

Network Pharmacology-Guided Identification of Kinase-Mediated Vascular Signalling Targets Underlying the Antihypertensive Potential of *Brassica rapa* L

Dipil Dhondsekar

Poona College of Pharmacy

Satish Mandlik

Poona College of Pharmacy

Shrikant Nilewar

Maliba Pharmacy College, Uka Tarsadia University

Deepa Mandlik

deepa_ingawale@yahoo.com

Poona College of Pharmacy

Research Article

Keywords: Hypertension, *Brassica rapa*, Network pharmacology, Molecular docking, Molecular dynamics simulation

Posted Date: March 5th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-8953804/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at In Silico Pharmacology on June 30th, 2026. See the published version at <https://doi.org/10.1007/s40203-026-00671-y>.

**Network Pharmacology-Guided Identification of Kinase-Mediated Vascular Signalling
Targets Underlying the Antihypertensive Potential of *Brassica rapa L***

Dipil Dhondsekar^a, Satish Mandlik^a, Shrikant Nilewar^b, Deepa Mandlik^{a*}

^{a, a*} Bharati Vidyapeeth (Deemed to be University), Poona College of Pharmacy, Erandwane,
Pune-411038, Maharashtra, India.

^b Maliba Pharmacy College, Uka Tarsadia University, Gujrat, 394350 India.

***Corresponding Author**

Deepa Mandlik

Department of Pharmacology,

Bharti Vidyapeeth (Deemed to be University),

Poona College of Pharmacy,

Erandwane, Pune-411038, Maharashtra, India

Mobile No. 9822504077

Email: deepa_ingawale@yahoo.com; deepa.mandlik@bharativedyapeeth.edu

Abstract

Hypertension is a complex cardiometabolic disorder involving oxidative stress, endothelial dysfunction, inflammation, and neurohormonal imbalance, which increase vascular resistance and remodeling. Consequently, single target treatment frequently has low long-term efficacy. *Brassica rapa* L. (BRL) turnip, a medicinal and dietary crucifer rich in glucosinolates, flavonoids, phenolic acids, offers significant potential for blood pressure modulation. Through a comprehensive *in-silico* method that combines network pharmacology, molecular docking, molecular dynamics simulation, and ADMET guided screening, this study examines the multitarget antihypertensive potentiation of BRL. In the list of the 189 phytoconstituents identified through extensive database, 9 drug-like candidates were ultimately selected utilizing SwissADME profiling and Lipinski's rule of 5. Predicted protein targets identified through SwissTargetPredication and the similarity ensemble approach were cross referenced with hypertension-associated genes from GeneCards and online mendelian inheritance in man, yielding 246 common targets. Protein-protein interaction analysis revealed a core module of 10 hub genes, such as EGFR, PIK3CA, FYN, PTK2, SRC, PTPN11, PIK3R1, CTNNB1, and AKT1 indicating a key role for kinase-driven vascular signaling. Functional enrichment analysis highlighted redox homeostasis, Vaso regulatory balance, and the PI3K-AKT and nitric/eNOS signaling pathways. AutoDock Vina docking identified quercetin (-11.4 kcal/mol), kaempferol and isorhamnetin (-11.2 kcal/mol), gluconasturtiin (-11.2 kcal/mol) as top ligands. Schrodinger molecular dynamics simulations over 100 ns confirmed the stability and energetically favorable nature of the protein-ligand interactions. Overall, BRL demonstrates strong multitarget antihypertensive potential, with prioritized lead molecules for further validation

Keywords

Hypertension; *Brassica rapa*; Network pharmacology; Molecular docking; Molecular dynamics simulation

1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of mortality and morbidity around the world. Hypertension (HTN) serves as the most significant and controllable risk factor for CVDs worldwide, (Fuchs and Whelton 2020a; Kengne et al. 2023; Poulter et al. 2020) estimated to cause 7.5 million deaths annually (Muntner et al. 2020). The clinical definition of hypertension has evolved from a systolic/diastolic blood pressure (SBP/DBP) threshold of $\geq 160/90$ mmHg in 1984 to $\geq 140/90$ mmHg in 1993 and $\geq 130/80$ mmHg in the 2017 American College of Cardiology/American Heart Association guidelines (Wu et al. 2022). Furthermore, the global prevalence and overall burden of HTN are steadily increasing, accompanied by a parallel rise in HTN-associated CVDs (Aggarwal et al. 2021). Effective HTN care could significantly lower the worldwide burden of HTN-associated CVS in addition to reducing age-related increases in blood pressure (BP) (Aggarwal et al. 2021).

As a result, natural goods and ethnomedical plants have gained more attention. Plants have served as both food and medicine throughout human history, and their unique pharmacological properties serve as the basis for ancient medical systems (Jain 2000; Pieroni et al. 2002). Traditional herbal remedies, which use both cultivated and wild plant species that have been used as natural sources of therapeutic compounds for generations, are still essential in many areas, particularly where access to modern healthcare is limited (Šarić-Kundalić et al. 2010). Recently, there has been increased interest in culinary and medicinal herbs because of their wide range of bioactive properties (Motti et al. 2022).

Cruciferous, particularly those of the *Brassica* genus which including turnip, broccoli, & cabbage [*Brassica rapa* L. (BRL)] are widely consumed and valued for their therapeutic potential (Hong and Kim 2008). In many Asian and Mediterranean locations, BRL, one of the earliest vegetables to be produced, has long been used as food and medicine to relieve exhaustion (Wang et al. 2023), hypoxia prevention (Liu et al. 2024), HTN (Abid et al. 2022a), and hepatic and renal disorders (Paul et al. 2019a). Phytochemical investigations reveal that BRL is rich in glucosinolates, isothiocyanates, phenolic compounds, flavonoids, organic acids, and sulfur-containing volatiles (Javed et al. 2019a; Padilla et al. 2007). Among these, gluconasturtiin and glucobrassicinapin are predominant glucosinolates, while β -phenylethyl isothiocyanate, kaempferol, and isorhamnetin glycosides represent major active derivatives. These metabolites exhibit antioxidant (Aires et al. 2011), anti-inflammatory (Semwal et al. 2021), nephroprotective (Paul et al. 2019b), anticancer (Higdon et al. 2007), osteoporosis and antihypertensive activities (Paul et al. 2019b). In particular, methanolic leaf extracts of BRL demonstrated significant angiotensin-converting enzyme (ACE) inhibition, supporting its

antihypertensive potential (Abid et al. 2022b; Cao et al. 2021a). BRL is a perfect option for computational research because of these bioactive characteristics. The intricate mechanisms and associations involved in drug discovery are better understood because to novel methods like network pharmacology, molecular docking, and molecular dynamics simulations. These methods link current research with traditional ethnopharmacological expertise. Numerous variables contribute to hypertension, such as oxidative stress, renin-angiotensin system dysfunction, endothelial dysfunction, and persistent inflammation. The development of effective medications is hampered by these difficulties (Gallo et al. 2022a). Vascular reactive oxygen species (ROS) are increased by oxidative stress, which compromises vessel function and raises HTN (Higashi 2022a). Overactivation of RAS increases angiotensin II, which causes inflammation, ROS production, and vasoconstriction. Nitric oxide availability is decreased by endothelial dysfunction, which also decreases vasodilation and raises blood pressure. Immune cells and cytokines are activated by inflammatory pathways, exacerbating HTN and causing further vascular tissue damage (Fodor et al. 2021). Because HTN comprises several interconnected pathways, such as oxidative stress, vascular inflammation, endothelial dysfunction, and RAS activation, single-target therapy is insufficient. Rapid investigation of multi-target interactions is made possible by *in-silico* techniques including network pharmacology, molecular docking, and MD. Network pharmacology maps the relationships between drugs, targets, and pathways to identify key hubs linked to HTN and signalling cascades including phosphatidylinositol 3-kinase-protein kinase B (PI3K-Akt) and nitric oxide pathways (Liu et al. 2022). Molecular docking and MD simulations then validate binding affinity and dynamic stability, confirming pose robustness within ACE or Angiotensin II type 1 receptor active sites (Ma et al. 2023a). These methods speed up the identification of antihypertensive leads while lowering experimental costs when combined with absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiling. Rich in isothiocyanates, flavonoids, glucosinolates, and phenolic acids, BRL is a therapeutic edible crucifer with anti-inflammatory and antioxidant properties that are directly related to HTN (Paul et al. 2019c). BRL's potential in RAS modulation was supported by a recent study that showed substantial ACE inhibitory action (~79%) of methanolic leaf extract compared to captopril (~86%) (Abid et al. 2022a). The chemical diversity of BRL provides inherent poly-pharmacology appropriate for network-based drug discovery, considering the multifactorial genesis of HTN. Key targets across oxidative-inflammatory and RAS pathways can be identified and validated by combining network pharmacology, docking, and MD simulations, indicating multitarget prospects for additional in-vivo investigation (Shahzadi et al. 2024). Although BRL have been

shown to have ACE inhibitory activity in earlier research, little is known about the larger kinase-mediated vascular signalling pathways that underlie this plant's capacity to lower blood pressure.

The current study focuses on assessing the multitarget modulation of PI3K-Akt (Nishida et al. 2012), SRC (Pullamsetti et al. 2012), and EGFR(Chen et al. 2020) signalling using an integrative in-silico approach, given the growing significance of these pathways in endothelial dysfunction and vascular remodelling. Previous investigation was limited to ACE inhibition (Abid et al. 2022a). However, kinase-mediated endothelial dysfunction and redox imbalance are major factors in the pathophysiology of hypertension. Using integrated network pharmacology and molecular dynamics, the current study explores kinase-centered vascular signalling modulation by BRL in a novel way.

Materials and Methods

1.1. Network Construction of BRL

All databases and software used in this study are publicly available. The chemical structures of BRL phytoconstituents were obtained from the Indian Medicinal Plant, Phytoconstituents and Therapeutics (IMPPAT) database (<https://cb.imsc.res.in/imppat/>) (Mohanraj et al. 2018), Dr. Dukes database (<https://phytochem.nal.usda.gov/>), and PubChem (Kim et al. 2023a). The canonical SMILES of each compound were used for target prediction. Molecular docking and visualization were carried out using AutoDock Vina v1.2.5 (Eberhardt et al. 2021a), Discovery Studio v4.5, and PyMOL v2.5.

2.1.1. Identification and Active Compounds Screening of BRL

The IMPPAT, Dr. Dukes, and PubChem databases were used to construct 189 phytoconstituents, which were subsequently then cross-referenced with existing literature. Duplicate entries were eliminated. Each compound was evaluated for drug-likeness using Lipinski's rule of five and ADMET parameters (Lipinski et al. 2001; Veber et al. 2002). Compounds violating more than two rules were excluded. Absorption, distribution, metabolism, and excretion (ADME) screening was performed through SwissADME (Daina et al. 2017). The remaining phytoconstituents were shortlisted for target prediction.

2.1.2. ADMET and Drug-likeness Prediction of BRL

The SwissADME online tool (<http://www.swissadme.ch/>) was employed to evaluate the drug-likeness of the selected BRL phytoconstituents. The SMILES notation for each compound was obtained from the PubChem database and submitted to SwissADME for analysis (Daina et al.

2017). Compounds were assessed based on Lipinski's rule of five, including molecular weight (<500 Da), hydrogen bond donors (≤ 5), and hydrogen bond acceptors (≤ 10), LogP (<5). Phytoconstituents meeting these criteria were considered to possess acceptable oral drug-likeness properties and were selected for subsequent computational studies (Chen et al. 2017; Daina et al. 2017; van de Waterbeemd and Gifford 2003).

2.1.3. Target Identification of BRL

The UniProt database was used to anticipate and then link the possible phytoconstituent targets to official gene symbols (Bateman et al. 2023). SwissTargetPrediction was used to predict the possible protein targets of the chosen phytoconstituents (Daina et al. 2019), Similarity Ensemble Approach (SEA) databases (Keiser et al. 2007), restricting the organism to Homo sapiens. SwissTargetPrediction possessed the probability threshold set to > 0.7 . In order to transform predicted protein IDs into official gene names, the UniProt database was utilised (Bateman et al. 2023). Redundant or non-human targets were discarded to obtain the final list of BRL-associated genes.

2.1.4. Hypertension-Related Target Collection

HTN-related genes were identified from GeneCards, OMIM, and Comparative Toxicogenomics Database (CTD) using the search terms "HTN" and "BP." Only genes with relevance scores > 10 (GeneCards) were retained (Amberger et al. 2019; Gao et al. 2021; Piñero et al. 2017; Stelzer et al. 2016). Gene names were standardised in UniProt and duplicates were eliminated. Venny 2.1.0 was used to identify the intersection of BRL targets and HTN-related genes; the overlapping genes were thought to be potential BRL therapeutic targets against HTN.

2.1.5. Network Construction and Analysis

A comprehensive interaction network has been established by integrating the intersecting targets between BRL phytoconstituents and hypertension. Using Cytoscape v3.10.2 (Shannon et al. 2003), A compound-target-disease network was developed to illustrate the relationships among BRL phytoconstituents, their potential targets, and hypertension (Barabási and Oltvai 2004a). To assess the relative significance of nodes inside the network, network topological characteristics such as degree, betweenness, and proximity centrality were computed. Higher degree nodes were thought to be important regulatory targets that might contribute to BRL's antihypertensive therapeutic effects.

2.1.6. Protein-Protein Interaction Network

Overlapping BRL-HTN target genes from the STRING database (<https://string-db.org/>) were used to build the protein-protein interaction (PPI) network (Szkarczyk et al. 2021). The organism was set to *Homo sapiens*, and a confidence score > 0.7 was applied to ensure high-confidence interactions. The interaction data were exported from STRING and visualized in Cytoscape v3.10.2 (Shannon et al. 2003). The network analyser tool was used to analyse the degree, betweenness, and closeness centrality of the network topology metrics (Assenov et al. 2008). Based on degree centrality, hub genes were found using the CytoHubba plugin (Chin et al. 2014), and the top 10 genes with the highest degree values were selected for subsequent molecular docking analysis (Barabási and Oltvai 2004b).

2.1.7. Functional Enrichment Analysis

Gene Ontology (GO) enrichment: ShinyGO v0.741 (<http://bioinformatics.sdstate.edu/go74/>) was used to functionally enrich the overlapping BRL-HTN targets. GO analysis was conducted across biological process enrichment (BPE), cellular component (CC), and molecular function (MF) categories to identify major biological activities. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis was carried out to determine the signalling cascades involved in the antihypertensive mechanism of BRL. Pathways related to RAS (Fyhrquist and Saijonmaa 2008), Hypoxia-inducible factor-1 (HIF-1) signalling (Haase 2006), calcium signalling (Touyz et al. 2018), PI3K-Akt signalling (Fulton et al. 1999a), oxidative stress regulation, and nitric oxide biosynthesis were prioritized. Significance thresholds were set at $p < 0.05$, and results were visualized as bar and bubble plots. KEGG pathway analysis: To determine the main signalling pathways connected to the anticipated targets, KEGG pathway enrichment analysis was also carried out. The statistical threshold for both analyses was set at $p < 0.05$. The top enriched GO terms and KEGG pathways were visualized using default plotting tools in ShinyGO for further interpretation (Kanehisa et al. 2023; Khatri et al. 2012).

2.2. Molecular Docking Studies

2.2.1. Ligand and protein preparation

The SMILES structures of the selected BRL phytoconstituents were obtained from the PubChem database (Kim et al. 2023b). Each compound was drawn using the RCSB PDB Chemical Sketch tool and downloaded in PDB format (Burley et al. 2021). Avogadro software's steepest descent technique was used to minimise the energy of the produced ligand structures in order to find the lowest energy conformations that could be docked (Hanwell et al. 2012).

From the Protein Data Bank (PDB), the top target proteins' three-dimensional crystal structures were obtained (Berman et al. 2000). PyMOL was used to eliminate non-essential heteroatoms and crystallographic water molecules from protein structures. Both ligand and protein files were then converted into PDBQT format using AutoDock Tools, with Kollman charges added to the proteins and polar hydrogens included where necessary (Morris et al. 2009).

2.2.2. Docking setup and visualization

Molecular docking was performed using AutoDock Vina v1.2.5 with default scoring and optimization parameters (Eberhardt et al. 2021b). PyMOL was used to process protein structures in order to eliminate non-essential heteroatoms and crystallographic water molecules (Seeliger and De Groot 2010a). All ligand-protein pairs were prepared and docked using uniform grid dimensions and exhaustiveness values to maintain consistency across targets (Forli et al. 2016). Based on anticipated binding affinity and appropriate binding within the active site, the optimal docking positions were chosen after docking (Seeliger and De Groot 2010b). Using PyMOL v2.5 and BIOVIA Discovery Studio Visualiser, the docked complexes were visualised and analysed to look at binding orientations and non-covalent interactions such as π - π stacking, hydrophobic contacts, and hydrogen bonding (Laskowski and Swindells 2011).

2.3. Molecular Dynamics Simulation

The dynamic stability of the docked protein-ligand complexes was confirmed by MD simulations using the DESMOND module of the Schrödinger Suite. During system construction, the OPLS2004 force field was used to prepare the solvent system. Prior to simulation, the complexes were brought up to energy minimization, followed by equilibration pursuant to the number of particles, pressure, and temperature ensemble for 100 ps each. The production MD simulation was then conducted for 100 ns at constant temperatures of 300 K and 1.01325 atm, respectively. To comprehend the stability and dynamic behaviour of the protein-ligand complexes, the trajectories generated during the simulation were analysed (Bowers et al. 2006).

