



Research

Network pharmacological approach predicts potential therapeutic targets for chronic myeloid leukemia

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Abstract: Cancer is an extremely complicated, multifaceted, organ-specific, and resilient illness. Chronic myeloid leukemia (CML), one of the most studied human diseases, has been associated with the Philadelphia (Ph) chromosome, a balanced, reciprocal translocation involving the long arms of chromosomes 9 and 22, for a number of reasons. Chronic phase (CP), accelerated phase (AP), and blast crisis (BC) are the clinical stages of CML, and each phase has a different kind of abnormality. We selected the CML gene expression dataset for this study. To identify differentially expressed genes (DEGs), we employed a gene expression dataset. Using the DEGs, we also discovered significant KEGG pathways to better understand the signaling cascades underpinning BC development. The most down-regulated genes were PRKY, TREX2, SRD5A1P1, CD40LG, RAP2C-AS1, APLN, H2BW3P, TMSB15A, ARM CX2, and TERF1P7, in addition to MAP1A, CDKN1A, SERPINE1, SLFN14, SYT11, HNRNPA1, ECM1, CCDC92, CASS4, CENPI, TREML2, UTP25, JDP2, APO-BEC3H, CDKN1A, SLFN14, SYT11, HNRNPA1, ECM1, CCDC92, CASS4, CENPI, TREML2, APO-BEC3H, and MMP2. The DEGs with the strongest linkages across the whole DEG network are NTRK1, FBL, APEX1, HSP90AB1, SSRP1, IMPDH2, EIF3A, DKC1, NAT10, HNRN-PA1, SYN-CRIP, PES1, EXOSC5, MYBBP1A, and IMP4. We can therefore conclude that these DEGs may be significant and the cause of changes in biological processes and gene expression. Furthermore, we observe that a number of potential signaling pathways, including as p53, PI3K-Akt, calcium signaling, ECM, Wnt, FoxO, cell cycle, and JAK-Stat signaling, were significantly enriched. We concluded that there was little chance that either drug would bind to MAP1A. Lastly, we conclude that Diosmin has a higher affinity for Apigenin based on the drug-target predictions. The top-ranked clustered proteins and the inferred proteins of the up-regulated genes did not bind the two medications in the same way as the inferred proteins of the top-ranked down-regulated genes. The drug that had the strongest affinity for both drugs was TREX2.

Keywords: Chronic myeloid leukemia; network pharmacology; Apigenin; Diosmin; molecular docking; gene expression profiling

1. Introduction

Cancer might be leukemia, lymphoma, sarcoma, carcinoma, melanoma, or glioma, depending on the organs. It is an extremely complex, multifaceted, and resilient illness. These varying degrees of complexity are believed to be the largest barrier to the creation of new therapeutic strategies or to the resistance of current ones. Stated differently, the low effectiveness of biomarker-based targeted cancer therapy may be due to the complexity and diversity of the intra-tumor cell population. The primary cause of normal cells turning into tumor cells is multi-level undesirable changes, including (epi)genetic modifications, transcriptional level changes, and aberrant signaling. To put it simply, cancer arises when multicellular organisms malfunction on multiple levels (owing to genetic flaws, metabolic abnormalities, and aberrant signaling). The cell is recognized as a cancer cell after such changes since it no longer resembles a normal cell[1-8].

For a number of reasons, CML is perhaps one of the most studied malignancies in humans. The Philadelphia (Ph) chromosome, a balanced, reciprocal translocation involving the long arms of chromosomes 9 and 22, has been connected to CML, the first recognized human cancer. CML is linked to several clinical stages. Most patients enter during the chronic phase (CP), when peripheral

blood myeloid progenitor cell numbers are higher but mature granulocyte production is still ongoing. As their condition deteriorates, patients go through an accelerated phase (AP) and a blast crisis (BC). Hematopoietic differentiation is halted during BC by the accumulation of immature blasts in the bone marrow (BM) that leak into the circulation. Because CP is long-lasting, researchers may look at cancer cells that behave in a "indolent" way and identify the changes associated with these cells changing into the "aggressive" blast crisis phenotype[9-19]. The development of CML is also distinct since it starts with a single genetic "hit," or lesion, in a hematopoietic stem cell. This lesion results in the fusion oncogene BCR-ABL, which encodes a protein tyrosine kinase necessary and sufficient for cell transformation[11, 13, 20-22]. Because the neoplastic clone is easily accessible and does not require invasive surgery, it makes it easier to collect samples for disease analysis. CML became the first hematological cancer to benefit from a targeted molecular treatment as a result of a methodical approach to medication development. Since the majority of leukemic stem cells in CP can still develop, there is an excess of adult granulocytes produced. The self-renewing juvenile blasts in advanced phase illness stop differentiating, most likely at the leukemia pro-genitor cell stage, which results in the "aggressive" disease phenotype. Leukemic clone stem and progenitor cells are thought to accumulate deleterious genetic events until a considerable number of secondary mutations take place, which causes the disease to proceed from a chronic to an advanced condition. These include increasing telomere shortening and a build-up of genomic instability brought on by disruption of DNA-repair proteins and genomic monitoring. In CP cells, essential proteins remain active, enabling the cells to undergo replicative senescence or perish. However, advanced phase blasts show signs of reduced TS function.

Patient populations that will benefit from targeted treatments can be found by stratifying patient cohorts using genetic markers. The best use of this concept has been in oncology, where most novel anticancer treatments are paired with a genetic marker, such as Iressa with an EGFR mutation or Vemurafenib with a BRAF mutation. Since mutations in a single gene can produce tumors in several locations, new targeted medications are often used with greater efficacy in multiple cancer indications than initially stated. The general problem with most, if not all, targeted cancer treatments is that they are not curative. Many people do not benefit from the drug, and resistance arises, even when they have the genetic changes or biomarker[9, 23-26].

In order to forecast the possible herbal medications that target the proteins for the assigned genes, we have concentrated on a straightforward method for gene expression analysis, network biology, and docking profiling. Apigenin and Diosmin were the medications used for this investigation since they are known to have anticancer properties[27-31].

