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ORIGINAL ARTICLE

Exploring the Therapeutic Potential of Curcumin in Colorectal Cancer: A Network Pharmacology and Molecular Docking Study

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ABSTRACT

Colorectal cancer remains a major health challenge that requires the exploration of new therapeutic agents. Previous studies have shown that Curcuminoids, the bioactive ingredients of turmeric (Curcuma longa), affect several cell signaling pathways, thereby putting forward the probable role of curcumin in modulating cancer development and progression. Here, we adopted a pharmacological network approach integrated with molecular docking to understand the mechanism of curcumin against colorectal cancer. Ten hub genes (PIK3R1, MAP2K2, PDGFRA, PDGFRB, NFKB1, HIF1A, PTPN11, SLC2A1, STAT1 and CCNE1) had been reported in this study to have high master candidate scores. Gene Ontologies and KEGG pathways enrichment analyses further proved that curcumin targeted many important pathways like Central carbon metabolism in cancer, Pathways in cancer, and PD-L1 expression and PD-1 checkpoint pathway establishing curcumin's broad anticancer potential. Molecular docking analysis demonstrated the docking between curcumin and the hub proteins, with PIK3R1, SLCIA and PTPN11 exhibiting the strongest binding energies of -9.5 kcal/mol, -9.2 kcal/mol and -8.8 kcal/mol, respectively, indicating that they play a central role in the mechanism of curcumin action. Our results highlight the action of curcumin in modulating key signaling pathways which are relevant to cancer metabolism, immune regulation, and tumour progression. The current work paves the way for a comprehensive understanding of the multi-target therapeutic potential of curcumin against colorectal cancer, opening research pathways for further experimental validation and clinical studies.

Keywords: *Colorectal cancer, Curcumin, Gene Ontologies, Molecular docking, Anticancer, Network Pharmacology.*

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INTRODUCTION

Cancer is a global health challenge responsible for the death of one out of six people in the world. Colorectal cancer is the third most common cancer in the world and the second most common cause of cancer-related death. The disease infects individuals of 50 years- and-more due to which symptoms remain unnoticed in the early stages. Age, dietary regime, physical inactivity, and lifestyle factors come under one or another risk factor. Effective screening and early detection can help determine the survival [1]. It is generally cited to occur on a large scale in Western and Northern Europe and USA and on a small scale in Africa, Asia, and India. Colorectal cancer is predicted to increase 60% by 2030, leading to more

than 1.1 million deaths. There have been many therapeutic protocols that were instituted, but the consideration of side effects that may occur during and after treatment is of equal importance [2*]. Symptoms are quite varied but can include diarrhea, constipation, blood in the stool, pain in the abdomen, unexplained weight loss, fatigue, and low iron levels. People often have no symptoms when the disease is in an early stage. A healthy lifestyle, which includes a healthy diet, physical activity, no smoking, and drinking alcohol, can lower the risk of getting colorectal cancer [3*]. Colorectal cancer targets the colon and rectum, essential parts of the digestive tract. By putting awareness towards areas affected by the illness, total implications for health profile and treatment options will be easy to conclude [4]. In recent years, several studies have suggested a dual role of gut microbiota, either as protectors of the host or as perpetuators of disease from the excessive presence of specific microbes that promote colon carcinogenesis. In this context, intestinal dysbiosis has been reported to correlate closely with colorectal inflammation and tumor development [5-7]. Treating cancer is a very complicated process. Though surgery, chemotherapy, and radiotherapy have a long history of use, recent advances include stem cell therapy, targeted therapy, ablation therapy, nanoparticles, natural antioxidants, radionics, chemodynamic therapy, sonodynamic therapy, and ferroptosis-based therapy [8]. Better understanding of the disease will lead to better prevention and treatment strategies. Increased interest in monomeric active compounds isolated from Chinese herbs in recent years has triggered new global research. A biologically active compound derived from rhizome turmeric, curcumin which is also known as the golden herb is an active ingredient of Chinese medicine belonging to the group of acidic polyphenolic compounds [9]. Because of perceived toxicity and high expense of modern therapies, global interest is redirected to finding possible natural products for cancer prevention that are safe, more viable, and that could be combined with conventional therapies currently offered to these patients [10]. Curcumin comes from the long herb Curcuma longa and represents one such option, which has a long-standing tradition of proved usages for a variety of chronic disorders, including cancers, in Ayurvedic traditional medicine as well as traditional Chinese medical practices. In the last few years, there has been increased focus on curcumin's ability to fight cancer; however, the anticancer mechanisms of drug action in curcumin are not yet fully understood. A vast body of research over the past twenty years suggests that curcuminoids, the bioactive ingredients of turmeric (*C. longa*), affect several cell signaling pathways, thereby putting forward the probable role of curcumin in modulating cancer development and progression [11,12]. Several studies reported that curcumin altered the non-coding RNAs expression in colorectal carcinoma cells [13].Network pharmacology is an approach that integrates bioinformatics and pharmacology. Through data integration and computational analysis, it systematically elucidates the relationship between drugs and diseases and explores the drug mechanisms [14].

In this study, we screened and predicted potential targets and signaling pathways from curcumin as a potential medicine for cancer cure, through the network pharmacological and molecular docking techniques and laid down a scientific basis for later drug development and clinical application.