3. Results

3.1. Compound Screening of Brassica rapa L.

A total of 189 phytoconstituents were initially collected from BRL through database mining. The SwissADME ADME evaluation and Lipinski's Rule of Five were used to select nine compounds with acceptable drug-likeness qualities for additional study. These compounds

included Ferulic acid, Linoleic acid, Quercetin, Kaempferol, Isorhamnetin, Caffeic acid, Sinapic acid, Glucoerucin, and Gluconasturtiin.

3.2. Mining of potential therapeutic targets of Brassica Rapa L. for the treatment of hypertension

The GeneCards database was used to acquire the targets of specific phytoconstituents (<https://www.genecards.org/>), GeneCards and similar databases were searched for genes linked to hypertension. Hub gene identification and downstream structural validation were limited to high-confidence overlapping targets determined from network topological analysis in order to reduce database-induced noise and improve biological specificity. From the SwissTargetPrediction database (<https://www.swisstargetprediction.ch/>), a total of 625 genes related to the phytoconstituents of BRL were collected. Then, 246 targets were screened by finding overlapping targets of BRL-associated targets and HTN-associated targets (Figure 1).

3.3 Protein-Protein Interaction Network Construction and Identification of Potential Hub Genes in Brassica rapa L. Related to Hypertension

To establish a PPI network, a total of 246 putative target genes of phytoconstituents of BRL that were retrieved for the treatment of HTN were entered into the STRING database (<https://string-db.org/>) with species restricted to "Homo sapiens" and a high confidence score > 0.700. The PPI network has 246 nodes and 1014 edges, according to the STRING analysis results (Figure 2A). To visualise targets, the acquired data were imported into the Cytoscape program (v3.10.2). Using the 12 CytoHubba algorithms in Cytoscape, including centrality and network metrics, we identified the top 10 hub genes for BRL in treating HTN (Figure 2C). The top 10 hub genes were calculated using 12 algorithms with 10 nodes and 45 edges (Figure 2C). Out of the top 10 hub genes, Epidermal Growth Factor Receptor (EGFR), Proto-oncogene Tyrosine-Protein Kinase Src (SRC), Catenin Beta 1 (CTNNB1), Protein Kinase B Alpha (AKT1), Signal Transducer and Activator of Transcription 3 (STAT3), had the highest degree value in the PPI network, as shown in Table 2. Figures 2D and 2E depict the network pharmacology analysis of BRL against HTN. Figure 2D presents the pathway-target interaction network related to hypertension, highlighting key signalling pathways and the top 10 hub gene targets identified by network topology. These genes play important roles in the development of hypertension. Figure 2E shows the integrated BRL compound-target-pathway-HTN network, which demonstrates how bioactive BRL phytoconstituents interact with their predicted molecular targets and hypertension-related pathways. This network reflects the multi-

component and multi-target mechanisms that may explain BRL's potential to lower blood pressure.

3.4. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes Pathway Enrichment Analysis of BRL in HTN

The 246 predicted overlapping target genes were subjected to GO and KEGG pathway enrichment analyses using ShinyGO (v0.741) (<http://bioinformatics.sdstate.edu/go74/>), a web-based gene-set enrichment analysis tool for plants and animals, in order to investigate the underlying molecular mechanisms of BRL in the treatment of HTN. The GO enrichment analysis categorized the targets into three functional groups: BPE, MF, and CC ($P < 0.05$). The biological significance of the targets was ascertained by identifying and analysing the top 10 significantly enriched phrases in each category (Figure 3A-C). The BPE terms were predominantly associated with vascular and inflammatory regulation, including “cellular response to chemical stress,” “response to oxidative stress,” “response to ROS,” “regulation of apoptotic signaling pathway,” and “regulation of vasoconstriction” (Figure 3A). The CC analysis indicated enrichment in “plasma membrane,” “receptor complex,” “synaptic membrane,” “cell junction,” and “cytoplasmic vesicle,” suggesting the involvement of transmembrane and signal transduction components (Figure 3B). The MF category mainly involved “G protein-coupled receptor binding,” “enzyme binding,” “ATP binding,” “protein kinase activity,” and “signaling receptor activity” (Figure 3C), indicating that the antihypertensive action of BRL may involve kinase-mediated signal transduction and receptor modulation. Subsequently, KEGG pathway enrichment analysis was conducted for the same 246 overlapping targets ($P < 0.05$), and the top 10 enriched signaling pathways were identified (Figure 2A and 2B). The results showed that BRL-targeted genes were significantly enriched in pathways associated with vascular function, inflammation, and oxidative stress, including: “Epidermal Growth Factor Receptor”, “Phosphoinositide-3-Kinase Regulatory Subunit 1 Alpha”, “Protein Tyrosine Kinase 2”, “SRC Proto-Oncogene Non-Receptor Tyrosine Kinase”, “Protein Tyrosine Phosphatase Non-Receptor Type 11”, “Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha”, “Signal Transducer and Activator of Transcription 3”, “Catenin Beta 1”, “FYN Proto-Oncogene Src Family Tyrosine Kinase”, “AKT Serine Threonine Kinase 1” (Figure 2C). The current study investigates kinase-centered vascular signalling modulation by BRL in a unique manner using integrated network pharmacology and molecular dynamics. Hypertension is driven by complex interactions between hormonal dysregulation, oxidative stress, and maladaptive intracellular signalling, all

of which were prominently enriched in the present analysis. Endothelial dysfunction and vascular remodelling in HTN are primarily caused by the renin-angiotensin-aldosterone system, sympathetic activation, and redox imbalance. BPEs include responses to hormones, oxygen-containing compounds, and chemical stimuli, as well as the regulation of cell proliferation and programmed cell death (Gallo et al. 2022b; Su et al. 2014). The enrichment of plasma membrane, receptor complex, membrane raft, and cytosolic components highlights the importance of angiotensin II type-1 receptor localization and lipid raft-dependent signal organization in amplifying hypertensive signalling cascades (Mehta and Griendling 2007). At the molecular level, enrichment of protein kinase activity, phosphotransferase activity, receptor activity, and oxidoreductase activity underscores the activation of kinase-dependent pathways (MAPKs, PKC, PI3K/Akt)(Fulton et al. 1999a; Touyz et al. 1999) and NADPH oxidase-derived reactive oxygen species(Cave et al. 2006; Touyz and Briones 2011), which together mediate vasoconstriction, inflammation, and structural vascular changes characteristic of HTN (Förstermann and Münzel 2006). Consistently, KEGG pathway analysis identified advanced glycation end-products binding to the receptor for advanced glycation end-products signalling (Wang et al. 2024), HIF-1 signalling (Pullamsetti et al. 2020), EGFR-associated signalling (Andresen et al. 2003), and nitrogen metabolism as key contributors, linking oxidative stress-induced inflammation, hypoxia-responsive vascular adaptation, angiotensin II-dependent receptor transactivation, and impaired nitric oxide bioavailability to sustained bP elevation and end-organ damage (Andresen et al. 2003; Förstermann and Münzel 2006; Pullamsetti et al. 2020).

3.5. Molecular docking interactions of BRL phytoconstituents with top 10 protein targets

The NCBI-PubChem database (<https://www.ncbi.nlm.nih.gov/>) provided the 3D structures of the phytoconstituents in SDF format (Figure 4). For the docking simulation, captopril was obtained as a standard medication from the RCSB NCBI PubChem database. The PDB Database (<https://www.rcsb.org/>) provided the 3D structures. AutoDock Vina v1.2.5 (<https://vina.scripps.edu>) was used to run the docking simulation with a few critical proteins. Discovery Studio software was used to prepare the receptor by removing co-crystallized ligands and water molecules. All ligands and receptors were stored in Protein Data Bank (PDB) format upon production. BIOVIA Discovery Studios (<https://discover.3ds.com/discovery-studio-visualizer-download>) and PyMOL 3.1 (<https://www.pymol.org/>) were used to display the docking results. Docking scores offer estimates of relative binding, but they should be

regarded with caution as estimates of binding affinity rather than as absolute measures of inhibitory potency.

Proto-oncogene tyrosine-protein kinase Src

For proto-oncogene tyrosine-protein kinase Src, docking analysis revealed binding energies ranging from -6.4 to -9.2 kcal/mol (Table 4), with Kaempferol (-9.2 kcal/mol) showing the strongest interaction and optimal stabilization within the Src active site, followed by Quercetin and Isorhamnetin (-8.7 kcal/mol), Gluconasturtiin (-8.2 kcal/mol), Glucoerucin (-6.8 kcal/mol), Ferulic acid and Caffeic acid (-6.6 kcal/mol), Linoleic acid (-6.5 kcal/mol), and Sinapic acid (-6.4 kcal/mol), indicating that kaempferol, Quercetin & Isorhamntin exhibits superior Src inhibitory potential among the tested compounds. The standard drug Captopril showed moderate binding affinity for Src, with a binding energy of -6.5 kcal/mol, serving as a reference for comparative evaluation. The detailed docking scores are summarized in Table 4, while the binding interactions and docking poses are illustrated in Figure 5.

Epidermal growth factor receptor

For EGFR, molecular docking analysis revealed binding energies ranging from -6.5 to -9.5 kcal/mol (Table 4), with Isorhamnetin and Kaempferol (-9.5 kcal/mol each) showing the strongest interactions and optimal stabilization within the EGFR active site, followed by Quercetin (-9.4 kcal/mol) and Gluconasturtiin (-9.2 kcal/mol). Sinapic acid (-7.7 kcal/mol), Glucoerucin (-7.6 kcal/mol), ferulic acid (-7.4 kcal/mol), and caffeic acid (-7.3 kcal/mol) all showed moderate binding affinities, whilst linoleic acid (-6.6 kcal/mol) showed a somewhat lower yet beneficial interaction. These results suggest that among the substances studied, flavonoid compounds in particular, isorhamnetin and kaempferol have the best EGFR inhibitory ability. As a benchmark for comparative analysis, the common medication captopril demonstrated a moderate binding affinity toward EGFR with a binding energy of -6.5 kcal/mol. Figure 6 shows the binding interactions and docking postures, and Table 4 summarises the detailed docking scores.

Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform

Docking analysis of Phosphatidylinositol 4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha Isoform (PIK3CA) showed binding energies ranging from -5.3 to -8.9 kcal/mol (Table 4), with Kaempferol (-8.9 kcal/mol) exhibiting the strongest interaction, followed by Isorhamnetin (-8.4 kcal/mol), Quercetin (-7.9 kcal/mol), and Gluconasturtiin (-7.8 kcal/mol). Ferulic acid (-6.7 kcal/mol), Caffeic acid (-6.6 kcal/mol), Sinapic acid (-6.3 kcal/mol), Glucoerucin (-6.1

kcal/mol), and Linoleic acid (-6.1 kcal/mol) showed moderate but favorable binding. As a reference control, the common medication captopril showed a relatively lower affinity for PIK3CA with a binding energy of -5.3 kcal/mol. Figure 7 shows the binding interactions and docking postures, and Table 4 summarises the detailed docking scores.

Phosphatidylinositol 3-kinase regulatory subunit alpha

Phosphatidylinositol 3-Kinase Regulatory Subunit Alpha (PIK3R1) docking analysis showed binding energies ranging from -5.8 to -8.7 kcal/mol (Table 4). The strongest interaction was shown by kaempferol (-8.7 kcal/mol), followed by isorhamnetin (-7.5 kcal/mol), quercetin (-7.4 kcal/mol), and gluconasturtiin (-7.0 kcal/mol). The binding affinities of ferulic acid and caffeic acid (-6.8 kcal/mol each), sinapic acid (-6.2 kcal/mol), glucoseerucin (-6.0 kcal/mol), and linoleic acid (-5.8 kcal/mol) were modest. As a comparison control, the common medication captopril showed a relatively lower affinity for PIK3R1 with a binding energy of -5.9 kcal/mol. Figure 8 shows the binding interactions and docking postures, and Table 4 summarises the detailed docking scores.

Focal adhesion kinase 1

The strongest interaction was shown by Kaempferol (-9.3 kcal/mol), followed by Gluconasturtiin (-8.9 kcal/mol), Isorhamnetin (-8.8 kcal/mol), and Quercetin (-8.7 kcal/mol), according to docking analysis of Focal Adhesion Kinase 1 (PTK2). Moderate binding was demonstrated by glucoseerucin (-7.8 kcal/mol), linoleic acid (-6.4 kcal/mol), ferulic acid and caffeic acid (-6.6 kcal/mol each), and sinapic acid (-6.8 kcal/mol). Captopril, a common medication, has a reduced affinity (-5.5 kcal/mol). Figure 9 shows the docking postures and binding interactions, while Table 4 summarises the detailed docking scores.

Tyrosine-protein phosphatase non-receptor type 11

Docking analysis of Tyrosine-Protein Phosphatase Non-Receptor Type 11 (PTPN11) revealed binding energies ranging from -5.5 to -9.6 kcal/mol, with Quercetin (-9.6 kcal/mol) showing the strongest interaction, followed by Isorhamnetin (-9.4 kcal/mol), Kaempferol (-9.3 kcal/mol), and Gluconasturtiin (-8.9 kcal/mol). Glucoerucin (-6.9 kcal/mol), Sinapic acid (-6.8 kcal/mol), Caffeic acid (-6.6 kcal/mol), and Ferulic acid (-6.2 kcal/mol) all showed moderate affinities. Captopril, a common medication, had modest binding (-6.7 kcal/mol). Figure 10 shows the binding interactions and docking postures, while Table 4 summarises the detailed docking scores.

Signal transducer and activator of transcription 3

The strongest interaction was shown by Kaempferol (-6.4 kcal/mol), followed by Isorhamnetin and Quercetin (-6.2 kcal/mol each) and Gluconasturtiin (-5.8 kcal/mol), according to docking analysis of Signal Transducer and Activator of Transcription 3 (STAT3), which revealed comparatively weaker binding energies ranging from -4.3 to -6.4 kcal/mol. Lower affinities were shown by other compounds. Captopril, a common medication, exhibited the least amount of interaction (-4.3 kcal/mol). Figure 11 shows the binding interactions and docking postures, while Table 4 summarises the detailed docking scores.

Catenin beta-1

Low binding affinities ranging from -3.0 to -4.6 kcal/mol were found in docking studies of Catenin Beta-1 (CTNNB1). The greatest interactions were found between Gluconasturtiin and Kaempferol (-4.6 kcal/mol each), followed by Isorhamnetin and Quercetin (-4.2 kcal/mol each). Linoleic acid (-3.0) showed weak binding to other chemicals. Captopril, a common medication, had a low affinity (-3.4 kcal/mol). Figure 12 shows the binding interactions and docking postures, while Table 4 summarises the detailed docking scores.

RAC-alpha serine/threonine-protein kinase

Strong binding energies ranging from -7.1 to -11.2 kcal/mol were revealed by docking analysis of RAC-Alpha Serine/Threonine-Protein Kinase (AKT1). Kaempferol (-11.2 kcal/mol) showed the strongest interaction, followed by isorhamnetin and quercetin (-10.6 kcal/mol each) and gluconasturtiin (-10.5 kcal/mol). Glucoerucin (-8.1 kcal/mol) and Sinapic acid (-7.9 kcal/mol) showed moderate affinities. Captopril, a common medication, had modest binding (-7.1 kcal/mol). Figure 12 shows the binding interactions and docking postures, while Table 4 summarises the detailed docking scores.

Tyrosine-protein kinase Fyn

Docking analysis of Tyrosine-Protein Kinase Fyn (FYN) revealed binding energies ranging from -6.0 to -9.6 kcal/mol, with Kaempferol (-9.6 kcal/mol) showing the strongest interaction, followed by Isorhamnetin and Quercetin (-9.3 kcal/mol each) and Gluconasturtiin (-8.6 kcal/mol). Moderate binding was observed for Ferulic acid (-7.5 kcal/mol) and Caffeic acid (-7.2 kcal/mol). The standard drug Captopril showed lower affinity (-6.2 kcal/mol). The detailed docking scores are summarized in Table 4, while the binding interactions and docking poses are illustrated in Figure 13.

3.6. Molecular Dynamics Simulation

To validate the docking results and assess the dynamic behaviour of the complexes under near-physiological conditions, we performed 100 ns molecular dynamics (MD) simulations for AKT1 and SRC with isorhamnetin, kaempferol, quercetin, and the reference drug captopril. These simulations evaluated structural stability, residue flexibility, interaction persistence, compactness, and binding energetics over time.

Stability of Protein-Ligand Complexes

In addition, RMSD analysis showed that all systems reached equilibrium within 10-20 ns and remained stable throughout the simulation. For AKT1, the protein RMSD values have remained within ~ 2.5 - 3.5 Å across all complexes. Ligand RMSD measurements indicated that the ligands isorhamnetin and kaempferol exhibited lower positional fluctuations than the drug captopril. Quercetin has shown consistent binding, with moderate fluctuations in ligand concentration during the production phase. In SRC complexes, the values of backbone RMSD ranged within ~ 2.0 - 3.0 Å, thus proving stability in structure. Among the tested compounds, flavonoid-bound systems showed a smoother progression of RMSD values compared to those of the captopril-bound complexes, which exhibited greater variability. The high variability observed in the captopril-bound complexes may arise from the size and binding properties of the inhibitors, which have a lower capacity to form extensive stabilizing interactions at the kinase's active sites. Overall, the RMSD profiles show that within the 100 ns time window, the chosen phytoconstituents hold a steady binding position in the catalytic pocket. The RMSD of AKT1 and SRC are illustrated in figure 14.

