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Deciphering the Anti-Colorectal Cancer Mechanisms of Piperine Using Network Pharmacology

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Abstract: *Colorectal cancer is one of the leading causes of cancer-related mortality worldwide, necessitating the development of safer and more effective therapeutic agents. Piperine, a major bioactive alkaloid isolated from Piper nigrum, has demonstrated significant pharmacological activities including anticancer, anti-inflammatory, and antioxidant effects. The present study aimed to elucidate the molecular mechanisms underlying the anti-colorectal cancer activity of Piperine using a network pharmacology approach integrated with bioinformatics analysis. The physicochemical properties, pharmacokinetic behavior, drug-likeness, and toxicity profile of Piperine were evaluated using Swiss ADME and ProTox-3.0 databases. Potential targets of Piperine were identified using Swiss Target Prediction, while colorectal cancer-associated targets were collected from Gene Cards database. Common targets between Piperine and colorectal cancer were identified and subjected to protein–protein interaction (PPI) network construction using STRING. Functional enrichment analysis including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis was performed using DAVID. The results demonstrated that Piperine exhibited favorable drug-likeness characteristics with high gastrointestinal absorption and acceptable bioavailability. A total of several common targets associated with colorectal cancer progression were identified, including MTOR, SRC, JAK2, CDK4, and PARP1. KEGG analysis revealed enrichment in MAPK, mTOR, and focal adhesion signaling pathways. The findings suggest that Piperine exerts anti-colorectal cancer activity through multitarget and multi-pathway mechanisms and may serve as a promising candidate for future anticancer drug development.*

Keywords: Colorectal Cancer, Network Pharmacology, Protein–Protein Interaction, KEGG Pathway Analysis, Gene Ontology, Swiss Target Prediction, Bioinformatics, Anticancer Activity, Molecular Targets.

I. INTRODUCTION

Colorectal Cancer is one of the most common and life-threatening malignancies worldwide and represents a major public health challenge due to its increasing incidence and mortality rates. Colorectal cancer (CRC) develops through a multistep process involving genetic mutations, epigenetic alterations, chronic inflammation, oxidative stress, abnormal cell proliferation, and dysregulation of multiple signaling pathways. Despite significant advances in surgery, chemotherapy, radiotherapy, immunotherapy, and targeted therapies, the prognosis of advanced colorectal cancer remains poor because of drug resistance, metastasis, recurrence, and severe adverse effects associated with conventional anticancer treatments. Therefore, the identification of safer and more effective therapeutic agents with multitarget actions has become an important area of cancer research.[1,2]

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Natural products and phytochemicals have gained considerable attention in recent years because of their broad pharmacological activities, lower toxicity profiles, and ability to modulate multiple molecular pathways simultaneously. Among these phytochemicals, Piperine, the major bioactive alkaloid isolated from Piper nigrum, has emerged as a promising therapeutic compound with diverse biological activities including antioxidant, anti-inflammatory, antimicrobial, immunomodulatory, neuroprotective, hepatoprotective, and anticancer properties. Piperine has been reported to inhibit tumor cell proliferation, induce apoptosis, suppress angiogenesis, regulate cell cycle progression, and reduce metastasis in various cancer models. Furthermore, Piperine is known to enhance the bioavailability of several drugs and phytoconstituents by modulating drug-metabolizing enzymes and membrane transporters.[3,4]

Cancer is a multifactorial disease involving complex interactions among genes, proteins, signaling pathways, and cellular networks. Traditional "one drug–one target" approaches are often insufficient for effectively managing complex diseases such as colorectal cancer. In this context, network pharmacology has emerged as a powerful systems biology-based approach that integrates pharmacology, bioinformatics, molecular biology, and computational science to understand the interactions between drugs, targets, pathways, and diseases at a holistic level. Network pharmacology enables the identification of multitarget mechanisms and signaling pathways involved in the therapeutic effects of bioactive compounds. The integration of protein–protein interaction (PPI) analysis, Gene Ontology (GO), and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis provides deeper insights into the molecular mechanisms underlying disease modulation.[5,6]