2. Methods

2.1. Data collection and processing: For this investigation, we have chosen the gene expression dataset (GSE177485[32]), which is freely accessible to the general public via Gene Expression Omnibus (GEO: <https://www.ncbi.nlm.nih.gov/geo>). Here, for a total of ten matched samples, gene expression profiling was carried out on CD34+ cells from five CML patients both untreated and three days after they received Meds433 100nM. These samples were generated by using Illumina NextSeq 500 (*Homo Sapiens*)[32]. We have used GEO2R available at GEO site and generated the fold changes and p-values[33]. We processed the raw data processing from quality check to gene expression profiling by using traditional approach for RNA-seq data processing and analysis that is quality check (FastQC), alignment (bowtie2), gene count (featurecount)[34-41]. To find significant differences between two sets of data (normal or control and cancer or target) for differential gene expression analysis, a conventional statistical t-test (matte, a MATLAB function) has been used. matte use a two-sample t-test to evaluate the variations in gene expression between two experimental conditions or phenotypes. A typical two-tailed, two-sample unpaired t-test for differential expression is applied to each gene, yielding a p-value for each gene. In our study, we have chosen the top-ranked genes to have strict conditions of selection based on fold change, so the fold changes are either extremely high or extremely low than the cutoff fold change. To do this, we first obtain the p-values from matte, then we proceed with p-value corrections and assign the p-value threshold. Finally, the volcano plot has been used for the calculation of fold change and the selection of genes with p-values less than 0.05 and fold changes within this range $\geq +2.0$ and ≤ -2.0 . We used the KEGG database for pathway analysis and wrote our own tool for network and pathway analysis. The fold change has been explained, and by default, we have applied the criterion for $FC > +2.0$ (up-regulated genes) and $FC \leq -2.0$ (down-regulated genes) to identify genes as DEGs. These DEGs have been taken into consideration for pathway enrichment analysis[31, 39, 41-49].

Throughout the project, FunCoup2.0 was utilized to generate the DEGs network, and Cytoscape was utilized to visualize the networks. We have utilized MATLAB for the majority of our computations and coding. Four categories of functional couplings or linkages, including protein complexes, physical interactions between proteins, metabolic processes, and signaling pathways, are predicted by FunCoup[30, 39, 41, 43-46, 48, 50, 51].

2.2. Ligand preparation: Both the structures for both the ligands (herbal drugs) were collected from PubChem database[52].

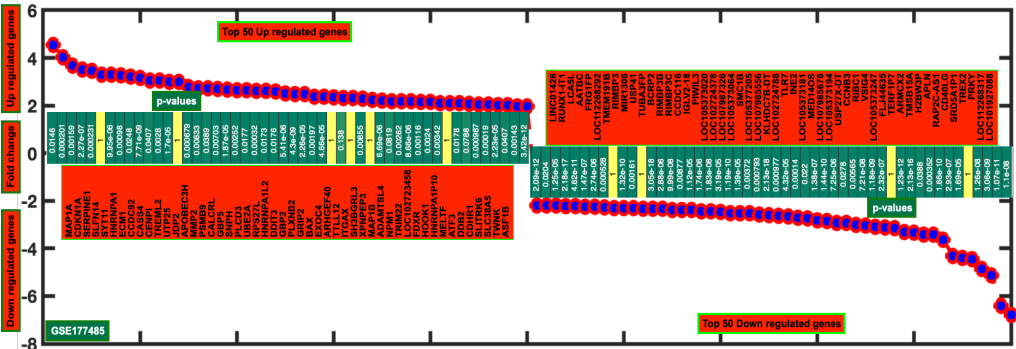
2.3. Preparation of receptors: The crystal structures of target proteins were retrieved from www.uniport.org where we selected the structures predicted by AlphaFold2[53-56].

2.4. Molecular docking: We used CB-DOCK2 (<https://cadd.labshare.cn/cb-dock2/>) for all the docking purpose and select the best binding cavity we used the lowest binding affinity value[57]. The UniProt database (www.uniprot.org) provided the protein sequences, which AlphaFold3 processed in order to predict their 3D structure. The 3D structures of pharmaceuticals in SDF format were obtained using PubChem. These files are processed internally because we used CB-Dock2, which only required us to upload the 3D structures of the proteins and medications. We choose Vina in the docking method after uploading the files. To select the docking complex, we used the binding affinity with lowest value.

3. Results

3.1. Gene expression profiling of CML data: We performed gene expression profiling for the gene expression dataset (GSE177485) which are publicly available at Gene Expression Omnibus (GEO: <https://www.ncbi.nlm.nih.gov/geo>). After performing the gene expression analysis, we predicted the DEGs and calculated the pathway enrichment analysis. For the DEGs, we plotted the top 100 DEGs followed by their fold changes and p-values (Figure 1). MAP1A, CDKN1A, SERPINE1, SLFN14, SYT11, HNRNPA1, ECM1, CCDC92, CASS4, CENPI, TREML2, UTP25, JDP2, APOBEC3H, and MMP2 were among the top-ranked up-regulated genes and LOC101927088, LOC112268317, PRKY, TREX2, SRD5A1P1, CD40LG, RAP2C-AS1, APLN, H2BW3P, TMSB15A , ARM CX2, TERF1P7, and FLJ44635 were among the top-ranked down regulated genes (Figure 1).

Figure 1. A plot to show the fold change and p-value of the top-ranked (50 up and 50 down regulated) DEGs. The positive values fold change represent the up regulated and the negative values of fold change represent the down regulated genes.



Most of these top-ranked DEGs are critical in terms of human cancers including CML. Thus, we further explored the biological functions. After analyzing the DEGs, the enriched pathways were calculated for all the DEGs, up regulated genes, and the down regulated genes (Table 1). In the overall enriched pathways (for all the DEGs (i.e., up and down regulated genes)). Neuroactive ligand-receptor interaction, Cytokine-cytokine receptor interaction, p53 signaling, PI3K-Akt signaling, Calcium signaling, Hippo signaling, Signaling pathways regulating pluripotency of stem cells, MAPK signaling, cAMP signaling, ECM-receptor interaction, Cell adhesion molecules (CAMs), Purine metabolism, FoxO signaling, Apoptosis, Wnt signaling, Focal adhesion, and Jak-Stat signaling were among the highly enriched pathways. In case of up regulated genes, p53, Apoptosis, Cytokine-cytokine receptor interaction, PI3K-Akt signaling, MAPK signaling, and Jak-Stat signaling were enriched while calcium signaling, hippo signaling, Signaling pathways regulating pluripotency of stem cells, CAMs, Wnt, ECM, PI3K-Akt, cAMP, and Adrenergic signaling in cardiomyocytes were enriched (Table 1). PI3K-Akt signaling was the only pathway which was enriched in both up and down regulated genes cases which means that in both the cases (light blue), there were higher number of genes up and down regulated.