Residue Flexibility Analysis

To evaluate local flexibility in the ligand-bound state, RMSF analysis was used. Increased fluctuations were mostly limited to solvent-exposed loops and terminal regions, which are naturally flexible, in both AKT1 and SRC systems. Conversely, residues in the ligand-binding pocket showed reduced RMSF values, suggesting that prolonged ligand interaction had limited their mobility. In contrast to captopril-bound systems, flavonoid-bound complexes showed less variation in important binding-site residues. This implies that localised stabilisation of catalytically important areas is facilitated by flavonoid binding, potentially improving the persistence of binding. The RMSF of AKT1 and SRC are illustrated in figure 15.

Structural Compactness and Secondary Structure Integrity

All complexes showed comparatively stable radius of gyration (Rg) profiles during the simulation, suggesting that ligand interaction did not cause structural destabilisation or global unfolding. Overall protein compactness is maintained when Rg variations are not significant. Analysis of secondary structure elements (SSEs) provided additional confirmation of structural integrity. In the 100 ns simulation, there was no indication of significant secondary structure loss, and the fraction of α -helices and β -strands stayed constant. Compared with the captopril complexes, flavonoid-bound systems showed stability that was either equal to or marginally better, confirming their structural compatibility with the kinase framework. Figure 16 illustrates the secondary structure evolution plots and detailed Rg trajectories for the AKT1 and SRC complexes.

Protein-Ligand Interaction Persistence

During the simulation, interaction profiling showed water-mediated bridges, π - π stacking, hydrophobic interactions, and persistent hydrogen bonds. Important residues found during docking continued to interact for a considerable amount of the trajectory, suggesting long-term binding as opposed to brief contact. In the binding pocket, flavonoids created extensive networks of interactions, especially through numerous hydrogen bond donors and acceptors and aromatic stacking. Captopril, in contrast, formed fewer long-lasting connections, which is in line with its more straightforward chemical structure. Stronger occupancy and interaction persistence for isorhamnetin, kaempferol, and quercetin in both AKT1 and SRC complexes were further validated by histogram analysis of interaction frequencies. Figure 17 provides a thorough overview of interaction trends and contact frequency distributions.

Binding Free Energy Estimation

MM-GBSA simulations on typical trajectory frames showed that all phytoconstituents had energetically advantageous binding. Among these, isorhamnetin, kaempferol, and quercetin showed better binding free energy values than the reference medication, confirming the stability patterns seen in RMSD and interaction studies. The projected binding modes are more reliable when docking scores, MM-GBSA estimates, and dynamic stability factors are consistent. The MD simulations demonstrate that the preferred BRL phytoconstituents bind to AKT1 and SRC, forming structurally compact and dynamically stable complexes. Strong dynamic support for the docking predictions is provided by the consistency between the RMSD, RMSF, interaction persistence, radius of gyration, and binding free energy

assessments. These results show that BRL's flavonoid components bind hypertension-associated kinase targets more strongly and persistently than the reference medication, warranting additional experimental confirmation. While single 100 ns simulations provide insight into dynamic stability, further replicate simulations and enhanced sampling approaches would strengthen the robustness of these observations.

4. Discussion

HTN is a prevalent chronic CVS and a major global source of morbidity and death (Mills et al. 2020). It does not result from a single molecular defect but arises from the combined effects of oxidative stress, endothelial dysfunction, vascular inflammation, and neurohormonal dysregulation, especially overactivation of the RAS. These mechanisms interact and reinforce each other, disrupting vascular homeostasis and maintaining elevated BP. Therefore, compared to single-target approaches, treatment techniques that target numerous disease pathways are expected to yield superior long-term blood pressure control (Fuchs and Whelton 2020b; Gallo et al. 2022b; Higashi 2022b).

In this work, the antihypertensive potential of BRL a cruciferous medicinal and edible plant well-known for its rich phytochemical content and related health benefits was investigated using an integrative in silico workflow that included network pharmacology, molecular docking, and MD dynamics simulations. Numerous bioactive classes, such as flavonoids, phenolic acids, glucosinolates, and isothiocyanates, are found in BRL, according to prior research. Many of these classes have shown anti-inflammatory and antioxidant properties that are directly related to vascular disorders (Cao et al. 2021b; Javed et al. 2019b). Crucially, BRL was shown to have potent ACE-inhibitory activity, indicating that it may work to modulate RAS and regulate blood pressure (Abid et al. 2022a).

In order to find drug-like candidates for additional analysis, 189 phytoconstituents were first gathered and screened using Lipinski's criteria and SwissADME. Because drug-likeness and ADME profiling prioritise molecules with acceptable physicochemical properties for oral bioavailability, they enhance the dependability of projected therapeutic leads, making this stage crucial in computational pharmacology investigations (Daina et al. 2017). Following screening, key phytoconstituents such as Quercetin, Kaempferol, Isorhamnetin, Sinapic Acid, Caffeic Acid, Ferulic Acid, and the characteristic Glucosinolate Gluconasturtiin were shortlisted. Flavonoids such as Quercetin and Kaempferol have been consistently reported as potent vascular protective agents due to their antioxidant properties and their ability to regulate multiple signalling pathways related to inflammation and endothelial integrity (Boots et al.

2008; M. Calderon-Montano et al. 2011). Since HTN pathogenesis is strongly linked to oxidative imbalance and inflammatory signalling, such phytochemicals represent biologically meaningful candidates for multitarget therapy.

A systems-level antihypertensive mechanism of BRL was further supported by the network pharmacology results of this investigation. A significant number of overlapping targets were obtained by intersecting plant-predicted targets with HTN-associated genes, supporting the idea that BRL active components may function through several nodes implicated in BP control. Among the primary hub targets found by the PPI network analysis were AKT1, SRC, EGFR, STAT3, PI3K family components, PTK2, and FYN. In vascular biology, these genes have significant mechanistic relevance. For instance, endothelial function, vascular relaxation, survival signalling, and nitric oxide synthesis are all critically dependent on PI3K-Akt signalling; disruptions in this axis can lead to endothelial dysfunction and elevated vascular resistance (Fulton et al. 1999b; Ma et al. 2023b). It is well known that Akt activation promotes endothelial nitric oxide production, which supports vasodilation and preserves vascular homeostasis (Fulton et al. 1999b). Similar to this, the Src family kinases SRC and FYN are crucial upstream signalling regulators that link membrane receptors to intracellular cascades that regulate vascular contractility, inflammation, and remodelling. While STAT3 is necessary for the activation of cytokine-mediated inflammation, which is increasingly identified as a key cause of chronic hypertension and endothelial dysfunction, EGFR signalling is also linked to vascular structural alterations and HTN remodelling processes (Gallo et al. 2022b; Ma et al. 2023b).

Thus, the discovery of these hubs implies that BRL phytochemicals may affect blood pressure regulation by concurrently focusing on inflammatory-vascular signalling networks and endothelial-protective pathways. The anticipated targets are linked to oxidative stress response, ROS regulation, chemical stress response, apoptotic regulation, and modulation of vasoconstriction, according to GO and KEGG enrichment studies, which offered further biological support. These enriched phrases are in line with contemporary HTN theories, which state that high ROS production lowers the bioavailability of nitric oxide, hinders endothelium-dependent relaxation, and encourages vascular dysfunction (Higashi 2022b). The concept that BRL can improve vascular function and restore endothelial integrity through coordinated signalling regulation as opposed to a single-enzyme inhibition strategy is further supported by the strong correlation with PI3K-Akt signalling.

Using AutoDock Vina, molecular docking was carried out against hub proteins to confirm the network-identified target interactions at the structural level. Several BRL phytochemicals

showed substantial binding affinities with several hub targets, according to the docking studies. Among important proteins, such as AKT1, EGFR, SRC, and FYN, quercetin, kaempferol, isorhamnetin, and gluconasturtiin consistently showed high binding scores. Crucially, these phytochemicals often displayed docking affinity values that were either superior to or equivalent to those of the reference medication, captopril. This suggests that BRL may have antihypertensive effects by modulating kinase-driven vascular signalling hubs in addition to blocking RAS. This interpretation supports the idea that the plant may have other upstream mechanisms that work together to improve BP regulation and is consistent with the documented ACE-inhibitory capability of BRL (Abid et al. 2022a). Furthermore, Gluconasturtiin's interaction potential highlights the importance of Brassica plants' glucosinolate-derived chemistry, which has been extensively linked to protective roles in chronic disease states through antioxidant and signalling regulatory actions (Cao et al. 2021b; Javed et al. 2019b). MD simulations were used to verify the stability of top-ranking ligand-protein complexes under dynamic biological settings because docking only offers a snapshot of a static interaction. The MD results revealed that protein-ligand complexes-maintained compactness, controlled residue flexibility, exhibited acceptable RMSD trends, and maintained ligand interactions throughout the trajectory. Such stability suggests that the docking-predicted binding conformations are probably dependable rather than just transient contacts. These results increase the likelihood that important phytochemicals like isorhamnetin, kaempferol, and quercetin may successfully interact with target binding sites and modify protein activity in a physiologically relevant setting.

Together, the current study offers compelling computational evidence that BRL may act as a multitarget antihypertensive plant by coordinating the modulation of pathways associated to endothelial function, inflammatory signalling, and oxidative stress. By combining network pharmacology with MD modelling and docking, the mechanistic interpretation is reinforced, and the idea that BRL phytochemicals can affect BP control through multi-pathway convergence is supported. It is important to note, nonetheless, that experimental validation is necessary for computational predictions. Future work should validate these findings using *in-vitro* studies focusing on endothelial nitric oxide signalling, oxidative biomarkers, and kinase-inhibition profiling, followed by *in-vivo* validation in standard HTN models such as N-nitro-L-arginine methyl ester, deoxycorticosterone acetate-salt, or two-kidney, one-clip. Additionally, pharmacokinetic evaluation is essential to confirm the systemic availability of lead bioactive. Overall, the study positions BRL as a promising nutraceutical source and a potential lead-compound reservoir for developing safer multitarget antihypertensive strategies.

5. Limitation

The approximative scoring systems employed in molecular docking, the predictive nature of target identification databases, and the use of single-run molecular dynamics simulations are the limitations of this study. Further limiting direct biological extrapolation is the lack of *in-vitro* and *in-vivo* validation. To validate the discovered interactions' pharmacological significance, more experimental research is required.

6. Conclusion

Using a comprehensive *in-silico* methodology that combines network pharmacology, molecular docking, MD simulation, and ADMET-based screening, this study ends with computational evidence pointing to possible multitarget interactions that need additional experimental confirmation. According to the results, BRL may include bioactive phytoconstituents that resemble drugs and can alter important molecular targets and pathways linked to hypertension. While network pharmacology identified key hub genes involved in vascular signalling and regulatory processes, enrichment analysis focused on important biological roles related to endothelial homeostasis, PI3K-Akt/NO-eNOS mediated Vaso regulatory mechanisms, and oxidative stress control. Additionally, flavonoids and glucosinolate-derived compounds, specifically quercetin, kaempferol, isorhamnetin, and gluconasturtiin, showed strong binding affinity toward multiple hub proteins and often showed better interaction potential than the reference drug captopril, according to molecular docking. Furthermore, MD simulations validated the lead ligand-protein complexes' stability and good interaction behaviour, boosting trust in their anticipated biological significance. Although additional *in-vitro* and *in-vivo* experimental validation is necessary to demonstrate efficacy, safety, and translational feasibility, our work positions BRL as a viable nutraceutical resource and a possible reservoir of lead candidates for multitarget HTN therapy.

Consent for publication

Not applicable.

Availability of data and materials

All data and materials are available upon request.

Competing interests

The authors declared no conflicts of interest.

Funding

No funding was received for this research work.

Author's contribution

DD and SN has performed the experimental parts. SM was responsible for literature research and drafting of a manuscript. DM has critically revised the manuscript. All authors have read and approved the manuscript.

Acknowledgement

We want to thank you, Dr. A. P. Pawar, Principal, Poona College of Pharmacy, Bharati Vidyapeeth (Deemed to be University), for providing the necessary facilities to carry out this research work.

Conflict of interest

We have no conflict of interest.

References

- Abid R, Islam M, Saeed H, Ahmad A, Imtiaz F, Yasmeen A, et al. Antihypertensive potential of Brassica rapa leaves: An in vitro and in silico approach. *Front. Pharmacol.* [Internet]. Frontiers Media S.A.; 2022a Sep 30 [cited 2025 Nov 4];13:996755. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9562470/>
- Abid R, Islam M, Saeed H, Ahmad A, Imtiaz F, Yasmeen A, et al. Antihypertensive potential of Brassica rapa leaves: An in vitro and in silico approach. *Front. Pharmacol.* [Internet]. Frontiers Media S.A.; 2022b Sep 30 [cited 2025 Nov 4];13:996755. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9562470/>
- Aggarwal R, Chiu N, Wadhera RK, Moran AE, Raber I, Shen C, et al. Racial/Ethnic Disparities in Hypertension Prevalence, Awareness, Treatment, and Control in the United States, 2013 to 2018. *Hypertension*. Lippincott Williams and Wilkins; 2021 Dec 1;78(6):1719–26.
- Aires A, Fernandes C, Carvalho R, Bennett RN, Saavedra MJ, Rosa EAS. Seasonal Effects on Bioactive Compounds and Antioxidant Capacity of Six Economically Important Brassica Vegetables. *Molecules* 2011, Vol. 16, Pages 6816–6832 [Internet]. Molecular Diversity Preservation International; 2011 Aug 10 [cited 2025 Nov 4];16(8):6816–32. Available from: <https://www.mdpi.com/1420-3049/16/8/6816/htm>
- Amberger JS, Bocchini CA, Scott AF, Hamosh A. OMIM.org: leveraging knowledge across phenotype–gene relationships. *Nucleic Acids Res.* [Internet]. Oxford Academic; 2019 Jan 8 [cited 2026 Jan 11];47(D1):D1038–43. Available from: <https://dx.doi.org/10.1093/nar/gky1151>
- Andresen BT, Linnoila JJ, Jackson EK, Romero GG. Role of EGFR transactivation in angiotensin II signaling to extracellular regulated kinase in preglomerular smooth muscle cells. *Hypertension* [Internet]. Hypertension; 2003 Mar 1 [cited 2026 Jan 29];41(3 Pt 2):781–6. Available from: <https://pubmed.ncbi.nlm.nih.gov/12623996/>
- Assenov Y, Ramírez F, Schelhorn SESE, Lengauer T, Albrecht M. Computing topological parameters of biological networks. *Bioinformatics* [Internet]. Oxford Academic; 2008 Jan 15 [cited 2026 Jan 11];24(2):282–4. Available from: <https://dx.doi.org/10.1093/bioinformatics/btm554>
- Barabási AL, Oltvai ZN. Network biology: understanding the cell’s functional organization. *Nature Reviews Genetics* 2004 5:2 [Internet]. Nature Publishing Group; 2004a Feb [cited 2026 Jan 11];5(2):101–13. Available from: <https://www.nature.com/articles/nrg1272>
- Barabási AL, Oltvai ZN. Network biology: understanding the cell’s functional organization. *Nature Reviews Genetics* 2004 5:2 [Internet]. Nature Publishing Group; 2004b Feb [cited 2026 Jan 11];5(2):101–13. Available from: <https://www.nature.com/articles/nrg1272>
- Bateman A, Martin MJ, Orchard S, Magrane M, Ahmad S, Alpi E, et al. UniProt: the Universal Protein Knowledgebase in 2023. *Nucleic Acids Res.* [Internet]. Oxford Academic; 2023 Jan 6 [cited 2026 Jan 11];51(D1):D523–31. Available from: <https://dx.doi.org/10.1093/nar/gkac1052>

Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, et al. The Protein Data Bank. *Nucleic Acids Res.* [Internet]. Oxford Academic; 2000 Jan 1 [cited 2026 Jan 11];28(1):235–42. Available from: <https://dx.doi.org/10.1093/nar/28.1.235>

Boots AW, Haenen GRMM, Bast A. Health effects of quercetin: From antioxidant to nutraceutical. *Eur. J. Pharmacol.* [Internet]. Eur J Pharmacol; 2008 May 13 [cited 2026 Jan 18];585(2–3):325–37. Available from: <https://pubmed.ncbi.nlm.nih.gov/18417116/>

Bowers KJ, Chow E, Xu H, Dror RO, Eastwood MP, Gregersen BA, et al. Scalable algorithms for molecular dynamics simulations on commodity clusters. *Proceedings of the 2006 ACM/IEEE Conference on Supercomputing, SC'06* [Internet]. 2006 [cited 2026 Jan 29]; Available from: [/doi/pdf/10.1145/1188455.1188544?download=true](https://doi.org/10.1145/1188455.1188544?download=true)

Burley SK, Bhikadiya C, Bi C, Bittrich S, Chen L, Crichlow G V., et al. RCSB Protein Data Bank: powerful new tools for exploring 3D structures of biological macromolecules for basic and applied research and education in fundamental biology, biomedicine, biotechnology, bioengineering and energy sciences. *Nucleic Acids Res.* [Internet]. Oxford Academic; 2021 Jan 8 [cited 2026 Jan 11];49(D1):D437–51. Available from: <https://dx.doi.org/10.1093/nar/gkaa1038>

