

ORIGINAL ARTICLE BREAST CANCER

Network Pharmacology and Preliminary In-Vitro Evaluation of *Piper Longum* (Indian Long Pepper) in Breast Cancer

Shivam Singh, PhD;^{1,2*} Ashok Sharma, PhD;³ Richa Tripathi, PhD;⁴ Vitthal Govindappa Huddar, MD, PhD;^{5*} Subhash Gupta, MD^{2*}

¹Department of Biotechnology, All India Institute of Medical Sciences, New Delhi, India, ²Department of Radiation Oncology, Dr. B. R. Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India, ³Department of Biochemistry, All India Institute of Medical Sciences, New Delhi, India, ⁴Department of Roga Nidan and Vikriti Vigyan (Pathology), All India Institute of Ayurveda (AIIA), New Delhi, India, ⁵Department of Kaya Chikitsa (Internal Medicine), All India Institute of Ayurveda (AIIA), Goa, India.

*Joint corresponding authors.



***Corresponding authors:**

Shivam Singh, Vitthal Govindappa Huddar, Subhash Gupta
shivam10singh2020@gmail.com
drvghuddar@gmail.com
drsubhashgupta72@gmail.com
All India Institute of Medical Sciences, New Delhi, India

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ABSTRACT

Background and Objectives: *Piper longum* (Indian Long Pepper) contains phytochemicals reported to have anticancer activity, but their targets and effects in breast-cancer models remain uncertain. This exploratory study combined network pharmacology, analysis of public breast cancer data, molecular docking, MCF-7 viability, DNA cell cycle, and apoptosis assays.

Methods: Nineteen compounds from *P. longum* fruit were identified using the literature and phytochemical databases. Target prediction tools and cancer gene databases were used to identify interactions with breast cancer genes. Protein-protein interaction, gene ontology, and pathway analyses highlighted key targets. Molecular docking was used to evaluate binding affinities, and *in vitro* assays assessed cytotoxicity in MCF-7 breast cancer cells.

Results: This study revealed 600 common gene targets between *P. longum* compounds and breast cancer. Compound-target-disease network analysis prioritized Norcepharadione B, Aristolodione, Pellitorine, Aristolactam AII, and N-isobutyl decadienamide as candidate compounds. Significant breast cancer genes (TP53, CTNNB1, STAT3, SMAD3, EGFR, and HSP90AA1) were central to these interactions. Notably, HSP90AA1 showed the most favorable predicted docking scores with Norcepharadione B and Aristolactam AII. Additionally, the aqueous extract of *P. longum* significantly inhibited the MCF-7 MTT signal, with an IC₅₀ of 3.75 µg/mL.

Conclusion and Implications for Translation: In this study, *Piper longum* phytochemicals were linked to key cancer genes. Molecular docking of the top five compounds with six genes showed that Norcepharadione B had the strongest affinity for HSP90AA1, indicating its potential to modulate HSP90AA1-mediated pathways, including ER and HER2 signaling. These interactions suggest therapeutic relevance. Furthermore, aqueous *P. longum* extract inhibited MCF-7 cellular metabolism at the IC₅₀ dose, possibly through cell-cycle arrest or apoptosis, which is currently under further investigation in our laboratory. These findings support further testing of defined *P. longum* compounds in breast-cancer models, but they do not yet establish therapeutic activity or mechanism.

Keywords: Breast Cancer; *Piper Longum*; Network Pharmacology; Molecular Docking; Cell Proliferation

INTRODUCTION

Background

Breast cancer continues to be a significant challenge in global health, as its complex development and varied clinical presentations pose substantial difficulties for effective treatment and

prevention.^[1] With the worldwide occurrence of this disease on the rise, it is crucial to explore the intricate nature of breast cancer to create successful therapeutic approaches.^[2]

Network pharmacology is widely used to prioritize compound-target relationships in complex mixtures, although its predictions require experimental validation. Unlike conventional single-target approaches, it enables the identification of multi-target mechanisms underlying the therapeutic effects of complex herbal medicines. In the present study, network pharmacology was employed to predict the potential molecular targets and biological pathways through which *Piper longum* phytochemicals may exert anti-breast cancer activity.

Piper longum (Indian long pepper) is a medicinal plant of the family Piperaceae that has long been used in traditional medicine and has attracted increasing attention for its anticancer potential.^[3] Experimental studies have shown that *P. longum* extracts and several of its bioactive constituents, including piperine and piperlongumine, inhibit breast cancer cell proliferation through mechanisms involving apoptosis, cell-cycle arrest, oxidative stress, and modulation of multiple oncogenic signaling pathways.^[4,5] However, the comprehensive molecular targets and interconnected signaling networks through which the diverse phytochemicals of *P. longum* exert their anti-breast cancer effects remain poorly understood. Therefore, this study used an integrated network pharmacology, molecular docking, and experimental approach to systematically identify the anti-breast cancer activity of *P. longum*.

Objectives

This study used network analysis to prioritize *P. longum* phytochemicals and breast-cancer-associated targets for further testing. The process involved several key steps, including gathering and organizing data on the chemical compounds present in *P. longum*, constructing a network using analytical methods, identifying key nodes through network analysis, computationally predicting results using molecular docking, and interpreting the findings to predict potential drug targets and therapeutic uses. In addition, the effect of *P. longum* aqueous extract on cancer cell proliferation was also assessed in the MCF-7 breast cancer cell line.

Aim

The study aimed to investigate different compounds found in *P. longum* as potential phytochemicals against breast cancer and to explore the effect of the aqueous extract of *P. longum* fruits on breast cancer cell proliferation.

METHODS

P. longum Bioactive Compounds Identification

Bioactive phytochemical constituents reported from the fruits of *Piper longum* were compiled using two independent sources: (i) the Indian Medicinal Plants, Phytochemistry and Therapeutics (IMPPAT) database (<https://cb.imsc.res.in/imppat/>; accessed on 25 April 2025), and (ii) a systematic literature survey of published phytochemical studies.^[6] The IMPPAT database was searched using the keyword "*Piper longum*" under the medicinal plant search option. All phytochemicals specifically annotated for the fruit of *P. longum* were retrieved. Literature searches were performed using combinations of the keywords "*Piper longum*," "*fruit*," "*phytochemical*," "*constituents*," "*secondary metabolites*," and "*chemical composition*."

The lists obtained from both sources were merged, and duplicate compounds were removed using compound names and PubChem Compound Identifiers (CID). Only compounds with a defined chemical structure and an available PubChem entry were retained for further analysis. Canonical SMILES and molecular structures were downloaded from PubChem and used as input for subsequent analyses (<https://pubchem.ncbi.nlm.nih.gov/>).^[7] All databases were accessed during 2024.

Screening of Potential Bioactive Compounds Using Absorption, Distribution, Metabolism, and Excretion (ADME) Analysis

The collected phytochemical compounds were subjected to pharmacokinetic evaluation using the SwissADME web server (<http://www.swissadme.ch/>) to assess their drug-likeness and suitability for oral administration.^[8] The canonical SMILES notation for each compound, obtained from the PubChem database, was uploaded to the SwissADME server for analysis. Several physicochemical and pharmacokinetic parameters relevant to drug discovery were evaluated, including molecular weight, hydrogen bond donor and acceptor counts, topological polar surface area (TPSA), XLOGP3 (octanol/water partition coefficient), predicted gastrointestinal (GI) absorption, Lipinski's Rule of Five compliance, and the predicted bioavailability score.^[4,9] These parameters were selected to assess the oral drug-likeness, pharmacokinetic behavior, and medicinal chemistry suitability of each phytochemical.

Compounds were screened using predefined inclusion criteria to select candidates with favorable pharmacokinetic properties. Only compounds with complete physicochemical

information in SwissADME, a canonical chemical structure available in the PubChem database, no violations of Lipinski's Rule of Five, a predicted bioavailability score ≥ 0.30 , and acceptable GI absorption were considered eligible for further analysis. The Lipinski rule is based on specific physicochemical properties, such as absorption, distribution, metabolism, and excretion, to predict drug pharmacokinetic properties such as (1) a maximum of five hydrogen bond donors, (2) a maximum of 10 hydrogen bond acceptors, (3) a molecular mass less than 500 Da, and (4) the partition coefficient, or XLOGP3, must not exceed 5 (Supplementary Table 2). The partition coefficient quantifies the relationship between a compound's lipophilicity (fat solubility) and hydrophilicity (water solubility). A compound with XLOGP3 > 5 is considered excessively lipophilic. Such compounds often suffer from several pharmacokinetic problems, including poor aqueous solubility in fluids such as GI fluids, reduced intestinal absorption, excessive tissue accumulation, and more. Conversely, compounds were excluded if they lacked complete structural or physicochemical information, were unavailable in the PubChem database, violated one or more of Lipinski's criteria, exhibited poor predicted GI absorption, or had a predicted bioavailability score below 0.30 because in early drug discovery, compounds with a bioavailability score of ≥ 0.3 are generally considered acceptable, whereas values > 0.5 are preferred for improved therapeutic efficacy and dose optimization.^[10] After applying these screening criteria, 19 phytochemical compounds were identified as potential bioactive constituents of *Piper longum* and were subsequently selected for downstream target prediction and network pharmacology analyses. Supplementary Figure 1 shows a brief flow diagram of the screening pipeline.

P. longum Potential Targets Prediction

The potential human protein targets of the 19 phytochemicals that passed the predefined ADME and drug-likeness criteria were predicted using three complementary in silico platforms: SuperPred (<https://prediction.charite.de/>; accessed on 10th May 2025), SwissTargetPrediction (<http://www.swisstargetprediction.ch/>; accessed on 10th May 2025), and DIGEP-Pred (<http://www.way2drug.com/ge/>; accessed on 10th May 2025).^[11–13] Canonical SMILES structures obtained from PubChem were used as input for target prediction. Targets meeting the predefined confidence criteria were retained for subsequent analysis. Specifically, predicted targets with a probability score > 0.80 in SuperPred, > 0.40 in SwissTargetPrediction, and > 0.50 in DIGEP-Pred were selected.^[14] The search was restricted to *Homo sapiens* targets. Predicted target names, UniProt identifiers, gene symbols, and

probability scores were retrieved. Duplicate targets predicted for multiple compounds were merged before downstream analyses. The resulting target lists from the three platforms were integrated to generate a comprehensive set of candidate targets associated with the selected *P. longum* phytochemicals. These targets represent computational predictions and database-derived associations and were not considered experimentally validated molecular targets.

Breast Cancer Screening Targets

Breast cancer-associated genes were retrieved from the Online Mendelian Inheritance in Man (OMIM) (<https://www.omim.org/>; accessed on 12th May 2025), Therapeutic Target Database (TTD) (<https://db.idrblab.net/ttd/>; accessed on 12th May 2025), and GeneCards (<https://www.genecards.org/>; accessed on 13th May 2025) (with a relevance score exceeding 30) using the keyword "Breast Cancer."^[15–17] The predefined database-specific criteria for human protein-coding genes were applied. Database-specific inclusion criteria were applied, gene symbols were standardized, and duplicate entries were removed. The resulting disease-associated gene set was then compared with the predicted phytochemical target set to identify shared candidate targets.

Shared Target Identification

The predicted *P. longum* phytochemical targets and breast cancer-associated genes were compared using Venny version 2.1.0 (<https://bioinfogp.cnb.csic.es/tools/venny/>; on 15th May 2025). The overlapping genes were considered shared candidate targets linking the selected phytochemicals with breast cancer. They were subsequently subjected to PPI-network construction, enrichment analysis, compound–target–disease network analysis, and molecular docking.

Construction and Analysis of Protein–Protein Interaction (PPI) Network

Protein-protein interactions (PPIs) play a crucial role in regulating cellular activities and biological functions across different organisms. Gaining insights into protein interactions can enhance our understanding of infection mechanisms and inform the development of effective drugs and treatment strategies. A PPI network was constructed using the STRING database (<https://string-db.org/>; 16th May 2025), focusing on *Homo sapiens* genes with high-confidence interaction scores of ≥ 0.7 , with disconnected nodes hidden.^[18] Next, network data from the STRING database were exported as a tab-separated values file to build the PPI network diagram and perform enrichment analysis

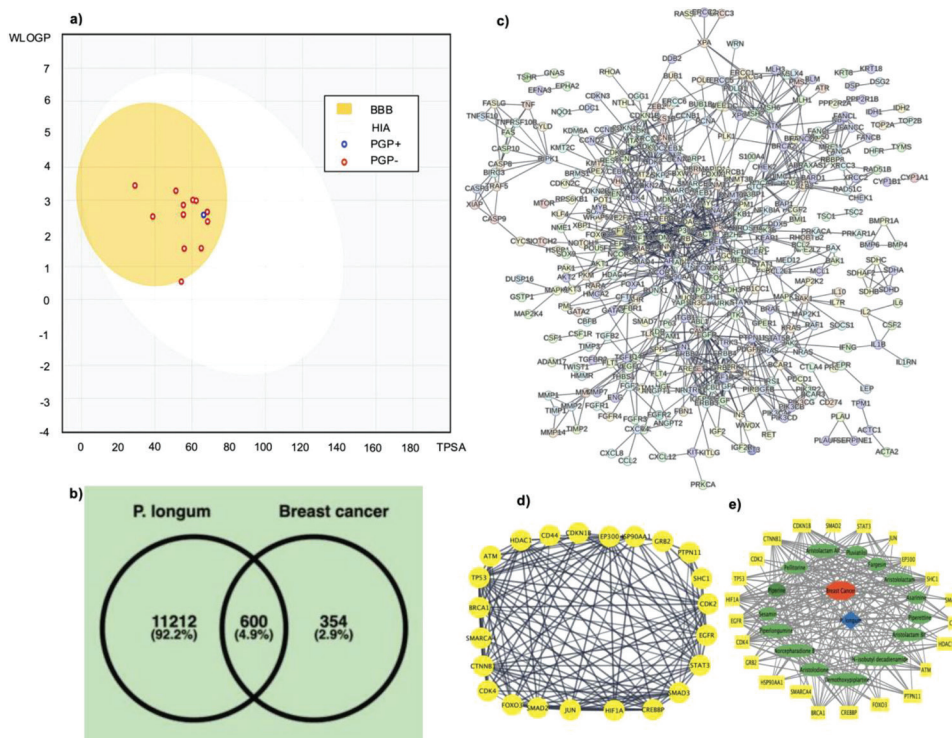


Figure 1. (a) Predicted BOILED-Egg diagram of the selected compounds. BBB - Blood Brain Barrier, HIA - Human Intestinal Absorption, PGP+ - substrate of P-glycoprotein and PGP- - non-substrate of P-glycoprotein. (b) Intersecting targets between the active phytochemical potential protein targets in *P. longum* and Breast cancer-related genes. (c) The PPI network of the 600 intersecting targets, (d) The PPI network of the top 23 target genes, and (e) Compound – Target – Disease network of breast cancer and *P. longum*.

using Cytoscape v3.9.1.^[19] Network topology was analyzed using the CytoNCA plugin by calculating Degree Centrality (DC), Betweenness Centrality (BC), and Closeness Centrality (CC) for each node. Degree centrality was used to identify highly connected proteins, while betweenness and closeness centrality were used to evaluate each node's relative influence and connectivity within the network.

Construction and Analysis of Compound, Target, and Disease (C-T-D) Network

A C-T-D network was developed using Cytoscape v3.9.1 (<https://cytoscape.org/>) to visualize interactions among the selected phytochemicals, predicted target genes, and breast cancer. We extracted nodes representing core genes, drugs, and diseases. By analyzing the nodes, we identified several targets based on their connectivity degree, which reflects their importance. We used the CytoNCA plugin to perform network topology analysis and loaded the C-T-D network map into Cytoscape version 3.9.1. Nodes were ranked by degree centrality. Degree was used as a network prioritization measure, not to test statistical significance.^[20] Nodes with higher degree values were considered more influential within the network, and the top-ranked phytochemicals were identified based on their connectivity to predicted target genes.