Several studies have suggested the anticancer potential of Piperine; however, its precise molecular mechanisms against colorectal cancer remain incompletely understood. Therefore, the present study was designed to investigate the anti-colorectal cancer mechanisms of Piperine using a network pharmacology approach. The study involved prediction of Piperine-associated targets, identification of colorectal cancer-related genes, screening of common therapeutic targets, construction of protein–protein interaction networks, and enrichment analysis of GO functions and KEGG pathways. In addition, pharmacokinetic properties, drug-likeness characteristics, and toxicity profiles of Piperine were evaluated using in silico platforms. The findings of the present study may provide a scientific basis for understanding the multitarget therapeutic mechanisms of Piperine and support its further development as a potential phytochemical candidate for colorectal cancer therapy.[7,8]

II. MATERIALS AND METHOD

Collection of Piperine Structure and ADME Analysis

The 2D and 3D structures of Piperine were retrieved from the PubChem Database in SDF format. The physicochemical properties, pharmacokinetic profile, drug-likeness, lipophilicity, water solubility, medicinal chemistry parameters, and bioavailability radar plot were evaluated using the SwissADME Tool. Parameters including molecular weight, topological polar surface area (TPSA), hydrogen bond acceptors and donors, rotatable bonds, gastrointestinal absorption, blood-brain barrier permeability, cytochrome P450 inhibition, and Lipinski's rule of five were analyzed to determine the drug-likeness characteristics of Piperine.[9,10]

Prediction of Potential Targets of Piperine

The canonical SMILES structure of Piperine obtained from PubChem was submitted to the SwissTargetPrediction Database for prediction of possible protein targets. The species was selected as "Homo sapiens." Predicted targets with significant probability values were collected and duplicate targets were removed. The identified targets were further categorized according to their target classes including kinases, enzymes, membrane receptors, phosphodiesterases, ion channels, proteases, and nuclear receptors.[10,11]

Identification of Colorectal Cancer-Related Targets

Targets associated with Colorectal Cancer were collected from publicly available disease databases including: GeneCards . The keyword "Colorectal Cancer" was used for target retrieval. Duplicate entries were removed, and overlapping targets between Piperine and colorectal cancer were identified using Venn diagram analysis.[11]

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Construction of Protein–Protein Interaction (PPI) Network

The common targets between Piperine and colorectal cancer were imported into the STRING Database to construct the protein–protein interaction (PPI) network. The organism was set to "Homo sapiens" with a medium confidence score of 0.4. [11]

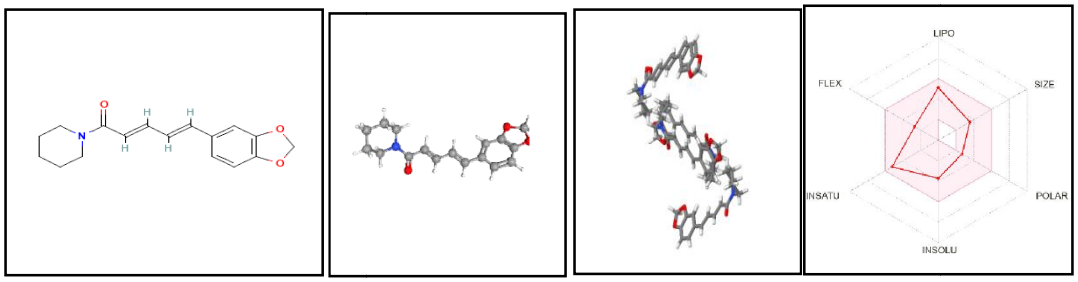
Toxicity Prediction Analysis

The toxicity profile of Piperine was predicted using the ProTox-3.0 Server. Organ toxicity, toxicity end points, nuclear receptor signaling pathways, stress response pathways, molecular initiating events, and cytochrome P450 metabolism-related toxicity predictions were evaluated. Toxicity radar charts were generated to visualize the toxicity confidence scores of Piperine.[12,13]