Cao Q, Wang G, Peng Y. A Critical Review on Phytochemical Profile and Biological Effects of Turnip (*Brassica rapa* L.). *Front. Nutr.* [Internet]. Frontiers Media S.A.; 2021a Jul 29 [cited 2025 Nov 4];8:721733. Available from: www.frontiersin.org

Cao Q, Wang G, Peng Y. A Critical Review on Phytochemical Profile and Biological Effects of Turnip (*Brassica rapa* L.). *Front. Nutr.* [Internet]. Frontiers Media S.A.; 2021b Jul 29 [cited 2026 Jan 18];8:721733. Available from: www.frontiersin.org

Cave AC, Brewer AC, Narayanapanicker A, Ray R, Grieve DJ, Walker S, et al. NADPH oxidases in cardiovascular health and disease. *Antioxid. Redox Signal.* [Internet]. Antioxid Redox Signal; 2006 May [cited 2026 Jan 29];8(5–6):691–728. Available from: <https://pubmed.ncbi.nlm.nih.gov/16771662/>

Chen DC, McCallum W, Sarnak MJ, Ku E. Intensive BP Control and eGFR Declines: Are These Events Due to Hemodynamic Effects and Are Changes Reversible? *Curr. Cardiol. Rep.* [Internet]. Springer; 2020 Oct 1 [cited 2026 Feb 13];22(10):117. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC7668315/>

Chen Y, De Bruyn Kops C, Kirchmair J. Data Resources for the Computer-Guided Discovery of Bioactive Natural Products. *J. Chem. Inf. Model.* [Internet]. American Chemical Society; 2017 Sep 25 [cited 2026 Jan 11];57(9):2099–111. Available from: <https://pubs.acs.org/doi/abs/10.1021/acs.jcim.7b00341>

Chin CH, Chen SH, Wu HH, Ho CW, Ko MT, Lin CY. cytoHubba: identifying hub objects and sub-networks from complex interactome. *BMC Systems Biology* 2014 8:4 [Internet]. BioMed Central; 2014 Dec 8 [cited 2026 Jan 11];8(4):S11-. Available from: <https://link.springer.com/article/10.1186/1752-0509-8-S4-S11>

Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports*

2017 7:1 [Internet]. Nature Publishing Group; 2017 Mar 3 [cited 2026 Jan 11];7(1):42717-. Available from: <https://www.nature.com/articles/srep42717>

Daina A, Michielin O, Zoete V. SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. *Nucleic Acids Res.* [Internet]. Oxford Academic; 2019 Jul 2 [cited 2026 Jan 11];47(W1):W357–64. Available from: <https://dx.doi.org/10.1093/nar/gkz382>

Eberhardt J, Santos-Martins D, Tillack AF, Forli S. AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings. *J. Chem. Inf. Model.* [Internet]. American Chemical Society; 2021a Aug 23 [cited 2026 Jan 11];61(8):3891–8. Available from: <https://pubs.acs.org/doi/abs/10.1021/acs.jcim.1c00203>

Eberhardt J, Santos-Martins D, Tillack AF, Forli S. AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings. *J. Chem. Inf. Model.* [Internet]. American Chemical Society; 2021b Aug 23 [cited 2026 Jan 11];61(8):3891–8. Available from: <https://pubs.acs.org/doi/abs/10.1021/acs.jcim.1c00203>

Fodor A, Tiperciuc B, Login C, Orasan OH, Lazar AL, Buchman C, et al. Endothelial Dysfunction, Inflammation, and Oxidative Stress in COVID-19—Mechanisms and Therapeutic Targets. *Oxid. Med. Cell. Longev.* [Internet]. John Wiley & Sons, Ltd; 2021 Jan 1 [cited 2025 Nov 4];2021(1):8671713. Available from: [/doi/pdf/10.1155/2021/8671713](https://doi/pdf/10.1155/2021/8671713)

Forli S, Huey R, Pique ME, Sanner MF, Goodsell DS, Olson AJ. Computational protein–ligand docking and virtual drug screening with the AutoDock suite. *Nature Protocols* 2016 11:5 [Internet]. Nature Publishing Group; 2016 Apr 14 [cited 2026 Jan 11];11(5):905–19. Available from: <https://www.nature.com/articles/nprot.2016.051>

Förstermann U, Münzel T. Endothelial nitric oxide synthase in vascular disease: from marvel to menace. *Circulation* [Internet]. Circulation; 2006 Apr [cited 2026 Jan 29];113(13):1708–14. Available from: <https://pubmed.ncbi.nlm.nih.gov/16585403/>

Fuchs FD, Whelton PK. High Blood Pressure and Cardiovascular Disease. *Hypertension*. Lippincott Williams and Wilkins; 2020a Feb 1;75(2):285–92.

Fuchs FD, Whelton PK. High Blood Pressure and Cardiovascular Disease. *Hypertension* [Internet]. Hypertension; 2020b Feb 1 [cited 2026 Jan 18];75(2):285–92. Available from: <https://pubmed.ncbi.nlm.nih.gov/31865786/>

Fulton D, Gratton JP, McCabe TJ, Fontana J, Fujio Y, Walsh K, et al. Regulation of endothelium-derived nitric oxide production by the protein kinase Akt. *Nature* 1999 399:6736 [Internet]. Nature Publishing Group; 1999a Jun 10 [cited 2026 Jan 11];399(6736):597–601. Available from: <https://www.nature.com/articles/21218>

Fulton D, Gratton JP, McCabe TJ, Fontana J, Fujio Y, Walsh K, et al. Regulation of endothelium-derived nitric oxide production by the protein kinase Akt. *Nature* [Internet]. Nature; 1999b Jun 10 [cited 2026 Jan 18];399(6736):597–601. Available from: <https://pubmed.ncbi.nlm.nih.gov/10376602/>

Fyhrquist F, Saijonmaa O. Renin-angiotensin system revisited. *J. Intern. Med.* [Internet]. John Wiley & Sons, Ltd; 2008 Sep 1 [cited 2026 Jan 11];264(3):224–36. Available from: [/doi/pdf/10.1111/j.1365-2796.2008.01981.x](https://doi/pdf/10.1111/j.1365-2796.2008.01981.x)

Gallo G, Volpe M, Savoia C. Endothelial Dysfunction in Hypertension: Current Concepts and Clinical Implications. *Front. Med. (Lausanne)*. [Internet]. Frontiers Media S.A.; 2022a Jan 20 [cited 2025 Nov 4];8:798958. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8811286/>

Gallo G, Volpe M, Savoia C. Endothelial Dysfunction in Hypertension: Current Concepts and Clinical Implications. *Front. Med. (Lausanne)*. [Internet]. Front Med (Lausanne); 2022b Jan 20 [cited 2026 Jan 18];8. Available from: <https://pubmed.ncbi.nlm.nih.gov/35127755/>

Gao X, Li S, Cong C, Wang Y, Xu L. A Network Pharmacology Approach to Estimate Potential Targets of the Active Ingredients of Epimedium for Alleviating Mild Cognitive Impairment and Treating Alzheimer's Disease. *Evid. Based. Complement. Alternat. Med.* [Internet]. Hindawi Limited; 2021 [cited 2026 Jan 11];2021:2302680. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC7861915/>

Haase VH. Hypoxia-inducible factors in the kidney. <https://doi.org/10.1152/ajprenal.00071.2006> [Internet]. American Physiological Society; 2006 [cited 2026 Jan 11];291(2):271–81. Available from: [/doi/pdf/10.1152/ajprenal.00071.2006?download=true](https://doi/pdf/10.1152/ajprenal.00071.2006?download=true)

Hanwell MD, Curtis DE, Lonie DC, Vandermeersch T, Zurek E, Hutchison GR. Avogadro: an advanced semantic chemical editor, visualization, and analysis platform. *Journal of Cheminformatics* 2012 4:1 [Internet]. BioMed Central; 2012 Aug 13 [cited 2026 Jan 11];4(1):17-. Available from: <https://link.springer.com/article/10.1186/1758-2946-4-17>

Higashi Y. Roles of Oxidative Stress and Inflammation in Vascular Endothelial Dysfunction-Related Disease. *Antioxidants* [Internet]. MDPI; 2022a Oct 1 [cited 2025 Nov 4];11(10):1958. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9598825/>

Higashi Y. Roles of Oxidative Stress and Inflammation in Vascular Endothelial Dysfunction-Related Disease. *Antioxidants (Basel)*. [Internet]. Antioxidants (Basel); 2022b Oct 1 [cited 2026 Jan 18];11(10). Available from: <https://pubmed.ncbi.nlm.nih.gov/36290681/>

Higdon J V., Delage B, Williams DE, Dashwood RH. Cruciferous vegetables and human cancer risk: epidemiologic evidence and mechanistic basis. *Pharmacol. Res.* [Internet]. Academic Press; 2007 Mar 1 [cited 2025 Nov 4];55(3):224–36. Available from: <https://www.sciencedirect.com/science/article/pii/S1043661807000321>

Hong E, Kim GH. Anticancer and antimicrobial activities of β -phenylethyl isothiocyanate in brassica rapa L. *Food Sci. Technol. Res.* 2008 Jul;14(4):377–82.

Jain SK. Human aspects of plant diversity. *Econ. Bot.* New York Botanical Garden Press; 2000;54(4):459–70.

Javed A, Ahmad A, Nouman M, Hameed A, Tahir A, Shabbir U. Turnip (*Brassica Rapa* L.): a natural health tonic. *Brazilian Journal of Food Technology* [Internet]. Instituto de Tecnologia de Alimentos - ITAL; 2019a [cited 2025 Nov 4];22:e2018253. Available from: <https://www.scielo.br/j/bjft/a/pH7R3CmhYrcSjxmCRzJmrVN/?format=html&lang=en>

Javed A, Ahmad A, Nouman M, Hameed A, Tahir A, Shabbir U. Turnip (*Brassica Rapa* L.): a natural health tonic. *Brazilian Journal of Food Technology* [Internet]. Instituto de

Tecnologia de Alimentos - ITAL; 2019b [cited 2026 Jan 18];22:e2018253. Available from: <https://www.scielo.br/j/bjft/a/pH7R3CmhYrcSjxmCRzJmrVN/?lang=en>

Kanehisa M, Furumichi M, Sato Y, Kawashima M, Ishiguro-Watanabe M. KEGG for taxonomy-based analysis of pathways and genomes. *Nucleic Acids Res.* [Internet]. Oxford Academic; 2023 Jan 6 [cited 2026 Jan 11];51(D1):D587–92. Available from: <https://dx.doi.org/10.1093/nar/gkac963>

Keiser MJ, Roth BL, Armbruster BN, Ernsberger P, Irwin JJ, Shoichet BK. Relating protein pharmacology by ligand chemistry. *Nature Biotechnology* 2007 25:2 [Internet]. Nature Publishing Group; 2007 Feb 7 [cited 2026 Jan 11];25(2):197–206. Available from: <https://www.nature.com/articles/nbt1284>

Kengne IC, Fankam AG, Yamako EK, Tamokou JDD. Phytochemical Analysis, Antifungal, and Antioxidant Properties of Two Herbs (*Tristemma mauritianum* and *Crassocephalum bogueyanum*) and One Tree (*Lavigeria macrocarpa*) Species. *Adv. Pharmacol. Pharm. Sci.* Hindawi Limited; 2023;2023.

Khatri P, Sirota M, Butte AJ. Ten Years of Pathway Analysis: Current Approaches and Outstanding Challenges. *PLoS Comput. Biol.* [Internet]. Public Library of Science; 2012 [cited 2026 Jan 11];8(2):e1002375. Available from: <https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1002375>

Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, et al. PubChem 2023 update. *Nucleic Acids Res.* [Internet]. Oxford Academic; 2023a Jan 6 [cited 2026 Jan 11];51(D1):D1373–80. Available from: <https://dx.doi.org/10.1093/nar/gkac956>

Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, et al. PubChem 2023 update. *Nucleic Acids Res.* [Internet]. Oxford Academic; 2023b Jan 6 [cited 2026 Jan 11];51(D1):D1373–80. Available from: <https://dx.doi.org/10.1093/nar/gkac956>

Laskowski RA, Swindells MB. LigPlot+: Multiple Ligand–Protein Interaction Diagrams for Drug Discovery. *J. Chem. Inf. Model.* [Internet]. American Chemical Society; 2011 Oct 24 [cited 2026 Jan 11];51(10):2778–86. Available from: <https://pubs.acs.org/doi/abs/10.1021/ci200227u>

Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* [Internet]. Elsevier; 2001 Mar 1 [cited 2026 Jan 11];46(1–3):3–26. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0169409X00001290?via%3Dihub>

Liu H, Mohammed SAD, Lu F, Chen P, Wang Y, Liu S. Network Pharmacology and Molecular Docking-Based Mechanism Study to Reveal Antihypertensive Effect of Gedan Jiangya Decoction. *Biomed Res. Int.* [Internet]. John Wiley & Sons, Ltd; 2022 Jan 1 [cited 2025 Nov 4];2022(1):3353464. Available from: [/doi/pdf/10.1155/2022/3353464](https://doi.org/10.1155/2022/3353464)

Liu W, Liu Z, Fan X, Li D, Zhao T, Niu Y, et al. *Brassica rapa* L. polysaccharide mitigates hypobaric hypoxia-induced oxidation and intestinal damage via microbiome modulation. *npj Science of Food* 2024 8:1 [Internet]. Nature Publishing Group; 2024 Dec 27 [cited 2026 Feb 3];8(1):112–. Available from: <https://www.nature.com/articles/s41538-024-00365-9>

M. Calderon-Montano J, Burgos-Moron E, Perez-Guerrero C, Lopez-Lazaro M. A review on the dietary flavonoid kaempferol. *Mini Rev. Med. Chem.* [Internet]. *Mini Rev Med Chem*; 2011 Apr 12 [cited 2026 Jan 18];11(4):298–344. Available from: <https://pubmed.ncbi.nlm.nih.gov/21428901/>

Ma J, Li Y, Yang X, Liu K, Zhang X, Zuo X, et al. Signaling pathways in vascular function and hypertension: molecular mechanisms and therapeutic interventions. *Signal Transduction and Targeted Therapy* 2023 8:1 [Internet]. Nature Publishing Group; 2023a Apr 20 [cited 2025 Nov 4];8(1):1–30. Available from: <https://www.nature.com/articles/s41392-023-01430-7>

Ma J, Li Y, Yang X, Liu K, Zhang X, Zuo X, et al. Signaling pathways in vascular function and hypertension: molecular mechanisms and therapeutic interventions. *Signal Transduct. Target. Ther.* [Internet]. *Signal Transduct Target Ther*; 2023b Dec 1 [cited 2026 Jan 18];8(1). Available from: <https://pubmed.ncbi.nlm.nih.gov/37080965/>

Mehta PK, Griendling KK. Angiotensin II cell signaling: physiological and pathological effects in the cardiovascular system. *Am. J. Physiol. Cell Physiol.* [Internet]. *Am J Physiol Cell Physiol*; 2007 Jan [cited 2026 Jan 29];292(1). Available from: <https://pubmed.ncbi.nlm.nih.gov/16870827/>

Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat. Rev. Nephrol.* *Nature Research*; 2020 Apr 1;16(4):223–37.

Mohanraj K, Karthikeyan BS, Vivek-Ananth RP, Chand RPB, Aparna SR, Mangalapandi P, et al. IMPPAT: A curated database of Indian Medicinal Plants, Phytochemistry And Therapeutics. *Scientific Reports* 2018 8:1 [Internet]. Nature Publishing Group; 2018 Mar 12 [cited 2026 Jan 11];8(1):4329-. Available from: <https://www.nature.com/articles/s41598-018-22631-z>

Morris GM, Ruth H, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, et al. Software news and updates AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *J. Comput. Chem.* [Internet]. John Wiley & Sons, Ltd; 2009 Dec 1 [cited 2026 Jan 11];30(16):2785–91. Available from: [/doi/pdf/10.1002/jcc.21256](https://doi.org/10.1002/jcc.21256)

Motti R, Paura B, Cozzolino A, Falco B de. Edible Flowers Used in Some Countries of the Mediterranean Basin: An Ethnobotanical Overview. *Plants*. MDPI; 2022 Dec 1;11(23).

Muntner P, Hardy ST, Fine LJ, Jaeger BC, Wozniak G, Levitan EB, et al. Trends in blood pressure control among US adults with hypertension, 1999-2000 to 2017-2018. *JAMA - Journal of the American Medical Association*. American Medical Association; 2020 Sep 22;324(12):1190–200.

Nishida H, Sohara E, Nomura N, Chiga M, Alessi DR, Rai T, et al. Phosphatidylinositol 3-Kinase/Akt Signaling Pathway Activates the WNK-OSR1/SPAK-NCC Phosphorylation Cascade in Hyperinsulinemic db/db Mice. *Hypertension* [Internet]. Lippincott Williams & WilkinsHagerstown, MD; 2012 Oct [cited 2026 Feb 13];60(4):981–90. Available from: [/doi/pdf/10.1161/HYPERTENSIONAHA.112.201509?download=true](https://doi.org/10.1161/HYPERTENSIONAHA.112.201509?download=true)

Padilla G, Cartea ME, Velasco P, de Haro A, Ordás A. Variation of glucosinolates in vegetable crops of *Brassica rapa*. *Phytochemistry* [Internet]. Pergamon; 2007 Feb 1 [cited

2025 Nov 4];68(4):536–45. Available from:

<https://www.sciencedirect.com/science/article/pii/S0031942206006947>

Paul S, Geng CA, Yang TH, Yang YP, Chen JJ. Phytochemical and Health-Beneficial Progress of Turnip (*Brassica rapa*). *J. Food Sci.* Blackwell Publishing Inc.; 2019a Jan 1;84(1):19–30.