Gene Ontology (GO) Analysis for Enrichment and Pathway Analysis

ShinyGO 0.7 (<http://bioinformatics.sdstate.edu/go/>; accessed on 20th May 2025) was utilized for the analysis of pathway and process enrichment.^[21] This tool encompasses a standard collection of ontologies for enrichment analysis, including Gene Ontology (GO) processes, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, Reactome gene sets, canonical pathways, and a thorough resource for mammalian protein complexes. GO and KEGG enrichment analyses were performed on the 23 top-ranked genes selected from the PPI network.^[22]

Analysis of Gene Expression

Gene expression analysis was performed using the Gene Expression Profiling Interactive Analysis 2 (GEPIA2, <http://gepia.cancer-pku.cn/>; accessed on 22nd May 2025), which integrates RNA-sequencing data from The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) projects.^[23] Breast Invasive Carcinoma (BRCA) tumor samples were compared with normal breast tissues using the GEPIA2 “Expression DIY” module. The differential expression cut-off parameters were set to $|\log_2FC| \geq 1$ and

$p < 0.01$, consistent with previous reports.^[24] At the time of analysis, the BRCA dataset comprised 1,085 tumor samples and 291 normal samples (TCGA and GTEx combined). Differential expression analysis was performed using the statistical methods implemented in the GEPIA2 platform. GEPIA2 uses ANOVA for differential expression between tumor and normal tissues and the log-rank test for survival analysis.

Analysis of Overall Survival and Heat Map of Survival

Overall survival analysis of the six hub genes was performed using the GEPIA2 survival module with the default parameters.^[25] Patients were automatically divided into high- and low-expression groups according to the default GEPIA2 expression cut-off (median expression), and survival differences were evaluated using Kaplan–Meier survival curves and the log-rank test. The GEPIA2 server generated hazard ratios with 95% confidence intervals. Because survival analysis was performed only for six predefined hub genes identified through the network analysis, no additional multiple-testing correction was applied.

Molecular Docking

The PDB structural data of the six hub genes were obtained from the Protein Data Bank (PDB) (<https://www.rcsb.org/>; accessed on 25th May 2025).^[26] The PyMOL Molecular Graphics System, Version 2.3.2, developed by Schrödinger, LLC (<http://www.pymol.org/pymol>), was then used to view the downloaded target structure files in .pdb format.^[27] Using PyMOL, water molecules and other heteroatoms, such as Ca, Cl, and Na, were removed from the structures before energy minimization. Then, using PubChem (<https://pubchem.ncbi.nlm.nih.gov/>), the top five bioactive compounds (ligands) from *P. longum* were converted into their corresponding 3D conformations in the .sdf file format.^[2] Subsequently, the target molecules in .pdb format and ligand molecules in .sdf format were loaded into the cavity-detection guided blind docking program CB-Dock2 (<http://cadd.labshare.cn/cb-dock2/>; accessed on 25th May 2025).^[28] CB-Dock2 automatically identifies potential ligand-binding cavities within the protein structure and ranks the predicted cavities according to their size. Based on the predicted cavities, the docking center and docking box dimensions are automatically determined according to the ligand structure. Molecular docking is subsequently performed using AutoDock Vina (<https://github.com/ccsb-scripps/AutoDock-Vina>). The resulting ligand-binding poses are ranked according to their predicted Vina scores, expressed in kcal/mol. These values represent the predicted binding affinity/docking scores of the corresponding protein–ligand complexes, with more negative values indicating a more favorable predicted interaction.

The top-ranked conformation for each protein–ligand complex was considered the optimal predicted binding pose. Finally, 2D schematic representations of predicted protein–ligand interactions were further visualized using two-dimensional interaction diagrams generated with the LIGPLOT tool (<https://www.ebi.ac.uk/thornton-srv/software/LigPlus/>; accessed on 25th May 2025) with standard Protein Data Bank file input.^[29] The result is a PostScript file, in color or black and white, that identifies hydrogen bonds, hydrogen-bond distances, interacting amino acid residues, and hydrophobic contacts between the ligands and the respective target proteins.

Extract Preparation

Dried fruits of *Piper longum* Linn. were procured from the pharmacy of the All India Institute of Ayurveda (AIIA), New Delhi, India. The plant material was authenticated in the Department of Dravyaguna, AIIA, before use in accordance with institutional quality-control procedures and the standards of the Ayurvedic Pharmacopoeia of India. The fruits were thoroughly washed with distilled water to remove adhering dust, foreign particles, and damaged plant material, then shade-dried at ambient temperature for approximately 20 days until a constant weight was achieved. The dried fruits were then pulverized into a coarse powder using an electric grinder and stored in airtight containers under dry conditions until extraction.

To compare different extraction approaches, aqueous and hydroalcoholic extracts were prepared using both cold maceration and Soxhlet extraction techniques at the Department of Rog Nidan and Vikriti Vigyan, AIIA. For cold maceration, 400 g of the powdered fruit material was suspended in 5 L of sterile double-distilled water (solid-to-solvent ratio, 1:12.5 w/v) and continuously stirred at room temperature ($25 \pm 2^\circ\text{C}$) for 12 hours to facilitate efficient extraction of water-soluble phytoconstituents. The extract was subsequently filtered through Whatman No. 1 filter paper to remove insoluble plant debris.

For Soxhlet extraction, coarsely powdered *P. longum* fruits were extracted separately with distilled water and a hydroalcoholic solvent (water, 1:1, v/v) until the extraction solvent in the siphon tube became colorless, indicating exhaustive extraction of soluble constituents. The resulting extracts were filtered through Whatman No. 1 filter paper to remove particulate matter.

The filtrates from all extraction methods were concentrated by evaporation in a hot-air oven at 55°C for 24 hours until a semisolid crude extract was obtained. The dried extracts were transferred to sterile airtight containers and stored at 4°C until further use. The extraction yield percentage was calculated as follows:

$$\text{Extraction yields (\%)} = \frac{\text{Weight of dried extract (g)}}{\text{Weight of dried plant material (g)}} \times 100$$

The extraction yields are given in (Supplementary Table 1).

HIGH PERFORMANCE THIN LAYER CHROMATOGRAPHY (HPTLC)

Piperine is one of the most abundant and essential alkaloids found in the Piperaceae family, such as *P. longum* and *P. nigrum*. Therefore, the selected extracts were chemically standardized by HPTLC using piperine as the reference marker before biological evaluation. A simple, rapid, quantitative HPTLC technique was used to validate the presence of piperine in various *P. longum* extracts mentioned above, following the HPTLC Association protocol for *P. longum* (www.hptlc-association.org). Briefly, 1 mg of test samples (cold maceration aqueous extract, aqueous, and hydro-alcoholic extracts by the Soxhlet method) was dissolved in 1 mL of methanol. Similarly, 1 g of dried fruit powder was dissolved in 10 mL of methanol, and 0.9 mg of standard piperine (Sigma-Aldrich, USA) was dissolved in 1 mL of methanol. Each standard and extract solution was sonicated for 10 minutes. The plate was prepared according to the HPTLC software. A mobile phase comprising Cyclohexane: Ethyl acetate (5:3 v/v) was prepared, and 20 mL of it was added to the chromatographic glass chamber. Two saturation pads were placed in the chamber for 20 minutes. Meanwhile, 7 µL of test samples and 3 µL of serially diluted piperine standard solutions were applied to pre-coated HPTLC Si 60 F₂₅₄ (Merck) plates. After loading and saturation, the silica gel plate was placed in the mobile phase to allow the samples to develop in the solvent. Following absorption, the plate was air-dried. The underivatized plate was viewed under UV light at 254 nm and 366 nm to compare piperine bands in test samples with standards. Piperine detection was also performed after derivatization.

Cell Culture

The human breast adenocarcinoma cell line MCF-7, obtained from the National Center for Cell Science (NCCS), Pune, India, was maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum (FBS), 100 U/mL penicillin, and 100 µg/mL streptomycin. Cells were cultured in a humidified incubator at 37°C with 5% CO₂ and 95% air. The culture medium was replaced every 2–3 days, and cells were passaged at approximately 70–80% confluency using 0.25% trypsin–EDTA. Cell viability was routinely assessed by the trypan blue exclusion assay, and only cultures with >95% viability

and no visible contamination were used for experiments. For treatment studies, cells were seeded at the required density and allowed to adhere for 24 hours before exposure to the test extracts.

Preparation of Extract Dilutions

A stock solution of the aqueous *P. longum* extract was prepared at 1 mg/mL in phosphate-buffered saline (pH 7.4) and filter-sterilized before use. Immediately before each experiment, serial working dilutions were freshly prepared from the stock solution using complete culture medium to obtain final treatment concentrations of 0.25, 0.5, 1.0, 2.5, 3.75, 5.0, 7.5, 10, 12.5, 15, 20, 25, 30, and 50 µg/mL. Cells treated with complete culture medium alone served as the untreated control.

MTT Assay

The cytotoxic effect of *Piper longum* aqueous extract on MCF-7 human breast cancer cells was evaluated using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Briefly, 1 × 10⁴ MCF-7 cells were seeded into 96-well flat-bottom tissue culture plates at an appropriate density and allowed to attach overnight under standard culture conditions. The next day, the culture medium was replaced with fresh complete medium containing different concentrations of *P. longum* aqueous extract. Untreated cells maintained in complete culture medium served as the negative control.

After 24 hours of treatment, 20 µL of MTT solution (5 mg/mL prepared in phosphate-buffered saline) was added to each well, followed by incubation for an additional 4 hours at 37°C in a humidified atmosphere containing 5% CO₂. During this period, metabolically active cells reduced the yellow tetrazolium salt to insoluble purple formazan crystals. At the end of the incubation period, the culture medium containing excess MTT reagent was carefully aspirated without disturbing the crystals, and 100 µL of dimethyl sulfoxide (DMSO) was added to each well to completely dissolve the formazan crystals. The plates were gently agitated for 10–15 minutes to ensure complete solubilization before measuring the absorbance at 570 nm using a microplate reader. Cell viability was expressed as the percentage of viable cells relative to the untreated control using the following equation:

$$\text{Cell viability (\%)} = \frac{\text{Absorbance of treated cells}}{\text{Absorbance of control cells}} \times 100$$

The concentration of *P. longum* aqueous extract required to inhibit 50% of cell viability (IC₅₀) was determined from the dose-response curve in GraphPad Prism version 10.

Each concentration was tested in [number] technical wells in each of [number] independent experiments. Data are presented as mean $\pm$ SD.

Statistical Analysis

All experiments were performed in three independent biological replicates, with each treatment and control analyzed in triplicate wells. Data are expressed as the mean $\pm$ standard deviation (SD). Statistical analyses were performed using GraphPad Prism version 10.0 (GraphPad Software, San Diego, CA, USA). The half-maximal inhibitory concentration (IC₅₀) of *P. longum* aqueous extract was determined by nonlinear regression analysis using a log(inhibitor) vs. normalized response (variable slope) dose-response curve model. A p-value of <0.05 was considered statistically significant.

RESULTS

P. longum Active Compounds

Literature review and IMPPAT database searches identified 82 bioactive compounds in *P. longum* fruit (Supplementary Table 2). All compounds were evaluated using SwissADME analysis to assess drug-likeness based on bioavailability score ≥ 0.3 and Lipinski's rule of five, which is used to predict the drug pharmacokinetic properties based on the facts such as (1) a maximum of five hydrogen bond donors, (2) a maximum of 10 hydrogen bond acceptors, (3) a molecular mass less than 500 Da, and (4) the partition coefficient, or XLOGP3, must not exceed 5 (Supplementary Table 3). This screening yielded 19 promising ligands (Supplementary Table 2). The selected compounds had calculated molecular weights of approximately 222–370 Da and XLOGP3 values of 1.23–4.70. Predicted GI absorption and blood-brain barrier penetration have also been reported separately for each compound in Supplementary Table 3. Additionally, most compounds were not P-glycoprotein (PGP) substrates, suggesting reduced efflux and enhanced bioavailability and reinforcing their potential as effective therapeutic candidates.

Breast Cancer and *P. longum* Potential Targets

Following the ADME analysis, the bioactive compounds underwent target prediction using the SuperPred, SwissTargetPrediction, and DIGEP-Pred databases, yielding 11,812 predicted targets. A thorough search using the keyword "Breast Cancer" in OMIM, the TTD, and GeneCards identified 954 target genes. After reviewing the target genes linked to *P. longum* and breast cancer, we found an overlap of 600 targets, as shown in Figure 1b and listed in Supplementary Table 4.

Protein-Protein Interaction (PPI) Network

Of the 600 overlapping targets, 516 were included in the STRING interaction network under the predefined high-confidence interaction threshold, whereas the remaining targets were excluded because they lacked qualifying interactions. To refine the analysis, we ranked nodes by degree and generated a focused PPI network of the top 23 genes using Cytoscape (Figure 1d). These genes included TP53, CTNNB1, STAT3, EP300, BRCA1, JUN, HDAC1, SMAD3, FOXO3, EGFR, HIF1A, CREBBP, HSP90AA1, CDK2, SMAD2, CDK4, SMARCA4, ATM, GRB2, CDKN1B, PTPN11, CD44, and SHC1.

The refined network consisted of 23 nodes and 139 edges, with an average of 12.1 neighbors per node. Degree centrality (DC), betweenness centrality (BC), and closeness centrality (CC) values are provided in Supplementary Table 5. DC quantifies the total number of direct connections a node possesses. DC reflects the number of direct connections, BC indicates a node's role in shortest paths, and CC measures proximity to all nodes.^[30] Six genes—TP53, CTNNB1, STAT3, SMAD3, EGFR, and HSP90AA1—showed above-average DC, BC, and CC, identifying them as hub genes (Supplementary Table 5). The network hierarchy for hub gene selection is as follows:

600 overlapping targets $\rightarrow$ 516 STRING-network nodes $\rightarrow$ Cytoscape $\rightarrow$ CytoNCA $\rightarrow$ Degree, Betweenness Centrality (BC), and Closeness Centrality (CC) $\rightarrow$ 23 top-ranked network genes $\rightarrow$ 6 final hub genes.

Construction and Analysis of C-T-D Network

The Cytoscape application was used to create a compound-target-disease network, enabling exploration of the complex interactions among compounds, targets, and breast cancer. Figure 1e depicts the C-T-D network, which encompasses 200 nodes and 400 edges, with an average of 4 neighboring nodes. Supplementary Table 6 presents the degree, betweenness, and closeness centralities for the top 15 bioactive compounds associated with breast cancer. The five compounds with the highest degree centrality were Pellitorine (20), Aristolodione (18), Aristolactam AII (18), Norcepharadione B (16), and N-isobutyl decadienamide (15).