MATERIAL AND METHODS

Potential target scanning

Smiles of curcumin is taken from (https://pubchem. ncbi.nlm.nih.gov/)[15] .The data of uniprot IDs of potential targets for the compound was retrieved from super- PRED (https://prediction.charite. de/subpages /target_ prediction. php) [16] on 24 December 2024, by using the SMILES taken from pubchem. These uniprot IDs were used in another online server STRING (https://string-db.org/ Version: 12.0) [17] to find the target genes for the compound by specifying species as “Homo sapiens”. Colorectal genes forget genes were downloaded from Gene Card (https://www.genecards.org/) [18] accessed on 24 December 2024.

Protein-Protein Interaction Network

The overlapping targets of compound and Colorectal cancer were achieved through Venny 2.1 **(**https://bioinfogp.cnb.csic.es/tools/venny/**)** [19]. A total of 33 overlapping predicted targets were imported into STRING (https://string-db.org/ Version: 12.0) for PPI network analysis.

Network Pharmacology and Hub genes

Finally, an input excel file having common targets and disease target pathways was prepared for cytoscape. The targets from each database were merged in cytoscape. The common-targets network was constructed to check the interaction of active genes within the complex biological system by using Cytoscape V3.10.3 on 26 December 2024 [20]. It was used to investigate the relationship between the titled compound and predicted overlapping targets. The Cytoscape software was used to visualize and analyze the network by calculating centrality and other parameters. Then the plugin CytoHubba [21] was used to identify the top 10 genes based on Maximal Clique Centrality (MCC), Degree, Edge Percolated

Component (EPC), Closeness, Radiality, Betweenness and Stress (MCC) as shown in Table 3. The high centrality value represented the important role in the network.

Molecular docking

To explore binding energy between the hub genes and Curcumin in more detail, molecular docking was performed. The main objective of the docking process was to find out the interactions between the hub genes and Curcumin. The molecular docking was carried out using CB-Dock2 (https://cadd.labshare.cn/cb-dock2/index.php) an online tool which automatically identifies active sites within a given protein, Cavity volume (Å3),Center,(x, y, z),Docking size(x, y, z) and Contact residues [22]. PDB IDs for docking were obtained from the Protein Data Bank (http://www.rcsb.org) [23]. Similarly, 3D structure of Curcumin was obtained using the Pub hem compound database (https://pubchem. ncbi.nlm.nih.gov/) [15]. These structures of protein and the ligand were used as inputs for CB-Dock2, where the docking analysis was performed to investigate the binding activities between the proteins and Curcumin. The ligand–protein interactions were extracted and visualized using the Discovery Studio 4.5 software [24].

RESULT AND DISCUSSION

Compound and Disease Target genes collection

Curcumin's Smiles COC1=C(C=CC(=C1)/C=C/C(=O)CC(=O)/C=C/C2=CC(=C(C=C2)O)OC)O is obtained from pubchem (https://pubchem.ncbi.nlm.nih.gov/compound/969516#section=SMILES) [15]. The smiles is further used to retrieve the list of predicted gene targets from Super pred (https://prediction. charite.de/subpages/target_prediction.php) [16]. Total 91 uniprot IDs of gene targets were obtained and these uniprot IDs were imported to String 12.0 database (https://string-db.org/) [17] to get the target genes. Organisms settings was done to *Homosapiens* , network type was used as full network so that all types of inthomosapiens, networkimental, co-expression, database and text mining can be included. Required score was set as medium confidence of 0.400 and FDR stringency was taken medium 5% to control the likelihood of false-positive interactions. Colorectal cancer genes were obtained from the gene cards database (https://www.genecards.org/) [18]. Total 13674 genes were retrieved. To shortlist them filter is applied to Gifts more than 65 and got a list of 713 disease target genes.

Protein-Protein Interaction (PPI) Network

To get the overlapping genes we have used Venny 2.1 and got 33 common genes as shown in Fig 1 (a). These 33 common genes are then imported to String 12.0 database to get the PPI network, Gene Ontology and KEGG Pathways. In PPI network the stats observed was, number of nodes: 33, number of edges (interactions): 84, average node degree: 5.09 which means that each protein interacts with ~5.09 other proteins, avg. local clustering coefficient: 0.511 which means that ~51.1% of the neighbors of a given protein are also connected to each other, expected number of edges: 37 and PPI enrichment p-value: 2.53e-11 shown in Fig 1(b). The extremely low p-value (<0.05) indicates that the network connectivity measured in the observed study is statistically valid and unlikely to arise due to random chance. Curcumin may exert its pharmacological action on colorectal cancer due to clusters of proteins with close connectivity and key biological pathways. The proteins identified with this network could serve as potential biomarkers or therapeutic targets for future experimental validation.