Paul S, Geng CA, Yang TH, Yang YP, Chen JJ. Phytochemical and Health-Beneficial Progress of Turnip (*Brassica rapa*). *J. Food Sci.* [Internet]. Blackwell Publishing Inc.; 2019b Jan 1 [cited 2026 Jan 30];84(1):19–30. Available from: [/doi/pdf/10.1111/1750-3841.14417](https://doi.org/10.1111/1750-3841.14417)

Paul S, Geng CA, Yang TH, Yang YP, Chen JJ. Phytochemical and Health-Beneficial Progress of Turnip (*Brassica rapa*). *J. Food Sci.* [Internet]. Blackwell Publishing Inc.; 2019c Jan 1 [cited 2025 Nov 4];84(1):19–30. Available from: [/doi/pdf/10.1111/1750-3841.14417](https://doi.org/10.1111/1750-3841.14417)

Pieroni A, Nebel S, Quave C, Münz H, Heinrich M. Ethnopharmacology of liakra: Traditional weedy vegetables of the Arbëreshë of the Vulture area in southern Italy. *J. Ethnopharmacol.* 2002;81(2):165–85.

Piñero J, Bravo Á, Queralt-Rosinach N, Gutiérrez-Sacristán A, Deu-Pons J, Centeno E, et al. DisGeNET: a comprehensive platform integrating information on human disease-associated genes and variants. *Nucleic Acids Res.* [Internet]. Oxford Academic; 2017 Jan 4 [cited 2026 Jan 11];45(D1):D833–9. Available from: <https://dx.doi.org/10.1093/nar/gkw943>

Poulter NR, Borghi C, Parati G, Pathak A, Toli D, Williams B, et al. Medication adherence in hypertension. *J. Hypertens.* Lippincott Williams and Wilkins; 2020 Apr 1;38(4):579–87.

Pullamsetti SS, Berghausen EM, Dabral S, Tretyn A, Butrous E, Savai R, et al. Role of Src tyrosine kinases in experimental pulmonary hypertension. *Arterioscler. Thromb. Vasc. Biol.* [Internet]. Lippincott Williams & Wilkins; Hagerstown, MD; 2012 Jun [cited 2026 Feb 13];32(6):1354–65. Available from: [/doi/pdf/10.1161/ATVBAHA.112.248500?download=true](https://doi.org/10.1161/ATVBAHA.112.248500?download=true)

Pullamsetti SS, Mamazhakypov A, Weissmann N, Seeger W, Savai R. Hypoxia-inducible factor signaling in pulmonary hypertension. *J. Clin. Invest.* [Internet]. American Society for Clinical Investigation; 2020 Nov 2 [cited 2026 Jan 29];130(11):5638. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC7598042/>

Šarić-Kundalić B, Dobeš C, Klatte-Asselmeyer V, Saukel J. Ethnobotanical study on medicinal use of wild and cultivated plants in middle, south and west Bosnia and Herzegovina. *J. Ethnopharmacol.* 2010 Aug;131(1):33–55.

Seeliger D, De Groot BL. Ligand docking and binding site analysis with PyMOL and Autodock/Vina. *Journal of Computer-Aided Molecular Design* 2010 24:5 [Internet]. Springer; 2010a Apr 17 [cited 2026 Jan 11];24(5):417–22. Available from: <https://link.springer.com/article/10.1007/s10822-010-9352-6>

Seeliger D, De Groot BL. Ligand docking and binding site analysis with PyMOL and Autodock/Vina. *Journal of Computer-Aided Molecular Design* 2010 24:5 [Internet]. Springer; 2010b Apr 17 [cited 2026 Jan 11];24(5):417–22. Available from: <https://link.springer.com/article/10.1007/s10822-010-9352-6>

Semwal BC, Singh N, Pathak S. Ethanol Extract of Brassica Rapa Attenuate the Complete Freund's Adjuvant-Induced Inflammation in Rats. *Biomedical and Pharmacology Journal*. Oriental Scientific Publishing Company; 2021;14(4):2337–45.

Shahzadi Z, Yousaf Z, Anjum I, Bilal M, Yasin H, Aftab A, et al. Network pharmacology and molecular docking: combined computational approaches to explore the antihypertensive potential of Fabaceae species. *Bioresources and Bioprocessing* 2024 11:1 [Internet]. SpringerOpen; 2024 May 20 [cited 2025 Nov 4];11(1):1–24. Available from: <https://bioresourcesbioprocessing.springeropen.com/articles/10.1186/s40643-024-00764-6>

Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: A Software Environment for Integrated Models of Biomolecular Interaction Networks. *Genome Res*. [Internet]. Cold Spring Harbor Laboratory Press; 2003 Nov 1 [cited 2026 Jan 11];13(11):2498–504. Available from: <http://genome.cshlp.org/content/13/11/2498.full>

Stelzer G, Rosen N, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, et al. The GeneCards Suite: From Gene Data Mining to Disease Genome Sequence Analyses. *Curr. Protoc. Bioinformatics* [Internet]. *Curr Protoc Bioinformatics*; 2016 [cited 2026 Jan 11];54:1.30.1-1.30.33. Available from: <https://pubmed.ncbi.nlm.nih.gov/27322403/>

Su Q, Qin DN, Wang FX, Ren J, Li HB, Zhang M, et al. Inhibition of reactive oxygen species in hypothalamic paraventricular nucleus attenuates the renin-angiotensin system and proinflammatory cytokines in hypertension. *Toxicol. Appl. Pharmacol.* [Internet]. Academic Press Inc.; 2014 Apr 15 [cited 2026 Jan 16];276(2):115–20. Available from: <https://pubmed.ncbi.nlm.nih.gov/24576725/>

Szklarczyk D, Gable AL, Nastou KC, Lyon D, Kirsch R, Pyysalo S, et al. The STRING database in 2021: customizable protein–protein networks, and functional characterization of user-uploaded gene/measurement sets. *Nucleic Acids Res*. [Internet]. Oxford Academic; 2021 Jan 8 [cited 2026 Jan 11];49(D1):D605–12. Available from: <https://dx.doi.org/10.1093/nar/gkaa1074>

Touyz RM, Alves-Lopes R, Rios FJ, Camargo LL, Anagnostopoulou A, Arner A, et al. Vascular smooth muscle contraction in hypertension. *Cardiovasc. Res*. [Internet]. Oxford Academic; 2018 Mar 15 [cited 2026 Jan 11];114(4):529–39. Available from: <https://dx.doi.org/10.1093/cvr/cvy023>

Touyz RM, Briones AM. Reactive oxygen species and vascular biology: implications in human hypertension. *Hypertens. Res*. [Internet]. *Hypertens Res*; 2011 Jan [cited 2026 Jan 29];34(1):5–14. Available from: <https://pubmed.ncbi.nlm.nih.gov/20981034/>

Touyz RM, El Mabrouk M, He G, Wu XH, Schiffrin EL. Mitogen-activated protein/extracellular signal-regulated kinase inhibition attenuates angiotensin II-mediated signaling and contraction in spontaneously hypertensive rat vascular smooth muscle cells. *Circ. Res*. [Internet]. *Circ Res*; 1999 Mar 19 [cited 2026 Jan 29];84(5):505–15. Available from: <https://www.ahajournals.org/doi/pdf/10.1161/01.RES.84.5.505?download=true>

Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J. Med. Chem.* [Internet]. American Chemical Society ; 2002 Jun 6 [cited 2026 Jan 11];45(12):2615–23. Available from: <https://pubs.acs.org/doi/abs/10.1021/jm020017n>

Wang B, Jiang T, Qi Y, Luo S, Xia Y, Lang B, et al. AGE-RAGE Axis and Cardiovascular Diseases: Pathophysiologic Mechanisms and Prospects for Clinical Applications. *Cardiovasc. Drugs Ther.* [Internet]. Springer; 2024 Dec 1 [cited 2026 Jan 29];39(6):1489. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC12717123/>

Wang C, Zhu H, Cheng Y, Guo Y, Zhao Y, Qian H. Aqueous Extract of *Brassica rapa* L.'s Impact on Modulating Exercise-Induced Fatigue via Gut-Muscle Axis. *Nutrients* [Internet]. Nutrients; 2023 Nov 1 [cited 2026 Feb 3];15(22). Available from: <https://pubmed.ncbi.nlm.nih.gov/38004133/>

van de Waterbeemd H, Gifford E. ADMET in silico modelling: towards prediction paradise? *Nature Reviews Drug Discovery* 2003 2:3 [Internet]. Nature Publishing Group; 2003 Mar [cited 2026 Jan 11];2(3):192–204. Available from: <https://www.nature.com/articles/nrd1032>

Wu S, Xu Y, Zheng R, Lu J, Li M, Chen L, et al. Hypertension Defined by 2017 ACC/AHA Guideline, Ideal Cardiovascular Health Metrics, and Risk of Cardiovascular Disease: A Nationwide Prospective Cohort Study. *Lancet Reg. Health West. Pac.* [Internet]. Elsevier; 2022 Mar 1 [cited 2025 Nov 4];20:100350. Available from: <https://www.sciencedirect.com/science/article/pii/S2666606521002595>

Table 1: Physicochemical Properties of Selected *Brassica rapa* L. Phytoconstituents Based on Lipinski's Rule of Five

Sr. No.	Compound Name	Molecular Weight (g/mol)	Log P	H-Bond Donors	H-Bond Acceptors
1	Ferulic acid	194.18	1.5	2	4
2	Linoleic acid	280.45	7.3	1	2
3	Quercetin	302.24	1.6	5	7
4	Kaempferol	286.24	1.9	4	6
5	Isorhamnetin	316.26	2.1	4	7
6	Caffeic acid	180.16	0.9	3	4
7	Sinapic acid	224.21	1.2	2	5
8	Glucoerucin	277.32	0.2	4	6
9	Gluconasturtiin	311.36	0.4	4	7

Table 2: Top 10 hub genes from the PPI network

Sr. No.	Gene Name	Gene Symbol	Degree	Betweenness Centrality	Closeness Centrality
1.	SRC Proto-Oncogene, Non-Receptor Tyrosine Kinase	SRC	95	0.068188927	0.655737705
2.	Epidermal Growth Factor Receptor	EGFR	99	0.048400563	0.664451827
3.	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha	PIK3CA	51	0.002799707	0.571428571
4.	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Regulatory Subunit Alpha	PIK3R1	46	0.001736985	0.561797753
5.	Protein Tyrosine Kinase 2	PTK2	36	0.002455398	0.546448087
6.	Protein Tyrosine Phosphatase Non-Receptor Type 11	PTPN11	42	0.002883579	0.552486188
7.	Signal Transducer and Activator of Transcription 3	STAT3	96	0.030216208	0.657894737
8.	Catenin Beta 1	CTNNB1	98	0.055136824	0.662251656
9.	FYN Proto-Oncogene, Src Family Tyrosine Kinase	FYN	43	0.006799762	0.547945205

10.	AKT Serine/Threonine Kinase 1	AKT1	128	0.09575394	0.735294118
-----	-------------------------------	------	-----	------------	-------------

Table 3: KEGG pathway enrichment of overlapping targets showing gene count, strength, FDR, and mapped hub proteins

Pathway	OGC	BGC	Strength	Signal	FDR	Genes
Fluid shear stress and atherosclerosis	6	129	1.96	3.9	0.000000000796	PIK3CA, PTK2, SRC, PIK3R1, AKT1, CTNNB1
VEGF signaling pathway	5	56	2.25	4.28	0.0000000002	PIK3CA, PTK2, SRC, PIK3R1, AKT1
Insulin resistance	5	106	1.97	3.49	0.00000000153	PIK3CA, STAT3, PIK3R1, AKT1, PTPN11
FoxO signaling pathway	5	126	1.89	3.25	0.00000000291	PIK3CA, STAT3, EGFR, PIK3R1, AKT1
AGE-RAGE signaling pathway in diabetic complications	4	96	1.91	2.8	0.0000000782	PIK3CA, STAT3, PIK3R1, AKT1
PI3K-Akt signaling pathway	5	349	1.45	1.92	0.000000231	PIK3CA, EGFR, PTK2, PIK3R1, AKT1
TNF signaling pathway	3	111	1.73	1.85	0.0000868	

						PIK3CA, PIK3R1, AKT1
AMPK signaling pathway	3	120	1.69	1.78	0.00011	PIK3CA, PIK3R1, AKT1
Aldosterone-regulated sodium reabsorption	2	37	2.03	1.69	0.00058	PIK3CA, PIK3R1
MAPK signaling pathway	2	286	1.14	0.65	0.0268	EGFR, AKT1
EGFR tyrosine kinase inhibitor resistance	6	77	2.19	4.73	0.0000000000808	PIK3CA, STAT3, EGFR, SRC, PIK3R1, AKT1
JAK-STAT signaling pathway	6	158	1.87	3.57	0.0000000002	PIK3CA, STAT3, EGFR, PIK3R1, AKT1, PTPN11
HIF-1 signaling pathway	5	102	1.98	3.54	0.0000000132	PIK3CA, STAT3, EGFR, PIK3R1, AKT1

Where OGC: Observed gene count, BGC: Background gene count, and FDR: False discovery rate.

Table 4. Binding Affinities (kcal/mol) of Selected *Brassica rapa* L. Phytoconstituents Docked with Top 10 Hub Protein Targets Using AutoDock Vina

Sr. No.	Receptor	Phytoconstituents	Binding Energy (Kcal/mol)
1	Proto-oncogene tyrosine-protein kinase Src (SRC)	Ferulic acid	-6.6
		Caffeic acid	-6.6
		Glucoerucin	-6.8
		Sinapic acid	-6.4
		Gluconasturtiin	-8.2
		Isorhamnetin	-8.7
		Kaempferol	-9.2
		Linoleic acid	-6.5
		Quercetin	-8.7
		Captopril	-6.5
2	Epidermal growth factor receptor	Ferulic acid	-7.4
		Caffeic acid	-7.3
		Sinapic acid	-7.7
		Glucoerucin	-7.6
		Gluconasturtiin	-9.2

	(EGFR)	Isorhamnetin	-9.5
		Kaempferol	-9.5
		Linoleic acid	-6.6
		Quercetin	-9.4
		Captopril	-6.5
3	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (PIK3CA)	Ferulic acid	-6.7
		Caffeic acid	-6.6
		Sinapic acid	-6.3
		Glucoerucin	-6.1
		Gluconasturtiin	-7.8
		Isorhamnetin	-8.4
		Kaempferol	-8.9
		Linoleic acid	-6.1
		Quercetin	-7.9
		Captopril	-5.3
4	Phosphatidylinositol 3-kinase regulatory subunit alpha (PIK3R1)	Ferulic acid	-6.8
		Caffeic acid	-6.8
		Sinapic acid	-6.2
		Glucoerucin	-6.0
		Gluconasturtiin	-7.0
		Isorhamnetin	-7.5
		Kaempferol	-8.7
		Linoleic acid	-5.8
		Quercetin	-7.4
		Captopril	-5.9
5	Focal adhesion kinase 1 (PTK2)	Ferulic acid	-6.6
		Caffeic acid	-6.6
		Sinapic acid	-6.8
		Glucoerucin	-7.8
		Gluconasturtiin	-8.9
		Isorhamnetin	-8.8
		Kaempferol	-9.3
		Linoleic acid	-6.4
		Quercetin	-8.7
		Captopril	-5.5
6	Tyrosine-protein phosphatase non-receptor type 11 (PTPN11)	Ferulic acid	-6.2
		Caffeic acid	-6.6
		Sinapic acid	-6.8
		Glucoerucin	-6.9
		Gluconasturtiin	-8.9
		Isorhamnetin	-9.4
		Kaempferol	-9.3
		Linoleic acid	-5.5
		Quercetin	-9.6
		Captopril	-6.7
		Ferulic acid	-5.0
		Caffeic acid	-5.2
		Sinapic acid	-5.0

7	Signal transducer and activator of transcription 3 (STAT3)	Glucoerucin	-5.0
		Gluconasturtiin	-5.8
		Isorhamnetin	-6.2
		Kaempferol	-6.4
		Linoleic acid	-4.8
		Quercetin	-6.2
		Captopril	-4.3
8	Catenin beta-1 (CTNNB1)	Ferulic acid	-3.6
		Caffeic acid	-3.6
		Sinapic acid	-3.6
		Glucoerucin	-3.9
		Gluconasturtiin	-4.6
		Isorhamnetin	-4.2
		Kaempferol	-4.6
		Linoleic acid	-3.0
		Quercetin	-4.2
		Captopril	-3.4
9	RAC-alpha serine/threonine-protein kinase (AKT1)	Ferulic acid	-7.8
		Caffeic acid	-7.6
		Sinapic acid	-7.9
		Glucoerucin	-8.1
		Gluconasturtiin	-10.5
		Isorhamnetin	-10.6
		Kaempferol	-11.2
		Linoleic acid	-7.7
		Quercetin	-10.6
		Captopril	-7.1
10	Tyrosine-protein kinase Fyn (FYN)	Ferulic acid	-7.5
		Caffeic acid	-7.2
		Sinapic acid	-6.8
		Glucoerucin	-6.0
		Gluconasturtiin	-8.6
		Isorhamnetin	-9.3
		Kaempferol	-9.6
		Linoleic acid	-7.1
		Quercetin	-9.3
		Captopril	-6.2

