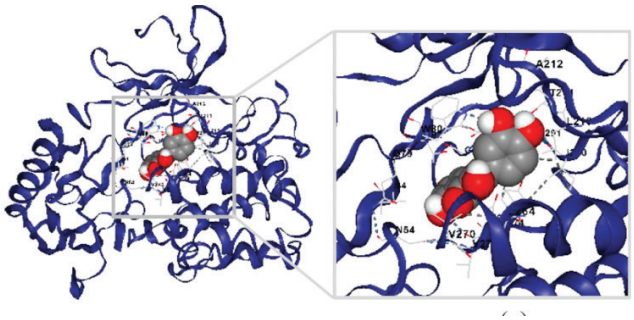
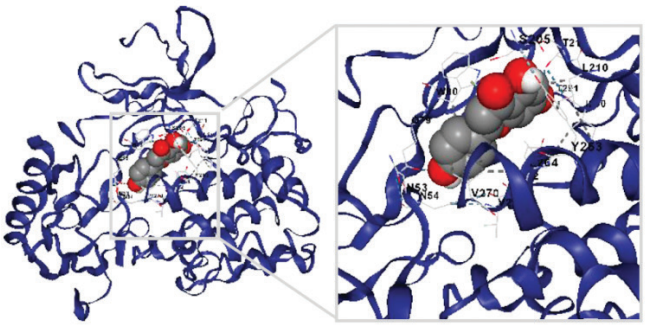
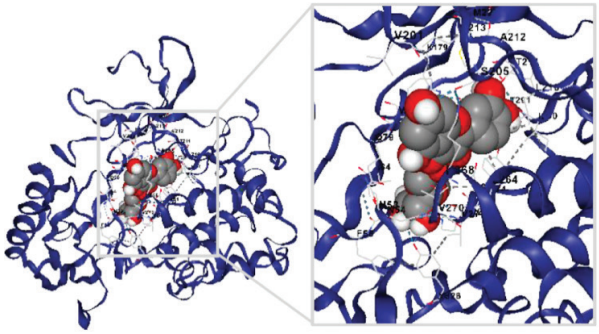
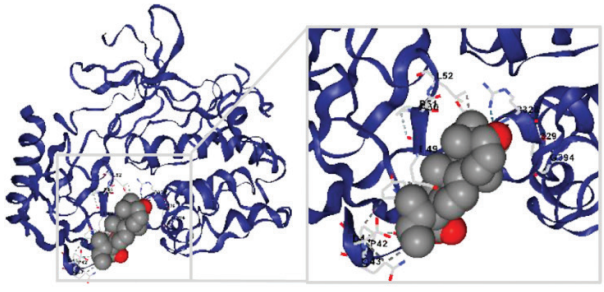
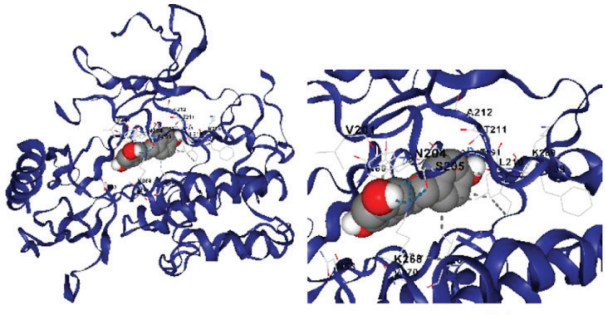
Continued