Gene Ontology (GO) Enrichment and KEGG Pathway Analysis

Targets of *P. longum* were analyzed using functional annotation and enrichment analyses, revealing key biological roles associated with its phytochemicals. Gene Ontology (GO) and KEGG enrichment analyses were performed on the 23 top-ranked genes selected from the PPI network. Gene Ontology (GO) analysis showed involvement in biological

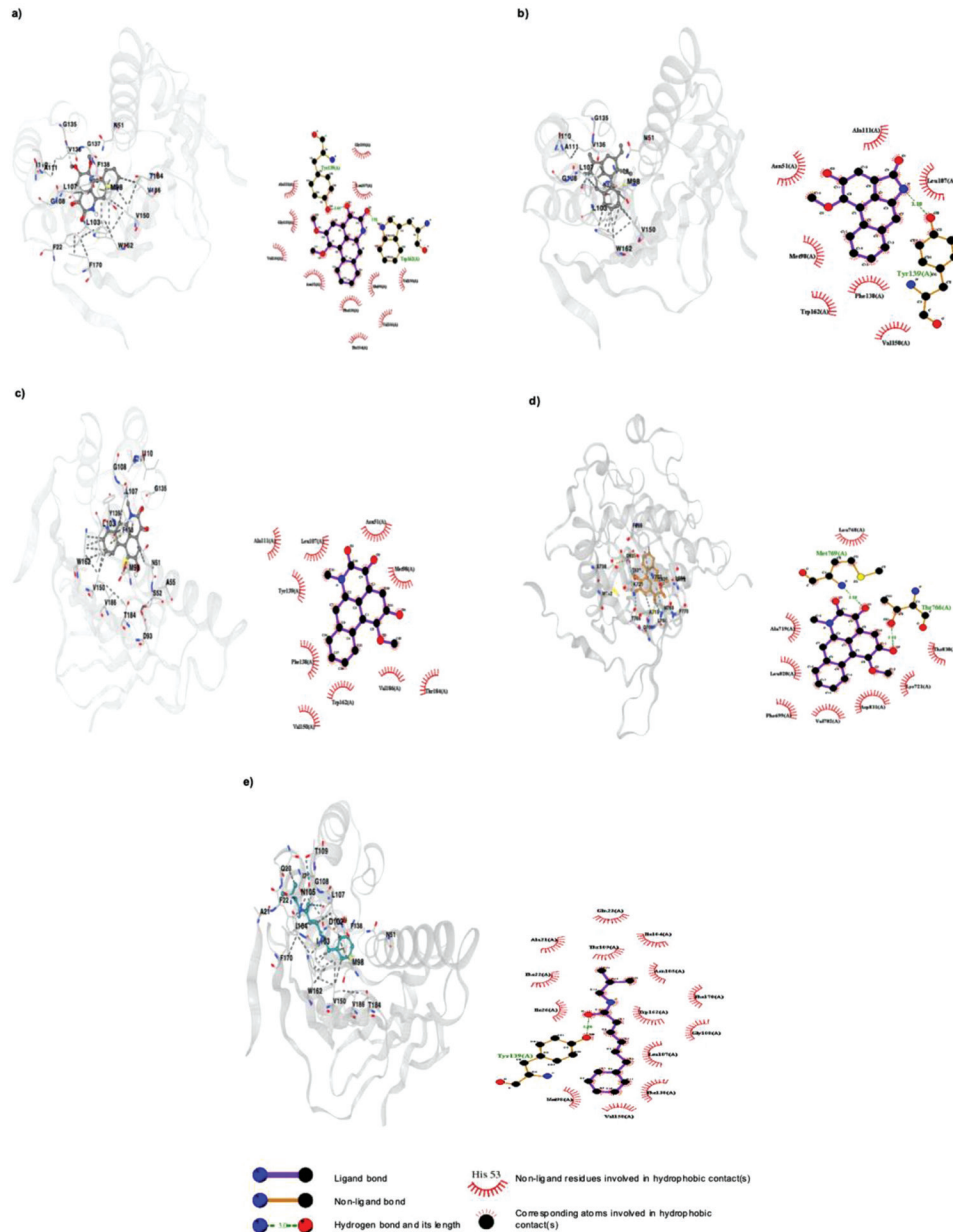


Figure 2. Molecular docking results of key bioactive compounds of *P. longum* with breast cancer hub genes. (a) HSP90AA1_Norcepharadione B; (b) HSP90AA1_Aristolactam AII; (c) HSP90AA1_Aristolodione; (d) EGFR_Aristolodione; (e) HSP90AA1_N-isobutyl decadienamide.

processes (BP) such as responses to growth factors, regulation of signal transduction, and responses to chemical and oxygen-containing stimuli. Cellular components (CC) included SMAD complexes, cyclin-dependent kinase complexes, transcription repressor complexes, euchromatin, DNA repair complexes, and chromosomes. Molecular functions (MF) comprised p53 binding, transcription coactivator binding, kinase and phosphatase binding, and transcription regulation. Using an FDR cutoff of 0.05, 631 BP, 19 CC, and 74 MF terms were identified across 23 genes (Supplementary Figure 2). KEGG pathway analysis revealed 101 associated

pathways, including cancer-related pathways, breast cancer, chronic myeloid leukemia, microRNAs in cancer, Forkhead box O (FOXO) signaling, PI3K-Akt signaling, cell cycle regulation, viral carcinogenesis, and hepatitis C. These findings highlight the therapeutic relevance of *P. longum*.

Unique Gene Expression

We assessed the expression levels of six breast cancer hub genes, including TP53, CTNNB1, STAT3, SMAD3, EGFR, and HSP90AA1, by comparing them with the BRCA dataset

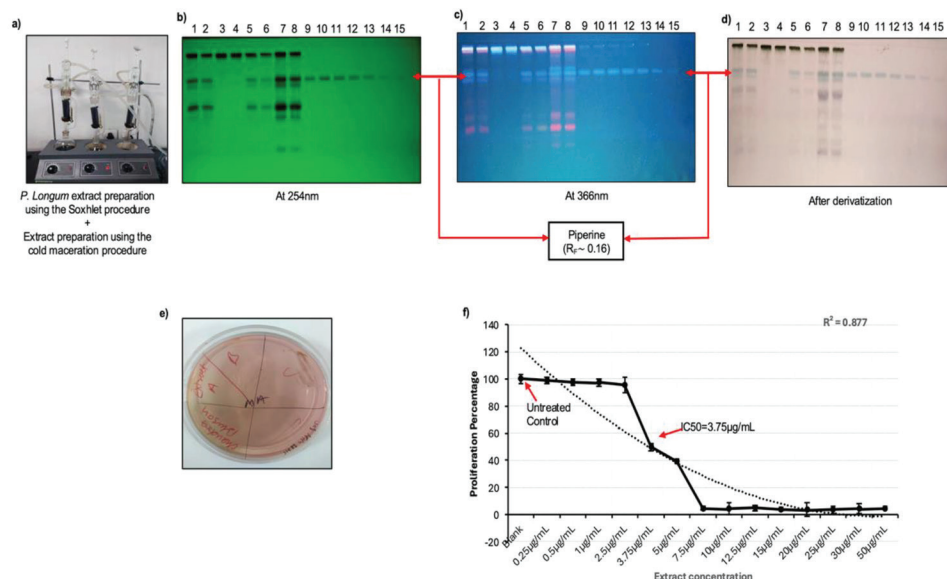


Figure 3. (a) Extract preparation. (b–d) HPTLC profile of standard and isolated piperine from different extraction methods and extract of *P. longum* dried fruits at 254nm (b), 366nm (c) and after derivatization (d) [1–2: Isolated Piperine from hydro-alcoholic Soxhlet method; 3–4: aqueous Soxhlet method; 5–6: cold maceration method; 7–8: *P. longum* dried fruit extract; 9–15: Piperine standard]. (e) Anti-microbial assessment of different extracts (A-Hydro-alcoholic extract by the Soxhlet method; B-aqueous extract by the Soxhlet method, and C-aqueous extract by the cold maceration method) on a Macconkey agar plate. (f) Line graph showing the effect of aqueous extract of *P. longum* on the growth of MCF-7 cell line using MTT assay.

using the GEPIA2 web tool (Supplementary Figure 3). The Cancer Genome Atlas-BRCA (TCGA_BRCA) dataset comprises expression data from 1,085 tumor tissues and 291 corresponding normal tissues related to BRCA. In the box plot, tumor samples are represented in red, while normal samples are shown in grey. A red asterisk indicates a statistically significant p-value (below 0.01), implying a potentially important difference in gene expression between tumor and normal tissues. The y-axis represents the mean log₂ (TPM + 1) values for gene expression levels. This transformation is commonly used in gene expression studies to stabilize variance across expression levels. At the stated cutoff, only EGFR and HSP90AA1 showed significant tumor-normal differences in the GEPIA2 analysis shown. HSP90AA1 was significantly upregulated and overexpressed in the TCGA_BRCA dataset. Additionally, TP53 was also overexpressed in the TCGA_BRCA dataset, but the difference was not significant ($p > 0.05$). In contrast, EGFR's expression was significantly downregulated in this dataset. Moreover, STAT3 and SMAD3 expression was downregulated ($p > 0.05$) (Supplementary Figure 4). CTNNB1 showed a negligible change in expression in the TCGA_BRCA dataset (Supplementary Figure 3).

Heat Maps and Survival Analysis of Unique Genes

Using GEPIA2, a survival analysis was conducted by comparing gene expression levels identified in the

survival heat map analysis with the TCGA_BRCA dataset (Supplementary Figure 4a). Among the six genes associated with breast cancer, HSP90AA1 and TP53 exhibited high expression levels in the BRCA dataset. Conversely, the remaining genes—CTNNB1, STAT3, SMAD3, and EGFR—demonstrated minimal expression in the BRCA dataset (Supplementary Figure 4a). A survival heatmap visually displays survival data, illustrating the relationship between specific variables (in this case, the six hub genes) and survival outcomes (such as overall survival time) across individuals or groups. The prognostic impact helps identify genes associated with improved or poorer survival, aiding the discovery of potential biomarkers for prognosis and treatment. Overall-survival analysis showed that the prognostic associations varied among the six hub genes. TP53 expression was significantly associated with poorer overall survival (HR = 1.4, $p = 0.038$), whereas the associations observed for HSP90AA1, CTNNB1, STAT3, SMAD3, and EGFR did not reach statistical significance under the analysis conditions used. Moreover, some genes exhibiting high expression levels and correlations with survival in BRCA patients included CTNNB1 (HR (Hazard ratio) = 0.94; $p = 0.71$), STAT3 (HR = 0.96; $p = 0.82$), SMAD3 (HR = 0.91; $p = 0.58$), and EGFR (HR = 0.9; $p = 0.53$). In contrast, the expression levels of TP53 (HR = 1.4, $p = 0.038$) and HSP90AA1 (HR = 1.3, $p = 0.079$) were associated with poorer prognoses and reduced survival rates among BRCA patients (Supplementary Figure 4b–g). The survival analysis

suggested a potential association between higher TP53 expression and poorer overall survival ($p = 0.038$), whereas the association observed for HSP90AA1 was weaker and did not reach statistical significance. These findings should therefore be considered exploratory and require validation in independent cohorts (Supplementary Figure 4).

Molecular Docking and Visualization Analysis

Molecular docking was employed to predict the potential interactions between the selected *P. longum* phytochemicals and six breast cancer-associated hub proteins. The protein structures used for docking were obtained from the Protein Data Bank (PDB) and included 4MZI (TP53), 8Y0G (CTNNB1), 6NUQ (STAT3), 1MJS (SMAD3), 1M17 (EGFR), and 4BQG (HSP90AA1).^[31–36] The predicted ligand docking score values for every hub gene are shown in Supplementary Table 7, in which the corresponding values, expressed in kcal/mol, represent the AutoDock Vina scores generated during the docking process and were used to rank the predicted binding poses. More negative Vina scores indicate more favorable predicted docking scores. Among the evaluated complexes, eleven protein–ligand interactions showed predicted binding affinities below -7 kcal/mol. These include HSP90AA1_Norcedaphadione B (-10.9 kcal/mol), HSP90AA1_Aristolactam AII (-10.7 kcal/mol), HSP90AA1_Aristolodione (-10.3 kcal/mol), EGFR_Aristolodione (-9.1 kcal/mol), HSP90AA1_N-isobutyl decadienamide (-9 kcal/mol), EGFR_Norcedaphadione B (-8.9 kcal/mol), EGFR_Aristolactam AII (-8.4 kcal/mol), STAT3_Aristolodione (-7.6 kcal/mol), HSP90AA1_Pellitorine (-7.5 kcal/mol), STAT3_Norcedaphadione B (-7.2 kcal/mol), and TP53_Aristolodione (-7.1 kcal/mol). Figure 2 illustrates representative 3D and 2D interaction plots of five selected protein–ligand complexes showing strong predicted binding affinities.

Piperine Assessment for Validation of Extracts

To evaluate the validation of different extracts of *P. longum*, the extracts were analyzed for the presence of piperine, one of the most abundant alkaloids found in *P. longum* fruits, using HPTLC (Figure 3a–d). As shown in Figure 3b–d, the HPTLC chromatogram indicated the presence of piperine in hydro-alcoholic extracts prepared by the Soxhlet method (lanes 1 and 2), aqueous extracts obtained through cold maceration (lanes 5 and 6), and dried fruit extract (lanes 7 and 8), all compared to piperine standards with an R_f value of approximately 0.16. The aforementioned extracts were then tested for microbial contamination at the Department of Microbiology, AIIA. Subsequently, a 1 mg/mL stock solution of this extract was prepared in PBS (pH 7.2–7.4) and stored at -20°C for use in *in vitro* experiments (Figure 3e). Notably, piperine was used solely as a phytochemical

marker for extract characterization and was not selected based on its network pharmacology ranking. In contrast, Norcedaphadione B and Aristolactam AII were prioritized independently through the computational network pharmacology and molecular docking analyses based on their predicted interactions with breast cancer-associated targets. Thus, HPTLC detection of piperine provides chemical evidence for the characteristic composition of the extract but should not be interpreted as experimental validation of the predicted activities of Norcedaphadione B, Aristolactam AII, or other computationally prioritized compounds.

Since we needed to treat the MCF-7 breast cancer cells with these extracts for subsequent experiments, we preferred to use the aqueous extract of *P. longum* prepared by cold maceration to minimize cell death caused by alcohol in the hydro-alcoholic extract.

Effect of *P. longum* Extract on MCF-7 MTT Signal

The effect of *P. longum* extract on MCF-7 MTT signal was analyzed after 24 hours of treatment using an MTT assay. The assay was conducted in both the extract-treated and untreated (control) groups. IC_{50} was reached at an extract concentration of $3.75\ \mu\text{g/mL}$ (Figure 3f) after 24 hours post-treatment. Interestingly, increasing *P. longum* extract concentration was associated with a decrease in MCF-7 cell MTT signal; data are presented as mean $\pm$ standard deviation (SD) (Supplementary Table 8).

DISCUSSION

Network pharmacology provides a systematic framework for investigating the multi-target and multi-pathway effects of phytochemicals in complex diseases such as breast cancer. By integrating phytochemical information, disease-associated genes, PPI networks, pathway enrichment, and molecular docking, this approach can identify potential molecular targets and generate mechanistic hypotheses for further experimental validation.^[37] In the present study, network pharmacology analysis identified several *Piper longum*-associated phytochemicals along with potential breast cancer-related targets, including TP53, CTNNB1, STAT3, SMAD3, EGFR, and HSP90AA1, which are involved in key biological processes regulating cell proliferation, survival, apoptosis, invasion, metastasis, and therapeutic resistance, thereby providing a computationally predicted basis for the potential anticancer activity of *P. longum*. These findings predicted *P. longum*-derived compounds and breast-cancer-associated targets that warrant direct experimental testing.

TP53 is among the most frequently altered genes in breast cancer and regulates cell-cycle progression, DNA damage responses, senescence, and apoptosis.^[38] Similarly, CTNNB1, which encodes β -catenin, is a central component

of Wnt signaling and has been associated with breast cancer progression and clinical outcome.^[39] Constitutive activation of STAT3 contributes to breast cancer cell proliferation, survival, metastasis, and resistance to therapy, whereas SMAD3 overexpression has been associated with breast tumor growth and metastatic potential.^[40–41] EGFR signaling is also involved in several downstream pathways, including JAK/STAT, PI3K/AKT, and RAS/RAF/MEK/ERK, which regulate cancer cell proliferation and survival and contribute to therapeutic resistance.^[42] Furthermore, HSP90AA1 has been implicated in breast cancer biology and has potential diagnostic and prognostic relevance.^[43] Thus, the network pharmacology analysis predicts that *P. longum* phytochemicals may modulate multiple oncogenic pathways rather than a single molecular target. These computational predictions require further experimental validation.