Table 1. Pathway enrichment analysis. The ligh blue color highlighted name of the pathway is meant for common pathway in up and down regulated DEGs.

Enriched pathways (DEGs)	p-values
KEGG_04080_Neuroactive_ligand-receptor_interaction	2.755732e-07
KEGG_04060_Cytokine-cytokine_receptor_interaction	2.755732e-06
KEGG_04115_p53_signaling	2.755732e-06
KEGG_04151_Pi3K-Akt_signaling	2.755732e-06
KEGG_04020_Calcium_signaling	2.480159e-05
KEGG_04392_Hippo_Signaling	2.480159e-05
KEGG_04550_Signaling_pathways_regulating_pluripotency_of_stem_cells	2.480159e-05
KEGG_04010_MAPK_signaling	1.984127e-04
KEGG_04024_cAMP_signaling_pathway_-_Homo_sapiens_(human)	1.388889e-03
KEGG_04512_ECM-receptor_interaction	1.388889e-03
KEGG_04514_Cell_adhesion_molecules_(CAMs)	1.388889e-03
KEGG_00230_Purine_metabolism	8.333333e-03
KEGG_04068_FoxO_signaling	8.333333e-03
KEGG_04210_Apoptosis	8.333333e-03
KEGG_04261_Adrenergic_signaling_in_cardiomyocytes	8.333333e-03

KEGG_04310_Wnt_signaling	8.333333e-03
KEGG_04510_Focal_adhesion	8.333333e-03
KEGG_00240_Pyrimidine_metabolism	4.166667e-02
KEGG_00350_Tyrosine_metabolism	4.166667e-02
KEGG_04072_Phospholipase_D_signaling	4.166667e-02
KEGG_04110_Cell_cycle	4.166667e-02
KEGG_04270_Vascular_smooth_muscle_contraction	4.166667e-02
KEGG_04630_Jak-STAT_signaling	4.166667e-02
KEGG_04722_Neurotrophin_signaling	4.166667e-02
KEGG_04742_Taste_transduction	4.166667e-02
KEGG_04750_Inflammatory_mediator_regulation_of_TRP_channels	4.166667e-02
KEGG_04916_Melanogenesis	4.166667e-02
Enriched pathways (UP regulated)	p-values
KEGG_04115_p53_signaling	2.480159e-05
KEGG_04060_Cytokine-cytokine_receptor_interaction	1.388889e-03
KEGG_00230_Purine_metabolism	8.333333e-03
KEGG_04151_PIK-Akt_signaling	8.333333e-03
KEGG_00240_Pyrimidine_metabolism	4.166667e-02
KEGG_04010_MAPK_signaling	4.166667e-02
KEGG_04210_Apoptosis	4.166667e-02
KEGG_04630_Jak-STAT_signaling	4.166667e-02
Enriched pathways (Down regulated)	p-values
KEGG_04080_Neuroactive_ligand-receptor_interaction	1.984127e-04
KEGG_04020_Calcium_signaling	1.388889e-03
KEGG_04392_Hippo_Signaling	1.388889e-03
KEGG_04550_Signaling_pathways_regulating_pluripotency_of_stem_cells	8.333333e-03
KEGG_04024_cAMP_signaling	4.166667e-02
KEGG_04151_PIK-Akt_signaling	4.166667e-02
KEGG_04261_Adrenergic_signaling_in_cardiomyocytes	4.166667e-02
KEGG_04310_Wnt_signaling	4.166667e-02
KEGG_04512_ECM-receptor_interaction	4.166667e-02
KEGG_04514_Cell_adhesion_molecules_(CAMs)	4.166667e-02
KEGG_04742_Taste_transduction	4.166667e-02

3.2. Network-level understanding: To better understand the DEGs, we applied network biology concept for which we used protein-protein interaction (PPI) network database i.e., FunCoup and retrieved the interaction among the DEGs. Here, we prepared the network of top 100 DEGs (50 up and 50 down regulated genes) and the network of all the DEGs and then predicted the top-ranked genes based on connectivity between the DEGs. In top-ranked DEGs network (Figure 2), we observe that CDKN1A, MMP2, BAX, NPM1, SH3BGRL3, HNRNPA1, HNRNPA1L2, UBE2A, SM1B, EXOC4, ASF1B, TTLL12, MAP1B, and SYT11 acts as the cyclic backbone of the network leading to the conclusion that they may act as the potential DEGs controlling the biological function. After analyzing the network of top DEGs, we have also analyzed the network of all the DEGs, where NTRK1, FBL, APEX1, HSP90AB1, SSRP1, IMPDH2, EIF3A, DKC1, NAT10, HNRNPA1, SYNCRIP, PES1, EXOSC5, MYBBP1A, and IMP4 are among the most connected DEGs (Figure 2). Thus, we could say that these DEGs could be highly important and the potential source of alterations in gene expression and in biological functions.

We also clustered every DEG network and conducted network analysis. Here were the top three clusters and an overview of the network statistics. The total number of nodes were 336 and the total edges were 1208. Average number of neighbors were 7.844, network diameter was 8, radius of the network was 5, 3.286, 0.211, 0.026, 1.231, 0.141, and 29 were characteristic path length, clustering coefficient, network density, network heterogeneity, network centralization, and connected components, respectively (Figure 2). APEX1, ASF1B, DDX10, DKC1, EIF3A, EXOSC5, FBL, HNRNPA1, IMP4, IMPDH2, LYAR, MYBBP1A, NAT10, NLE1, PES1, RAD23B, RPS27L, SSRP1, SYNCRIP, WDR12, and WDR43 were genes presented in top cluster i.e., cluster and these genes were highly connected. ATP1B1, ATP2B2, CCDC103, CYP2J2, DLGAP1, KCNB4, KIF1A, MAP1A, PTPN5, RAPGEF4, and SNPH were present in second top cluster (cluster 2). RAPGEF4, SNPH, CYP2J2, ATP1B1, and ATP2B2 were among the highly connected genes. EIF3D, HSP90AB1, NTRK1, RRP12, and TTLL12 were present in cluster 3.