	TP53	
Quercetin		**Pocket: C5 & Score: -7.7** **Chain B**: SER96 VAL97 SER99 GLN100 LYS101 SER166 GLN167 HIS168 MET169 THR170 GLU171 VAL172 ASN210 THR211 PHE212 GLY245 MET246 ASN247 ARG249 **Chain C**: LEU114 LYS120 SER121 VAL122 THR123 GLN136 LEU137 ALA138 LYS139 THR140 PRO142 SER185 ASP186 ARG196 GLU198 GLY199 GLU224 CYS229 THR231 HIS233 ASN235
Apigenin		**Pocket: C5 & Score: -7.5** **Chain B**: SER96 VAL97 SER99 GLN100 LYS101 SER166 GLN167 HIS168 MET169 THR170 GLU171 VAL172 ASN210 THR211 PHE212 ASN247 ARG249 **Chain C**: LEU114 LYS120 SER121 VAL122 THR123 GLN136 ALA138 LYS139 THR140 PRO142 ASP186 ARG196 GLU198 GLY199 GLU224 SER227 CYS229 THR231 HIS233 ASN235 CYS277
Rutin		**Pocket: C4 & Score: -9.7** **Chain B**: SER96 VAL97 GLN167 HIS168 MET169 THR170 GLU171 VAL172 ARG174 ARG209 ASN210 THR211 PHE212 ARG213 HIS214 ARG249 **Chain C**: ALA138 LYS139 THR140 SER183 ASP184 SER185 ASP186 GLY187 LEU188 ARG196 VAL197 GLU198 GLY199 ASN200 LEU201 ARG202 VAL203 ASN235 MET237
Ursolic Acid		**Pocket: C4 & Score: -9.0** **Chain B**: SER96 VAL97 THR170 GLU171 VAL172 ARG174 ARG209 ASN210 THR211 PHE212 **Chain C**: ALA138 LYS139 THR140 SER185 ASP186 GLY187 LEU188 ARG196 VAL197 GLU198 GLY199 ASN200 LEU201 ARG202 VAL203 VAL218 PRO219 GLU221 THR230 THR231 ILE232 HIS233 ASN235 MET237
Resveratrol		**Pocket: C5 & Score: -6.8** **Chain B**: GLN167 HIS168 MET169 THR170 GLU171 VAL172 ASN210 THR211 PHE212 ASN247 ARG249 **Chain C**: SER121 THR123 GLN136 ALA138 LYS139 THR140 ASP186 ARG196 GLU198 GLY199 ASN235

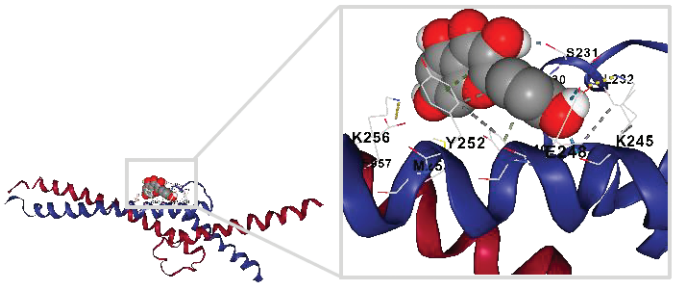
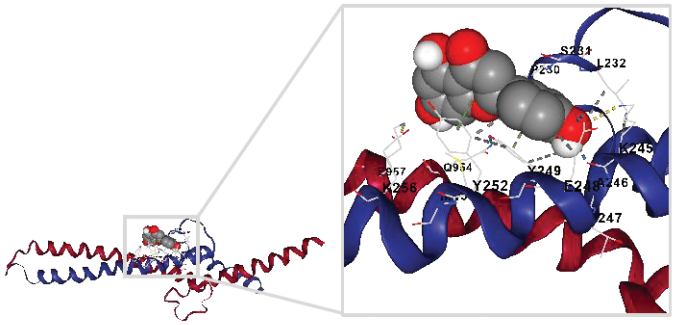
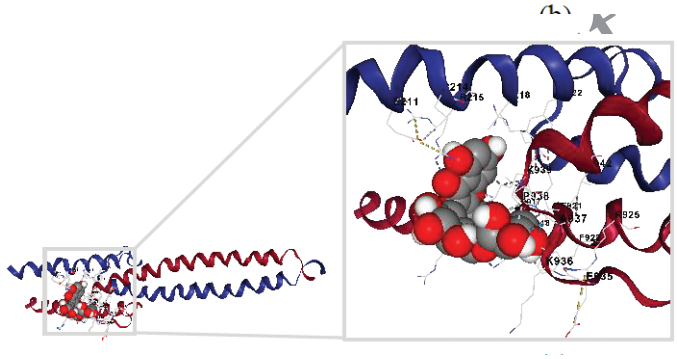
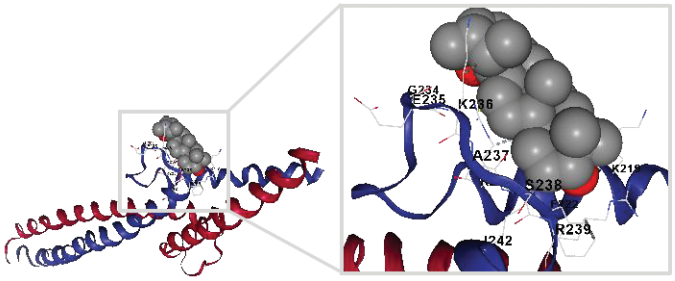
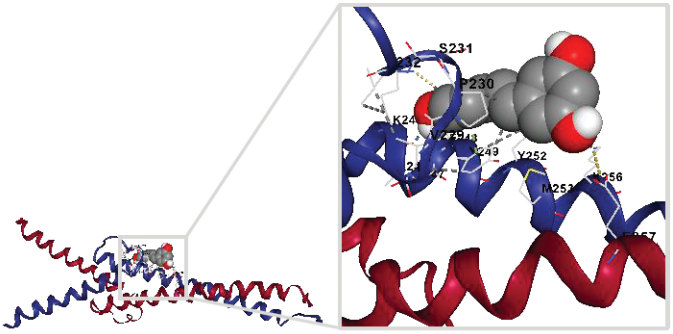
Continued