Functional and KEGG Pathway Enrichment Analysis

Functional enrichment analysis of the common targets associated with the anti-colorectal cancer activity of Piperine was performed using the ShinyGO v0.80 web server and the DAVID database. Gene Ontology (GO) enrichment analysis was carried out under three categories, namely Biological Process (BP), Cellular Component (CC), and Molecular Function (MF). In addition, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis was conducted to identify the major signaling pathways involved in the therapeutic mechanism of Piperine against colorectal cancer. Enrichment results with a p-value < 0.05 were considered statistically significant. The significantly enriched GO terms and KEGG pathways were ranked according to enrichment score and gene count, and the top enriched pathways and biological functions were visualized graphically using ShinyGO.[14]

III. RESULTS AND DISCUSSION



A B C D

Fig 1: A) 2D Structure B) 3D Conformer C) Crystal Structures from PubChem database and D) Radar plot of bioavailability of Piperine from Swiss ADME

Table 1: Physicochemical Properties of Piperine from Swiss ADME

Category	Parameter	Value
Physicochemical Properties	Molecular Formula	C17H19NO3
	Molecular Weight	285.34 g/mol
	Number of Heavy Atoms	21
	Number of Aromatic Heavy Atoms	6
	Fraction Csp3	0.35
	Number of Rotatable Bonds	4
	Number of H-Bond Acceptors	3
	Number of H-Bond Donors	0
	Molar Refractivity	85.47
	TPSA	38.77 Å²
Lipophilicity	Log Po/w (iLOGP)	3.38
	Log Po/w (XLOGP3)	3.46

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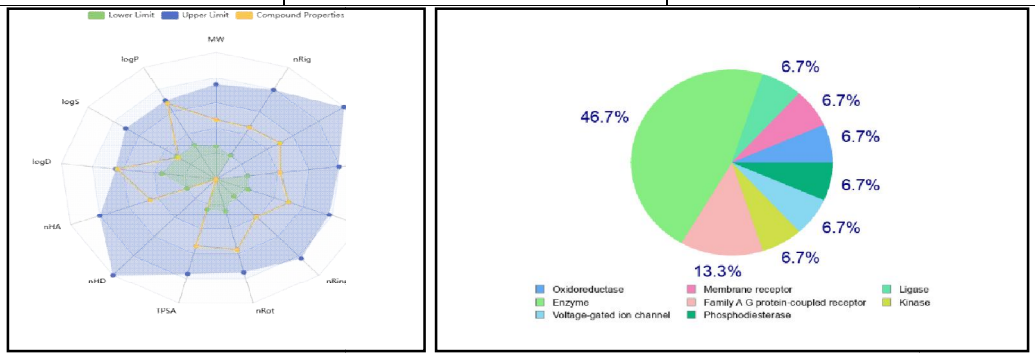
	Log Po/w (WLOGP)	2.51
	Log Po/w (MLOGP)	2.39
	Log Po/w (SILICOS-IT)	3.41
	Consensus Log Po/w	3.03
Water Solubility	Log S (ESOL)	-3.74
	Solubility (ESOL)	5.24×10^{-2} mg/ml ; 1.84×10^{-4} mol/l
	Class (ESOL)	Soluble
	Log S (Ali)	-3.96
	Solubility (Ali)	3.16×10^{-2} mg/ml ; 1.11×10^{-4} mol/l
	Class (Ali)	Soluble
	Log S (SILICOS-IT)	-3.00
	Solubility (SILICOS-IT)	2.87×10^{-1} mg/ml ; 1.00×10^{-3} mol/l
	Class (SILICOS-IT)	Soluble
Pharmacokinetics	GI Absorption	High
	BBB Permeant	Yes
	P-gp Substrate	No
	CYP1A2 Inhibitor	Yes
	CYP2C19 Inhibitor	Yes
	CYP2C9 Inhibitor	Yes
	CYP2D6 Inhibitor	No
	CYP3A4 Inhibitor	No
	Log Kp (Skin Permeation)	-5.58 cm/s
Drug likeness	Lipinski Rule	Yes; 0 violation
	Ghose Filter	Yes
	Veber Rule	Yes
	Egan Rule	Yes
	Muegge Rule	Yes
	Bioavailability Score	0.55
Medicinal Chemistry	PAINS Alerts	0 alert
	Brenk Alerts	2 alerts: michael_acceptor_1, polyene
	Leadlikeness	Yes
	Synthetic Accessibility	2.92