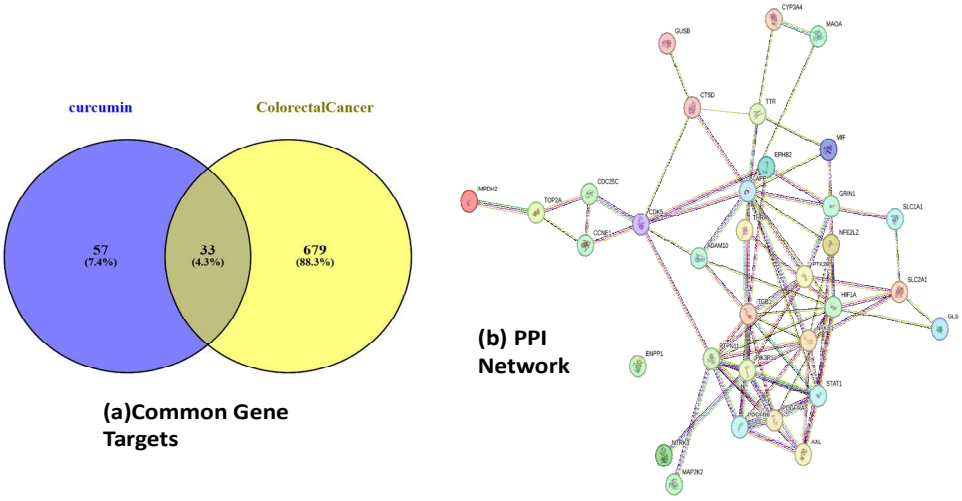


Fig 1(a) Venn Diagram of Curcumin and colorectal cancer common genes. (b) PPI network

Merged Network and Hub genes

Afterwards common target genes and disease target pathways are imported to Cytoscape 3.10.3. for getting the merged network and Hubb genes. The "Curcumin" target genes network and "colorectal cancer" targets network are shown in Fig 2(a) & (b).

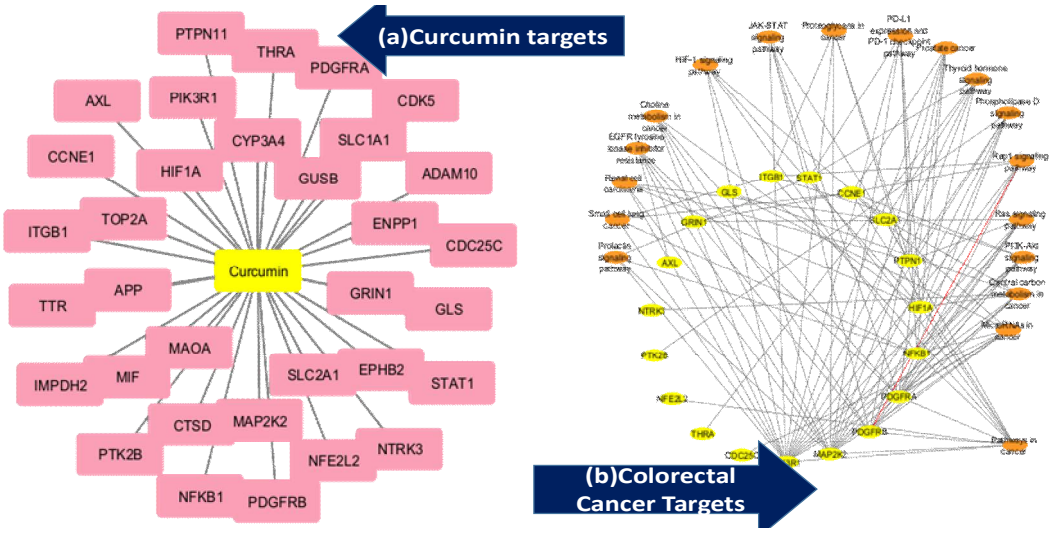


Fig2 (a) Curcumin targets of 33 Genes with 34 nodes and 33 edges (b) Colorectal Cancer target pathways with 37 nodes and 109 edges.

To identify the hub genes CytoHubba plugin in Cytoscape was used based on Maximum Clique Centrality (MCC)score ≥ 3 within the network as shown in Table 1 . The **MCC score** is a metric used to rank nodes or sub networks in biological and other complex networks.

Table 1 Top 10 Hub genes according to cyto hubba based on MCC score

Gene name	MCC	Degree	EPC	Closeness	Radiality	Betweenness	Stress
PIK3R1	19	19	19.021	35	2.45098	327.037	3002
MAP2K2	17	17	18.866	33.66667	2.37255	252.5561	2424
PDGFRA	12	12	17.532	30.33333	2.17647	124.1604	1234
PDGFRB	12	12	17.263	30.33333	2.17647	124.1604	1234
NFKB1	10	10	15.992	29	2.09804	102.0268	932
HIF1A	9	9	14.721	28.33333	2.05882	84.18573	772
PTPN11	7	7	12.474	27	1.98039	60.18176	506
SLC2A1	6	6	12.45	26.33333	1.94118	42.45874	394
STAT1	6	6	12.299	26.33333	1.94118	47.84725	408
CCNE1	6	6	13.457	26.33333	1.94118	40.86605	372