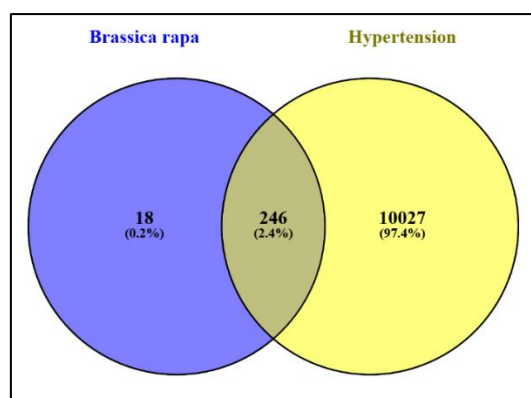


Figure 1: Venn diagram of the potential therapeutic target of BRL in treating HTN

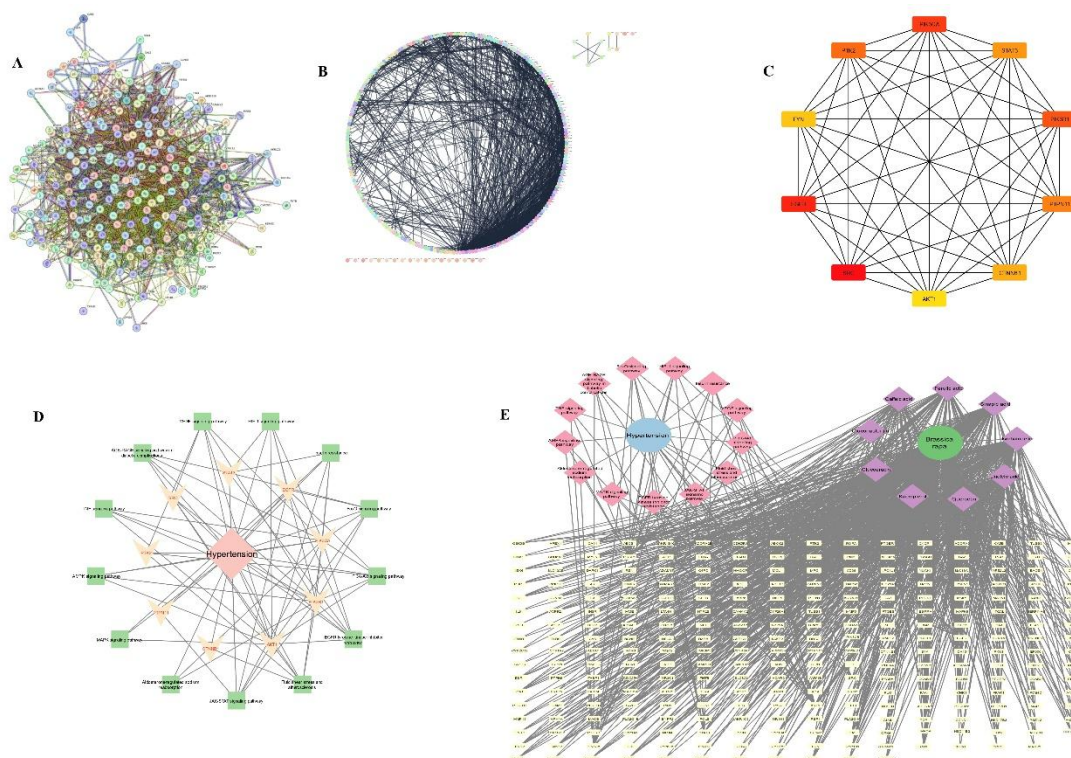


Figure 2: Protein-protein interaction network, hub genes, and drug-disease-compound-target-pathway network of BRL active phytoconstituents against HTN

Proteins, genes, or biological entities are represented by nodes, whereas linkages and interactions are represented by edges. (A) PPI network retrieved from the STRING database for potential targets of BRL against HTN. (B) PPI network reconstructed and visualized in Cytoscape. (C) Top 10 hub genes identified using the Degree algorithm in Cytoscape. (D) HTN network showing disease (HTN), top 10 core targets, and their related key pathways. (E) Integrated BRL-HTN-Compound-Target-Pathway network representing BRL (drug), HTN (disease), active phytoconstituents, corresponding targets, and enriched pathways. The PPI network's top ten hub genes were chosen based on centrality and degree metrics. These highly interconnected nodes may serve as key regulators of HTN-associated signalling pathways.

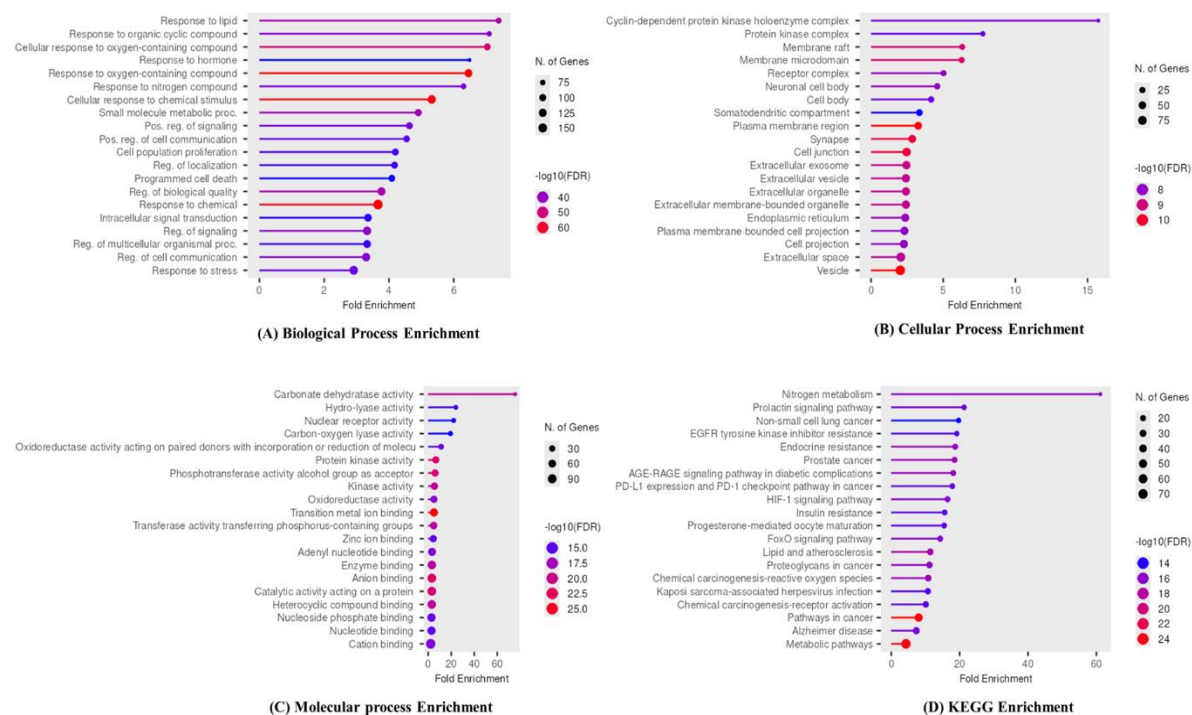


Figure 3: GO analysis results

The biological process, cellular component, molecular function, and KEGG enrichment are shown in (A), (B), and (C), respectively. The number of genes is indicated on the X-axis, while the Y-axis displays enriched GO keywords. Bar colours indicate the $-\log_{10}$ P-value. Enrichment study of overlapping HTN-related BRL targets using the KEGG pathway. Table 3 lists the phytoconstituents, which comprise mapped hub proteins, enrichment strength, signal, false detection rate, observed gene count, and background gene count.

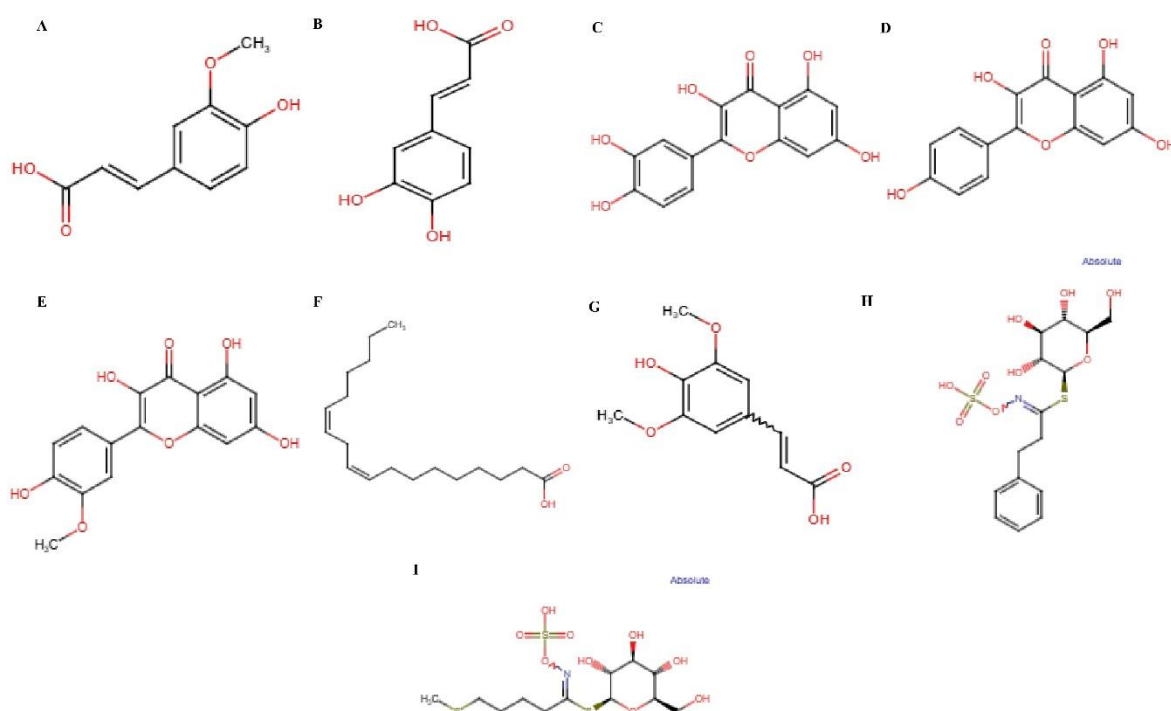


Figure 4: Chemical structures of BRL bioactive compounds used for molecular docking

The 2D chemical structures of selected BRL phytoconstituents included in the study are shown: (A) Ferulic acid, (B) Caffeic acid, (C) Quercetin, (D) Kaempferol, (E) Isorhamnetin, (F) linoleic acid, (G) Sinapic acid, (H) Gluconasturtiin, (I) Glucoerucin. (A-I) representative ligands used for target prediction, PPI network analysis, and molecular docking simulations against HTN-related targets. Molecular docking was performed to evaluate the binding efficiency of the selected BRL phytoconstituents against the top 10 hub protein targets. Table 4 represents the binding affinity scores obtained from AutoDock Vina, along with Captopril as the reference standard.

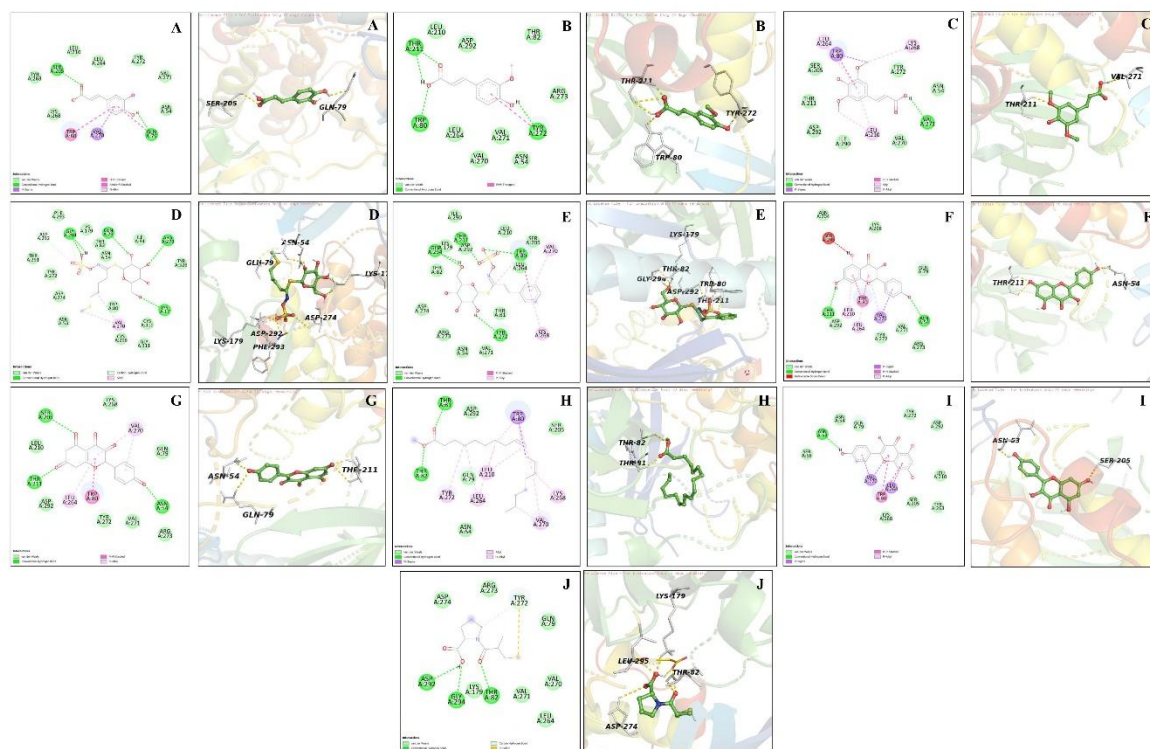


Figure 5: Molecular docking interactions of phytochemicals with proto-oncogene tyrosine-protein kinase SRC

Panels A-J represent the 2D ligand-protein interaction maps (left) and corresponding 3D binding conformations (right) of Src docked with (A) Ferulic acid, (B) Caffeic acid, (C) Sinapic acid (D) Glucoerucin, (E) Gluconasturtiin, (F) Isorhamnetin, (G) Kaempferol, (H) Linoleic acid, (I) Quercetin, and (J) Captopril (Standard drug).

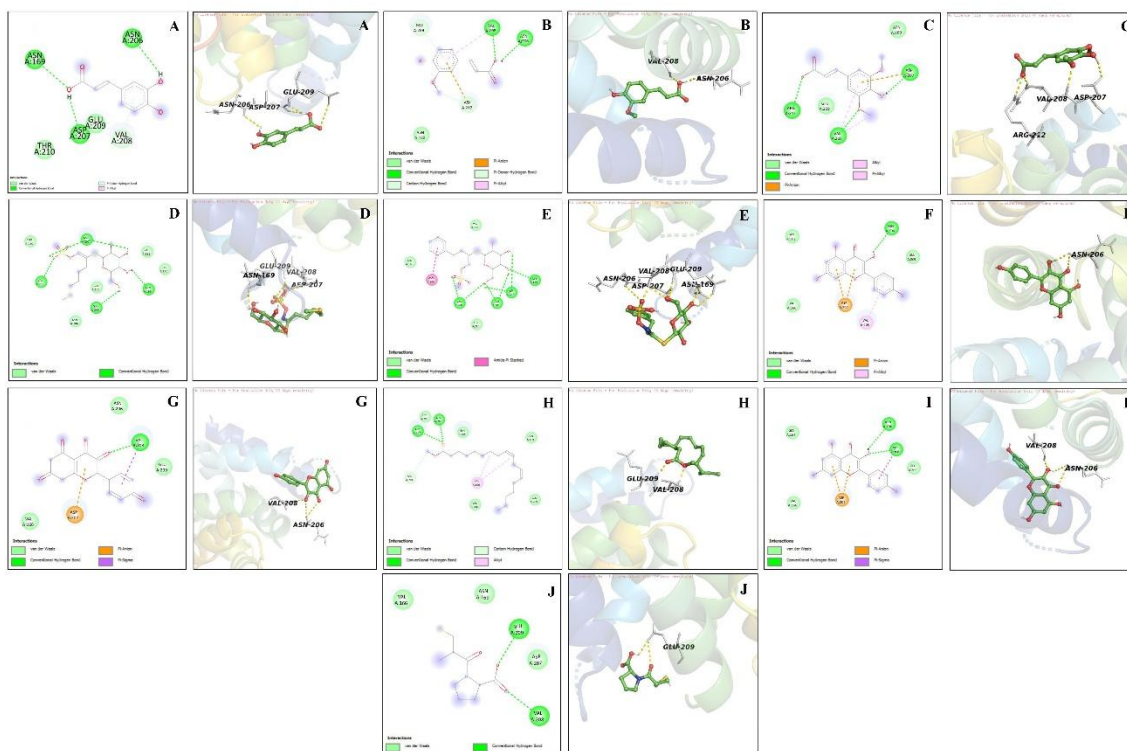


Figure 6: Molecular docking interactions of phytochemicals with epidermal growth factor receptor (EGFR)

Panels A-J represent the 2D ligand-protein interaction maps (left) and corresponding 3D binding conformations (right) of EGFR docked with (A) Ferulic acid, (B) Caffeic acid, (C) Sinapic acid (D) Glucoerucin, (E) Gluconasturtiin, (F) Isorhamnetin, (G) Kaempferol, (H) Linoleic acid, (I) Quercetin, and (J) Captopril (Standard drug).