A B

Fig 2: Target Classes of Piperine from Swiss Target prediction

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Table 2: Targets of Piperine from Swiss Target prediction

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*
Monoamine oxidase B	MAOB	P27338	CHEMBL2039	Oxidoreductase	1
Sigma opioid receptor	SIGMAR1	Q99720	CHEMBL287	Membrane receptor	0.114337559
Acetyl-CoA carboxylase 2	ACACB	O00763	CHEMBL4829	Ligase	0.097874534
PI4-kinase beta subunit	PI4KB	Q9UBF8	CHEMBL3268	Enzyme	0.097874534
PI4-kinase alpha subunit	PI4KA	P42356	CHEMBL3667	Enzyme	0.097874534
Adenosine A2a receptor	ADORA2A	P29274	CHEMBL251	Family A G protein-coupled receptor	0.097874534
Steryl-sulfatase	STS	P08842	CHEMBL3559	Enzyme	0.097874534
Macrophage colony stimulating factor receptor	CSF1R	P07333	CHEMBL1844	Kinase	0.097874534
Anandamide amidohydrolase	FAAH	O00519	CHEMBL2243	Enzyme	0.097874534
6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3	PFKFB3	Q16875	CHEMBL2331053	Enzyme	0.097874534
N-acylsphingosine-amidohydrolase	NAAA	Q02083	CHEMBL4349	Enzyme	0.097874534
Acid ceramidase	ASAH1	Q13510	CHEMBL5463	Enzyme	0.097874534
Transient receptor potential cation channel subfamily M member 8 (by homology)	TRPM8	Q7Z2W7	CHEMBL1075319	Voltage-gated ion channel	0.097874534
Adenosine A3 receptor	ADORA3	P0DMS8	CHEMBL256	Family A G protein-coupled receptor	0.097874534
Phosphodiesterase 4D	PDE4D	Q08499	CHEMBL288	Phosphodiesterase	0.097874534
Poly [ADP-ribose] polymerase-1	PARP1	P09874	CHEMBL3105	Enzyme	0.097874534
Cathepsin L	CTSL	P07711	CHEMBL3837	Protease	0.097874534
Cathepsin (B and K)	CTSB	P07858	CHEMBL4072	Protease	0.097874534
Diacylglycerol O-acyltransferase 1	DGAT1	O75907	CHEMBL6009	Enzyme	0.097874534
Serine/threonine-protein kinase Aurora-B	AURKB	Q96GD4	CHEMBL2185	Kinase	0.097874534
Cyclin-dependent kinase 1	CDK1	P06493	CHEMBL308	Kinase	0.097874534
Sodium channel protein type IX alpha subunit	SCN9A	Q15858	CHEMBL4296	Voltage-gated ion channel	0.097874534

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Serine/threonine-protein kinase Aurora-A	AURKA	O14965	CHEMBL4722	Kinase	0.097874534
Adenosine A1 receptor	ADORA1	P30542	CHEMBL226	Family A G protein-coupled receptor	0.097874534
Endothelin receptor ET-A (by homology)	EDNRA	P25101	CHEMBL252	Family A G protein-coupled receptor	0.097874534
CDC7/DBF4 (Cell division cycle 7-related protein kinase/Activator of S phase kinase)	DBF4 CDC7	Q9UBU7 O00311	CHEMBL2111377	Kinase	0.097874534
CDC7/DBF4 (Cell division cycle 7-related protein kinase/Activator of S phase kinase)	CDC7	O00311	CHEMBL5443	Kinase	0.097874534
Acetylcholinesterase	ACHE	P22303	CHEMBL220	Hydrolase	0.097874534
Dopamine D2 receptor	DRD2	P14416	CHEMBL217	Family A G protein-coupled receptor	0.097874534
Serine/threonine-protein kinase Chk2	CHEK2	O96017	CHEMBL2527	Kinase	0.097874534
Phosphodiesterase 7A	PDE7A	Q13946	CHEMBL3012	Phosphodiesterase	0.097874534
Ribosomal protein S6 kinase 1	RPS6KB1	P23443	CHEMBL4501	Kinase	0.097874534
Sodium/glucose cotransporter 1	SLC5A1	P13866	CHEMBL4979	Electrochemical transporter	0.097874534
Nicotinamide phosphoribosyltransferase	NAMPT	P43490	CHEMBL1744525	Enzyme	0.097874534
p53-binding protein Mdm-2	MDM2	Q00987	CHEMBL5023	Other nuclear protein	0.097874534
Glucose-dependent insulinotropic receptor	GPR119	Q8TDV5	CHEMBL5652	Family A G protein-coupled receptor	0.097874534
Xanthine dehydrogenase	XDH	P47989	CHEMBL1929	Oxidoreductase	0.097874534
Nerve growth factor receptor Trk-A	NTRK1	P04629	CHEMBL2815	Kinase	0.097874534
Acyl coenzyme A:cholesterol acyltransferase 1	SOAT1	P35610	CHEMBL2782	Enzyme	0.097874534
Cathepsin (V and K)	CTSV	O60911	CHEMBL3272	Protease	0.097874534
DNA topoisomerase II alpha	TOP2A	P11388	CHEMBL1806	Isomerase	0.097874534
Ribosomal protein S6 kinase alpha 3	RPS6KA3	P51812	CHEMBL2345	Kinase	0.097874534