Functional enrichment analysis further supported this multi-target mechanism. The shared targets between *P. longum* phytochemicals and breast cancer were enriched in biological processes associated with growth-factor responses, responses to endogenous and chemical stimuli, and signal transduction. These findings are consistent with the established role of the tumor microenvironment in regulating cancer-cell metabolism, nutrient availability, and signaling. KEGG pathway analysis further identified enrichment of the PI3K–AKT, FOXO, microRNA, cancer-related, proteoglycan, and viral carcinogenesis pathways. Among these, the PI3K–AKT pathway is particularly relevant because it regulates proliferation, growth, survival, apoptosis, and migration and is frequently dysregulated in breast cancer. FOXO transcription factors are also closely linked to cellular stress responses, apoptosis, cancer-cell survival, and resistance to targeted therapies. In addition, microRNAs and proteoglycans may influence post-transcriptional gene regulation and extracellular-matrix-mediated processes involved in tumor invasion and metastasis.^[44]

Molecular docking provided computational predictions regarding the potential interactions between selected *P. longum* phytochemicals and breast cancer-associated hub proteins. Among the evaluated interactions, Norcepharadione B showed the strongest predicted docking score toward HSP90AA1 (–10.9 kcal/mol), followed by Aristolactam AII (–10.7 kcal/mol) and Aristolodione (–10.3 kcal/mol). HSP90AA1 is a molecular chaperone that contributes to the stabilization and functional regulation of multiple oncogenic proteins.^[45] Therefore, the favorable docking scores observed for these phytochemicals indicate that HSP90AA1 may represent a potential molecular target for future investigation. However, the present docking analysis does not demonstrate direct binding or modulation of HSP90AA1-mediated signaling, and these predicted interactions require biochemical and functional validation.

Importantly, the present study also reported experimental assessment of the effect of the aqueous *P. longum* extract on MCF-7 breast cancer cells. The growth-inhibitory effect was observed in the MTT assay. Previous studies have reported that piperlongumine, an individual constituent of *P. longum*, inhibits proliferation and induces cell-cycle arrest through ROS accumulation and suppression of IKK β signaling. Although the precise mechanisms may differ, these published findings support the possibility that *P. longum*-derived phytochemicals influence cellular metabolism.^[46] Additionally, piperine has also been reported to inhibit breast cancer cell growth and induce apoptosis, accompanied by caspase-3 activation.^[4] Further, Prajapati et al.^[5] explained that the combination of piperine and piperlongumine induces apoptosis in breast cancer cells by inhibiting STAT3 activation.^[5] These findings are particularly relevant to the present network pharmacology results, in which STAT3 was predicted to be one of the major breast cancer-associated targets. Nevertheless, because the present study did not directly measure STAT3 activity or downstream apoptotic proteins, this mechanistic relationship should be considered a hypothesis requiring further validation. These observations are broadly consistent with the current findings and suggest that members of the *Piperaceae* family may exert anticancer activity through coordinated regulation of cell-cycle progression and apoptotic pathways. However, the differences in the specific cell-cycle phase affected by different *Piper* species and preparations highlight the importance of extract composition, extraction method, dose, and cellular context.

Strengths and Limitations

Taken together, the findings support a model in which the aqueous *P. longum* extract might exert anticancer activity through a multi-level mechanism. Network pharmacology predicted several cancer-associated molecular targets and pathways, while molecular docking prioritized putative compound-target interactions for further investigation. An *in vitro* study in MCF-7 cells demonstrated that the aqueous extract of *P. longum* significantly inhibits the MTT signal of the breast cancer cell line. These results suggest that the anticancer effects of *P. longum* may arise from the coordinated modulation of multiple signaling pathways involved in proliferation and survival.

The present study has several limitations that should be acknowledged. First, although the aqueous *P. longum* extract was characterized using HPTLC with piperine as a marker compound, comprehensive chemical standardization and quantitative estimation of the prioritized phytochemicals identified through network pharmacology, including Norcepharadione B and Aristolactam AII, were not performed. Therefore, the biological activity observed in the present study cannot be directly attributed to any

individual constituent of the extract. Second, the *in vitro* experiments used only a single breast cancer cell line (MCF-7). Validation in additional breast cancer subtypes, including triple-negative and HER2-positive cell lines, would improve the generalizability of the findings. Third, the present study did not include a non-tumorigenic human breast epithelial cell line as a normal-cell comparator. Consequently, the selectivity of the extract toward cancer cells relative to normal cells could not be assessed. Finally, although the MTT assay demonstrated a significant reduction in cellular metabolic activity following treatment with the aqueous *P. longum* extract, plant-derived compounds may occasionally interfere with tetrazolium-based colorimetric assays through direct chemical reduction or intrinsic color. To minimize this possibility, the MTT findings should be complemented with independent cell-cycle and Annexin V/PI apoptosis assays, which consistently demonstrated cell-cycle arrest and increased apoptotic cell death. Nevertheless, additional orthogonal viability assays (such as ATP-based luminescence or live-cell imaging assays) would further strengthen these observations. An additional limitation of the present network pharmacology approach is that hub-gene prioritization was based on network topology analysis. Centrality measures, including degree, betweenness, and closeness centrality, preferentially identify highly connected and extensively studied genes within biological interaction networks. Consequently, these metrics do not necessarily identify the most disease-specific, biologically causal, or therapeutically druggable targets. Therefore, the hub genes identified in this study should be regarded as computationally prioritized candidates for further investigation rather than experimentally validated therapeutic targets. Future studies integrating functional genomics, target validation, and pharmacological experiments are needed to establish their biological significance and clinical relevance.

In brief, the computational predictions should not be interpreted as experimentally confirmed molecular mechanisms. Direct validation of the predicted interactions and pathways through target-specific approaches, including quantitative PCR, Western blotting, assessment of protein phosphorylation, and functional target inhibition or rescue experiments, will be warranted and will be carried out in our lab in the near future.

CONCLUSION AND IMPLICATIONS FOR TRANSLATION

The present study integrated network pharmacology and molecular docking to identify potential phytochemicals, molecular targets, and biological pathways that may contribute to the anticancer activity of *Piper longum* against breast cancer. The computational analyses generated hypotheses about compound–target interactions. At the

same time, the *in vitro* experiments demonstrated that the aqueous *P. longum* extract reduces the MTT signal in MCF-7 cells. However, these findings should not be interpreted as evidence that specific phytochemicals directly interact with the predicted molecular targets or as proof of therapeutic efficacy. Instead, the present work provides a rational starting point for future compound-specific studies involving chemical standardization, target validation, mechanistic investigations, and comprehensive preclinical evaluation. Such studies will be essential to determine the biological relevance and translational potential of the identified phytochemicals before clinical application can be considered.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of Interest: The authors declare no competing interests. **Financial Disclosure:** Nothing to declare. **Funding/Supported:** The study was financially supported by the ICMR (5/13/58/2020/NCD-III). **Ethics Approval:** Not Applicable. **Use of Artificial Intelligence (AI)-Assisted Technology for Manuscript Preparation:** The author(s) confirm that there was no use of AI-Assisted Technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI. **Disclaimer:** None.

Key Messages

1) *Piper longum* shows promising anticancer potential because its bioactive phytochemicals may act on multiple breast cancer-related targets and signaling pathways. 2) Experimental findings support this potential, with the aqueous extract demonstrating growth-inhibitory and pro-apoptotic effects in MCF-7 breast cancer cells. 3) Findings provide a foundation for plant-derived, multi-target therapeutic development, but further compound-specific validation, mechanistic studies, and comprehensive preclinical evaluation are required before clinical potential can be established.

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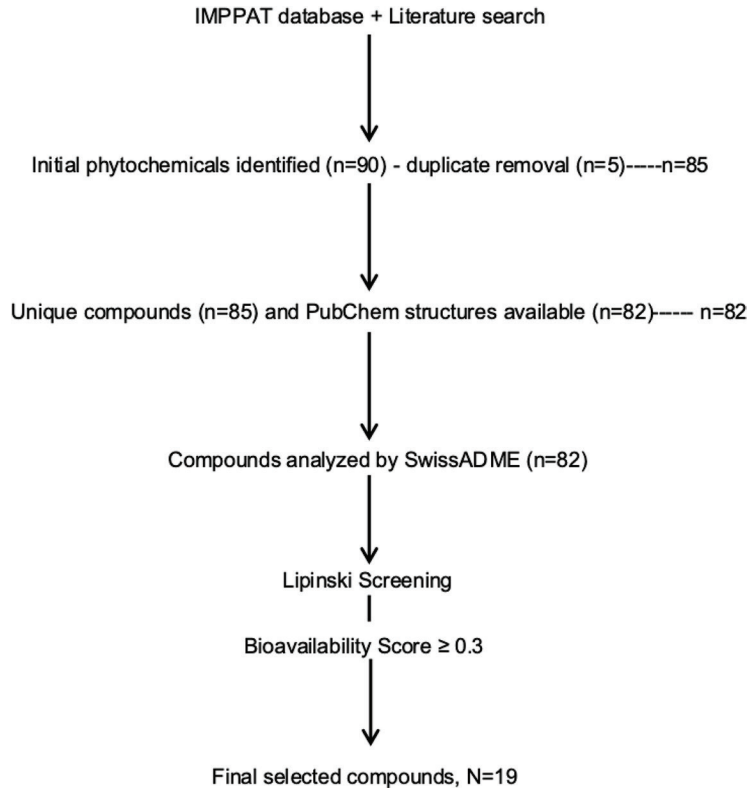
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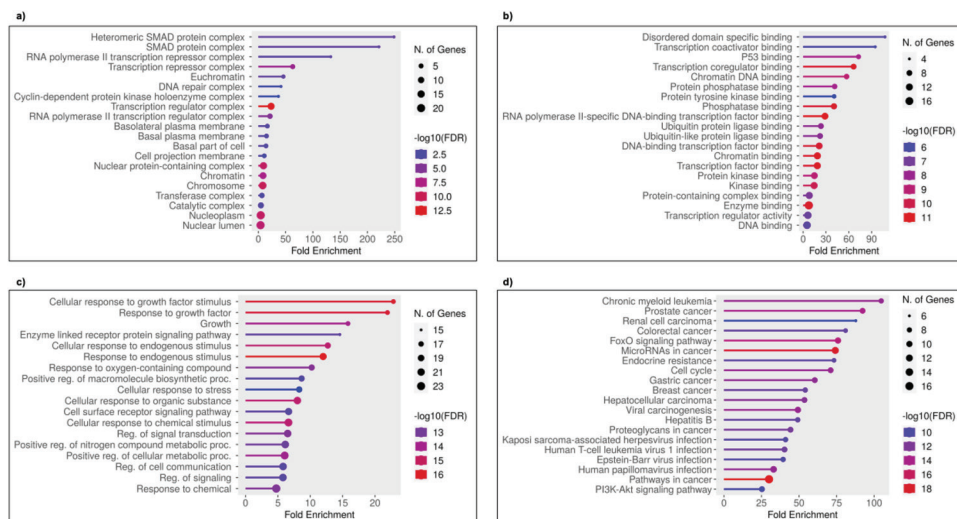
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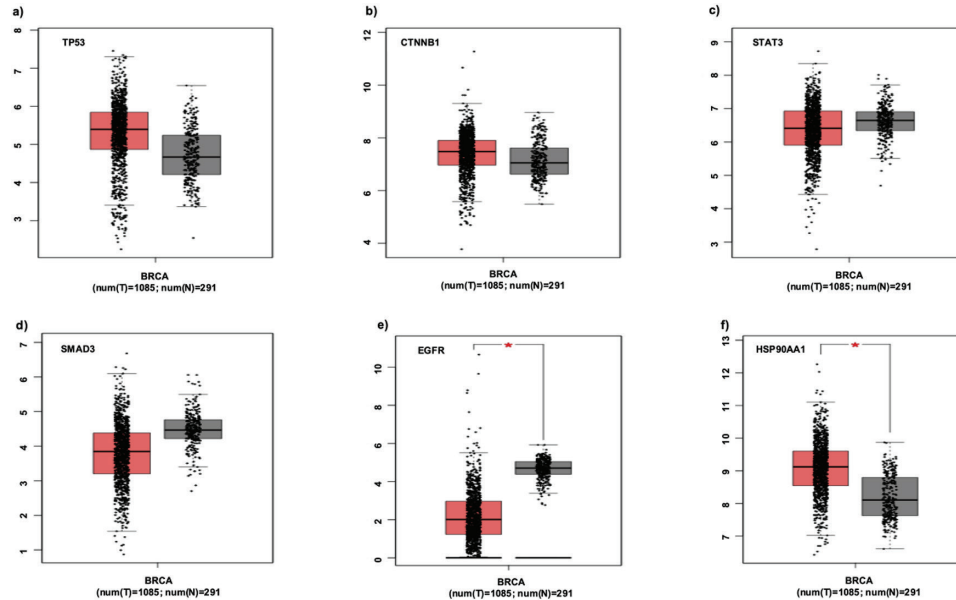
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SUPPLEMENTARY FIGURES

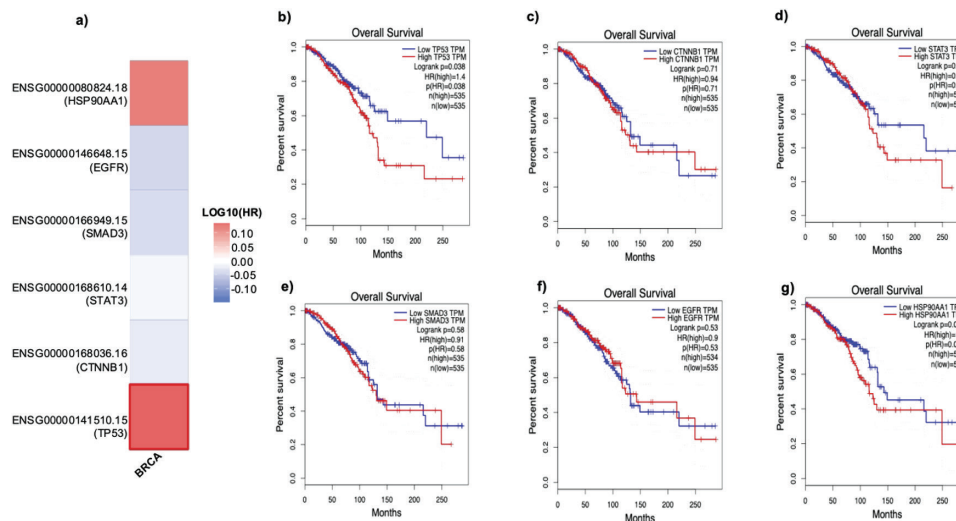


Supplementary Figure 1: Flow diagram demonstrating the screening pipeline for compound selection.

Supplementary Figure 2: Top 23 GO terms and KEGG pathways associated with *P. longum* and breast cancer. (a) Cellular Components, (b) Molecular Functions, (c) Biological Processes, and (d) KEGG pathway.



Supplementary Figure 3: Box plots encode the six breast cancer-associated gene expression levels [(a) TP53, (b) CTNNB1, (c) STAT3, (d) SMAD3, (e) EGFR, and (f) HSP90AA1] in BRCA compared with normal cells. Tumor tissues are marked in red color, and noncancerous or normal tissues are marked in grey color.



Supplementary Figure 4: Survival analysis demonstrating (a) the survival heat map representing the prognostic impacts of unique gene expression levels based on the TCGA_BRCA dataset. The heat map represents the hazard ratios on a log10 scale for the breast cancer-associated genes. Red color represents higher risks, and blue color indicates lower risks. The darkened rectangular frames indicate significant favorable and unfavorable results in prognostic analyses, and (b-g) breast cancer-associated unique genes and their prognostic value, as represented by overall survival analyses (Kaplan-Meier plots and log-rank tests) based on TCGA_BRCA using GEPIA2. The dashed lines denote upper and lower confidence intervals. (b) TP53, (c) CTNNB1, (d) STAT3, (e) SMAD3, (f) EGFR, and (g) HSP90AA1.