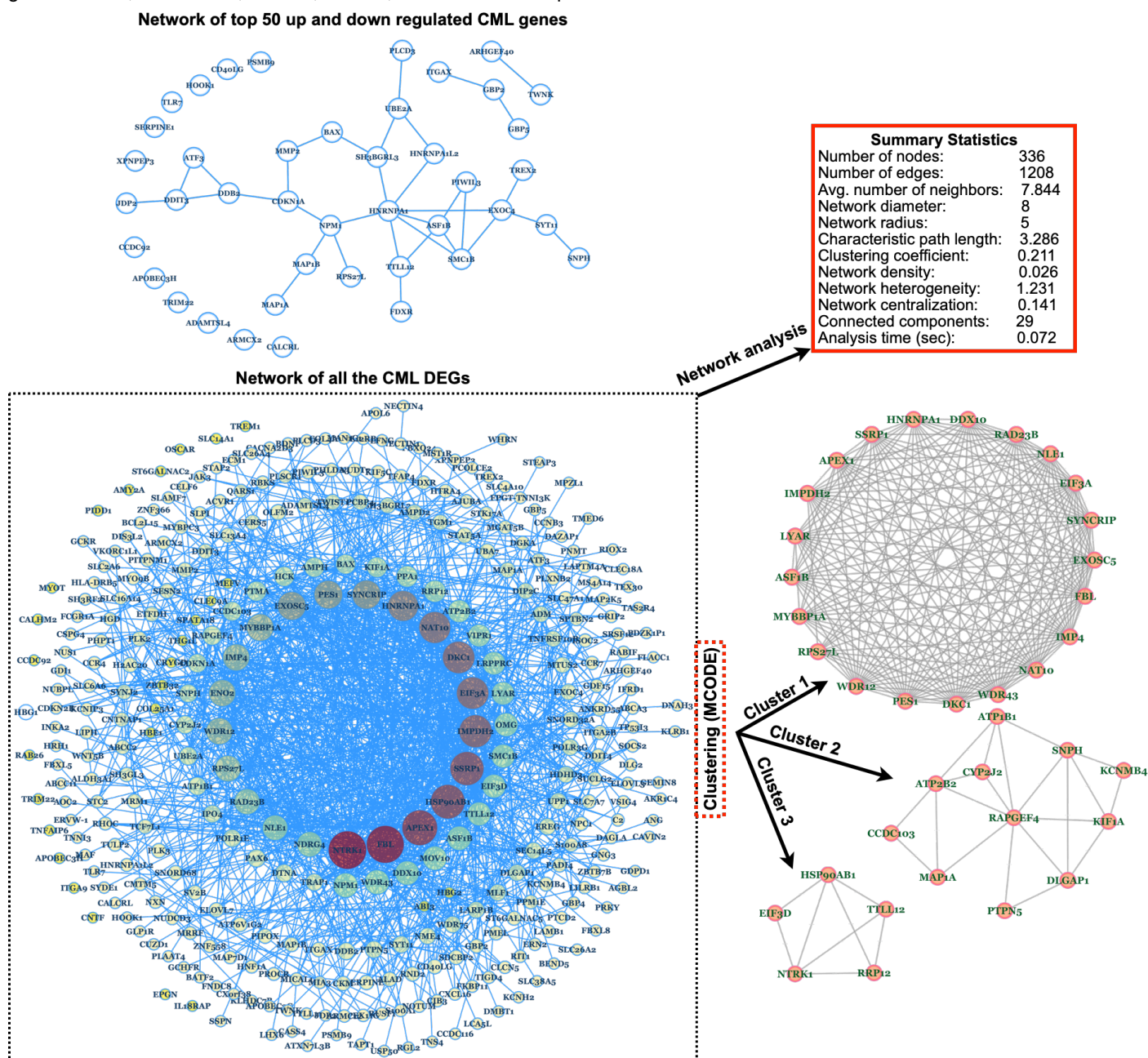


Figure 2. Networks of the top DEGs and all the DEGs for the selected CML dataset. The red color to light yellow color in the network of all the DEGs means the higher connectivity to lesser connectivity. We also performed network analysis and clustering of all the DEGs network. The summary of network statistics and the top three clusters were shown here.

Moreover, we explored the biological functions of the top-ranked DEGs by mapping the inferred KEGG pathways from KEGG pathway database (Table 2). Here, we could clearly observe that a large number of signaling pathways from the inferred pathways list directly link with human cancer including the CML. Out of these pathways, there are cancer specific pathways also such as pathways in

cancer, CML, colorectal cancer, bladder cancer, melanogenesis, melanoma, and prostate cancer. The well-established cancer associated pathways were: apoptosis, cell cycle, p53, FoxO, PI3K-Akt, NF- κ B, TLR, hippo, MAPK, regulation of actin cytoskeleton, ErbB, TCR, CAMs, cytokine signaling, Wnt, etc.

Table 2. Inferred KEGG pathways for the top 50 up and down regulated genes mapped from KEGG database.

DEGs	Pathways
CALCRL	KEGG_04080_Neuroactive_ligand-receptor_interaction
CALCRL	KEGG_04270_Vascular_smooth_muscle_contraction
UBE2A	KEGG_04120_Ubiquitin_mediated_proteolysis
SMC1B	KEGG_04110_Cell_cycle
SMC1B	KEGG_04111_Cell_cycle_-_yeast
BAX	KEGG_04115_p53_signaling_pathway
BAX	KEGG_04210_Apoptosis
BAX	KEGG_04722_Neurotrophin_signaling_pathway
BAX	KEGG_05014_Amyotrophic_lateral_sclerosis_(ALS)
BAX	KEGG_05020_Prion_diseases
BAX	KEGG_05200_Pathways_in_cancer
BAX	KEGG_05210_Colorectal_cancer
MMP2	KEGG_04670_Leukocyte_transendothelial_migration
MMP2	KEGG_04912_GnRH_signaling_pathway
MMP2	KEGG_05200_Pathways_in_cancer
MMP2	KEGG_05219_Bladder_cancer
PRKY	KEGG_04010_MAPK_signaling_pathway
PRKY	KEGG_04020_Calcium_signaling_pathway
PRKY	KEGG_04210_Apoptosis
PRKY	KEGG_04310_Wnt_signaling_pathway
PRKY	KEGG_04340_Hedgehog_signaling_pathway
PRKY	KEGG_04540_Gap_junction
PRKY	KEGG_04720_Long-term_potentiation
PRKY	KEGG_04740_Olfactory_transduction
PRKY	KEGG_04742_Taste_transduction
PRKY	KEGG_04910_Insulin_signaling_pathway
PRKY	KEGG_04912_GnRH_signaling_pathway
PRKY	KEGG_04914_Progesterone-mediated_oocyte_maturation
PRKY	KEGG_04916_Melanogenesis
CD40LG	KEGG_04060_Cytokine-cytokine_receptor_interaction
CD40LG	KEGG_04514_Cell_adhesion_molecules_(CAMs)
CD40LG	KEGG_04660_T_cell_receptor_signaling_pathway
CD40LG	KEGG_04672_Intestinal_immune_network_for_IgA_production
CD40LG	KEGG_05310_Asthma
CD40LG	KEGG_05320_Autoimmune_thyroid_disease
CD40LG	KEGG_05322_Systemic_lupus_erythematosus
CD40LG	KEGG_05330_Allograft_rejection