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Sphingosine 1-phosphate receptor Edg-1	S1PR1	P21453	CHEMBL4333	Family A G protein-coupled receptor	0.097874534
Tyrosine-protein kinase ABL	ABL1	P00519	CHEMBL1862	Kinase	0.097874534
Tyrosine-protein kinase LCK	LCK	P06239	CHEMBL258	Kinase	0.097874534
15-hydroxyprostaglandin dehydrogenase [NAD+]	HPGD	P15428	CHEMBL1293255	Enzyme	0.097874534
Epoxide hydratase	EPHX2	P34913	CHEMBL2409	Protease	0.097874534
Pyruvate kinase isozymes M1/M2	PKM	P14618	CHEMBL1075189	Enzyme	0.097874534
Inhibitor of nuclear factor kappa B kinase beta subunit	IKBKB	O14920	CHEMBL1991	Kinase	0.097874534
Beta secretase 2	BACE2	Q9Y5Z0	CHEMBL2525	Protease	0.097874534
Dipeptidyl peptidase IV	DPP4	P27487	CHEMBL284	Protease	0.097874534
Phosphodiesterase 10A	PDE10A	Q9Y233	CHEMBL4409	Phosphodiesterase	0.097874534
Vasopressin V1a receptor	AVPR1A	P37288	CHEMBL1889	Family A G protein-coupled receptor	0.097874534
Cytochrome P450 11B1	CYP11B1	P15538	CHEMBL1908	Cytochrome P450	0.097874534
MAP kinase-activated protein kinase 2	MAPKAPK2	P49137	CHEMBL2208	Kinase	0.097874534
Cytochrome P450 11B2	CYP11B2	P19099	CHEMBL2722	Cytochrome P450	0.097874534
MAP kinase signal-integrating kinase 2	MKNK2	Q9HBH9	CHEMBL4204	Kinase	0.097874534
Dynamin-1	DNM1	Q05193	CHEMBL4958	Enzyme	0.097874534
Adenosine A2b receptor	ADORA2B	P29275	CHEMBL255	Family A G protein-coupled receptor	0.097874534
Proteinase-activated receptor 1	F2R	P25116	CHEMBL3974	Family A G protein-coupled receptor	0.097874534
Cystic fibrosis transmembrane conductance regulator	CFTR	P13569	CHEMBL4051	Other ion channel	0.097874534
Corticotropin releasing factor receptor 1	CRHR1	P34998	CHEMBL1800	Family B G protein-coupled receptor	0.097874534
Thrombin	F2	P00734	CHEMBL204	Protease	0.097874534
Cyclin-dependent kinase 2/cyclin E	CCNE2 CDK2 CCNE1	O96020 P24941 P24864	CHEMBL2094126	Other cytosolic protein	0.097874534