SUPPLEMENTARY TABLES

Supplementary Table 1: Extraction yields.				
S. no.	Extraction method	Starting powder	Dried extract	Yield (%)
1	Cold aqueous	400 g	48.2 g	12.05
2	Soxhlet aqueous	400 g	39.8 g	9.95
3	Soxhlet hydroalcoholic	400 g	66.4 g	16.6

Supplementary Table 2: The list of compounds identified and their respective SMILES sequence from the fruit of <i>P. longum</i> .			
S. no.	Compounds in fruit	Canonical/isomeric SMILES	PubChem compounds (CIDs)
1	(-)-alpha-Cadinol	<chem>CC1=C[C@H]2[C@@H](CC[C@@]([C@H]2CC1)(C)O)C(C)C</chem>	10398656
2	(+)-alpha-Gurjunene	<chem>C[C@H]1CC[C@H]2[C@H](C2(C)C)C3=C(CC[C@@H]13)C</chem>	15560275
3	(+)-beta-Phellandrene	<chem>CC(C)[C@@H]1CCC(=C)C=C1</chem>	442484
4	(1R)-2-methyl-5-propan-2-ylbicyclo[3.1.0]hex-2-ene	<chem>CC1=CC[C@]2([C@@H]1C2)C(C)C</chem>	637518
5	(E)-beta-ocimene	<chem>CC(=CC/C=C(\C)/C=C)C</chem>	5281553
6	(Z)-beta-Ocimene	<chem>CC(=CC[C@@H]1[C@@](O1)(C)C=C)C</chem>	5320250
7	(Z)-gamma-bisabolene	<chem>CC1=CC/C(=C/C)\CCC=C(C)C/CC1</chem>	3033866
8	1-methylhexyl acetate	<chem>CCCCC(C)OC(=O)C</chem>	80018
9	1-pentadecene	<chem>CCCCCCCCCCCCC=C</chem>	25913
10	2-nonanone	<chem>CCCCCCCC(=O)C</chem>	13187
11	2-phenylethanol	<chem>C1=CC=C(C=C1)CCO</chem>	6054
12	2-tridecanone	<chem>CCCCCCCCCCCC(=O)C</chem>	11622
13	2-undecanone	<chem>CCCCCCCCC(=O)C</chem>	8163
14	4'-methoxyacetophenone	<chem>CC(=O)C1=CC=C(C=C1)OC</chem>	7476
15	5-[3-(1,3-benzodioxol-5-yl)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c]furan-6-yl]-1,3-benzodioxole	<chem>C1C2C(COC2C3=CC4=C(C=C3)OCO4)C(O1)C5=CC6=C(C=C5)OCO6</chem>	5204
16	9-Eicosyne	<chem>CCCCCCCCCCCC#CCCCCCCCC [1, 2]</chem>	557019
17	alpha-Eudesmol	<chem>CC1=CCC[C@]2([C@H]1C[C@@H](CC2)C(C)(C)O)C</chem>	92762
18	alpha-Murolene	<chem>CC1=C[C@@H]2[C@H](CC1)C(=CC[C@H]2C(C)C)C</chem>	12306047
19	alpha-Phellandrene	<chem>CC1=CCC(C=C1)C(C)C</chem>	7460
20	alpha-Pinene	<chem>CC1=CCC2CC1C2(C)C</chem>	6654
21	alpha-Terpineol	<chem>CC1=CCC(CC1)C(C)(C)O</chem>	17100
22	alpha-Terpinyl acetate	<chem>CC1=CCC(CC1)C(C)(C)OC(=O)C</chem>	111037
23	Aristolactam AII	<chem>COC1=C(C=C2C3=C1C4=CC=CC=C4C3NC2=O)O</chem>	148657
24	Aristolactam BII	<chem>COC1=C(C2=C3C(=C1)C(=O)NC3=CC4=CC=CC=C42)OC</chem>	162739
25	Aristolodione	<chem>CN1C2=CC3=CC=CC=C3C4=C2C(=CC(=C4OC)O)C(=O)C1=O</chem>	184116
26	Aristololactam	<chem>COC1=CC=CC2=C3C4=C(C=C21)NC(=O)C4=CC5=C3OCO5</chem>	96710
27	beta-Caryophyllene	<chem>C/C1=C\CCC(=C)[C@H]2CC([C@@H]2CC1)(C)C</chem>	5281515
28	beta-Cubebene	<chem>CC(C)[C@@H]1CC[C@H]([C@H]2[C@]13[C@@H]2C(=C)CC3)C(C)C [1]</chem>	93081

(Continued)

Supplementary Table 2: (Continued)

S. no.	Compounds in fruit	Canonical/isomeric SMILES	PubChem compounds (CIDs)
29	beta-Elemene	<chem>CC(=C)[C@@H]1CC[C@@]([C@@H](C1)C(=C)C)(C)C=C</chem>	6918391
30	beta-Eudesmol	<chem>C[C@]12CCCC(=C)[C@@H]1C[C@@H](CC2)C(C)(C)O</chem>	91457
31	beta-Patchoulene	<chem>CC1CCC2=C1CC3CCC2(C3(C)C)C</chem>	101731
32	beta-Pinene	<chem>CC1(C2CCC(=C)C1C2)C</chem>	14896
33	Bornyl acetate	<chem>CC(=O)O[C@@H]1C[C@@H]2CC[C@]1(C2(C)C)C</chem>	93009
34	Cadinane	<chem>C[C@H]1CC[C@H]2[C@H](CC[C@H]([C@@H]2C1)C(C)C)C</chem>	9548708
35	Camphene	<chem>CC1(C2CCC(C2)C1=C)C</chem>	6616
36	Caryophyllene oxide	<chem>C[C@@]12CC[C@@H]3[C@H](CC3(C)C)C(=C)CC[C@H]1O2</chem>	1742210
37	Copaene	<chem>CC1=CC[C@H]2[C@H]3[C@@H]1[C@@]2(CC[C@H]3C(C)C)C</chem>	12303902
38	Decanal	<chem>CCCCCCCCC=O</chem>	8175
39	Dehydropiersonalinaline	<chem>C1CCN(CC1)C(=O)/C=C/C=CC/C=C/C2=CC3=C(C=C2)OCO3</chem>	6439947
40	delta-Cadinol	<chem>CC1=C[C@H]2[C@@H](CC[C@@]([C@H]2CC1)(C)O)C(C)C</chem>	3084311
41	delta-Elemene	<chem>CC(C)C1=C[C@@H]([C@@](CC1)(C)C=C)C(=C)C</chem>	12309449
42	Dihydrocarveol	<chem>CC1CCC(CC1O)C(=C)C</chem>	12072
43	Dodecanal	<chem>CCCCCCCCCCCCC=O</chem>	8194
44	Eicosane	<chem>CCCCCCCCCCCCCCCCCCCC</chem>	8222
45	Elemol	<chem>CC(=C)[C@@H]1C[C@@H](CC[C@@]1(C)C=C)C(C)(C)O</chem>	92138
46	Eucalyptol	<chem>CC1(C2CCC(O1)(CC2)C)C</chem>	2758
47	Fargesin	<chem>COC1=C(C=C(C=C1)[C@H]2[C@H]3CO[C@@H]([C@H]3CO2)C4=CC5=C(C=C4)OCO5)OC</chem>	10926754
48	gamma-Elemene	<chem>CC(=C1CC[C@]([C@H](C1)C(=C)C)(C)C=C)C</chem>	12309452
49	gamma-Murolene	<chem>CC1=C[C@H]2[C@H](CC1)C(=C)CC[C@H]2C(C)C</chem>	12313020
50	Guineensine	<chem>CC(C)CNC(=O)/C=C/C=CCCCC/C=C/C1=CC2=C(C=C1)OCO2</chem>	6442405
51	Heneicosane	<chem>CCCCCCCCCCCCCCCCCCCC</chem>	12403
52	Heptadecane	<chem>CCCCCCCCCCCCCCCCC</chem>	12398
53	Hexadecane	<chem>CCCCCCCCCCCCCCCCC</chem>	11006
54	Humulene	<chem>C/C1=C\CC(/C=C/C/C/C(=C/CC1)/C)(C)C</chem>	5281520
55	Isobutyramide	<chem>CC(C)C(=O)N</chem>	68424
56	Limonene	<chem>CC1=CCC(CC1)C(=C)C</chem>	22311
57	Linalool	<chem>CC(=CCCC(C)(C=C)O)C</chem>	6549
58	Myrcene	<chem>CC(=CCCC(=C)C=C)C</chem>	31253
59	Nerolidol	<chem>CC(=CCC/C(=C/CCC(C)(C=C)O)/C)C</chem>	5284507
60	Nonadecane	<chem>CCCCCCCCCCCCCCCCC</chem>	12401
61	Norcepharadione B	<chem>COC1=C(C2=C3C(=C1)C(=O)C(=O)NC3=CC4=CC=CC=C42)OC</chem>	189168
62	Octadecane	<chem>CCCCCCCCCCCCCCCCC</chem>	11635
63	p-Cymene	<chem>CC1=CC=C(C=C1)C(C)C</chem>	7463
64	Pellitorine	<chem>CCCCC/C=C/C=C/C(=O)NCC(C)C</chem>	5318516
65	Pentadecane	<chem>CCCCCCCCCCCCCCC</chem>	12391

(Continued)

Supplementary Table 2: (Continued)

S. no.	Compounds in fruit	Canonical/isomeric SMILES	PubChem compounds (CIDs)
66	Piperidine	C1CCNCC1	8082
67	Piperine	C1CCN(CC1)C(=O)/C=C/C=C/C2=CC3=C(C=C2)OCO3	638024
68	Piperlongumine	COC1=CC(=CC(=C1OC)OC)/C=C/C(=O)N2CCC=CC2=O	637858
69	Piperlonguminine	CC(C)CNC(=O)/C=C/C=C/C1=CC2=C(C=C1)OCO2	5320621
70	Pipernonaline	C1CCN(CC1)C(=O)/C=C/CCCC/C=C/C2=CC3=C(C=C2)OCO3	9974595
71	Piperocetadecalidine	CCCC=CCCCCCCCCCC=CC=CC(=O)N1CCCCC1 [1, 2]	177604078
72	Piperolein B	C1CCN(CC1)C(=O)CCCCC/C=C/C2=CC3=C(C=C2)OCO3	21580213
73	Piperundecalidine	C1CCN(CC1)C(=O)/C=C/C=C/CCCC/C=C/C2=CC3=C(C=C2)OCO3	44453654
74	Pluviatilol	COC1=C(C=CC(=C1)[C@@H]2[C@@H]3CO[C@H]([C@@H]3CO2)C4=CC5=C(C=C4)OCO5)O	70695727
75	Terpinolene	CC1=CCC(=C(C)C)CC1	11463
76	Tridecane	CCCCCCCCCCCCC	12388
77	Zingiberene	CC1=CC[C@@H](C=C1)[C@@H](C)CCC=C(C)C	92776
78	Longamide B	C1C(N2C(=CC(=C2Br)Br)C(=O)N1)O	11602770
79	N-isobutyl decadienamide	CCCCC=CC=CC(=O)NCC(C)C	3009280
80	Sesamin	C1[C@H]2[C@H](CO[C@@H]2C3=CC4=C(C=C3)OCO4)[C@H](O1)C5=CC6=C(C=C5)OCO6	72307
81	Tetrahydropiperine	O=C(CCCCC1=CC(OCO2)=C2C=C1)N3CCCCC3	581676
82	Tetrahydropiperic acid	OC(=O)CCCCC1=CC2=C(OCO2)C=C1	5321853

Supplementary Table 3: ADME properties of the selected phytochemicals of *P. longum* following the Lipinski's rule of five and bioavailability score.

Name of the compound	MW*	MR [†]	Rotatable bonds	XLOGP3 [‡]	H-bond acceptors	H-bond donors	Bioavailability score	GI absorption [#]	BBB penetration [!]
Norcepharadione B	307.3	90.02	2	3.16	4	1	0.55	High	Yes
Piperine	285.3	85.47	4	3.46	3	0	0.55	High	Yes
Aristolodione	307.3	90.45	1	3.02	4	1	0.55	High	Yes
Aristolactam BII	279.3	83.75	2	3.28	3	1	0.55	High	Yes
Dehydropipernonaline	339.4	104.23	7	4.7	3	0	0.55	High	Yes
Piperlongumine	317.3	89.47	6	2.07	5	0	0.55	High	Yes
Pluviatilol	356.4	92.45	3	2.48	6	1	0.55	High	Yes
Aristolactam	293.3	83.32	1	3.12	4	1	0.55	High	Yes
Fargesin	370.4	96.92	4	2.81	6	0	0.55	High	Yes
Pellitorine	223.4	71.47	9	4.39	1	1	0.55	High	Yes
Aristolactam AII	265.3	79.28	1	2.95	3	2	0.55	High	Yes
Longamide	352	67.28	2	1.23	3	2	0.85	High	Yes
Tetrahydropiperic acid	222.2	58.47	5	2.54	4	1	0.85	High	Yes
Piperettine	311.4	94.61	5	4.11	3	0	0.55	High	Yes

(Continued)

Supplementary Table 3: (Continued)

Name of the compound	MW*	MR [†]	Rotatable bonds	XLOGP3*	H-bond acceptors	H-bond donors	Bioavailability score	GI absorption [‡]	BBB penetration [‡]
Asarinine	354.4	90	2	2.68	6	0	0.55	High	Yes
Demethoxy pipartine	287.3	82.98	5	2.1	4	0	0.55	High	Yes
N-isobutyl decadienamide	223.4	71.47	9	3.69	1	1	0.55	High	Yes
Tetrahydro piperine	289.4	85.63	6	3.52	3	0	0.55	High	Yes
Sesamin	354.4	90	2	2.68	6	0	0.55	High	Yes

*Molecular weight; [†]Number of rotatable bonds; [‡]Partition coefficient; [‡]Gastrointestinal absorption; and Blood-Brain Barrier Penetration.

Supplementary Table 4: Complete list of target genes linked with *P. longum* and breast cancer.

S. no.	Gene name	Gene symbol	HGNC ID
1	ATP binding cassette subfamily A member 1	ABCA1	HGNC:29
2	ATP binding cassette subfamily B member 1	ABCB1	HGNC:40
3	ATP binding cassette subfamily C member 1 (ABCC1 blood group)	ABCC1	HGNC:51
4	ATP binding cassette subfamily C member 4 (PEL blood group)	ABCC4	HGNC:55
5	ATP binding cassette subfamily G member 2 (JR blood group)	ABCG2	HGNC:74
6	ABL proto-oncogene 1, non-receptor tyrosine kinase	ABL1	HGNC:76
7	Abraxas 1, BRCA1 A complex subunit	ABRAXAS1	HGNC:25829
8	Actin alpha 2, smooth muscle	ACTA2	HGNC:130
9	Actin beta	ACTB	HGNC:132
10	Actin alpha cardiac muscle 1	ACTC1	HGNC:143
11	ADAM metalloproteinase domain 17	ADAM17	HGNC:195
12	Adrenoceptor beta 2	ADRB2	HGNC:286
13	Argonaute RISC catalytic component 2	AGO2	HGNC:3263
14	Aryl hydrocarbon receptor	AHR	HGNC:348
15	AKT serine/threonine kinase 1	AKT1	HGNC:391
16	AKT serine/threonine kinase 2	AKT2	HGNC:392
17	AKT serine/threonine kinase 3	AKT3	HGNC:393
18	Angiopoietin 1	ANGPT1	HGNC:484
19	Angiopoietin 2	ANGPT2	HGNC:485
20	APC regulator of Wnt signaling pathway	APC	HGNC:583
21	Androgen receptor	AR	HGNC:644
22	Amphiregulin	AREG	HGNC:651
23	AT-rich interaction domain 1A	ARID1A	HGNC:11110
24	ATM serine/threonine kinase	ATM	HGNC:795
25	ATPase copper transporting beta	ATP7B	HGNC:870
26	ATR checkpoint kinase	ATR	HGNC:882
27	Aurora kinase A	AURKA	HGNC:11393
28	AXL receptor tyrosine kinase	AXL	HGNC:905
29	BCL2 antagonist/killer 1	BAK1	HGNC:949
30	BRAF-activated non-protein coding RNA	BANCR	HGNC:43877

(Continued)

Supplementary Table 4: (Continued)