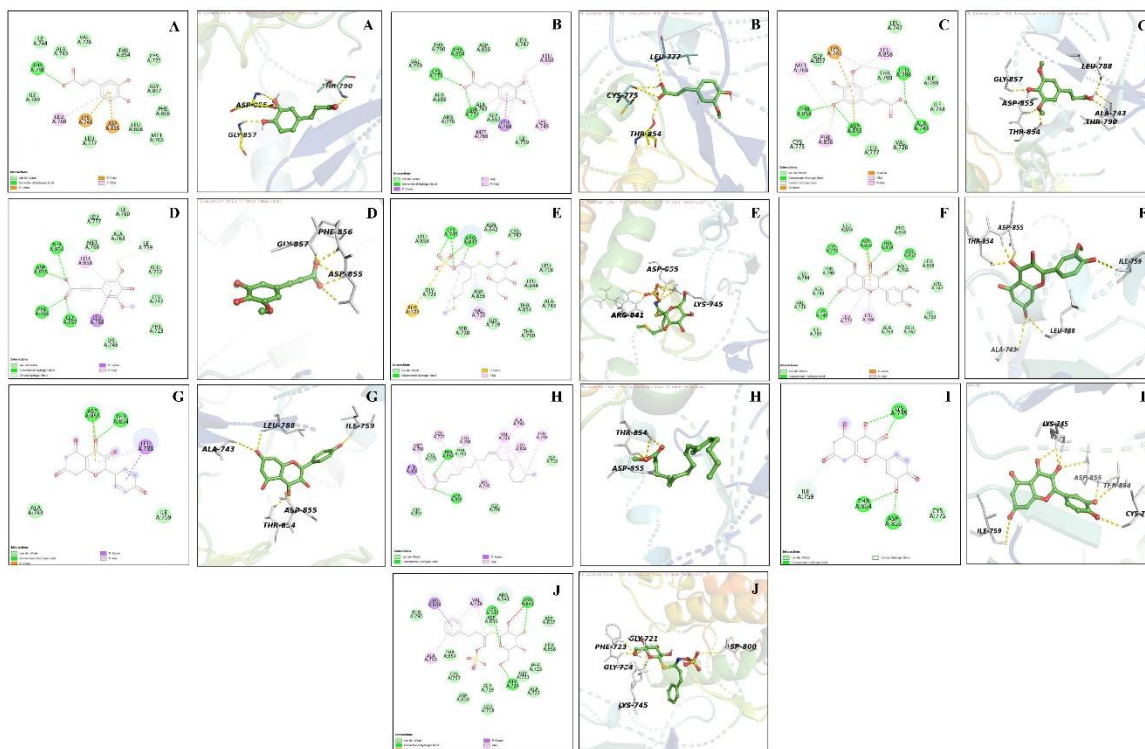


Figure 7: Molecular docking interactions of phytochemicals with Phosphatidylinositol 4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha Isoform (PIK3CA)

Panels A-J represent the 2D ligand-protein interaction maps (left) and corresponding 3D binding conformations (right) of PIK3CA docked with (A) Ferulic acid, (B) Caffeic acid, (C) Sinapic acid (D) Glucoerucin, (E) Gluconasturtiin, (F) Isorhamnetin, (G) Kaempferol, (H) Linoleic acid, (I) Quercetin, and (J) Captopril (Standard drug).

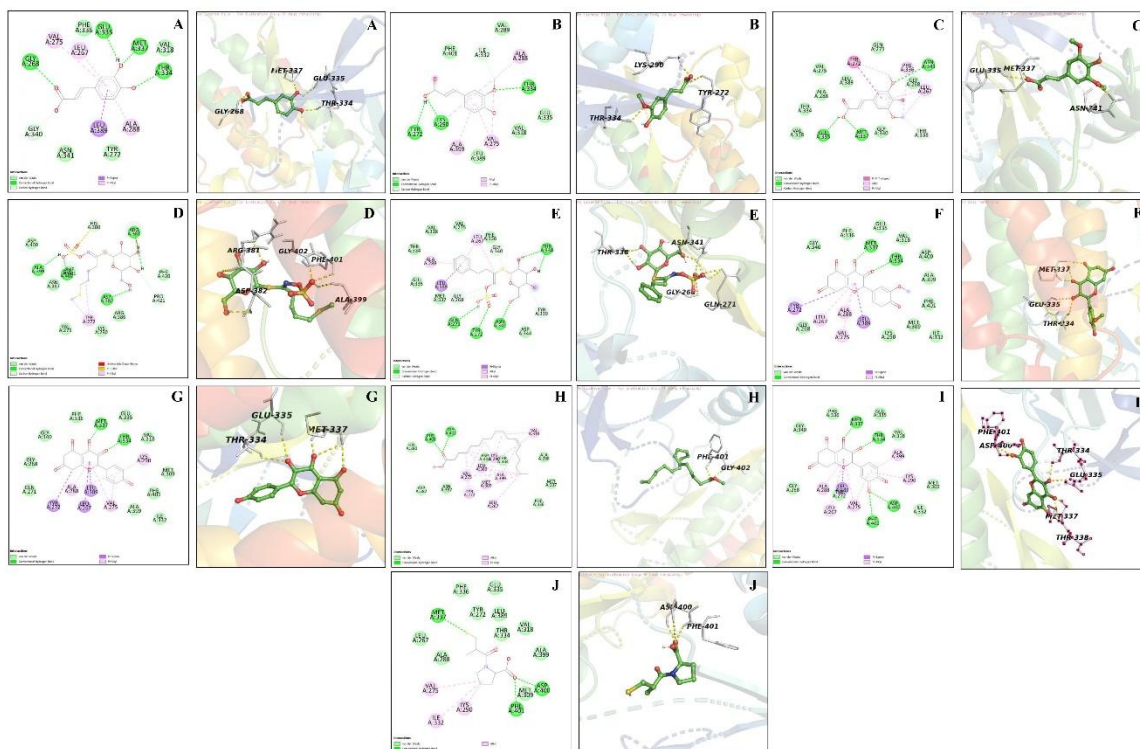


Figure 8: Molecular docking interactions of phytochemicals with Phosphatidylinositol 3-Kinase Regulatory Subunit Alpha (PIK3R1)

Panels A-J represent the 2D ligand-protein interaction maps (left) and corresponding 3D binding conformations (right) of PIK3R1 docked with (A) Ferulic acid, (B) Caffeic acid, (C) Sinapic acid (D) Glucoerucin, (E) Gluconasturtiin, (F) Isorhamnetin, (G) Kaempferol, (H) Linoleic acid, (I) Quercetin, and (J) Captopril (Standard drug).

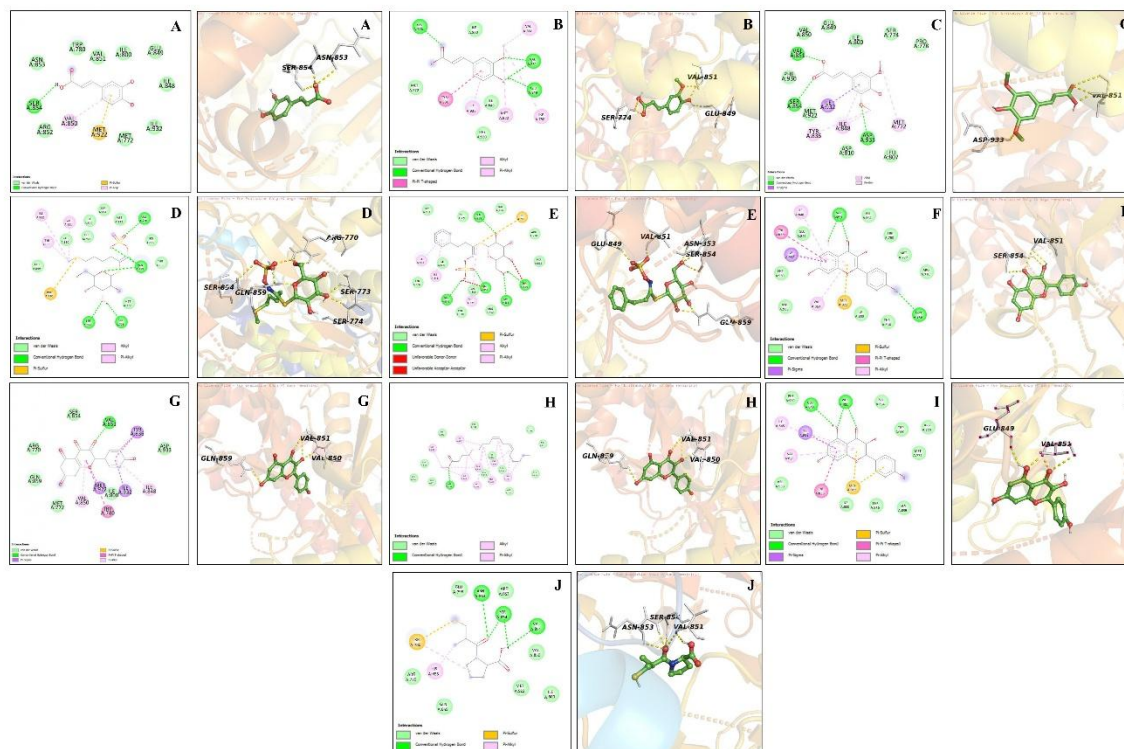


Figure 8: Molecular docking interactions of phytochemicals with Focal Adhesion Kinase 1 (PTK2)

Panels A-J represent the 2D ligand-protein interaction maps (left) and corresponding 3D binding conformations (right) of PIK3R1 docked with (A) Ferulic acid, (B) Caffeic acid, (C) Sinapic acid (D) Glucoerucin, (E) Gluconasturtiin, (F) Isorhamnetin, (G) Kaempferol, (H) Linoleic acid, (I) Quercetin, and (J) Captopril (Standard drug).

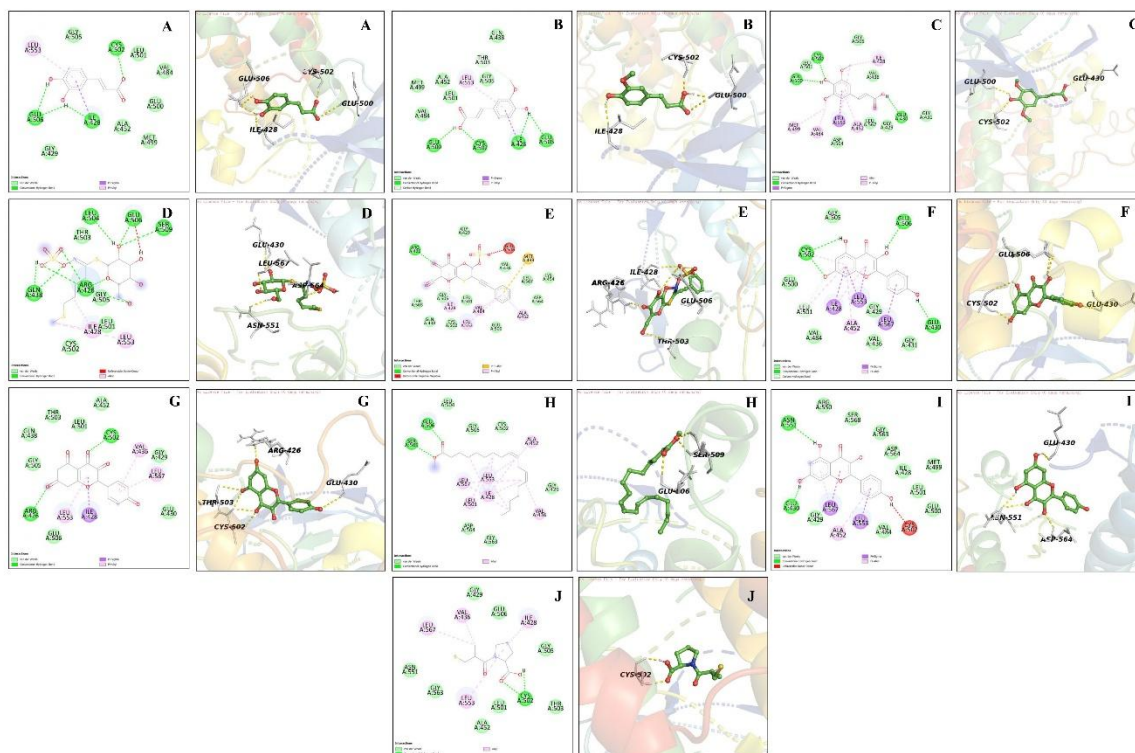


Figure 11: Molecular docking interactions of phytochemicals with Signal transducer and activator of transcription 3

Panels A-J represent the 2D ligand-protein interaction maps (left) and corresponding 3D binding conformations (right) of PIK3R1 docked with (A) Ferulic acid, (B) Caffeic acid, (C) Sinapic acid (D) Glucoerucin, (E) Gluconasturtiin, (F) Isorhamnetin, (G) Kaempferol, (H) Linoleic acid, (I) Quercetin, and (J) Captopril (Standard drug).

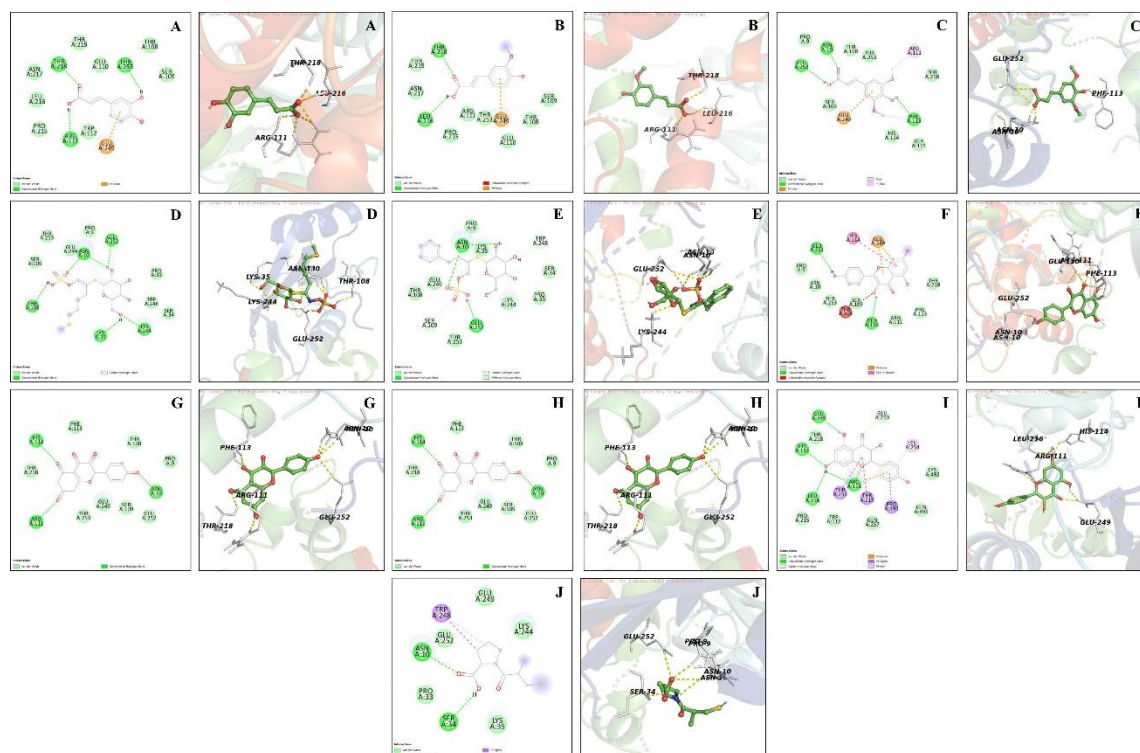


Figure 10: Molecular docking interactions of phytochemicals with Catenin beta-1

Panels A-J represent the 2D ligand-protein interaction maps (left) and corresponding 3D binding conformations (right) of PIK3R1 docked with (A) Ferulic acid, (B) Caffeic acid, (C) Sinapic acid (D) Glucoerucin, (E) Gluconasturtiin, (F) Isorhamnetin, (G) Kaempferol, (H) Linoleic acid, (I) Quercetin, and (J) Captopril (Standard drug).