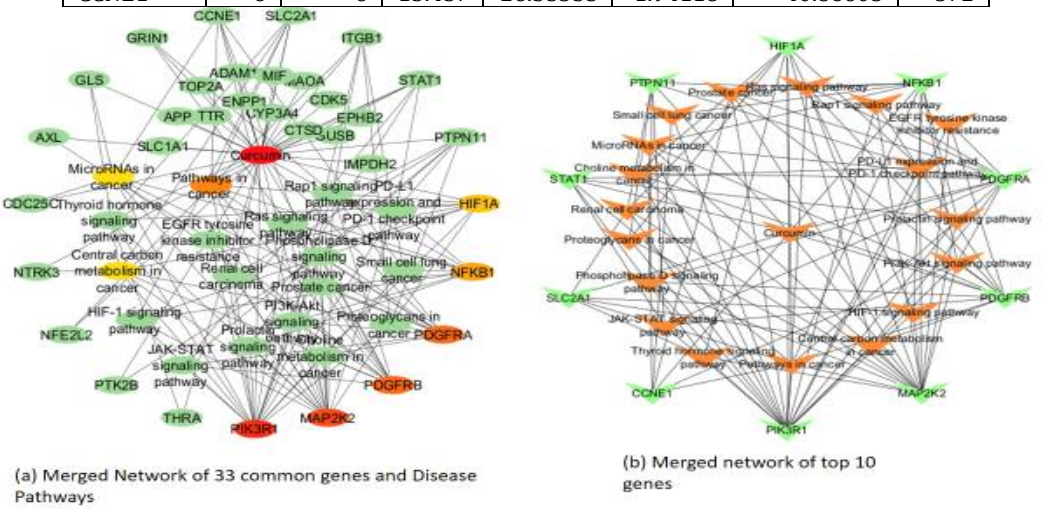
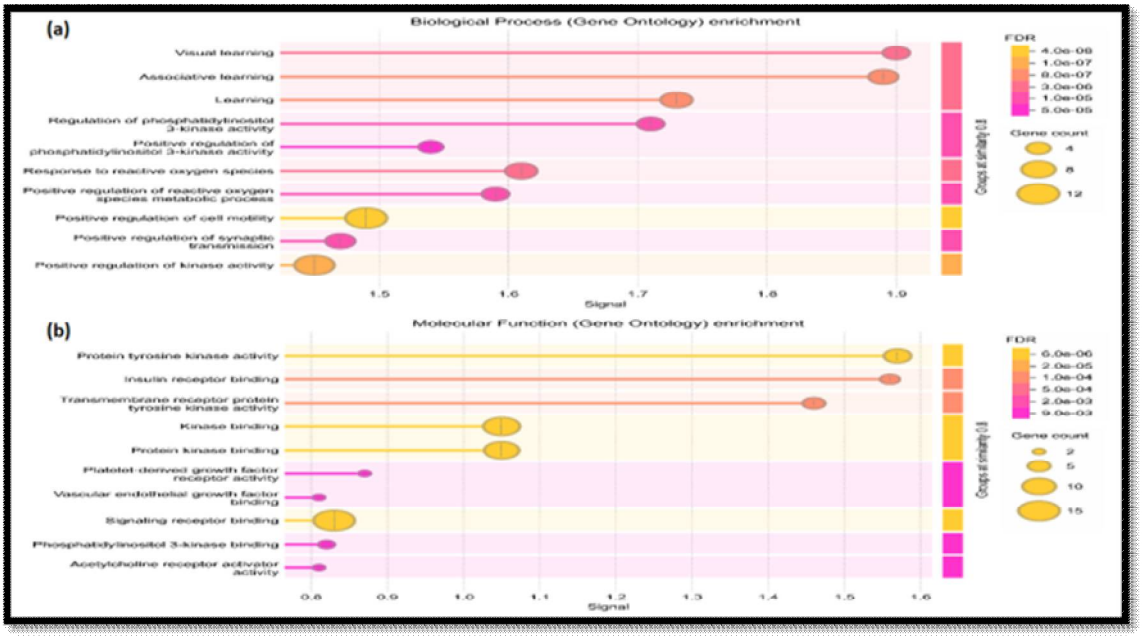


Fig 3 (a) Cluster 1: Merged network of common genes and related pathways with 52 nodes and 142 edges. Cluster 2: Expanded Merged Network of top 10 genes interactions based on MCC having 52 nodes and 142 edges.

Gene Ontology and KEGG analysis

Gene Ontology (GO) and KEGG pathways enrichment analysis was done by using string 12.0 version**.** The bubble charts depicting **gene enrichment analysis results** across biological processes or pathways, molecular function, cellular component and pathway enrichment are shown in Fig 5 (a),(b),(c) &(d) respectively. For analyzing this data Maximum **False Discovery Rate (**FDR) shown is taken ≤ 0.05, Minimum signal shown ≥ 0.01, Minimum strength shown ≥ 0.01, similarity ≥0.8 and Minimum count in network is 2. The color gradient represents the **False Discovery Rate (FDR),** which indicates the significance of enrichment [25]. The colors range from yellow to pink, representing FDR values, with yellow indicating the lowest FDR values (most significant) and pink indicating higher FDR values (less significant). The size of the bubbles corresponds to the gene count associated with each category. The largest bubbles within these regions indicate pathways with more genes contributing to their enrichment. In contrast, pathways in **dark pink regions** have lower significance (higher FDR) and generally smaller bubbles, meaning fewer genes are enriched. In biological process positive regulation of cell communication and positive regulation of kinase activity **enrichments** are most significant as shown in Fig 4 (a). In molecular function (Gene Ontology) enrichment, Signaling receptor binding, Protein binding and Kinase binding are most significant as they have least FDR value shown in Fig 4 (b). In Cellular Component (Gene Ontology) enrichment, Axon, Receptor complex and Cell surface are most significant Fig 4 (c).Top 10 KEGG pathways enrichment is shown in Fig 4 (d) and related genes are shown in Table 2. Central carbon metabolism in cancer has highest significance as it has lowest FDR value 1.0e-10 . Other pathways of significance are MicroRNAs in cancer with FDR value of 4.33e-08 , Pathways in cancer has (FDR 5.55e-08), PD-L1 expression and PD-1 checkpoint pathway in cancer (FDR 7.82e-070, Prostate cancer (1.16e-06),Thyroid hormone signaling pathway (3.24e-06), Ras signaling pathway (FDR 4.49e-06) and Renal cell carcinoma with 4.49E-06 FDR. On comparing table 1 and 2, we can say that top 10 hub genes are closely related to these pathways. The pathway enrichment analysis, provide insight into the molecular mechanisms for curcumin's anticancer activity. Further experimental validation of these interactions is needed to confirm the therapeutic value of curcumin for colorectal cancer.