S. no.	Gene name	Gene symbol	HGNC ID
31	BRCA1 associated deubiquitinase 1	BAP1	HGNC:950
32	BRCA1 associated RING domain 1	BARD1	HGNC:952
33	BCL2 associated X, apoptosis regulator	BAX	HGNC:959
34	BCAR1 scaffold protein, Cas family member	BCAR1	HGNC:971
35	BCAR3 adaptor protein, NSP family member	BCAR3	HGNC:973
36	Brain enriched myelin associated protein 1	BCAS1	HGNC:974
37	BCL2 apoptosis regulator	BCL2	HGNC:990
38	BCL2 like 1	BCL2L1	HGNC:992
39	Brain cytoplasmic RNA 1	BCYRN1	HGNC:1022
40	Baculoviral IAP repeat containing 3	BIRC3	HGNC:591
41	Baculoviral IAP repeat containing 5	BIRC5	HGNC:593
42	BLM RecQ like helicase	BLM	HGNC:1058
43	Bridge-like lipid transfer protein family member 2	BLTP2	HGNC:28960
44	BMI1 proto-oncogene, polycomb ring finger	BMI1	HGNC:1066
45	Bone morphogenetic protein 4	BMP4	HGNC:1071
46	Bone morphogenetic protein 6	BMP6	HGNC:1073
47	Bone morphogenetic protein receptor type 1A	BMPRI1A	HGNC:1076
48	B-Raf proto-oncogene, serine/threonine kinase	BRAF	HGNC:1097
49	BRCA1 DNA repair associated	BRCA1	HGNC:1100
50	BRCA2 DNA repair associated	BRCA2	HGNC:1101
51	BRCA1 interacting DNA helicase 1	BRIP1	HGNC:20473
52	BRMS1 transcriptional repressor and anoikis regulator	BRMS1	HGNC:17262
53	BUB1 mitotic checkpoint serine/threonine kinase	BUB1	HGNC:1148
54	BUB1 mitotic checkpoint serine/threonine kinase B	BUB1B	HGNC:1149
55	Calcium voltage-gated channel auxiliary subunit alpha2delta 1	CACNA2D1	HGNC:1399
56	Cancer susceptibility 15	CASC15	HGNC:28245
57	Caspase 10	CASP10	HGNC:1500
58	Caspase 3	CASP3	HGNC:1504
59	Caspase 8	CASP8	HGNC:1509
60	Caspase 9	CASP9	HGNC:1511
61	Caveolin 1	CAV1	HGNC:1527
62	Core-binding factor subunit beta	CBFB	HGNC:1539
63	Cbl proto-oncogene	CBL	HGNC:1541
64	C-C motif chemokine ligand 2	CCL2	HGNC:10618
65	Cyclin A2	CCNA2	HGNC:1578
66	Cyclin B1	CCNB1	HGNC:1579
67	Cyclin D1	CCND1	HGNC:1582
68	Cyclin D2	CCND2	HGNC:1583
69	Cyclin D3	CCND3	HGNC:1585
70	Cyclin E1	CCNE1	HGNC:1589
71	CD274 molecule	CD274	HGNC:17635

(Continued)

Supplementary Table 4: (Continued)

S. no.	Gene name	Gene symbol	HGNC ID
72	CD3 gamma subunit of T-cell receptor complex	CD3G	HGNC:1675
73	CD44 molecule (IN blood group)	CD44	HGNC:1681
74	CD82 molecule	CD82	HGNC:6210
75	Cell division cycle 25A	CDC25A	HGNC:1725
76	Cell division cycle 73	CDC73	HGNC:16783
77	Cadherin 1	CDH1	HGNC:1748
78	Cadherin 3	CDH3	HGNC:1762
79	Cyclin dependent kinase 1	CDK1	HGNC:1722
80	Cyclin dependent kinase 2	CDK2	HGNC:1771
81	Cyclin dependent kinase 4	CDK4	HGNC:1773
82	Cyclin dependent kinase 6	CDK6	HGNC:1777
83	Cyclin dependent kinase inhibitor 1A	CDKN1A	HGNC:1784
84	Cyclin dependent kinase inhibitor 1B	CDKN1B	HGNC:1785
85	Cyclin dependent kinase inhibitor 1C	CDKN1C	HGNC:1786
86	Cyclin dependent kinase inhibitor 2A	CDKN2A	HGNC:1787
87	Cyclin dependent kinase inhibitor 2B	CDKN2B	HGNC:1788
88	Cyclin dependent kinase inhibitor 2C	CDKN2C	HGNC:1789
89	Cyclin dependent kinase inhibitor 3	CDKN3	HGNC:1791
90	CEA cell adhesion molecule 5	CEACAM5	HGNC:1817
91	CCAAT enhancer binding protein alpha	CEBPA	HGNC:1833
92	CF transmembrane conductance regulator	CFTR	HGNC:1884
93	Checkpoint kinase 1	CHEK1	HGNC:1925
94	Checkpoint kinase 2	CHEK2	HGNC:16627
95	Cholinergic receptor nicotinic alpha 7 subunit	CHRNA7	HGNC:1960
96	CDC28 protein kinase regulatory subunit 1B	CKS1B	HGNC:19083
97	Collagen type III alpha 1 chain	COL3A1	HGNC:2201
98	Catechol-O-methyltransferase	COMT	HGNC:2228
99	cAMP responsive element binding protein 1	CREB1	HGNC:2345
100	CREB binding lysine acetyltransferase	CREBBP	HGNC:2348
101	Colorectal neoplasia differentially expressed	CRNDE	HGNC:37078
102	Colony stimulating factor 1	CSF1	HGNC:2432
103	Colony stimulating factor 1 receptor	CSF1R	HGNC:2433
104	Colony stimulating factor 2	CSF2	HGNC:2434
105	CCCTC-binding factor	CTCF	HGNC:13723
106	Cytotoxic T-lymphocyte associated protein 4	CTLA4	HGNC:2505
107	Catenin alpha 1	CTNNA1	HGNC:2509
108	Catenin beta 1	CTNNB1	HGNC:2514
109	Cathepsin D	CTSD	HGNC:2529
110	C-X-C motif chemokine ligand 12	CXCL12	HGNC:10672
111	C-X-C motif chemokine ligand 8	CXCL8	HGNC:6025
112	C-X-C motif chemokine receptor 4	CXCR4	HGNC:2561

(Continued)

Supplementary Table 4: (Continued)

S. no.	Gene name	Gene symbol	HGNC ID
113	Cytochrome c, somatic	CYCS	HGNC:19986
114	CYLD lysine 63 deubiquitinase	CYLD	HGNC:2584
115	Cytochrome P450 family 1 subfamily A member 1	CYP1A1	HGNC:2595
116	Cytochrome P450 family 1 subfamily B member 1	CYP1B1	HGNC:2597
117	Cytochrome P450 family 2 subfamily D member 6 (gene/pseudogene)	CYP2D6	HGNC:2625
118	Cytoskeleton regulator RNA	CYTOR	HGNC:28717
119	DCC netrin 1 receptor	DCC	HGNC:2701
120	Dynactin subunit 5	DCTN5	HGNC:24594
121	Damage specific DNA binding protein 2	DDB2	HGNC:2718
122	Discoidin domain receptor tyrosine kinase 1	DDR1	HGNC:2730
123	DEAD-box helicase 5	DDX5	HGNC:2746
124	Dihydrofolate reductase	DHFR	HGNC:2861
125	Dicer 1, ribonuclease III	DICER1	HGNC:17098
126	DIS3 like 3'-5' exoribonuclease 2	DIS3L2	HGNC:28648
127	DLC1 Rho GTPase activating protein	DLC1	HGNC:2897
128	DNA methyltransferase 1	DNMT1	HGNC:2976
129	DNA methyltransferase 3 alpha	DNMT3A	HGNC:2978
130	DNA methyltransferase 3 beta	DNMT3B	HGNC:2979
131	Dihydropyrimidine dehydrogenase	DPYD	HGNC:3012
132	Drosha ribonuclease III	DROSHA	HGNC:17904
133	Desmoglein 2	DSG2	HGNC:3049
134	Desmoplakin	DSP	HGNC:3052
135	E2F transcription factor 1	E2F1	HGNC:3113
136	E2F transcription factor 4	E2F4	HGNC:3118
137	Ephrin A3	EFNA3	HGNC:3223
138	Epidermal growth factor	EGF	HGNC:3229
139	Epidermal growth factor receptor	EGFR	HGNC:3236
140	ELAV like RNA binding protein 1	ELAVL1	HGNC:3312
141	Endoglin	ENG	HGNC:3349
142	EP300 lysine acetyltransferase	EP300	HGNC:3373
143	Epithelial cell adhesion molecule	EPCAM	HGNC:11529
144	EPH receptor A2	EPHA2	HGNC:3386
145	EPH receptor B2	EPHB2	HGNC:3393
146	EPH receptor B4	EPHB4	HGNC:3395
147	erb-b2 receptor tyrosine kinase 2	ERBB2	HGNC:3430
148	erb-b2 receptor tyrosine kinase 3	ERBB3	HGNC:3431
149	erb-b2 receptor tyrosine kinase 4	ERBB4	HGNC:3432
150	ERCC excision repair 1, endonuclease non-catalytic subunit	ERCC1	HGNC:3433
151	ERCC excision repair 2, TFIIH core complex helicase subunit	ERCC2	HGNC:3434
152	ERCC excision repair 3, TFIIH core complex helicase subunit	ERCC3	HGNC:3435
153	ERCC excision repair 4, endonuclease catalytic subunit	ERCC4	HGNC:3436

(Continued)

Supplementary Table 4: (Continued)

S. no.	Gene name	Gene symbol	HGNC ID
154	ERCC excision repair 5, endonuclease	ERCC5	HGNC:3437
155	ERCC excision repair 6, chromatin remodeling factor	ERCC6	HGNC:3438
156	Endogenous retrovirus group 48 member 1, envelope	ERVH48-1	HGNC:17216
157	Estrogen receptor 2	ESR2	HGNC:3468
158	ETS proto-oncogene 1, transcription factor	ETS1	HGNC:3488
159	Exocyst complex component 2	EXOC2	HGNC:24968
160	Exostosin glycosyltransferase 1	EXT1	HGNC:3512
161	Enhancer of zeste 2 polycomb repressive complex 2 subunit	EZH2	HGNC:3527
162	FA complementation group A	FANCA	HGNC:3582
163	FA complementation group B	FANCB	HGNC:3583
164	FA complementation group C	FANCC	HGNC:3584
165	FA complementation group D2	FANCD2	HGNC:3585
166	FA complementation group I	FANCI	HGNC:25568
167	FA complementation group L	FANCL	HGNC:20748
168	Fas cell surface death receptor	FAS	HGNC:11920
169	Fas ligand	FASLG	HGNC:11936
170	Fatty acid synthase	FASN	HGNC:3594
171	Fibrillin 1	FBN1	HGNC:3603
172	F-box protein 32	FBXO32	HGNC:16731
173	F-box and WD repeat domain containing 7	FBXW7	HGNC:16712
174	Fibroblast growth factor 2	FGF2	HGNC:3676
175	Fibroblast growth factor receptor 1	FGFR1	HGNC:3688
176	Fibroblast growth factor receptor 2	FGFR2	HGNC:3689
177	Fibroblast growth factor receptor 3	FGFR3	HGNC:3690
178	Fibroblast growth factor receptor 4	FGFR4	HGNC:3691
179	Fumarate hydratase	FH	HGNC:3700
180	Fragile histidine triad diadenosine triphosphatase	FHIT	HGNC:3701
181	Folliculin	FLCN	HGNC:27310
182	Fms related receptor tyrosine kinase 1	FLT1	HGNC:3763
183	Fms related receptor tyrosine kinase 3	FLT3	HGNC:3765
184	Fms related receptor tyrosine kinase 4	FLT4	HGNC:3767
185	Fibronectin 1	FN1	HGNC:3778
186	Fos proto-oncogene, AP-1 transcription factor subunit	FOS	HGNC:3796
187	Forkhead box A1	FOXA1	HGNC:5021
188	Forkhead box M1	FOXM1	HGNC:3818
189	Forkhead box O1	FOXO1	HGNC:3819
190	Forkhead box O3	FOXO3	HGNC:3821
191	Polypeptide N-acetylgalactosaminyltransferase 12	GALNT12	HGNC:19877
192	Growth arrest specific 5	GAS5	HGNC:16355
193	GATA binding protein 2	GATA2	HGNC:4171
194	GATA binding protein 3	GATA3	HGNC:4172

(Continued)

Supplementary Table 4: (Continued)

S. no.	Gene name	Gene symbol	HGNC ID
195	Glutaminase	GLS	HGNC:4331
196	GNAS complex locus	GNAS	HGNC:4392
197	Gonadotropin releasing hormone 1	GNRH1	HGNC:4419
198	Glypican 3	GPC3	HGNC:4451
199	G protein-coupled estrogen receptor 1	GPBR1	HGNC:4485
200	G protein signaling modulator 2	GPSM2	HGNC:29501
201	Growth factor receptor bound protein 2	GRB2	HGNC:4566
202	Growth regulating estrogen receptor binding 1	GREB1	HGNC:24885
203	Gremlin 1, DAN family BMP antagonist	GREM1	HGNC:2001
204	Glycogen synthase kinase 3 beta	GSK3B	HGNC:4617
205	Glutathione S-transferase mu 1	GSTM1	HGNC:4632
206	Glutathione S-transferase pi 1	GSTP1	HGNC:4638
207	Glutathione S-transferase theta 1	GSTT1	HGNC:4641
208	H19 imprinted maternally expressed transcript	H19	HGNC:4713
209	HOXD antisense growth-associated long non-coding RNA	HAGLR	HGNC:43755
210	Histone deacetylase 1	HDAC1	HGNC:4852
211	Histone deacetylase 4	HDAC4	HGNC:14063
212	Homeostatic iron regulator	HFE	HGNC:4886
213	Hepatocyte growth factor	HGF	HGNC:4893
214	Hypoxia inducible factor 1 subunit alpha	HIF1A	HGNC:4910
215	HIF1A antisense RNA 2	HIF1A-AS2	HGNC:43015
216	High mobility group AT-hook 2	HMG2	HGNC:5009
217	Hyaluronan mediated motility receptor	HMMR	HGNC:5012
218	HNF1 homeobox A	HNF1A	HGNC:11621
219	HOX transcript antisense RNA	HOTAIR	HGNC:33510
220	HOXA cluster antisense RNA 2	HOXA-AS2	HGNC:43745
221	Homeobox B13	HOXB13	HGNC:5112
222	HR lysine demethylase and nuclear receptor corepressor	HR	HGNC:5172
223	HRas proto-oncogene, GTPase	HRAS	HGNC:5173
224	Hydroxysteroid 17-beta dehydrogenase 1	HSD17B1	HGNC:5210
225	Heat shock protein 90 alpha family class A member 1	HSP90AA1	HGNC:5253
226	Heat shock protein family B (small) member 1	HSPB1	HGNC:5246
227	Intercellular adhesion molecule 1	ICAM1	HGNC:5344
228	Isocitrate dehydrogenase (NADP(+)) 1	IDH1	HGNC:5382
229	Isocitrate dehydrogenase (NADP(+)) 2	IDH2	HGNC:5383
230	Interferon gamma	IFNG	HGNC:5438
231	Insulin like growth factor 1 receptor	IGF1R	HGNC:5465
232	Insulin like growth factor 2	IGF2	HGNC:5466
233	Insulin like growth factor 2 receptor	IGF2R	HGNC:5467
234	Insulin like growth factor binding protein 3	IGFBP3	HGNC:5472
235	Interleukin 10	IL10	HGNC:5962

(Continued)

Supplementary Table 4: (Continued)