	MAPK3
Quercetin	 **Pocket: C2 & Score: -8.7** **Chain B**: ILE48 GLY49 GLU50 GLY51 TYR53 VAL56 ALA69 LYS71 ILE73 GLU88 ILE101 GLN122 ASP123 LEU124 MET125 GLU126 THR127 ASP128 LYS131 LYS168 SER170 ASN171 LEU173 ILE174 CYS183 ASP184
Apigenin	 **Pocket: C1 & Score: -8.5** **Chain A**: ILE48 GLY49 GLU50 GLY51 TYR53 VAL56 ALA69 LYS71 ILE73 GLU88 LEU92 ILE101 GLN122 ASP123 LEU124 MET125 GLU126 THR127 ASP128 LYS131 SER170 ASN171 LEU173 CYS183 ASP184
Rutin	 **Pocket: C4 & Score: -9.7** **Chain A**: HIS158 ASN161 ALA191 ASP192 PRO193 TYR222 THR223 LYS224 SER225 ILE226 ILE228 PRO315 ASN316 LYS317 ARG318 ILE319 THR320 VAL321 GLU322 GLU323 **Chain B**: ARG108 ALA109 SER110 THR111 PHE365 ALA369 ARG370 PHE371 GLN372 PRO373 GLY374
Ursolic Acid	 **Pocket: C4 & Score: -8.4** **Chain A**: THR223 LYS224 SER225 PRO315 ASN316 LYS317 ARG318 ILE319 THR320 GLU323 **Chain B**: ARG108 SER110 PHE365 GLN366 ALA369 ARG370 GLN372 PRO373
Resveratrol	 **Pocket: C1 & Score: -8.2** **Chain A**: ILE48 GLY49 GLU50 GLY51 TYR53 VAL56 ALA69 LYS71 ILE73 TYR81 ARG84 THR85 LEU86 GLU88 ILE101 ILE120 GLN122 ASP123 LEU124 MET125 GLU126 THR127 ASP128 LYS131 SER170 ASN171 LEU173 ILE174 CYS183 ASP184 GLY186