CD40LG	KEGG_05416_Viral_myocarditis
SERPINE1	KEGG_04115_p53_signaling_pathway
SERPINE1	KEGG_04610_Complement_and_coagulation_cascades
CDKN1A	KEGG_04012_ErbB_signaling_pathway
CDKN1A	KEGG_04110_Cell_cycle
CDKN1A	KEGG_04115_p53_signaling_pathway
CDKN1A	KEGG_05200_Pathways_in_cancer
CDKN1A	KEGG_05214_Glioma
CDKN1A	KEGG_05215_Prostate_cancer
CDKN1A	KEGG_05218_Melanoma
CDKN1A	KEGG_05219_Bladder_cancer
CDKN1A	KEGG_05220_Chronic_myeloid_leukemia
EXOC4	KEGG_04530_Tight_junction
DDB2	KEGG_04115_p53_signaling_pathway
DDB2	KEGG_04120_Ubiquitin_mediated_proteolysis
ITGAX	KEGG_04810_Regulation_of_actin_cytoskeleton
CCNB3	KEGG_04110_Cell_cycle
CCNB3	KEGG_04115_p53_signaling_pathway
CCNB3	KEGG_04914_Progesterone-mediated_oocyte_maturation
PLCD3	KEGG_00562_Inositol_phosphate_metabolism
PLCD3	KEGG_04020_Calcium_signaling_pathway
PLCD3	KEGG_04070_Phosphatidylinositol_signaling_system
APLN	KEGG_04080_Neuroactive_ligand-receptor_interaction
DDIT3	KEGG_04010_MAPK_signaling_pathway
PIWIL3	KEGG_04320_Dorso-ventral_axis_formation
PLXNB2	KEGG_04360_Axon_guidance
TLR7	KEGG_04620_Toll-like_receptor_signaling_pathway
PSMB9	KEGG_03050_Proteasome
SERPINE1	KEGG_04392_Hippo_Signaling_Pathway
BAX	KEGG_04141_Protein_processing_in_endoplasmic_reticulum
DDIT3	KEGG_04141_Protein_processing_in_endoplasmic_reticulum
DDB2	KEGG_03420_Nucleotide_excision_repair
SERPINE1	KEGG_04371_Apelin_signaling_pathway_- _Homo_sapiens_(human)
APLN	KEGG_04371_Apelin_signaling_pathway_- _Homo_sapiens_(human)
CD40LG	KEGG_04064_NF-kappa_B_signaling_pathway_- _Homo_sapiens_(human)
CDKN1A	KEGG_04066_HIF-1_signaling_pathway_- _Homo_sapiens_(human)
SERPINE1	KEGG_04066_HIF-1_signaling_pathway_- _Homo_sapiens_(human)
CDKN1A	KEGG_04068_FoxO_signaling_pathway_- _Homo_sapiens_(human)
CCNB3	KEGG_04068_FoxO_signaling_pathway_- _Homo_sapiens_(human)
BAX	KEGG_04071_Sphingolipid_signaling_pathway_- _Homo_sapiens_(human)
CDKN1A	KEGG_04151_PI3K-Akt_signaling_pathway_- _Homo_sapiens_(human)
BAX	KEGG_04211_Longevity_regulating_pathway

MMP2	KEGG_04915_Estrogen_signaling_pathway
CDKN1A	KEGG_04921_Oxytocin_signaling_pathway
PLCD3	KEGG_04919_Thyroid_hormone_signaling_pathway
MMP2	KEGG_05418_Fluid_shear_stress_and_atherosclerosis

3.3. Docking of top-ranked proteins with Apigenin and Diosmin: In previous step, we predicted the genes acting as hub genes based on network profiling and clustering. Thus, we performed docking studies of top 10 DEGs with Apigenin and Diosmin. In case of up regulated genes, Apigenin showed -7.8 kcal/mol with ROA1, -7.7 kcal/mol with SLFN14, -7.6 kcal/mol with SYT11, and -5.9 kcal/mol with MAP1A. Diosmin showed highest binding affinity (delta G) -9.2 kcal/mol with SLFN14 and ROA1, -8.4 kcal/mol with SYT11, -7.4 kcal/mol with CDKN1A, and lowest -6.7 kcal/mol with MAP1A (Figure 3). Thus, we could conclude that Diosmin has higher binding affinity with respect to Apigenin and both the drugs have lowest binding possibility with MAP1A. In case of top-ranked down regulated genes, their inferred proteins showed binding affinity with the two drugs different than the up regulated genes. TREX2 had binding affinity maximum for both the drugs (Apigenin with TREX2 = -7.9 kcal/mol and Diosmin with TREX2 = -9.2 kcal/mol) (Figure 4).