S. no.	Gene name	Gene symbol	HGNC ID
236	Interleukin 12B	IL12B	HGNC:5970
237	Interleukin 1 beta	IL1B	HGNC:5992
238	Interleukin 1 receptor antagonist	IL1RN	HGNC:6000
239	Interleukin 2	IL2	HGNC:6001
240	Interleukin 6	IL6	HGNC:6018
241	Interleukin 7 receptor	IL7R	HGNC:6024
242	Inosine monophosphate dehydrogenase 1	IMPDH1	HGNC:6052
243	Insulin	INS	HGNC:6081
244	Interferon regulatory factor 1	IRF1	HGNC:6116
245	Insulin receptor substrate 1	IRS1	HGNC:6125
246	Itchy E3 ubiquitin protein ligase	ITCH	HGNC:13890
247	Integrin subunit beta 1	ITGB1	HGNC:6153
248	Janus kinase 1	JAK1	HGNC:6190
249	Janus kinase 2	JAK2	HGNC:6192
250	Jun proto-oncogene, AP-1 transcription factor subunit	JUN	HGNC:6204
251	KCNQ1 opposite strand/antisense transcript 1	KCNQ1OT1	HGNC:6295
252	Lysine demethylase 4B	KDM4B	HGNC:29136
253	Lysine demethylase 6A	KDM6A	HGNC:12637
254	Kinase insert domain receptor	KDR	HGNC:6307
255	Kelch like ECH associated protein 1	KEAP1	HGNC:23177
256	KISS-1 metastasis suppressor	KISS1	HGNC:6341
257	KIT proto-oncogene, receptor tyrosine kinase	KIT	HGNC:6342
258	KIT ligand	KITLG	HGNC:6343
259	kinesin light chain 1	KLC1	HGNC:6387
260	KLF3 antisense RNA 1	KLF3-AS1	HGNC:25796
261	KLF transcription factor 4	KLF4	HGNC:6348
262	KLF transcription factor 6	KLF6	HGNC:2235
263	Kallikrein related peptidase 3	KLK3	HGNC:6364
264	Lysine methyltransferase 2A	KMT2A	HGNC:7132
265	Lysine methyltransferase 2C	KMT2C	HGNC:13726
266	Lysine methyltransferase 2D	KMT2D	HGNC:7133
267	KRas proto-oncogene, GTPase	KRAS	HGNC:6407
268	Keratin 18	KRT18	HGNC:6430
269	Keratin 19	KRT19	HGNC:6436
270	Keratin 20	KRT20	HGNC:20412
271	Keratin 5	KRT5	HGNC:6442
272	Keratin 7	KRT7	HGNC:6445
273	Keratin 8	KRT8	HGNC:6446
274	Lymphocyte cytosolic protein 1	LCP1	HGNC:6528
275	Low density lipoprotein receptor	LDLR	HGNC:6547
276	Lymphoid enhancer binding factor 1	LEF1	HGNC:6551

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Supplementary Table 4: (Continued)

S. no.	Gene name	Gene symbol	HGNC ID
277	Leptin	LEP	HGNC:6553
278	Leptin receptor	LEPR	HGNC:6554
279	Long independently transcribed non-coding RNA 472	LINC00472	HGNC:21380
280	Long independently transcribed non-coding RNA 1116	LINC01116	HGNC:49259
281	LDL receptor related protein 1B	LRP1B	HGNC:6693
282	Lung cancer associated transcript 1	LUCAT1	HGNC:48498
283	Metastasis associated lung adenocarcinoma transcript 1	MALAT1	HGNC:29665
284	Mitogen-activated protein kinase kinase 1	MAP2K1	HGNC:6840
285	Mitogen-activated protein kinase kinase 2	MAP2K2	HGNC:6842
286	Mitogen-activated protein kinase kinase 4	MAP2K4	HGNC:6844
287	Mitogen-activated protein kinase kinase kinase 1	MAP3K1	HGNC:6848
288	Mitogen-activated protein kinase kinase kinase 6	MAP3K6	HGNC:6858
289	Mitogen-activated protein kinase 1	MAPK1	HGNC:6871
290	Mitogen-activated protein kinase 10	MAPK10	HGNC:6872
291	Mitogen-activated protein kinase 14	MAPK14	HGNC:6876
292	Mitogen-activated protein kinase 8	MAPK8	HGNC:6881
293	MYC associated transcriptional regulator X	MAX	HGNC:6913
294	Melanocortin 1 receptor	MC1R	HGNC:6929
295	Melanocortin 4 receptor	MC4R	HGNC:6932
296	MCL1 apoptosis regulator, BCL2 family member	MCL1	HGNC:6943
297	MDM2 proto-oncogene	MDM2	HGNC:6973
298	MDM4 regulator of p53	MDM4	HGNC:6974
299	Mediator complex subunit 1	MED1	HGNC:9234
300	Mediator complex subunit 12	MED12	HGNC:11957
301	Maternally expressed 3	MEG3	HGNC:14575
302	Maternal embryonic leucine zipper kinase	MELK	HGNC:16870
303	Menin 1	MEN1	HGNC:7010
304	MET proto-oncogene, receptor tyrosine kinase	MET	HGNC:7029
305	O-6-methylguanine-DNA methyltransferase	MGMT	HGNC:7059
306	Myocardial infarction associated transcript	MIAT	HGNC:33425
307	microRNA 106b	MIR106B	HGNC:31495
308	microRNA 10b	MIR10B	HGNC:31498
309	microRNA 125a	MIR125A	HGNC:31505
310	microRNA 126	MIR126	HGNC:31508
311	microRNA 127	MIR127	HGNC:31509
312	microRNA 132	MIR132	HGNC:31516
313	microRNA 135b	MIR135B	HGNC:31760
314	microRNA 139	MIR139	HGNC:31526
315	microRNA 141	MIR141	HGNC:31528
316	microRNA 143	MIR143	HGNC:31530
317	microRNA 146a	MIR146A	HGNC:31533

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Supplementary Table 4: (Continued)

S. no.	Gene name	Gene symbol	HGNC ID
318	microRNA 149	MIR149	HGNC:31536
319	microRNA 15a	MIR15A	HGNC:31543
320	microRNA 15b	MIR15B	HGNC:31544
321	microRNA 17	MIR17	HGNC:31547
322	microRNA 182	MIR182	HGNC:31553
323	microRNA 183	MIR183	HGNC:31554
324	microRNA 192	MIR192	HGNC:31562
325	microRNA 196b	MIR196B	HGNC:31790
326	microRNA 200a	MIR200A	HGNC:31578
327	microRNA 200b	MIR200B	HGNC:31579
328	microRNA 200c	MIR200C	HGNC:31580
329	microRNA 20a	MIR20A	HGNC:31577
330	microRNA 21	MIR21	HGNC:31586
331	microRNA 210	MIR210	HGNC:31587
332	microRNA 22	MIR22	HGNC:31599
333	microRNA 221	MIR221	HGNC:31601
334	microRNA 24-1	MIR24-1	HGNC:31607
335	microRNA 25	MIR25	HGNC:31609
336	microRNA 30a	MIR30A	HGNC:31624
337	microRNA 30b	MIR30B	HGNC:31625
338	microRNA 30e	MIR30E	HGNC:31629
339	microRNA 320a	MIR320A	HGNC:31632
340	microRNA 342	MIR342	HGNC:31778
341	microRNA 34a	MIR34A	HGNC:31635
342	microRNA 34b	MIR34B	HGNC:31636
343	microRNA 34c	MIR34C	HGNC:31637
344	microRNA 424	MIR424	HGNC:31881
345	microRNA 425	MIR425	HGNC:31882
346	microRNA 494	MIR494	HGNC:32084
347	microRNA 497	MIR497	HGNC:32088
348	microRNA 542	MIR542	HGNC:32534
349	MIR7-3 host gene	MIR7-3HG	HGNC:30049
350	microRNA 92a-1	MIR92A1	HGNC:31643
351	microRNA 93	MIR93	HGNC:31645
352	microRNA 96	MIR96	HGNC:31648
353	microRNA 98	MIR98	HGNC:31649
354	microRNA 99a	MIR99A	HGNC:31650
355	microRNA let-7b	MIRLET7B	HGNC:31479
356	microRNA let-7d	MIRLET7D	HGNC:31481
357	microRNA let-7e	MIRLET7E	HGNC:31482
358	microRNA let-7g	MIRLET7G	HGNC:31485

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Supplementary Table 4: (Continued)

S. no.	Gene name	Gene symbol	HGNC ID
359	Melanocyte inducing transcription factor	MITF	HGNC:7105
360	Marker of proliferation Ki-67	MKI67	HGNC:7107
361	MutL homolog 1	MLH1	HGNC:7127
362	MutL homolog 3	MLH3	HGNC:7128
363	Matrix metalloproteinase 1	MMP1	HGNC:7155
364	Matrix metalloproteinase 14	MMP14	HGNC:7160
365	Matrix metalloproteinase 2	MMP2	HGNC:7166
366	Matrix metalloproteinase 7	MMP7	HGNC:7174
367	Matrix metalloproteinase 9	MMP9	HGNC:7176
368	MRE11 double strand break repair nuclease	MRE11	HGNC:7230
369	MutS homolog 2	MSH2	HGNC:7325
370	MutS homolog 6	MSH6	HGNC:7329
371	Macrophage scavenger receptor 1	MSR1	HGNC:7376
372	Metastasis associated 1	MTA1	HGNC:7410
373	Methylenetetrahydrofolate reductase	MTHFR	HGNC:7436
374	Mechanistic target of rapamycin kinase	MTOR	HGNC:3942
375	5-methyltetrahydrofolate-homocysteine methyltransferase	MTR	HGNC:7468
376	Mucin 1, cell surface associated	MUC1	HGNC:7508
377	Mucin 16, cell surface associated	MUC16	HGNC:15582
378	MAX interactor 1, dimerization protein	MXI1	HGNC:7534
379	MYB proto-oncogene, transcription factor	MYB	HGNC:7545
380	MYC proto-oncogene, bHLH transcription factor	MYC	HGNC:7553
381	N-acetyltransferase 2	NAT2	HGNC:7646
382	Nibrin	NBN	HGNC:7652
383	Nuclear receptor coactivator 3	NCOA3	HGNC:7670
384	Nuclear receptor corepressor 1	NCOR1	HGNC:7672
385	Nuclear receptor corepressor 2	NCOR2	HGNC:7673
386	Nuclear paraspeckle assembly transcript 1	NEAT1	HGNC:30815
387	NIMA related kinase 2	NEK2	HGNC:7745
388	neurofibromin 1	NF1	HGNC:7765
389	NFE2 like bZIP transcription factor 2	NFE2L2	HGNC:7782
390	Nuclear factor kappa B subunit 1	NFKB1	HGNC:7794
391	NFKB inhibitor alpha	NFKBIA	HGNC:7797
392	NK2 homeobox 1	NKX2-1	HGNC:11825
393	NME/NM23 nucleoside diphosphate kinase 1	NME1	HGNC:7849
394	NNT antisense RNA 1	NNT-AS1	HGNC:49005
395	Nitric oxide synthase 2	NOS2	HGNC:7873
396	Notch receptor 1	NOTCH1	HGNC:7881
397	Notch receptor 2	NOTCH2	HGNC:7882
398	Notch receptor 3	NOTCH3	HGNC:7883
399	Nucleophosmin 1	NPM1	HGNC:7910

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Supplementary Table 4: (Continued)

S. no.	Gene name	Gene symbol	HGNC ID
400	NAD(P)H quinone dehydrogenase 1	NQO1	HGNC:2874
401	N-ribosyldihydronicotinamide:quinone dehydrogenase 2	NQO2	HGNC:7856
402	Nuclear receptor subfamily 3 group C member 1	NR3C1	HGNC:7978
403	NRAS proto-oncogene, GTPase	NRAS	HGNC:7989
404	Neuregulin 1	NRG1	HGNC:7997
405	Nth like DNA glycosylase 1	NTHL1	HGNC:8028
406	Neurotrophic receptor tyrosine kinase 1	NTRK1	HGNC:8031
407	Neurotrophic receptor tyrosine kinase 2	NTRK2	HGNC:8032
408	Neurotrophic receptor tyrosine kinase 3	NTRK3	HGNC:8033
409	Ornithine decarboxylase 1	ODC1	HGNC:8109
410	8-oxoguanine DNA glycosylase	OGG1	HGNC:8125
411	Phenylalanine hydroxylase	PAH	HGNC:8582
412	p21 (RAC1) activated kinase 1	PAK1	HGNC:8590
413	Partner and localizer of BRCA2	PALB2	HGNC:26144
414	Palladin, cytoskeletal associated protein	PALLD	HGNC:17068
415	Poly(ADP-ribose) polymerase 1	PARP1	HGNC:270
416	Polybromo 1	PBRM1	HGNC:30064
417	Polycomb group ring finger 2	PCGF2	HGNC:12929
418	Proliferating cell nuclear antigen	PCNA	HGNC:8729
419	Programmed cell death 1	PDCD1	HGNC:8760
420	Platelet derived growth factor subunit B	PDGFB	HGNC:8800
421	Platelet derived growth factor receptor alpha	PDGFRA	HGNC:8803
422	Prohibitin 1	PHB1	HGNC:8912
423	Paired like homeobox 2B	PHOX2B	HGNC:9143
424	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	PIK3CA	HGNC:8975
425	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta	PIK3CB	HGNC:8976
426	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta	PIK3CD	HGNC:8977
427	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma	PIK3CG	HGNC:8978
428	Phosphoinositide-3-kinase regulatory subunit 1	PIK3R1	HGNC:8979
429	Phosphoinositide-3-kinase regulatory subunit 2	PIK3R2	HGNC:8980
430	Pyruvate kinase M1/2	PKM	HGNC:9021
431	Plasminogen activator, urokinase	PLAU	HGNC:9052
432	Plasminogen activator, urokinase receptor	PLAUR	HGNC:9053
433	Polo like kinase 1	PLK1	HGNC:9077
434	PML nuclear body scaffold	PML	HGNC:9113
435	PMS1 homolog 1, mismatch repair system component	PMS1	HGNC:9121
436	PMS1 homolog 2, mismatch repair system component	PMS2	HGNC:9122
437	DNA polymerase delta 1, catalytic subunit	POLD1	HGNC:9175
438	DNA polymerase epsilon, catalytic subunit	POLE	HGNC:9177
439	Protection of telomeres 1	POT1	HGNC:17284
440	POU class 5 homeobox 1	POU5F1	HGNC:9221

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Supplementary Table 4: (Continued)

S. no.	Gene name	Gene symbol	HGNC ID
441	Peroxisome proliferator activated receptor gamma	PPARG	HGNC:9236
442	Protein phosphatase, Mg ²⁺ /Mn ²⁺ dependent 1D	PPM1D	HGNC:9277
443	Protein phosphatase, Mg ²⁺ /Mn ²⁺ dependent 1L	PPM1L	HGNC:16381
444	Protein phosphatase 2 scaffold subunit Abeta	PPP2R1B	HGNC:9303
445	Protein phosphatase 2 regulatory subunit Balpha	PPP2R2A	HGNC:9304
446	Protein regulator of cytokinesis 1	PRC1	HGNC:9341
447	Protein kinase cAMP-activated catalytic subunit alpha	PRKACA	HGNC:9380
448	Protein kinase cAMP-dependent type I regulatory subunit alpha	PRKAR1A	HGNC:9388
449	Protein kinase C alpha	PRKCA	HGNC:9393
450	Protein kinase, DNA-activated, catalytic subunit	PRKDC	HGNC:9413
451	Parkin RBR E3 ubiquitin protein ligase	PRKN	HGNC:8607
452	Prolactin receptor	PRLR	HGNC:9446
453	Phosphatase and tensin homolog	PTEN	HGNC:9588
454	Prostaglandin F receptor	PTGFR	HGNC:9600
455	Prostaglandin-endoperoxide synthase 2	PTGS2	HGNC:9605
456	Parathyroid hormone like hormone	PTH1H	HGNC:9607
457	Protein tyrosine kinase 2	PTK2	HGNC:9611
458	Protein tyrosine phosphatase non-receptor type 11	PTPN11	HGNC:9644
459	Protein tyrosine phosphatase non-receptor type 3	PTPN3	HGNC:9655
460	RAB, member of RAS oncogene family like 3	RABL3	HGNC:18072
461	Rac family small GTPase 1	RAC1	HGNC:9801
462	RAD50 double strand break repair protein	RAD50	HGNC:9816
463	RAD51 recombinase	RAD51	HGNC:9817
464	RAD51 paralog B	RAD51B	HGNC:9822
465	RAD51 paralog C	RAD51C	HGNC:9820
466	RAD54 like	RAD54L	HGNC:9826
467	Raf-1 proto-oncogene, serine/threonine kinase	RAF1	HGNC:9829
468	Retinoic acid receptor alpha	RARA	HGNC:9864
469	Ras association domain family member 1	RASSF1	HGNC:9882
470	RB transcriptional corepressor 1	RB1	HGNC:9884
471	RB1 inducible coiled-coil 1	RB1CC1	HGNC:15574
472	RB binding protein 8, endonuclease	RBBP8	HGNC:9891
473	Reversion inducing cysteine rich protein with kazal motifs	RECK	HGNC:11345
474	RecQ like helicase	RECQL	HGNC:9948
475	RecQ like helicase 4	RECQL4	HGNC:9949
476	RELA proto-oncogene, NF-kB subunit	RELA	HGNC:9955
477	RE1 silencing transcription factor	REST	HGNC:9966
478	Ret proto-oncogene	RET	HGNC:9967
479	Rhomoid 5 homolog 2	RHBDF2	HGNC:20788
480	Ras homolog family member A	RHOA	HGNC:667
481	Rho related BTB domain containing 2	RHOBTB2	HGNC:18756