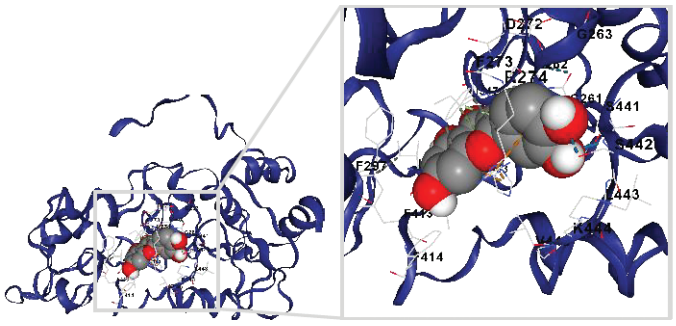
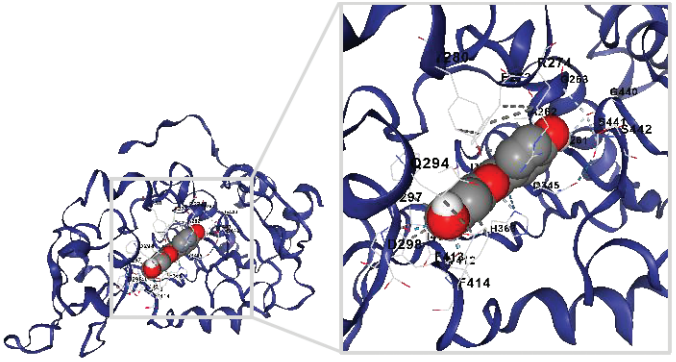
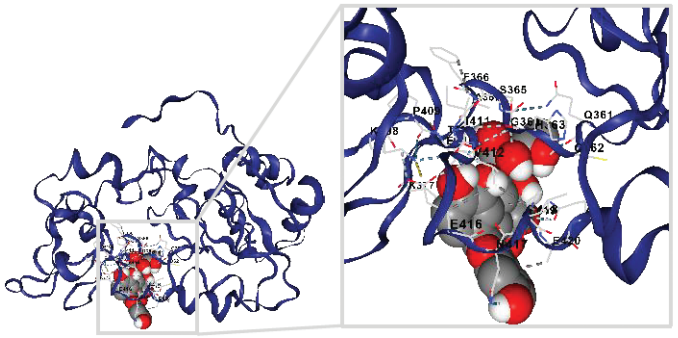
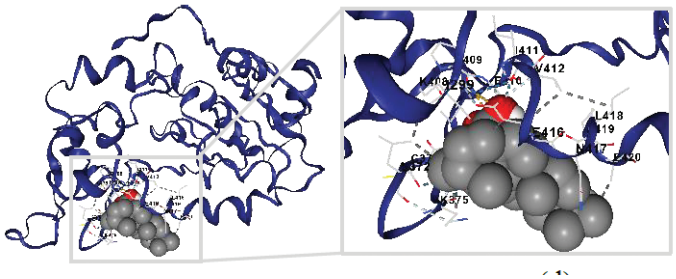
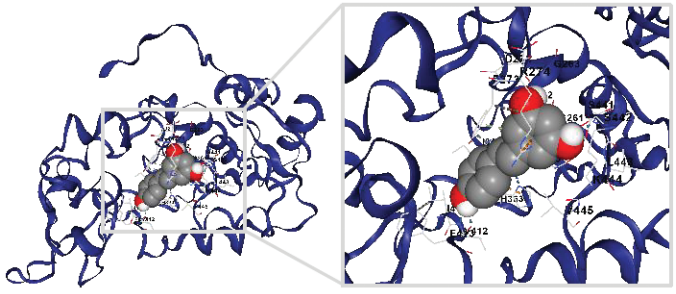
Continued

	AKT1
Quercetin	 **Pocket: C1 & Score: -9.5** **Chain A**: TYR18 ASN53 ASN54 GLN79 TRP80 THR82 ILE84 LYS179 VAL201 SER205 PHE209 LEU210 THR211 ALA212 LEU213 MET227 TYR263 LEU264 LYS268 VAL270 VAL271 TYR272 ARG273 ASP274 ASN279 LYS289 ILE290 THR291 ASP292 PHE293 GLY294 LEU295 CYS296 LYS297 GLU298
Apigenin	 **Pocket: C1 & Score: -9.0** **Chain A**: TYR18 ASN53 ASN54 GLN79 TRP80 THR82 ILE84 LYS179 VAL201 SER205 LEU210 THR211 TYR263 LEU264 LYS268 VAL270 VAL271 TYR272 ARG273 ASP274 ASN279 ILE290 THR291 ASP292 PHE293 GLY294 CYS296 LYS297 GLU298 TYR326
Rutin	 **Pocket: C1 & Score: -11.4** **Chain A**: GLU17 TYR18 ASN53 ASN54 PHE55 SER56 VAL57 ALA58 GLN59 CYS77 LEU78 GLN79 TRP80 THR81 THR82 VAL83 ILE84 GLU85 ARG86 LYS179 ASN199 VAL201 LEU202 ASN204 SER205 LEU210 THR211 ALA212 LEU213 SER216 PHE225 MET227 TYR263 LEU264 LYS268 VAL270 VAL271 TYR272 ARG273 ASP274 ASN279 ILE290 THR291 ASP292 PHE293 GLY294 LEU295 CYS296 LYS297 GLU298 TYR326
Ursolic Acid	 **Pocket: C4 & Score: -8.7** **Chain A**: ILE36 GLY37 TYR38 LYS39 GLU40 PRO42 GLN43 ASP44 GLU49 ALA50 PRO51 LEU52 PHE55 PRO318 GLU319 GLU322 ASN324 ASP325 TYR326 GLY327 ARG328 ALA329 ILE361 LEU362 MET363 LYS386 ASP387 PRO388 LYS389 ARG391 GLY393 GLY394 GLY395 SER396 ASP398
Resveratrol	 **Pocket: C1 & Score: -8.2** **Chain A**: ASN53 ASN54 GLN79 TRP80 THR81 THR82 ILE84 LYS179 VAL201 ASN204 SER205 ARG206 HIS207 PHE209 LEU210 THR211 ALA212 LEU213 MET227 TYR263 LEU264 LYS268 VAL270 VAL271 TYR272 ARG273 ASP274 ASN279 LYS289 ILE290 THR291 ASP292 PHE293 GLY294