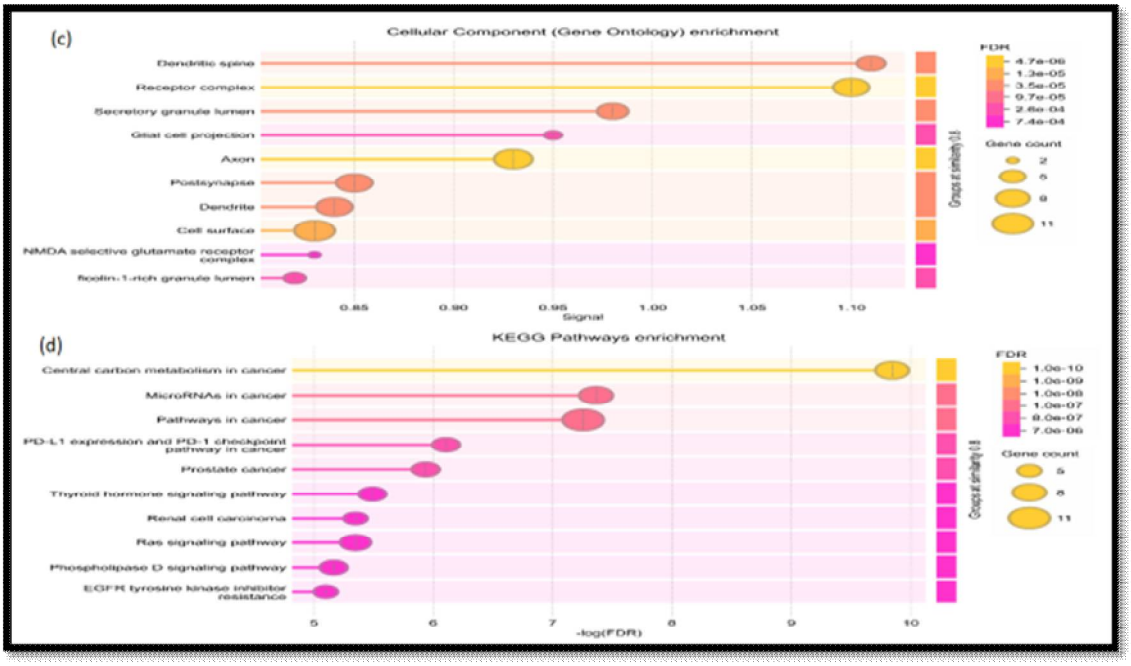


Fig 5 (a)Top10 Biological process enrichment, (b) Top 10 Molecular function enrichment (c) Top 10 Cellular Component enrichment and (d) Top 10 KEGG Pathways Enrichment

Table 2 Top 10 Pathways and related genes

ID	Description	Observed gene count	False discovery rate	Matching proteins in your network (labels)
hsa05230	Central carbon metabolism in cancer	8	1.43E-10	PDGFRA,PDGFRB,MAP2K2,GLS,NTRK3,SLC2A1,PIK3R1,HIF1A
hsa05206	MicroRNAs in cancer	8	4.33E-08	NFKB1,PDGFRA,PDGFRB,CCNE1,MAP2K2,GLS,CDC25C,PIK3R1
hsa05200	Pathways in cancer	11	5.55E-08	NFKB1,PDGFRA,PDGFRB,CCNE1,MAP2K2,STAT1,ITGB1,NFE2L2,SLC2A1,PIK3R1,HIF1A
hsa05235	PD-L1 expression and PD-1 checkpoint pathway in cancer	6	7.82E-07	NFKB1,MAP2K2,STAT1,PIK3R1,HIF1A,PTPN11
hsa05215	Prostate cancer	6	1.16E-06	NFKB1,PDGFRA,PDGFRB,CCNE1,MAP2K2,PIK3R1
hsa04919	Thyroid hormone signaling pathway	6	3.24E-06	MAP2K2,THRA,STAT1,SLC2A1,PIK3R1,HIF1A
hsa04014	Ras signaling pathway	7	4.49E-06	NFKB1,PDGFRA,PDGFRB,MAP2K2,GRIN1,PIK3R1,PTPN11
hsa05211	Renal cell carcinoma	5	4.49E-06	MAP2K2,SLC2A1,PIK3R1,HIF1A,PTPN11
hsa04072	Phospholipase D signaling pathway	6	6.85E-06	PDGFRA,PDGFRB,MAP2K2,PTK2B,PIK3R1,PTPN11
hsa01521	EGFR tyrosine kinase inhibitor resistance	5	7.97E-06	PDGFRA,PDGFRB,MAP2K2,AXL,PIK3R1
hsa05161	Hepatitis B	6	8.45E-06	NFKB1,CCNE1,MAP2K2,STAT1,PTK2B,PIK3R1