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Interleukin-8 receptor B	CXCR2	P25025	CHEMBL2434	Family A G protein-coupled receptor	0.097874534
Glucocorticoid receptor	NR3C1	P04150	CHEMBL2034	Nuclear receptor	0.097874534
c-Jun N-terminal kinase 1	MAPK8	P45983	CHEMBL2276	Kinase	0.097874534
Serine/threonine-protein kinase mTOR	MTOR	P42345	CHEMBL2842	Kinase	0.097874534
Protein-tyrosine phosphatase 4A3	PTP4A3	O75365	CHEMBL4162	Phosphatase	0.097874534
Leucine-rich repeat serine/threonine-protein kinase 2	LRRK2	Q5S007	CHEMBL1075104	Kinase	0.097874534
Stem cell growth factor receptor	KIT	P10721	CHEMBL1936	Kinase	0.097874534
Platelet-derived growth factor receptor alpha	PDGFRA	P16234	CHEMBL2007	Kinase	0.097874534
Alpha-1b adrenergic receptor	ADRA1B	P35368	CHEMBL232	Family A G protein-coupled receptor	0.097874534
Tyrosine-protein kinase SRC	SRC	P12931	CHEMBL267	Kinase	0.097874534
Focal adhesion kinase 1	PTK2	Q05397	CHEMBL2695	Kinase	0.097874534
Tyrosine-protein kinase JAK2	JAK2	O60674	CHEMBL2971	Kinase	0.097874534
Rho-associated protein kinase 2	ROCK2	O75116	CHEMBL2973	Kinase	0.097874534
Rho-associated protein kinase 1	ROCK1	Q13464	CHEMBL3231	Kinase	0.097874534
Heat shock protein HSP 90-alpha	HSP90AA1	P07900	CHEMBL3880	Other cytosolic protein	0.097874534
cAMP-dependent protein kinase alpha-catalytic subunit	PRKACA	P17612	CHEMBL4101	Kinase	0.097874534
Acyl-CoA desaturase	SCD	O00767	CHEMBL5555	Enzyme	0.097874534
Type-1 angiotensin II receptor	AGTR1	P30556	CHEMBL227	Family A G protein-coupled receptor	0.097874534
Lysosomal Pro-X carboxypeptidase	PRCP	P42785	CHEMBL2335	Protease	0.097874534
Hepatocyte growth factor receptor	MET	P08581	CHEMBL3717	Kinase	0.097874534
Neuropeptide Y receptor type 1	NPY1R	P25929	CHEMBL4777	Family A G protein-coupled receptor	0.097874534
Perforin-1	PRF1	P14222	CHEMBL5480	Other ion channel	0.097874534

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Lysine-specific demethylase 4D-like	KDM4E	B2RXH2	CHEMBL1293226	Eraser	0.097874534
Lysine-specific demethylase 5C	KDM5C	P41229	CHEMBL2163176	Eraser	0.097874534
ADAMTS4	ADAMTS4	O75173	CHEMBL2318	Protease	0.097874534
Cyclin-dependent kinase 2	CDK2	P24941	CHEMBL301	Kinase	0.097874534
CDK2/Cyclin A	CCNA2 CDK2	P20248 P24941	CHEMBL3038469	Kinase	0.097874534
Cyclin-dependent kinase 4	CDK4	P11802	CHEMBL331	Kinase	0.097874534
Lysine-specific demethylase 4A	KDM4A	O75164	CHEMBL5896	Eraser	0.097874534
Lysine-specific demethylase 4D	KDM4D	Q6B0I6	CHEMBL6138	Eraser	0.097874534
Lysine-specific demethylase 4C	KDM4C	Q9H3R0	CHEMBL6175	Eraser	0.097874534

Table 3: toxicity prediction of Piperine from ProTox 3.0

Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	dili	Inactive	0.91
Organ toxicity	Neurotoxicity	neuro	Active	0.66
Organ toxicity	Nephrotoxicity	nephro	Inactive	0.54
Organ toxicity	Respiratory toxicity	respi	Active	0.83
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.77
Toxicity end points	Carcinogenicity	carcino	Active	0.53
Toxicity end points	Immunotoxicity	immuno	Active	0.96
Toxicity end points	Mutagenicity	mutagen	Inactive	0.96
Toxicity end points	Cytotoxicity	cyto	Inactive	0.53
Toxicity end points	BBB-barrier	bbb	Active	0.98
Toxicity end points	Ecotoxicity	eco	Inactive	0.51
Toxicity end points	Clinical toxicity	clinical	Active	0.69
Toxicity end points	Nutritional toxicity	nutri	Inactive	0.61
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Active	0.99
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_aromatase	Inactive	0.98
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Active	0.99