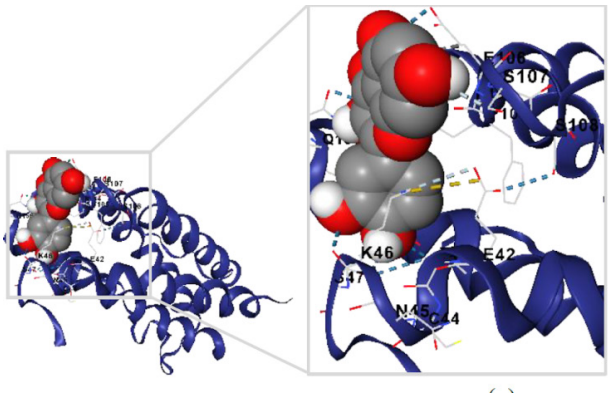
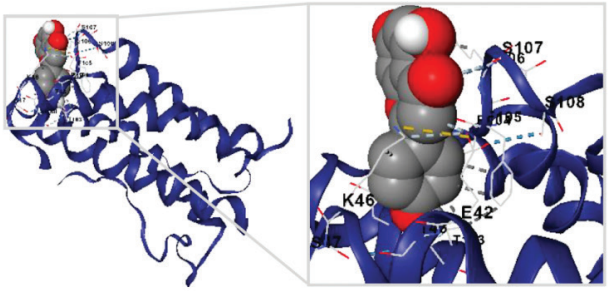
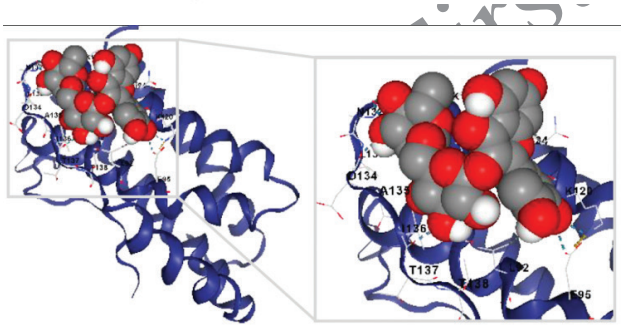
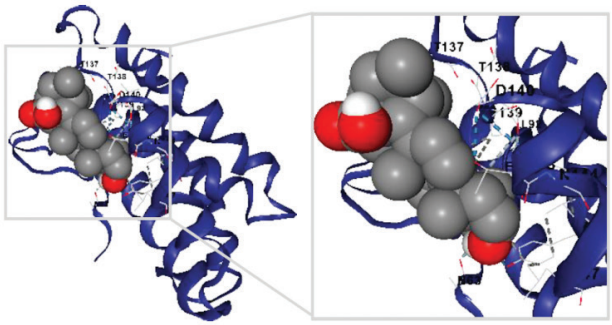
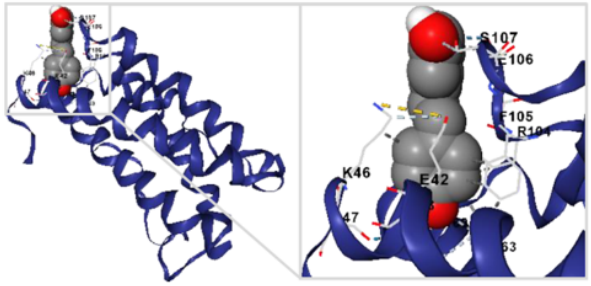
Continued