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Supplementary Table 4: (Continued)

S. no.	Gene name	Gene symbol	HGNC ID
482	RAD50 interactor 1	RINT1	HGNC:21876
483	Receptor interacting serine/threonine kinase 1	RIPK1	HGNC:10019
484	Rhabdomyosarcoma 2 associated transcript	RMST	HGNC:29893
485	Ribonuclease L	RNASEL	HGNC:10050
486	Ring finger protein 43	RNF43	HGNC:18505
487	Ribosomal protein S6 kinase B1	RPS6KB1	HGNC:10436
488	RUNX family transcription factor 1	RUNX1	HGNC:10471
489	S100 calcium binding protein A4	S100A4	HGNC:10494
490	Succinate dehydrogenase complex flavoprotein subunit A	SDHA	HGNC:10680
491	Succinate dehydrogenase complex assembly factor 2	SDHAF2	HGNC:26034
492	Succinate dehydrogenase complex iron sulfur subunit B	SDHB	HGNC:10681
493	Succinate dehydrogenase complex subunit C	SDHC	HGNC:10682
494	Succinate dehydrogenase complex subunit D	SDHD	HGNC:10683
495	Septin 9	SEPTIN9	HGNC:7323
496	Serpin family E member 1	SERPINE1	HGNC:8583
497	SET domain containing 2, histone lysine methyltransferase	SETD2	HGNC:18420
498	SHC adaptor protein 1	SHC1	HGNC:10840
499	S-phase kinase associated protein 2	SKP2	HGNC:10901
500	Solute carrier family 19 member 1	SLC19A1	HGNC:10937
501	Solute carrier family 2 member 1	SLC2A1	HGNC:11005
502	Solute carrier family 39 member 6	SLC39A6	HGNC:18607
503	SLX4 structure-specific endonuclease subunit	SLX4	HGNC:23845
504	SMAD family member 2	SMAD2	HGNC:6768
505	SMAD family member 3	SMAD3	HGNC:6769
506	SMAD family member 4	SMAD4	HGNC:6770
507	SMAD family member 7	SMAD7	HGNC:6773
508	SWI/SNF related BAF chromatin remodeling complex subunit ATPase 4	SMARCA4	HGNC:11100
509	SWI/SNF related BAF chromatin remodeling complex subunit B1	SMARCB1	HGNC:11103
510	SWI/SNF related BAF chromatin remodeling complex subunit E1	SMARCE1	HGNC:11109
511	Smoothed, frizzled class receptor	SMO	HGNC:11119
512	Snail family transcriptional repressor 1	SNAI1	HGNC:11128
513	Snail family transcriptional repressor 2	SNAI2	HGNC:11094
514	Small nucleolar RNA host gene 1	SNHG1	HGNC:32688
515	Small nucleolar RNA host gene 12	SNHG12	HGNC:30062
516	Small nucleolar RNA host gene 15	SNHG15	HGNC:27797
517	Small nucleolar RNA host gene 7	SNHG7	HGNC:28254
518	Suppressor of cytokine signaling 1	SOCS1	HGNC:19383
519	Superoxide dismutase 2	SOD2	HGNC:11180
520	SRY-box transcription factor 2	SOX2	HGNC:11195
521	SOX2 overlapping transcript	SOX2-OT	HGNC:20209
522	SRY-box transcription factor 9	SOX9	HGNC:11204

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Supplementary Table 4: (Continued)

S. no.	Gene name	Gene symbol	HGNC ID
523	Sp1 transcription factor	SP1	HGNC:11205
524	Spen family transcriptional repressor	SPEN	HGNC:17575
525	Secreted phosphoprotein 1	SPP1	HGNC:11255
526	ST8SIA6 antisense RNA 1	ST8SIA6-AS1	HGNC:44880
527	STAG2 cohesin complex component	STAG2	HGNC:11355
528	Signal transducer and activator of transcription 1	STAT1	HGNC:11362
529	Signal transducer and activator of transcription 3	STAT3	HGNC:11364
530	Signal transducer and activator of transcription 5B	STAT5B	HGNC:11367
531	Steroid sulfatase	STS	HGNC:11425
532	STXBP5 antisense RNA 1	STXBP5-AS1	HGNC:44183
533	SUFU negative regulator of hedgehog signaling	SUFU	HGNC:16466
534	T-box transcription factor 3	TBX3	HGNC:11602
535	Transcription factor 7 like 2	TCF7L2	HGNC:11641
536	TEK receptor tyrosine kinase	TEK	HGNC:11724
537	Telomerase reverse transcriptase	TERT	HGNC:11730
538	Transforming growth factor alpha	TGFA	HGNC:11765
539	Transforming growth factor beta 1	TGFB1	HGNC:11766
540	Transforming growth factor beta 2	TGFB2	HGNC:11768
541	Transforming growth factor beta receptor 1	TGFBR1	HGNC:11772
542	Transforming growth factor beta receptor 3	TGFBR3	HGNC:11774
543	Thrombospondin 1	THBS1	HGNC:11785
544	TIMP metalloproteinase inhibitor 1	TIMP1	HGNC:11820
545	TIMP metalloproteinase inhibitor 2	TIMP2	HGNC:11821
546	TIMP metalloproteinase inhibitor 3	TIMP3	HGNC:11822
547	Toll like receptor 4	TLR4	HGNC:11850
548	Transmembrane protein 127	TMEM127	HGNC:26038
549	Tumor necrosis factor	TNF	HGNC:11892
550	TNF receptor superfamily member 10b	TNFRSF10B	HGNC:11905
551	TNF superfamily member 10	TNFSF10	HGNC:11925
552	Tankyrase	TNKS	HGNC:11941
553	DNA topoisomerase I	TOP1	HGNC:11986
554	DNA topoisomerase II alpha	TOP2A	HGNC:11989
555	DNA topoisomerase II beta	TOP2B	HGNC:11990
556	Tumor protein p53	TP53	HGNC:11998
557	Tumor protein p53 binding protein 1	TP53BP1	HGNC:11999
558	Tumor protein p63	TP63	HGNC:15979
559	Tumor protein p73	TP73	HGNC:12003
560	Trophoblast glycoprotein	TPBG	HGNC:12004
561	Tropomyosin 1	TPM1	HGNC:12010
562	TNF receptor associated factor 5	TRAF5	HGNC:12035
563	Tripartite motif containing 24	TRIM24	HGNC:11812

(Continued)

Supplementary Table 4: (Continued)

S. no.	Gene name	Gene symbol	HGNC ID
564	TSC complex subunit 1	TSC1	HGNC:12362
565	TSC complex subunit 2	TSC2	HGNC:12363
566	Tumor susceptibility 101	TSG101	HGNC:15971
567	Thyroid stimulating hormone receptor	TSHR	HGNC:12373
568	Tubulin beta class I	TUBB	HGNC:20778
569	Taurine up-regulated 1	TUG1	HGNC:26066
570	Twist family bHLH transcription factor 1	TWIST1	HGNC:12428
571	Thymidine phosphorylase	TYMP	HGNC:3148
572	Thymidylate synthetase	TYMS	HGNC:12441
573	Urothelial cancer associated 1	UCA1	HGNC:37126
574	Ubiquitin interaction motif containing 1	UIMC1	HGNC:30298
575	Vitamin D receptor	VDR	HGNC:12679
576	Vascular endothelial growth factor A	VEGFA	HGNC:12680
577	Vascular endothelial growth factor C	VEGFC	HGNC:12682
578	von Hippel-Lindau tumor suppressor	VHL	HGNC:12687
579	Vimentin	VIM	HGNC:12692
580	WEE1 G2 checkpoint kinase	WEE1	HGNC:12761
581	Wnt family member 5A	WNT5A	HGNC:12784
582	WD repeat containing antisense to TP53	WRAP53	HGNC:25522
583	WRN RecQ like helicase	WRN	HGNC:12791
584	WT1 transcription factor	WT1	HGNC:12796
585	WW domain containing oxidoreductase	WWOX	HGNC:12799
586	X-box binding protein 1	XBP1	HGNC:12801
587	X-linked inhibitor of apoptosis	XIAP	HGNC:592
588	X inactive specific transcript	XIST	HGNC:12810
589	XPA, DNA damage recognition and repair factor	XPA	HGNC:12814
590	XPC complex subunit, DNA damage recognition and repair factor	XPC	HGNC:12816
591	X-ray repair cross complementing 1	XRCC1	HGNC:12828
592	X-ray repair cross complementing 2	XRCC2	HGNC:12829
593	X-ray repair cross complementing 3	XRCC3	HGNC:12830
594	Yes1 associated transcriptional regulator	YAP1	HGNC:16262
595	Zinc finger E-box binding homeobox 1	ZEB1	HGNC:11642
596	Zinc finger E-box binding homeobox 2	ZEB2	HGNC:14881
597	ZNFX1 antisense RNA 1	ZFAS1	HGNC:33101
598	Zinc finger homeobox 3	ZFHX3	HGNC:777
599	Zinc finger protein 226	ZNF226	HGNC:13019
600	Apurinic/apyrimidinic endodeoxyribonuclease 1	APEX1	HGNC:587

Supplementary Table 5: The DC, BC and CC values of the top 23 genes with high node degrees.

S. no.	Gene	Degree	Betweenness	Closeness
1	TP53	20	36.55488	0.9166667
2	CTNNB1	17	22.947418	0.8148148
3	STAT3	16	35.14751	0.78571427
4	EP300	15	6.983542	0.7586207
5	BRCA1	15	8.865761	0.7586207
6	JUN	15	6.3675547	0.7586207
7	HDAC1	14	7.10359	0.73333335
8	SMAD3	14	11.143892	0.73333335
9	FOXO3	14	9.667524	0.73333335
10	EGFR	14	30.097809	0.73333335
11	HIF1A	13	4.958153	0.7096774
12	CREBBP	13	3.048002	0.7096774
13	HSP90AA1	13	14.258073	0.7096774
14	CDK2	13	6.858516	0.6875
15	SMAD2	11	5.4929295	0.6666667
16	CDK4	11	5.385622	0.64705884
17	SMARCA4	10	3.1275735	0.62857145
18	ATM	10	4.311977	0.61111111
19	GRB2	7	6.6081953	0.5945946
20	CDKN1B	7	4.7634	0.5945946
21	PTPN11	6	3.5929294	0.5641026
22	CD44	6	0.7151515	0.57894737
23	SHC1	4	0	0.5

Supplementary Table 6: The DC, BC and CC values of the top 15 compounds with node degrees.

S. no.	Compound	Degree	Betweenness	Closeness
1	Norcepharadione B	16	0.044930636	0.569231
2	Piperine	10	0.007306859	0.480519
3	Aristolodione	18	0.084677764	0.606557
4	Aristolactam BII	12	0.021652833	0.506849
5	Piperlongumine	11	0.017921943	0.493333
6	Pluviatilol	15	0.034154909	0.55223881
7	Aristololactam	12	0.032323994	0.506849
8	Fargesin	11	0.012610539	0.49333333
9	Pellitorine	20	0.163497384	0.64912281
10	Aristolactam AII	18	0.085932008	0.60655738
11	Piperettine	10	0.007306859	0.48051948
12	Asarinine	11	0.012222268	0.49333333
13	Demethoxyplartine	10	0.015304632	0.480519
14	N-isobutyl decadienamide	15	0.058820693	0.552239
15	Sesamin	11	0.01244779	0.493333

Supplementary Table 7: List of protein-ligand complexes with top 5 binding affinities.		
S. no.	Protein-ligand complex	Predicted docking scores (kcal/mol)
1	TP53_Norcepharadione B	-6.7
2	TP53_Aristolodione	-7.1
3	TP53_Pellitorine	-5.1
4	TP53_Aristolactam AII	-6.6
5	TP53_N-isobutyl decadienamide	-5.8
6	CTNNB1_Norcepharadione B	-6.4
7	CTNNB1_Aristolodione	-6.9
8	CTNNB1_Pellitorine	-4.8
9	CTNNB1_Aristolactam AII	-6.3
10	CTNNB1_N-isobutyl decadienamide	-5.6
11	HSP90AA1_Norcepharadione B	-10.9
12	HSP90AA1_Aristolodione	-10.3
13	HSP90AA1_Pellitorine	-7.5
14	HSP90AA1_Aristolactam AII	-10.7
15	HSP90AA1_N-isobutyl decadienamide	-9
16	SMAD3_Norcepharadione B	-7
17	SMAD3_Aristolodione	-6.7
18	SMAD3_Pellitorine	-5.2
19	SMAD3_Aristolactam AII	-6.6
20	SMAD3_N-isobutyl decadienamide	-6.3
21	STAT3_Norcepharadione B	-7.2
22	STAT3_Aristolodione	-7.6
23	STAT3_Pellitorine	-5.5
24	STAT3_Aristolactam AII	-6.9
25	STAT3_N-isobutyl decadienamide	-6.5
26	EGFR_Norcepharadione B	-8.9
27	EGFR_Aristolodione	-9.1
28	EGFR_Pellitorine	-5.3
29	EGFR_Aristolactam AII	-8.4
30	EGFR_N-isobutyl decadienamide	-6.4

Supplementary Table 8: MTT analysis data.					
Extract concentration	Proliferation percentages			Mean	Standard deviation
	Replicate 1	Replicate 2	Replicate 3		
Blank	100	100	100	100	0
0.25 µg/mL	96.07	98.87	99.97	98.3033333	2.01080415
0.5 µg/mL	99.29	98.43	94.76	97.4933333	2.40587475
1 µg/mL	98.81	99.06	94.42	97.43	2.60973179
2.5 µg/mL	99.46	98.37	88.76	95.53	5.888268
3.75 µg/mL	47.66	49.17	52.19	49.6733333	2.3065631

(Continued)

Supplementary Table 8: (Continued)

Extract concentration	Proliferation percentages			Mean	Standard deviation
	Replicate 1	Replicate 2	Replicate 3		
5 µg/mL	39.48	41.1	37.89	39.49	1.60502336
7.5 µg/mL	3.71	4.42	5.91	4.68	1.12280898
10 µg/mL	3.35	5.06	10.55	6.32	3.76174162
12.5 µg/mL	3.75	6.44	8.06	6.08333333	2.17702396
15 µg/mL	3.1	3.18	5.73	4.00333333	1.4958721
20 µg/mL	1.04	9.72	2.56	4.44	4.63534249
25 µg/mL	4.03	6.42	1.76	4.07	2.3302575
30 µg/mL	7.94	4.03	2.19	4.72	2.93644343
50 µg/mL	5.89	4.39	3.87	4.71666667	1.04887241