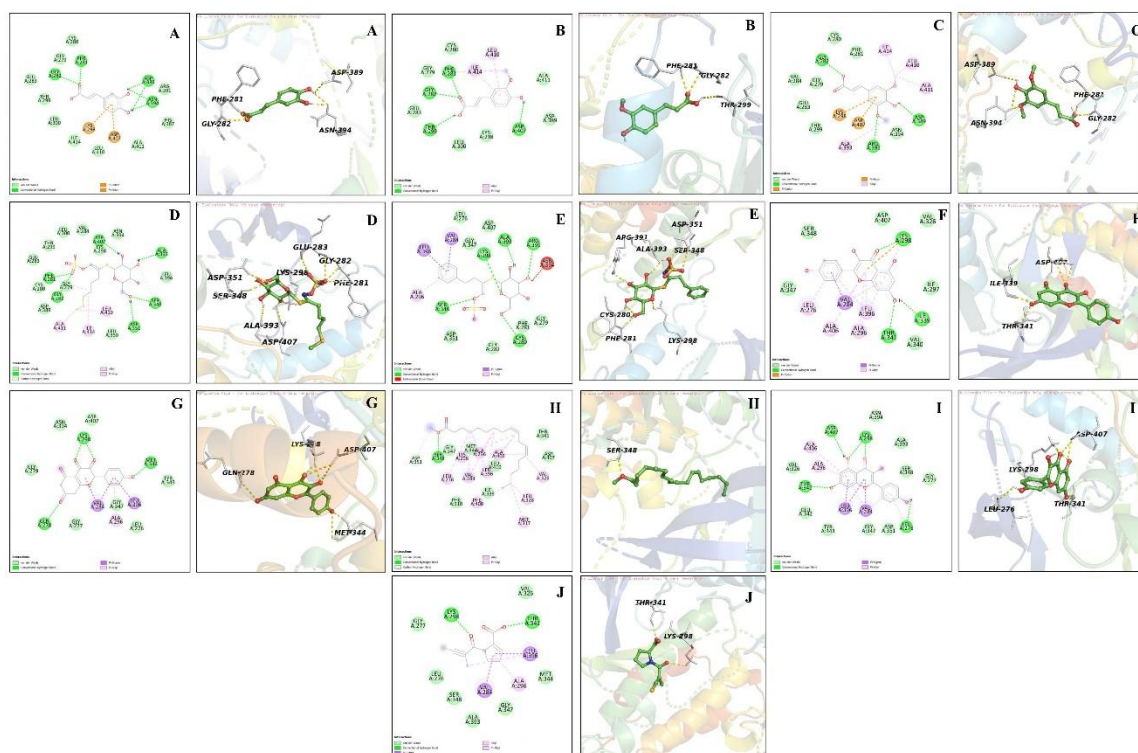


Figure 11: Molecular docking interactions of phytochemicals with RAC-alpha serine/threonine-protein kinase

Panels A-J represent the 2D ligand-protein interaction maps (left) and corresponding 3D binding conformations (right) of PIK3R1 docked with (A) Ferulic acid, (B) Caffeic acid, (C) Sinapic acid (D) Glucoerucin, (E) Gluconasturtiin, (F) Isorhamnetin, (G) Kaempferol, (H) Linoleic acid, (I) Quercetin, and (J) Captopril (Standard drug).

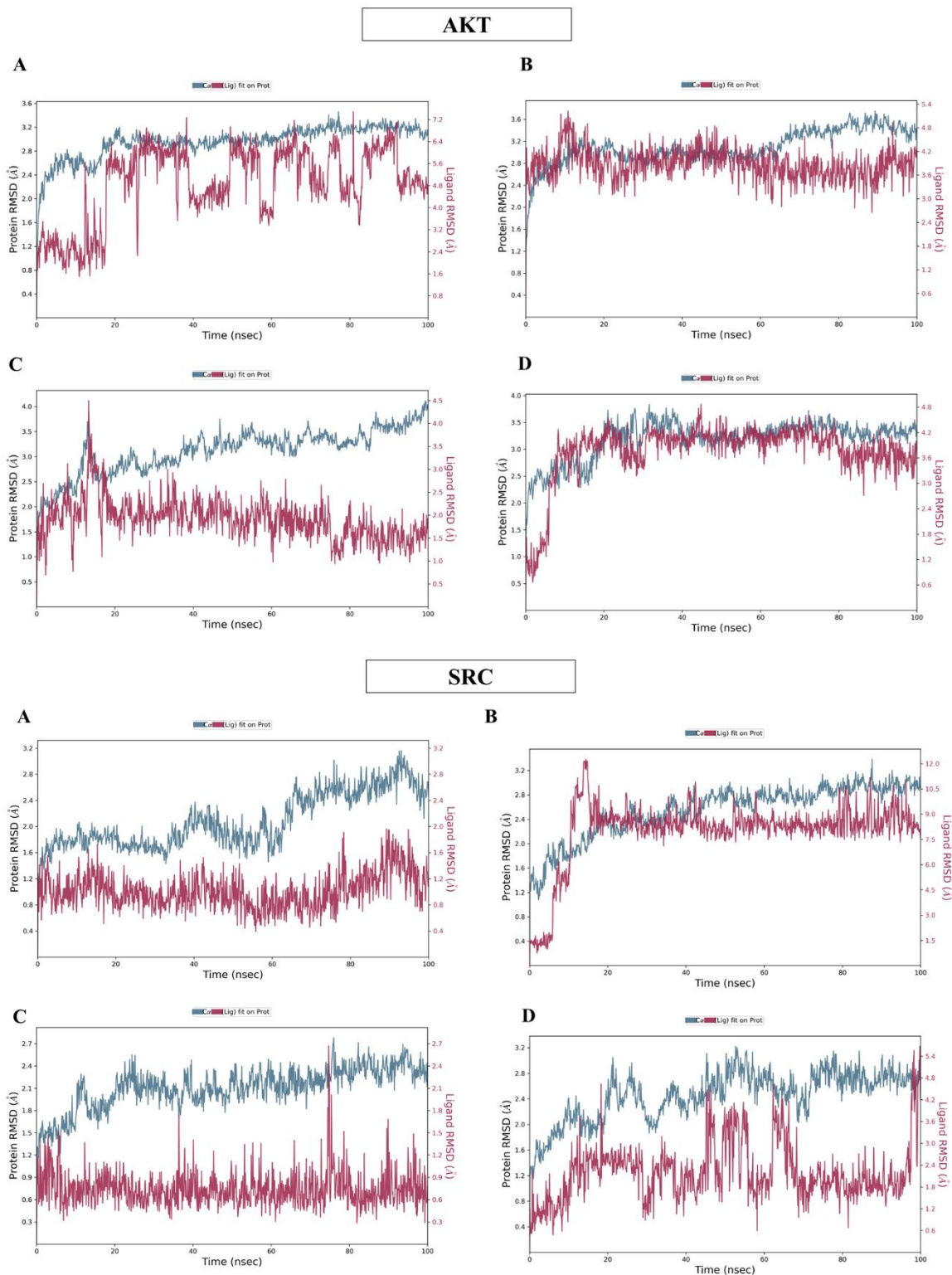


Figure 14: Protein backbone and ligand RMSD profiles of AKT1 and SRC

The RMSD of AKT1 & SRC complexes with the standard drug captopril and the top-ranked compounds (Isorhamnetin, Kaempferol, and Quercetin) during the 100 ns molecular dynamics simulation in which Panel A-D represents (A) Isorhamnetin, (B) Kaempferol (C) Quercetin (D) Captopril

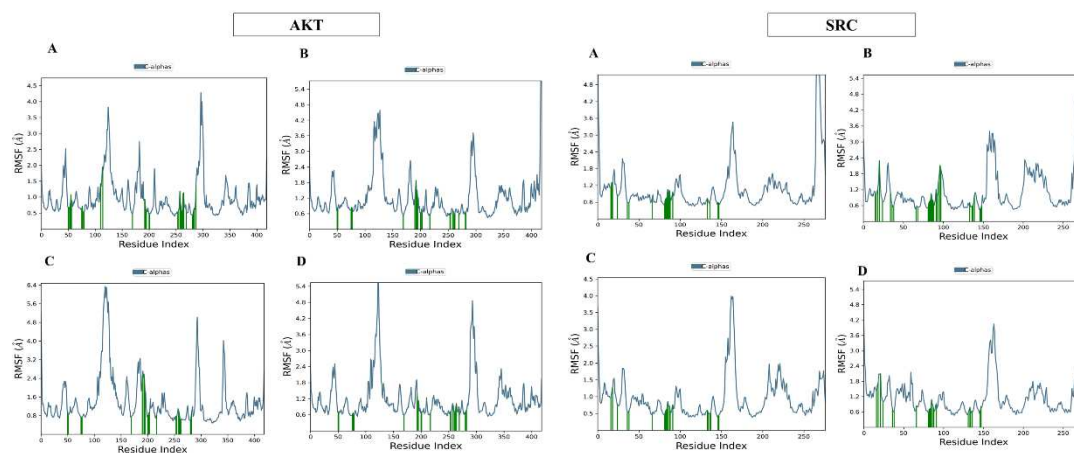


Figure 15: Residue-wise flexibility of AKT1 and SRC

The RMSF of AKT1 & SRC complexes with the standard drug captopril and the top-ranked compounds (Isorhamnetin, Kaempferol, and Quercetin) during the 100 ns molecular dynamics simulation in which Panel A-D represents (A) Isorhamnetin, (B) Kaempferol (C) Quercetin (D) Captopril

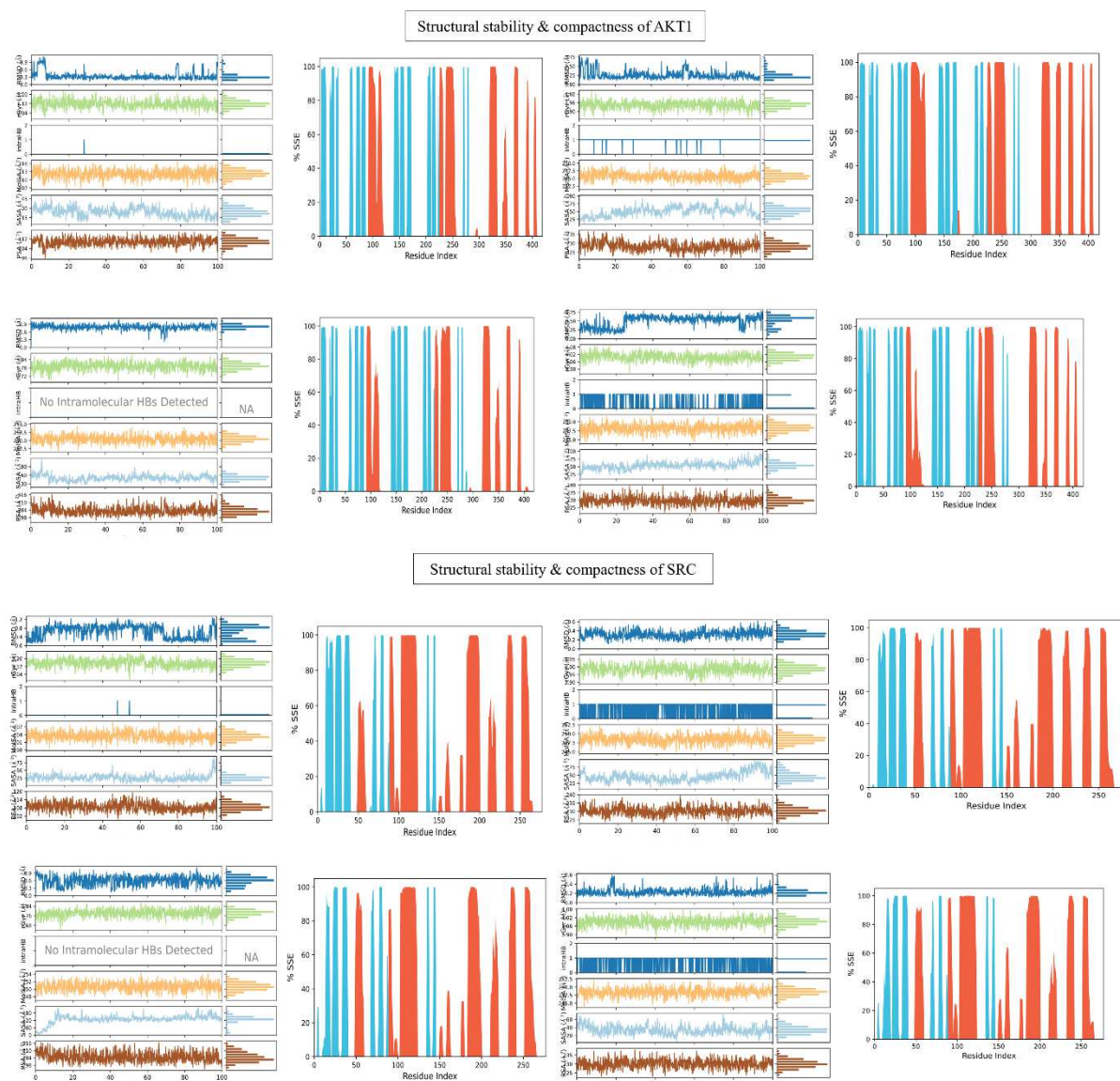
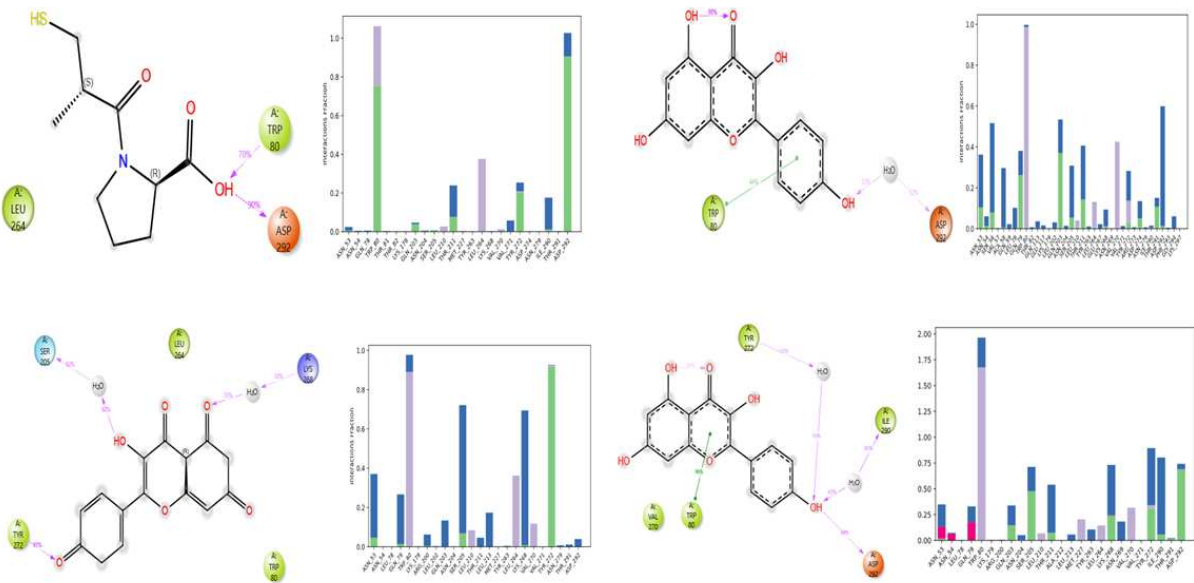


Figure 16: Structural stability analysis of AKT1 and SRC during MD simulation

(A, C) radius of gyration and (B, D) secondary structure element (SSE) distribution for the standard drug and the best-performing compound (Isorhamnetin, Kaempferol, and Quercetin).

Protein-Ligand Interactions of AKT1



Protein-Ligand Interactions of SRC

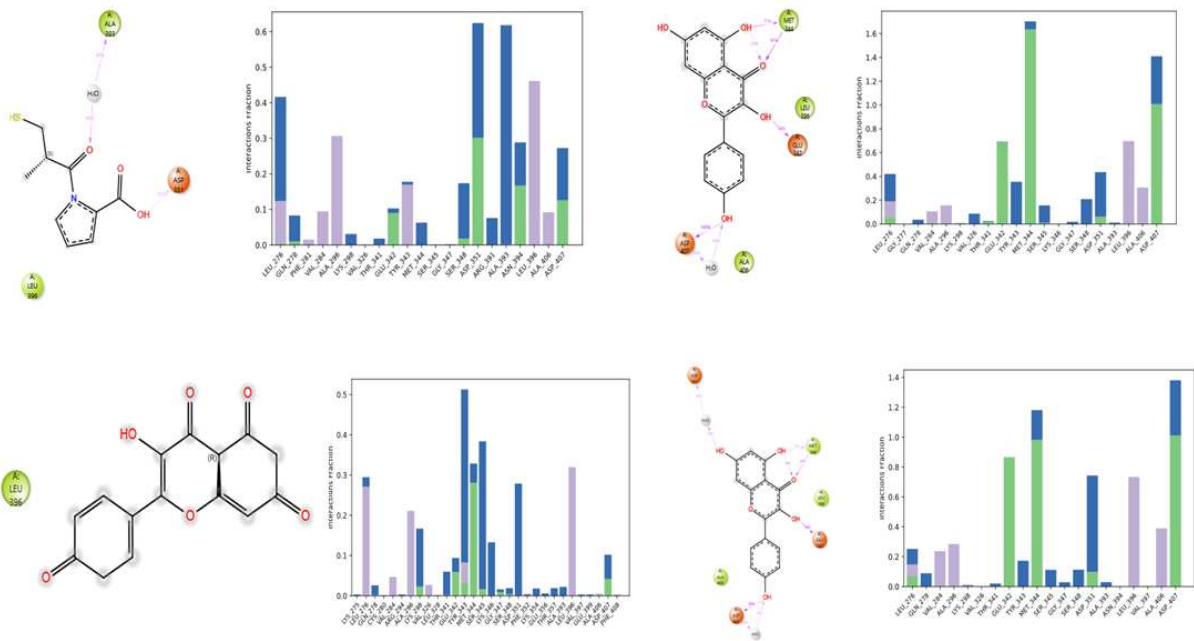


Figure 17: Protein-ligand interaction analysis of AKT1 and SRC complexes during MD simulation

(A, C) Two-dimensional summary of protein-ligand interactions for the best-performing compound. (B, D) Histogram depicting the frequency and persistence of protein-ligand contacts compared with the standard drug.