	MYC
Quercetin	 **Pocket: C3 & Score: -6.9** **Chain A**: GLN954 GLU957 **Chain B**: VAL229 PRO230 SER231 LEU232 LYS245 ALA246 THR247 GLU248 TYR249 GLN251 TYR252 MET253 ARG255 LYS256
Apigenin	 **Pocket: C3 & Score: -6.8** **Chain A**: GLN954 GLU957 GLN958 **Chain B**: VAL229 PRO230 SER231 LEU232 LYS245 ALA246 THR247 GLU248 TYR249 GLN251 TYR252 MET253 ARG255 LYS256
Rutin	 **Pocket: C1 & Score: -6.9** **Chain A**: GLU910 ARG911 ARG913 ARG914 ASN915 LEU917 LYS918 PHE921 PHE922 ARG925 GLU935 LYS936 ALA937 PRO938 LYS939 ILE942 **Chain B**: GLU211 ARG212 ARG214 ARG215 ASP216 ILE218 LYS219 PHE222 HIS223 ARG226 ALA237 SER238 ARG239 ILE242
Ursolic Acid	 **Pocket: C2 & Score: -6.6** **Chain A**: ARG913 **Chain B**: ILE218 LYS219 PHE222 HIS223 ARG226 ASP227 GLY234 GLU235 LYS236 ALA237 SER238 ARG239 ILE242
Resveratrol	 **Pocket: C3 & Score: -6.1** **Chain A**: GLU957 **Chain B**: VAL229 PRO230 SER231 LEU232 GLU235 LYS236 ALA237 GLN241 LYS245 ALA246 THR247 GLU248 TYR249 TYR252 MET253 ARG255 LYS256

Continued

	SIRT1	
Quercetin		**Pocket: C1 & Score: -9.2** **Chain B**: GLY261 ALA262 GLY263 GLY269 ILE270 PRO271 ASP272 PHE273 ARG274 GLY278 ILE279 ARG282 LEU283 ASP286 PHE287 PHE297 PHE312 LYS314 GLU315 ILE316 TYR317 PRO318 GLY319 GLN320 PHE321 GLN345 ASN346 ILE347 ASP348 HIS363 ILE411 VAL412 PHE413 PHE414 GLY440 SER441 SER442 LEU443 LYS444 VAL445 ILE510 THR511 GLU512
Apigenin		**Pocket: C1 & Score: -9.0** **Chain B**: GLY261 ALA262 GLY263 GLY269 ILE270 PRO271 ASP272 PHE273 ARG274 ILE279 TYR280 ARG282 ASP286 GLN294 PHE297 ASP298 PHE312 GLU315 ILE316 TYR317 GLN320 PHE321 GLN345 ASN346 ILE347 ASP348 HIS363 ILE411 VAL412 PHE413 PHE414 GLY415 GLU416 ASN417 LEU418 GLY440 SER441 SER442 LEU443 LYS444 VAL445 ARG446 PRO447 GLU512
Rutin		**Pocket: C2 & Score: -8.5** **Chain B**: ILE299 ARG303 GLN361 CYS362 HIS363 GLY364 SER365 PHE366 ALA367 THR368 ALA369 SER370 CYS371 LEU372 ILE373 LYS375 TYR376 LYS377 ASP379 MET407 LYS408 PRO409 GLU410 ILE411 VAL412 PHE413 GLY415 GLU416 ASN417 LEU418 PRO419 GLU420 GLN421 ARG424
Ursolic Acid		**Pocket: C2 & Score: -9.1** **Chain B**: ILE299 PHE302 ARG303 ILE359 ILE360 GLN361 CYS362 GLY364 SER365 THR368 SER370 CYS371 LEU372 LYS375 LYS377 ASP379 LYS408 PRO409 GLU410 ILE411 VAL412 GLY415 GLU416 ASN417 LEU418 PRO419 GLU420 GLN421 PHE422 HIS423
Resveratrol		**Pocket: C1 & Score: -8.3** **Chain B**: GLY261 ALA262 GLY263 GLY269 ILE270 PRO271 ASP272 PHE273 ARG274 SER275 ILE279 TYR280 ARG282 PHE297 PHE312 GLU315 ILE316 TYR317 PRO318 GLY319 GLN320 PHE321 GLN345 ASN346 ILE347 ASP348 HIS363 ILE411 VAL412 PHE413 PHE414 GLY440 SER441 SER442 LEU443 LYS444 VAL445 ASN465 ARG466