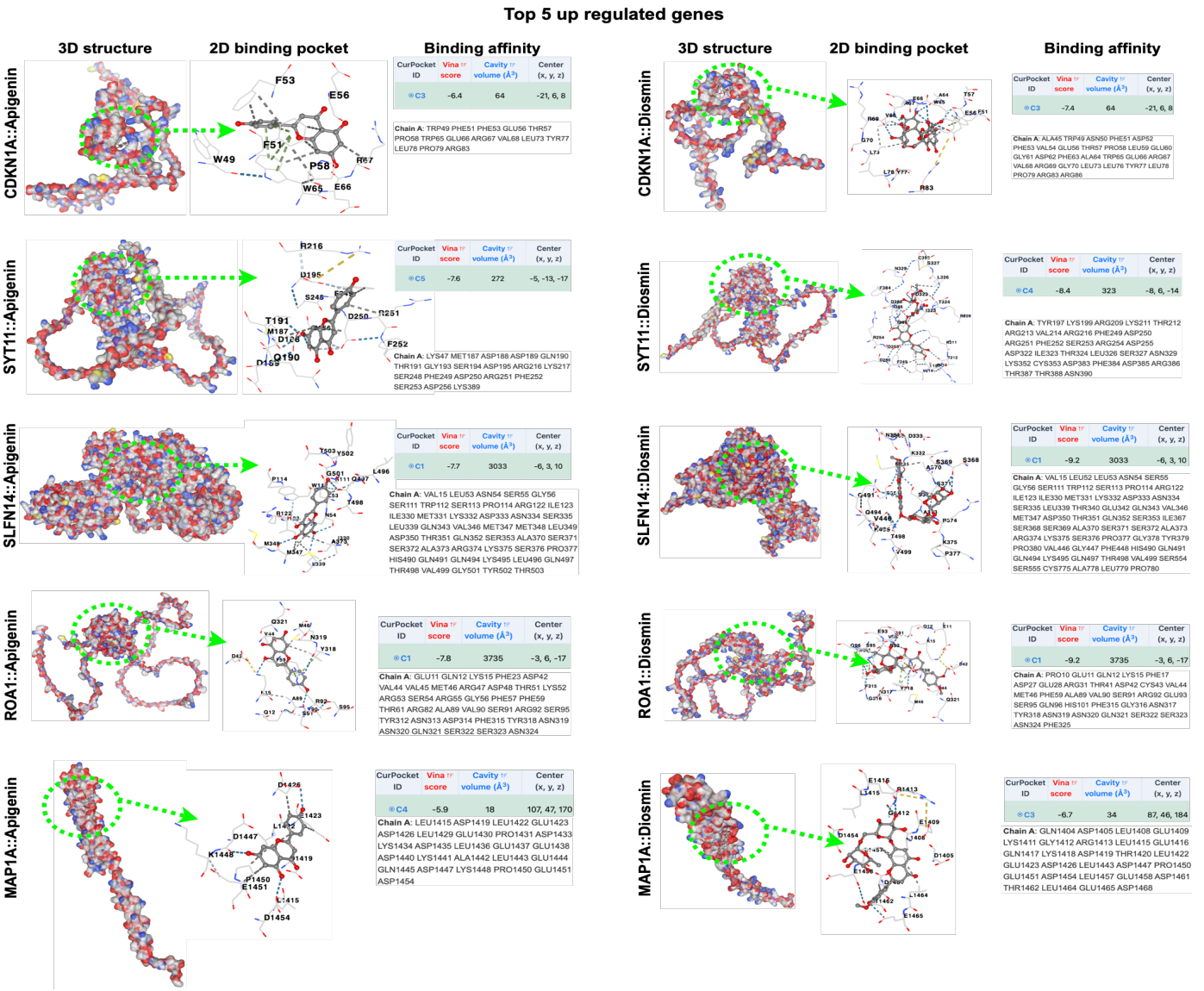


Figure 3. Docking profiling of the proteins for the respective top-ranked up regulated DEGs with Apigenin and Diosmin. Here, the protein docked with the drugs was represented by the 3D structure. The binding pocket and sites were represented by the 2D structure. Additionally, we listed the number of cavities, the binding affinity (delta G in kcal/mol), and the amino acids that are present in the binding cavity.

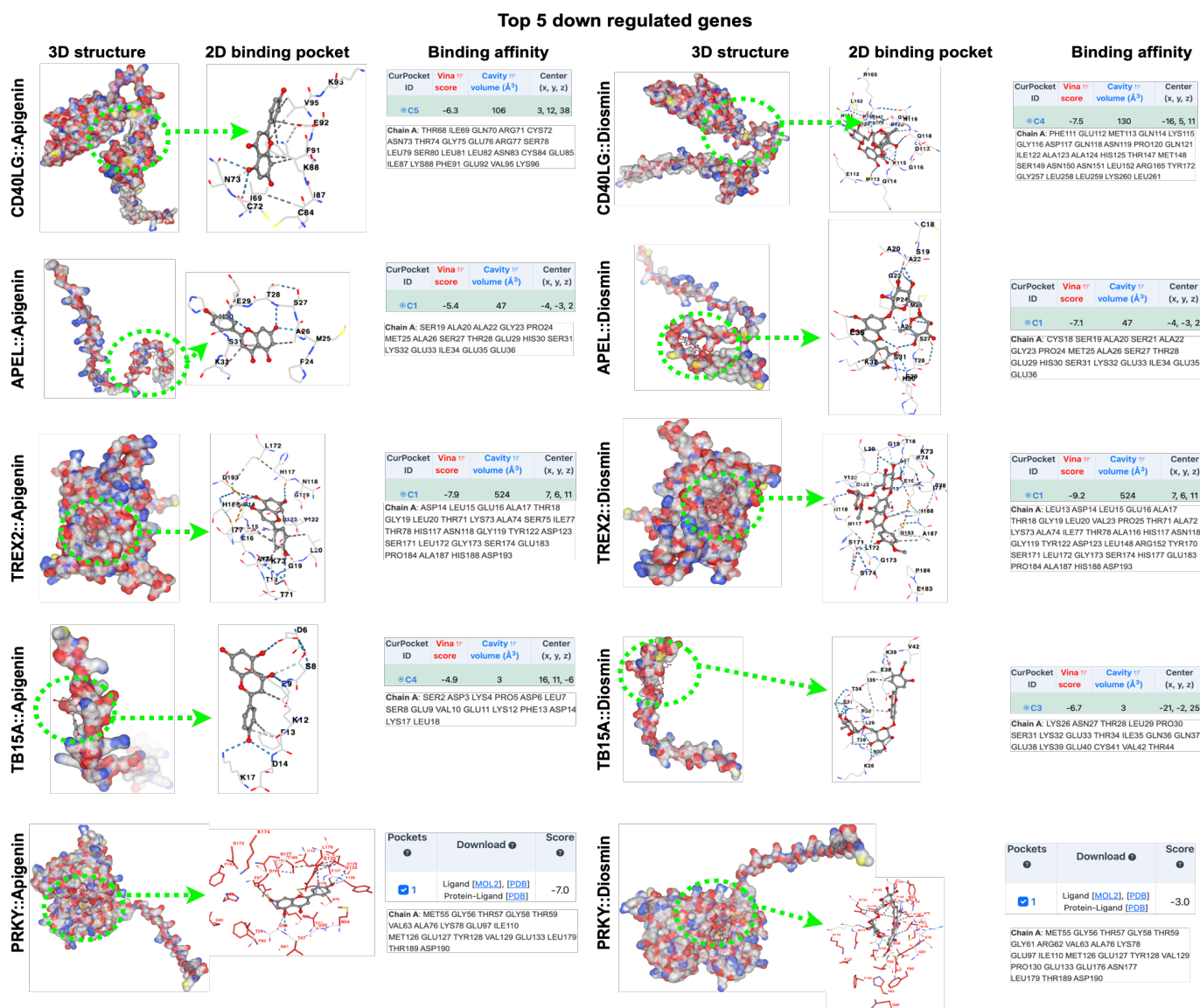


Figure 4. Docking profiling of the proteins for the respective top-ranked down regulated DEGs with Apigenin and Diosmin. In this case, the 2D structure depicted the binding pocket and the sites. The 3D structure shows the protein docked with the medications. The cavity number, binding affinity (delta G in kcal/mol), and amino acids that were present in the binding cavity have also been included.