Molecular Docking

To verify our results for the drug-target interactions, these ten hub genes were selected as a target for molecular docking analysis. Table 3 shows the result of docking analysis of 10 proteins, which was performed by using CB-Dock2 . Binding energy less than -5 kcal/mol is usually considered to be a sign of improved target-ligand binding affinity, which in turn supports improved pharmacological activity [24]. The docking studies showed that all of the complexes between top 10 proteins with Curcumine had binding energies below -5 kcal/mol. The protein targets towards which the best binding energy is shown are PIK3R1 (PDB ID: 4JPS) (-9.5 kcal/mol), PDGFRA (PDB ID: 7LBF) (-8.0 kcal/mol) , SLC2A1 (PDBID:6THA)(-9.2 kcal/mol) and PTPN11 (PDB ID: 5EHR) (-8.8 kcal/mol). All the interacting residues

are also shown in Table 3. Fig 6 shows the 3-D and 2-D views of all interactions between Curcumin and top 10 Proteins. Also, the figure elucidates various types of interactions which are contributing to ligand stabilization in the binding pocket (Figure 6).

Table 3 Binding enegies of Top 10 proteins with Curcumin and Contact residues.

Protein Name	**PDB ID**	**Binding Energy (kcal/mol)**	**Cavity volume (Å³)**	**Center (x, y, z)**	**Docking size (x, y, z)**	**Contact residues**
PIK3R1	4JPS	-9.5	4691	-2, -30, 13	26, 34, 26	TYR165 VAL166 TYR167 PRO168 PRO169 ASN170 ASP258 GLU259 LYS271 GLN296 LEU297 PRO298 ASP300 ASP626 SER629 GLN630 TYR631 LEU632 ILE633 GLN661 ARG662 PHE666 HIS670 CYS695 GLY696 MET697 TYR698 HIS701 LEU752 LEU755 ASN756 PRO757 ALA758 HIS759 GLN760 MET811 LEU812 LEU814 GLN815 ARG818 PRO835 TYR836 GLY837 CYS838 LEU839 GLU849
MAP2K2	1S9I	-7.8	1150	41, 99, 48	26, 26, 26	LEU78 GLY79 ALA80 GLY81 ASN82 GLY83 GLY84 VAL86 ALA99 LYS101 ILE103 LEU119 LEU122 ILE145 MET147 GLU148 HIS149 MET150 ASP151 GLY153 SER154 GLN157 ARG193 ASP194 LYS196 SER198 ASN199 LEU201 CYS211 ASP212 PHE213 GLY214 VAL215 SER216 GLY217 LEU219 ILE220 MET223 VAL228 GLY229 THR230 ARG231 TYR233 ARG238 GLU106
PDGFRA	7LBF	-8.0	1779	188, 146, 114	26, 26, 35	ALA96 ASN97 SER98 GLN91 TYR92 TYR93 ILE94 LEU95 ALA96 ILE99 ASP110 TYR112 SER113 GLN115 LEU116 ARG117 LYS118 PRO119 ALA120 TYR122 VAL144 PRO145 TYR188 VAL189 GLY190 ARG212 GLN215 PHE222 TYR223 ASN226 ALA227 ARG230 ASN231 PHE233 ARG234 VAL235 LYS237 ILE239 GLN58 LEU97 THR99 THR107 GLU108 GLU109 ASN110 GLU111 LEU112 TYR118 ARG151 ARG175 GLN176
PDGFRB	3MJG	-7.9	1082	18, -49, 5	26, 26,26	GLU21 CYS49 SER50 GLY51 CYS52 CYS53 ASN54 ASN55 ARG56 VAL58 GLN59 CYS60 ARG61 VAL102 VAL22 GLU24 ILE25 SER26 ARG27 ARG28 LEU38 VAL39 TRP40 PRO42 CYS43 TYR207 GLU241 ASP263 PHE264 LEU265 ASP267 MET268 TYR270
NFKB1	1SVC	-7.0	175	44, 33, 36	26, 26, 26	PHE56 ARG57 PHE58 ARG59 TYR60 VAL61 ALA62 GLU63 GLY64 PRO65 HIS67 GLY68 ALA111 HIS112 SER113 VAL115 GLY116 ASP121 GLY122 LEU140 GLY141 ILE142 LEU143 HIS144 VAL145 THR146 LYS147 LYS148 LYS149 GLU152 THR153 ALA156 ARG157 GLU160 MET208 ASP209 LEU210 SER211 ASP242 LYS244 ALA245 PRO246 ASN247
HIF1A	4H6J	-7.6	292	7, -27, -21	26, 26, 26	LEU248 ILE324 TYR325 ASN326 THR327 LYS328 ASN329 GLN331 PRO332 GLN333 CYS334 VAL357 CYS358 GLN359 PRO360 THR361 ARG362 SER424 MET426 GLU435 TRP436 LEU437 TRP438 ARG440 THR441 SER442 THR460 THR462 ASN463 VAL464 LYS465 ASN466