Continued

	IL6
Quercetin	 **Pocket: C5 & Score: -7.1** **Chain A**: GLU42 THR43 CYS44 ASN45 LYS46 SER47 ARG104 PHE105 GLU106 SER107 SER108 GLN156 GLN159 ASP160 THR163
Apigenin	 **Pocket: C5 & Score: -6.7** **Chain A**: GLU42 THR43 LYS46 SER47 ARG104 PHE105 GLU106 SER107 SER108 GLN156 TRP157 ASP160 THR163
Rutin	 **Pocket: C3 & Score: -7.0** **Chain A**: ILE88 LEU91 LEU92 GLU93 GLU95 VAL96 GLU99 THR119 LYS120 VAL121 ILE123 GLN124 GLN127 LYS128 ALA130 LYS131 ASN132 LEU133 ASP134 ALA135 ILE136 THR137 THR138 PRO139 ASP140 PRO141 ASN144
Ursolic Acid	 **Pocket: C1 & Score: -6.9** **Chain A**: ASN63 LEU64 PRO65 THR89 LEU92 GLU93 PHE94 GLU95 VAL96 TYR97 GLU99 GLN116 LYS120 THR137 THR138 PRO139 ASP140 PRO141 THR143 ASN144 LEU147
Resveratrol	 **Pocket: C5 & Score: -6.1** **Chain A**: GLU42 THR43 CYS44 LYS46 SER47 LEU101 ARG104 PHE105 GLU106 SER107 GLN156 ASP160 THR163

Alongside neural aging, mitochondrial dysfunction represents another intrinsic factor that accelerates aging. As a cellular powerhouse, mitochondria generate ATP through redox processes that can lead to the accumulation of reactive oxygen species, mutation in mitochondrial DNA, and progressive mitochondrial decay [51]. This dysfunction is linked with increased oxidative stress, aberrant apoptosis regulation, and energy deficits in aging tissues. Notably, aging brains show increased neurons with cytochrome c oxidase deficiency in areas such as the substantia nigra and hippocampus, further implicating mitochondrial failure in neurodegeneration. *Centella asiatica*, through its antioxidant constituents, may help ameliorate these mitochondrial effects by reducing oxidative stress and supporting mitochondrial integrity [51,52].

Furthermore, the vascular system is another major target of aging-related deterioration. Endothelial dysfunction, vascular inflammation, and reduced nitric oxide (NO) bioavailability are prominent features that contribute to cardiovascular diseases in the elderly. In our ClueGO analysis, nitric oxide synthase activity emerged as one of the most significantly enriched molecular functions targeted by *C. asiatica*'s bioactive compounds. Nitric oxide plays a key role in maintaining vascular tone, inhibiting platelet aggregation, and preventing leukocyte adhesion. Dysregulation of NO pathways leads to impaired vasodilation and heightened inflammatory responses, which accelerate vascular aging and increase the risk of oxidative stress [53]. *Centella asiatica* may help preserve endothelial function and vascular homeostasis. These molecular insights are consistent with prior studies, showing *C. asiatica*'s cardioprotective effects, including attenuation of cardiac hypertrophy, fibrosis, and ischemia-reperfusion injury. The plant's antioxidant, anti-inflammatory, and vasomodulatory properties make it a promising candidate for mitigating cardiovascular aging and its related pathologies [53].

The therapeutic potential of *C. asiatica* lies in its rich repertoire of bioactive compounds, particularly the combination of polyphenols—such as Quercetin, Apigenin, and Rutin—and triterpenoid, including Ursolic Acid, Asiaticoside, Madecassoside, and Asiatic Acid. These compounds act on various molecular targets, many of which are associated with aging hallmarks, particularly cellular senescence and inflammatory signaling [9]. Among the 28 core proteins identified in this study, several—including TP53, AKT1, PTEN, IL6, and SIRT1—are modulated by multiple compounds, suggesting coordinated regulation across intersecting pathways.

Among these compounds, Quercetin, Apigenin, Rutin, and Ursolic Acid emerged as the most relevant based on network analysis results. Their potential synergy with more abundant triterpenoids found in *C. asiatica*, such as Asiaticoside, Madecassoside, and Asiatic Acid, further highlights the value of exploring this plant as a multi-component anti-aging agent. Quercetin, Apigenin, and Rutin are known for their strong antioxidant and anti-inflammatory properties [9]. They modulate pathways involved in DNA repair, apoptosis, and cytokine suppression, contributing to delayed cellular senescence. Meanwhile, triterpenoids such as Ursolic Acid and Asiaticoside exhibit pronounced sirtuin-activiting properties. Sirtuins, especially SIRT1 and SIRT2, are key regulators of chromatin remodeling, DNA repair, metabolic homeostasis, and mitochondrial integrity. The activation of these proteins has been linked to increased cellular longevity and improved stress resistance [54,55].