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Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_gamma	Inactive	0.99
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.96
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.96
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.95
Tox21-Stress response pathways	Phosphoprotein (Tumor Supressor) p53	sr_p53	Inactive	0.99
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Active	1
Molecular Initiating Events	Thyroid hormone receptor alpha (THRα)	mie_thr_alpha	Inactive	0.90
Molecular Initiating Events	Thyroid hormone receptor beta (THRβ)	mie_thr_beta	Inactive	0.78
Molecular Initiating Events	Transtyretrin (TTR)	mie_ttr	Inactive	0.97
Molecular Initiating Events	Ryanodine receptor (RYR)	mie_ryr	Inactive	0.98
Molecular Initiating Events	GABA receptor (GABAR)	mie_gabar	Inactive	0.96
Molecular Initiating Events	Glutamate N-methyl-D-aspartate receptor (NMDAR)	mie_nmdar	Inactive	0.92
Molecular Initiating Events	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate receptor (AMPAR)	mie_ampar	Inactive	0.97
Molecular Initiating Events	Kainate receptor (KAR)	mie_kar	Inactive	0.99
Molecular Initiating Events	Achetylcholinesterase (AChE)	mie_ache	Inactive	0.91
Molecular Initiating Events	Constitutive androstane receptor (CAR)	mie_car	Inactive	0.98
Molecular Initiating Events	Pregnane X receptor (PXR)	mie_pxr	Inactive	0.92
Molecular Initiating Events	NADH-quinone oxidoreductase (NADHOX)	mie_nadhox	Inactive	0.97
Molecular Initiating Events	Voltage gated sodium channel (VGSC)	mie_vgsc	Inactive	0.95
Molecular Initiating Events	Na+/I- symporter (NIS)	mie_nis	Inactive	0.98
Metabolism	Cytochrome CYP1A2	CYP1A2	Inactive	0.71
Metabolism	Cytochrome CYP2C19	CYP2C19	Inactive	0.91

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Metabolism	Cytochrome CYP2C9	CYP2C9	Inactive	0.73
Metabolism	Cytochrome CYP2D6	CYP2D6	Active	0.87
Metabolism	Cytochrome CYP3A4	CYP3A4	Inactive	0.53
Metabolism	Cytochrome CYP2E1	CYP2E1	Inactive	1

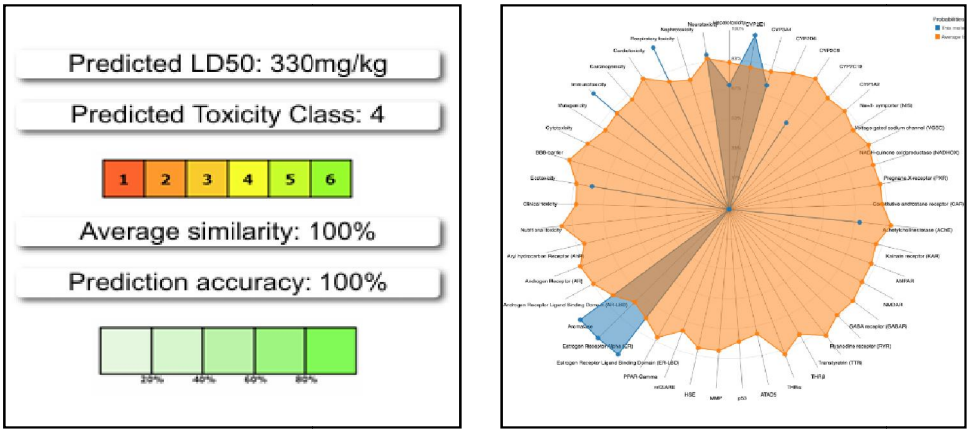

Fig 3: The toxicity radar chart is intended to quickly illustrate the confidence of positive toxicity results compared to the average of its class. from ProTox 3.0