Furthermore, we performed docking (Figure 5) of Apigenin and Diosmin with the inferred proteins of top DEGs based on clustering (by using MCODE tool of Cytoscape). Interestingly, Diosmin again appeared as the promising drug by showing comparatively much higher binding affinity in comparison with Apigenin with four out of five top proteins. Diosmin displayed -10.7, -10.5, -9.8, and -9.6 kcal/mol with RAPGEF4, CYP2J2, APEX1, and DDX10, respectively and even the number of contact residues were higher for the stronger binding affinity. While Apigenin had higher binding affinity -7.7, 7.7, and 7.6 kcal/mol with RAPGEF4, DDX10, and APEX1, respectively.

Top 5 genes based on clustering

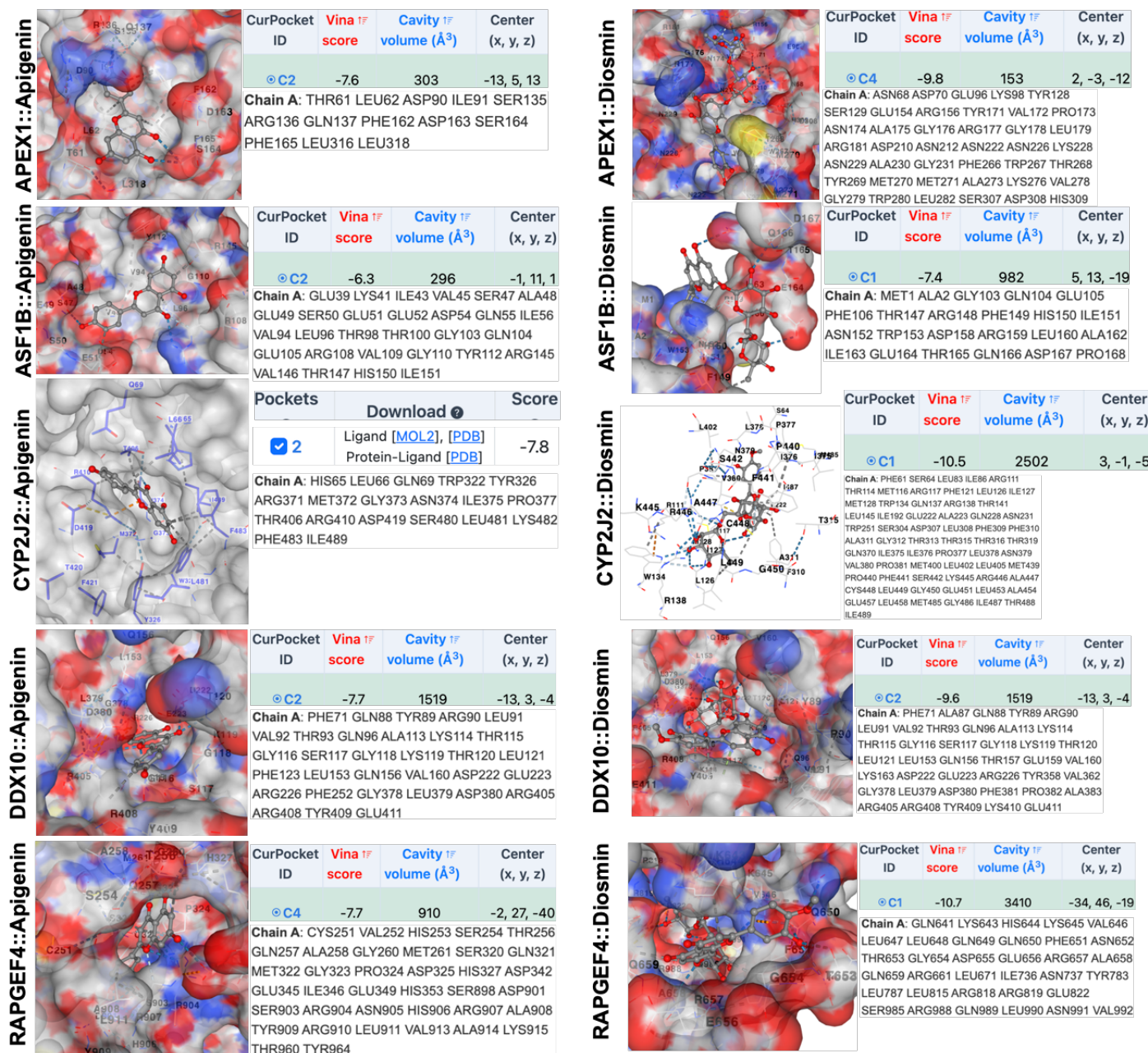


Figure 5. Docking study of the inferred proteins of top five DEGs obtained by running MCODE of Cytoscape. Here, we have shown the binding sites and the binding residues with both the drugs.

4. Discussion

We predicted the DEGs following the gene expression analysis and computed the pathway enrichment analysis. We showed the top 100 DEGs for the DEGs, together with their p-values and fold changes (Figure 1). The top-ranked down-regulated genes were LOC101927088, LOC112268317, PRKY, TREX2, SRD5A1P1, CD40LG, RAP2C-AS1, APLN, H2BW3P, TMSB15A, ARM CX2, TERF1P7, and FLJ44635, while the top-ranked up-regulated genes were MAP1A, CDKN1A, SERPINE1, SLFN14, SYT11, HNRNPA1, ECM1, CCDC92, CASS4, CENPI, TREML2, UTP25, JDP2, APOBEC3H, and MMP2 (Figure 1). The majority of these highly listed genes are essential for both CML and other malignancies[14-19, 58-68]. The most interconnected DEGs in the entire DEGs network are NTRK1, FBL, APEX1, HSP90AB1, SSRP1, IMPDH2, EIF3A, DKC1, NAT10, HNRNPA1, SYNCRIP, PES1, EX-OSC5, MYBBP1A, and IMP4. Therefore, we may conclude that these DEGs may be very significant and the cause of changes in biological processes and gene expression.