The interplay among these mechanisms is largely mediated by telomerase regulation. Telomerase, via its catalytic subunit TERT, maintains telomere length and delays replicative senescence. Evidence from studies on *C. asiatica* extract DLBS1649 shows that it prevents age-related telomerase suppression and maintains TERT expression, indicating potential for delaying telomere-driven senescence. The interaction between telomerase activation, p53 modulation, and sirtuin signaling supports a multi-layered protective effect that balances prosurvival signals with genomic surveillance [11].

Importantly, this combinatorial mechanism underscores the unique advantage of *Centella asiatica* as an anti-aging agent. Herbal extracts that contain only individual components, such as Quercetin or Ursolic Acid alone, may not replicate this synergistic effect. The integrated action of both polyphenols and triterpenoids appears essential for comprehensive protection against cellular aging, particularly in maintaining genome integrity and preventing chronic inflammation.

Nevertheless, despite the promising biological activities of *C. asiatica* compounds, pharmaceutical application requires careful consideration of pharmacokinetic challenges. Many of the key bioactive compounds, such as Rutin and Ursolic Acid, possess high molecular weight or high lipophilicity (logP>5), which may limit aqueous solubility and oral bioavailability. Nevertheless, these barriers can be addressed through formulation strategies such as cyclodextrin complexation, lipid-based nanocarriers, or solid dispersion systems to enhance solubility and intestinal absorption [56].

To strengthen the pharmacological relevance of the network analysis, molecular docking analysis was performed. The results demonstrated that Quercetin, Apigenin, Rutin, and Ursolic Acid exhibit strong binding affinity (AG < –5 kcal/mol) to senescence-associated proteins [17]. These interactions reinforce the functional relevance of the network pharmacology predictions, confirming that the identified compounds have not only theoretical but also structural compatibility with their protein targets. However, as with any blind docking approach, the results should be interpreted with caution due to limitations such as reliance on predicted cavities. Nonetheless, this method provides a valuable first step for exploring potential binding regions on targets that are still underexplored.

Together, these findings suggest that the anti-aging potential of *C. asiatica* is supported by both biological plausibility and computational validation. Its bioactive compounds potentially act through multiple pathways—particularly senescence regulation, sirtuin activation, and telomerase maintenance—and can be optimized for therapeutic use through formulation science. This integrated, multi-target approach strengthens the rationale for further investigation and development of *C. asiatica*-based anti-aging interventions.

CONCLUSION

Based on current findings, *C. asiatica* bioactive compounds, which are predicted to have the most relevant anti-

aging features, are Quercetin, Apigenin, Rutin, and Ursolic Acid—which act on key proteins within the cellular senescence pathway, including PTEN, TP53, MAPK3, AKT1, MYC, SIRT1, and IL6. These compounds are predicted to have potency as anti-aging through the cellular senescence pathway, in which they contribute to the regulation of cellular senescence, apoptosis, dysfunctional mitochondrial, and telomerase activity in ways that promote cellular homeostasis and longevity. Notably, the synergistic action between polyphenols and triterpenoids—especially sirtuin-activating compounds like Asiaticoside and Madecassoside—further reinforces *Centella asiatica*'s multifaceted anti-aging effects, including its neuroprotective and vasoprotective potential.

Additionally, molecular docking supports the network pharmacology findings, with all four compounds showing strong binding affinity to senescence-related targets. These findings provide a strong foundation for future *in vitro* and *in vivo* research regarding specific bioactive compounds of *C. asiatica* as anti-aging agents, thereby enabling a more focused and efficient longevity experimental design to validate their efficacy and mechanism of action. The exploratory nature of these findings has been acknowledged, and network pharmacology and enrichment analyses are recognized as providing a systems-level perspective on potential molecular mechanisms, forming the basis for subsequent biological validation.

LIST OF ABBREVIATIONS

ADME: Absorption, distribution, metabolism, and excretion; BC: Betweenness centrality; DC: Degree centrality; KEGG: Kyoto Encyclopedia of Genes and Genomes; MAPK3: Mitogen-activated protein Kinase 3; PI3K: Phosphoinositide 3-Kinase; PPI: Protein–Protein Interaction; PTEN: Phosphatase and Tensin Homolog; SASP: Senescence-Associated Secretory Phenotype; SIRT1: Sirtuin 1.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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CONFLICTS OF INTEREST

This study was conducted within PT Dexa Medica, which funded the research through internal support. The authors are affiliated with the company and did not receive any external or third-party funding. In accordance with ICMJE guidelines, no conflicts of interest are declared.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

PUBLISHER'S NOTE

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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