PTPN11	5EHR	-8.8	1273	23, 42, 3	26,26,26	THR108 GLU110 ARG111 PHE113 HIS114 GLY115 HIS116 LEU117 LEU125 LEU216 ASN217 THR218 THR219 ARG229 GLU232 LEU233 LYS235 LEU236 ALA237 GLY246 GLU249 GLU250 THR253 LEU254 GLN257 ASP489 PRO491 LYS492 THR493 GLN495
SLC2A1	6THA	-9.2	1275	20, 56, 14	26, 26, 26	PHE26 THR30 SER73 GLY76 SER80 PHE81 VAL83 GLY134 THR137 GLY138 PRO141 MET142 HIS160 GLN161 ILE164 VAL165 ILE168 GLN282 GLN283 ILE287 ASN288 PHE291 TYR292 ASN317 THR321 SER324 PHE379 GLU380 GLY384 PRO385 TRP388 PHE389 ILE404 ALA405 ALA407 GLY408 PHE409 ASN411 TRP412 ASN415
STAT1	1YVL	-7.0	1328	-27, -27, 191	26, 26,26	LYS150 VAL153 MET154 GLU157 HIS158 ILE160 LYS161 GLU164 ASP165 GLU268 SER269 GLN271 GLN272 ARG274 GLN275 GLN276 LYS278 LYS279 PHE309 GLU353 GLN441 PRO442 LEU444 LYS1350 GLN1352 GLU1353 LEU1354 ASN1355 TYR1356 ASN1357 LYS1388 VAL1389 ASN1391 MET1392 GLU1393 GLU1394 ASN1397 GLY1398 SER1399 ALA1401 ALA1402 GLU1403 ARG1405 CYS1440 GLN1441 PRO1442
CCNE1	1W98	-7.1	3735	24, 1, -18	35, 26, 26	ARG50 SER53 LEU54 ARG122 ALA149 ARG150 ALA151 PHE152 GLY153 VAL154 PRO155 VAL156 ARG157 THR158 TYR159 TYR179 LYS108 TYR144 LYS145 LEU146 HIS147 ARG148 GLU149 LEU153 LEU187 GLU188 GLU189 ILE190 TYR191 LEU226 SER227 PRO228 LEU229 THR230 VAL232 SER233 ASN236 VAL237 GLN240 PRO253 GLN254 TYR255 GLN257 PHE260 GLY336 VAL337 ALA338 GLU340 ASP341 HIS343 ASN344 ILE345

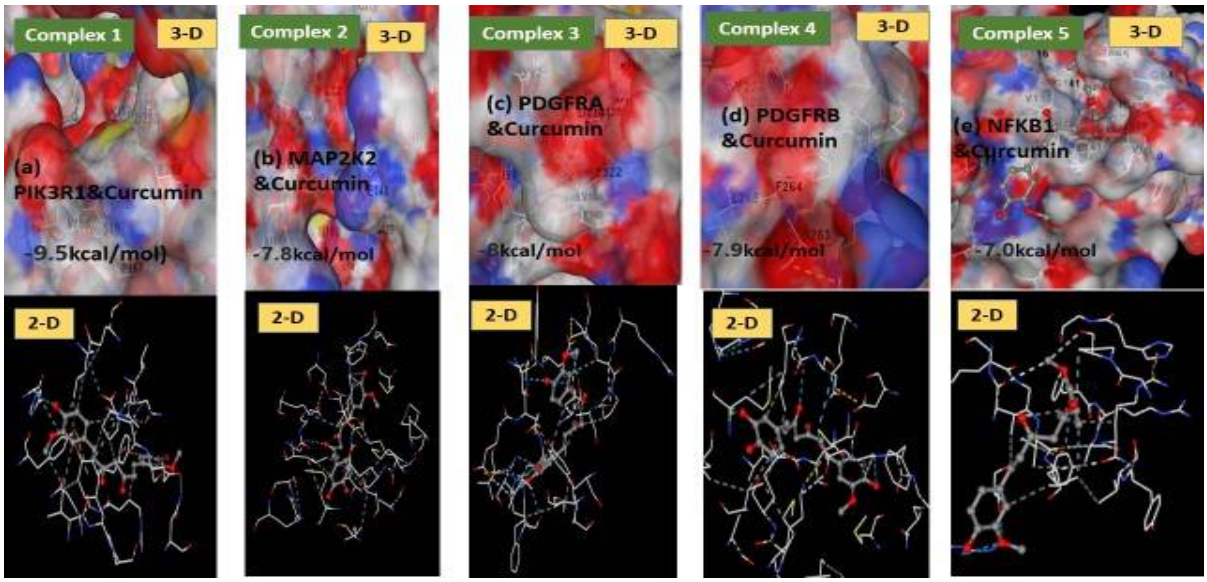


Fig 6 (a) complex of PIK3R1&Curcumin with binding energy -9.5kcal/mol) (b) MAP2K2 &Curcumin binding energy is -7.8kcal/mol (c) PDGFRA &Curcumin binding energy is -8kcal/mol (d) PDGFRB &Curcumin binding energy is -7.9kcal/mol, (e) NFKB1 &Curcumin binding energy is -7.0kcal/mol.