Calcium signaling, PI3K-Akt signaling, p53 signaling, cytokine-cytokine receptor interaction, neuroactive ligand-receptor interaction, hippocampal signaling, Apoptosis, FoxO signaling, Purine metabolism, ECM-receptor interaction, MAPK signaling, cAMP

signaling, cell adhesion molecules (CAMs), Jak-Stat signaling, Wnt signaling, focal adhesion, and pluripotency of stem cells were among the highly enriched signaling pathways. In the case of up-regulated genes, the following were enriched: calcium signaling, hippo signaling, signaling pathways regulating pluripotency of stem cells, CAMs, Wnt, ECM, PI3K-Akt, cAMP, and Adrenergic signaling in cardiomyocytes; p53, Apoptosis, Cytokine-cytokine receptor interaction, PI3K-Akt signaling, MAPK signaling, and Jak-Stat signaling were enriched (Table 1). There were more genes that were up-regulated and down-regulated in both cases since PI3K-Akt signaling was the only pathway that was enriched in both situations. Majority of these enriched pathways are known to be associated with many cancers including CML[2, 69-89].

Apigenin displayed -7.8 kcal/mol with ROA1, -7.7 kcal/mol with SLFN14, -7.6 kcal/mol with SYT11, and -5.9 kcal/mol with MAP1A in the case of up-regulated genes. Diosmin's binding affinity (delta G) was lowest with MAP1A (-6.7 kcal/mol), greatest with SLFN14 and ROA1 (-9.2 kcal/mol), followed by SYT11 (-8.4 kcal/mol), and CDKN1A (-7.4 kcal/mol) (Figure 3). We may therefore draw the conclusion that Diosmin has a greater affinity for Apigenin and that both medications have the lowest potential for binding to MAP1A. The inferred proteins of the top-ranked down-regulated genes had a different binding affinity for the two medicines than those of the up-regulated genes. For both medications, TREX2 exhibited the highest binding affinity (Diosmin with TREX2 = -9.2 kcal/mol and Apigenin with TREX2 = -7.9 kcal/mol).

In the previous studies, the potentials of these drugs were explored by using in-vitro approach in different types of cancers[27-31, 90-98]. These cancers are hepatocellular carcinoma, breast cancer, colorectal cancer, etc. These research works and reviews explored the role of Diosmin and Apigenin in different cancer cell lines and including the signaling pathways and the drug targets. The targets of the drugs include the proteins which are known to be linked with CML progression[9, 23, 99-105].

Most CML patients enter during the chronic phase (CP), which is marked by a persisting production of mature granulocytes but an increase in peripheral blood myeloid progenitor cells. As the illness progresses, patients go through an accelerated phase (AP) and a blast crisis (BC). Haematopoietic differentiation is halted by the buildup of immature blasts in the bone marrow (BM) and their release into the bloodstream during BC[9, 17, 106-108]. The general prognosis for people with chronic myeloid leukemia (CML) was either unchanged or barely improved for much too long. Even after numerous studies examining splenic irradiation, radioactive phosphorous (P32), splenectomy, chemotherapy with one or more medications, and regimens combining multiple modalities were conducted, this remained the case. For younger patients whose siblings had the same genetic makeup, allogeneic bone marrow transplantation eventually emerged as the preferred treatment. The treatment toolkit now includes interferon alfa (IFN- α) therapy, which can be administered either by itself or in combination with cytarabine. Treatment for CML patients at every stage of the disease was significantly altered by imatinib mesylate, the first tyrosine kinase inhibitor (TKI) to precisely target the BCR-ABL1 oncoprotein[13, 21, 109-111]. Using improved population-based Swedish registries, previous researchers assessed the age, sex, and geographical evolution of the outcome for 3,173 CML patients diagnosed in Sweden between 1973 and 2008[112-116]. They sought to evaluate trends in short- and long-term excess mortality as well as patient survival for all patients during these 36 years, whether or not they were included in clinical trials. At the beginning of the experiment, busulfan was the most commonly used therapy drug. IFN- α , hydroxyurea, and allogeneic stem-cell transplantation (SCT) were then introduced, and hydroxyurea was utilized more extensively. Most importantly, imatinib mesylate was approved by regulators and added to trial protocols.

5. Conclusions

From gene expression to network-level comprehension and the identification of potential therapeutic targets, we have presented our findings in this article in the most straightforward manner possible. The most down-regulated genes were LOC101927088, LOC112268317, PRKY, TREX2, SRD5A1P1, CD40LG, RAP2C-AS1, APLN, H2BW3P, TMSB15A, ARM CX2, TERF1P7, and FLJ44635, along with MAP1A, CDKN1A, SERPINE1, SLFN14, SYT11, HNRNPA1, ECM1, CCDC92, CASS4, CENPI, TREML2, UTP25, JDP2, APOBEC3H, and MMP2. CML and other malignancies require the majority of these highly listed genes. The DEGs with the strongest linkages across the whole DEG network are NTRK1, FBL, APEX1, HSP90AB1, SSRP1, IMPDH2, EIF3A, DKC1, NAT10, HNRNPA1, SYNCRIP, PES1, EXOSC5, MYBBP1A, and IMP4. We can therefore conclude that these DEGs may be very important and the cause of changes in biological processes and gene expression. Apoptosis, FoxO signaling, purine metabolism, ECM-receptor interaction, MAPK signaling, cAMP signaling, cell adhesion molecules (CAMs), Jak-Stat signaling, Wnt signaling, focal adhesion, Calcium signaling, PI3K-Akt signaling, p53 signaling, cytokine-cytokine receptor interaction, neuroactive ligand-receptor interaction, and stem cell pluripotency were among the highly enriched signaling pathways. Based on the drug-target predictions and the molecular docking results, we deduced that Diosmin has a greater affinity for Apigenin and that both medications have the least propensity to bind to MAP1A. The predicted proteins of the top-ranked down-regulated genes showed a different binding affinity for the two drugs than the up-regulated genes. For both medications, TREX2 exhibited the highest binding affinity.

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Abbreviations

The following abbreviations are used in this manuscript:

CML	Chronic myeloid leukemia
CP	Chronic phase
AP	Accelerated phase
BC	Blast crisis
GEO	Gene expression omnibus
DEGs	Differentially expressed genes

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