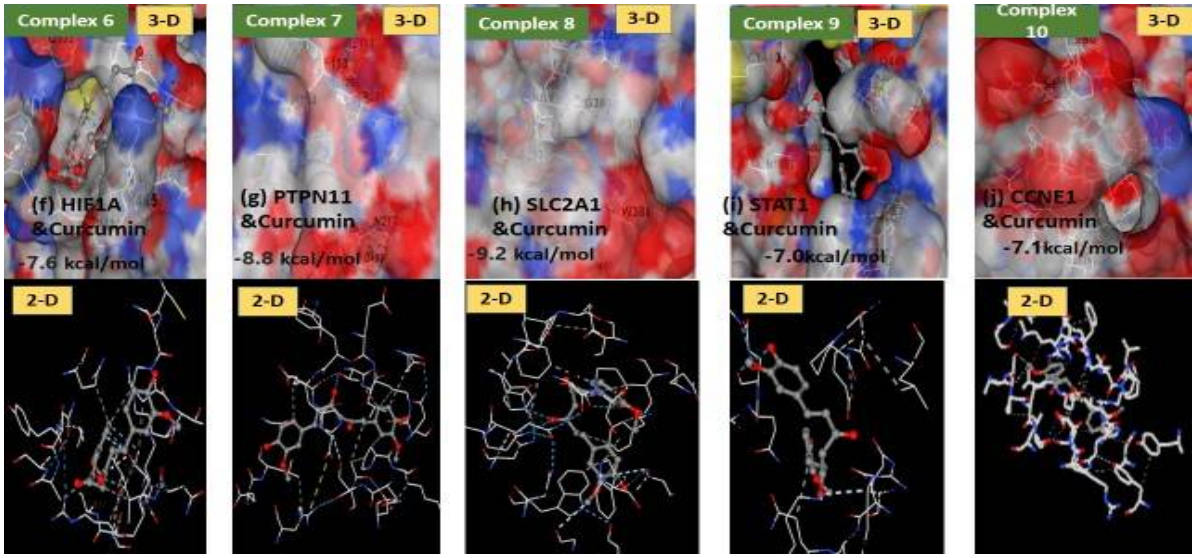


Fig 6 (f) HIF1A &Curcumin binding energy -7.6 kcal/mol, (g) PTPN11 &Curcumin binding energy -8.8 kcal/mol, (h) SLC2A1 &Curcumin binding energy -9.2 kcal/mol, (i) STAT1 &Curcumin binding energy -7.0kcal/mol and (j) CCNE1 &Curcumin binding energy -7.1kcal/mol

CONCLUSIONS AND FUTURE PROSPECTS

Our study aimed at predicting the complete target of Curcumin and its relevant pathways in the treatment of colorectal Cancer. We used the network pharmacology investigations of curcumin on colorectal cancer to derive 10 hub genes -PIK3R1, MAP2K2, PDGFRA, PDGFRB, NFKB1, HIF1A, PTPN11, SLC2A1, STAT1, and CCNE1-based on their MCC scores which tells the centrality of their roles in molecular mechanisms underlying colon cancer.

Gene Ontology (GO) and KEGG pathway enrichment analyses further spoke of the possible mechanisms by which curcumin modulates cancer-related pathways. The central pathways are Central Carbon Metabolism in Cancer (FDR=1.43E-10), involving genes PDGFRA, PDGFRB, MAP2K2, and HIF1A, indicating curcumin's role in interfering with metabolic reprogramming in cancer cells. MicroRNAs in Cancer (FDR=4.33E-08)-involving genes NFKB1, CCNE1, MAP2K2, suggests that curcumin has an effect on miRNA-mediated gene regulation.

Pathways in Cancer (FDR=5.55E-08), which include many hub genes like STAT1, PIK3R1, and NFKB1, as point to a wide action of curcumin on cancer-related signaling networks. Other pathways of significance include PD-L1 Expression and PD-1 Checkpoint Pathway in Cancer (FDR=7.82E-07), implicating genes STAT1 and PIK3R1, which support curcumin's action in modulating immune checkpoint pathways. Other important pathways included Ras Signaling, Thyroid Hormone Signaling, and EGFR Tyrosine Kinase Inhibitor Resistance-very critical for the development and treatment resistance of colorectal cancer. Moreover, in our docking study, both PIK3R1 (-9.5 kcal/mol) and SLC2A1 (-9.2 kcal/mol) showed very intense interactions with curcumin, representatively making them leading targets. PTPN11 showed an entertaining binding affinity (-8.8 kcal/mol), a place for taking its action in mechanism with curcumin. Proteins which have shown moderate binding energy are PDGFRA, PDGFRB, and MAP2K2 (-7.8 to -8.0 kcal/mol). They are further validated as potential targets.NFKB1, STAT1, and CCNE1 showed relatively low binding affinities (-7.0 to -7.1 kcal/mol), although they also do remain important. Molecular docking studies support the results of curcumin binding to other hub proteins involved with colorectal cancer, which possibly validate its status as a multi-target therapeutic agent corresponding to PIK3R1, SLC2A1, and PTPN11. These results, together with pathway enrichment analysis, provide insight into the molecular mechanisms for curcumin's anticancer activity. Further experimental validation of these interactions is needed to confirm the therapeutic value of curcumin for colorectal cancer. Collectively, we can say that these studies indicate curcumin might exert anti-tumor effects in colorectal cancer treatment through modulating key regulatory pathways on cellular metabolism, immune pathways, signaling pathways, and tumor progression. This study provides a solid basis for future experimental and clinical investigations to validate those identified hub genes and pathways as prospective therapeutic targets of curcumin in treating colorectal cancer.

CONFLICTS OF INTEREST
The authors declare that they have no conflict of interest.

ETHICAL APPROVAL
Not applicable.

CONSENT TO PUBLICATION
All the authors consented to publish the manuscript.

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