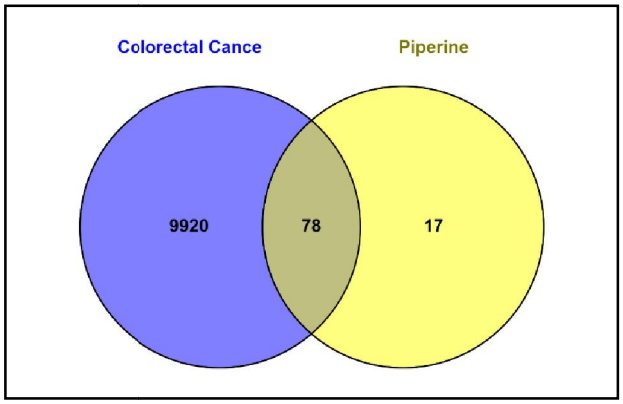

Fig 4: Common targets of Colorectal Cancer and Piperine (Venny 2.0)

Table 4: Common targets of Colorectal Cancer and Piperine (Venny 2.0)

Disease	Compound	Common Targets
Colorectal Cancer	Piperine	CHEK2, MET, KIT, PDGFRA, CDK4, MTOR, MDM2, SRC, AURKA, NTRK1, PTK2, PARP1, JAK2, CFTR, CDK2, CDK1, TOP2A, HSP90AA1, ABL1, PKM, MAPK8, RPS6KB1, AURKB, PRKACA, CTSB, CSF1R, IKBKB, CXCR2, PTP4A3, ROCK1, DPP4, PRF1, HPGD, LCK, NR3C1, CTSL, F2R, KDM5C, NAMPT, PFKFB3, EDNRA, LRRK2, KDM4C, AGTR1, XDH, TRPM8, ROCK2, F2, SCD, STS, DRD2, S1PR1, MAPKAPK2, KDM4A, ASAH1, EPHX2, RPS6KA3, CDC7, ADORA2A, SOAT1, ACHE, PDE4D, SLC5A1, CTSV, ADORA3, PI4KB, ADORA2B, MKNK2, FAAH, ADORA1, CRHR1, SCN9A, ACACB, SIGMAR1, ADAMTS4, GPR119, ADRA1B, MAOB

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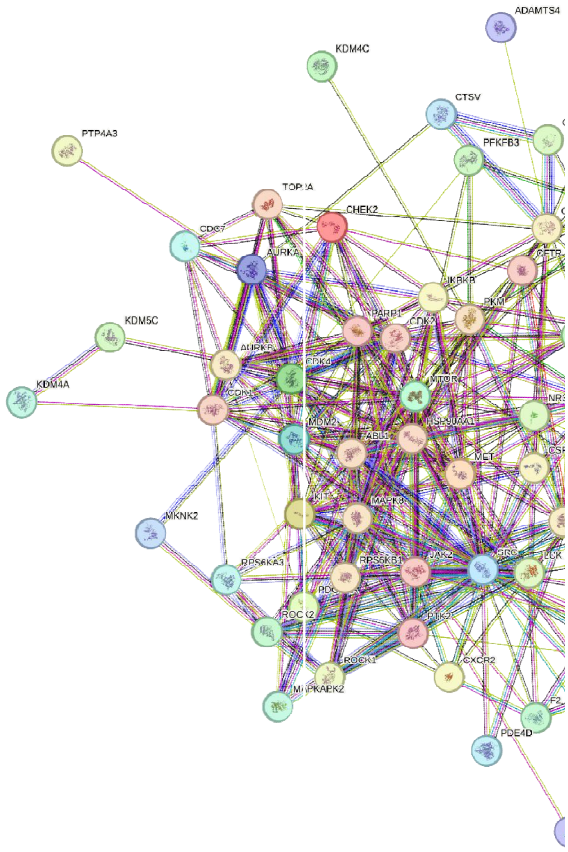

Fig 5: Protein- protein interaction (STRING)

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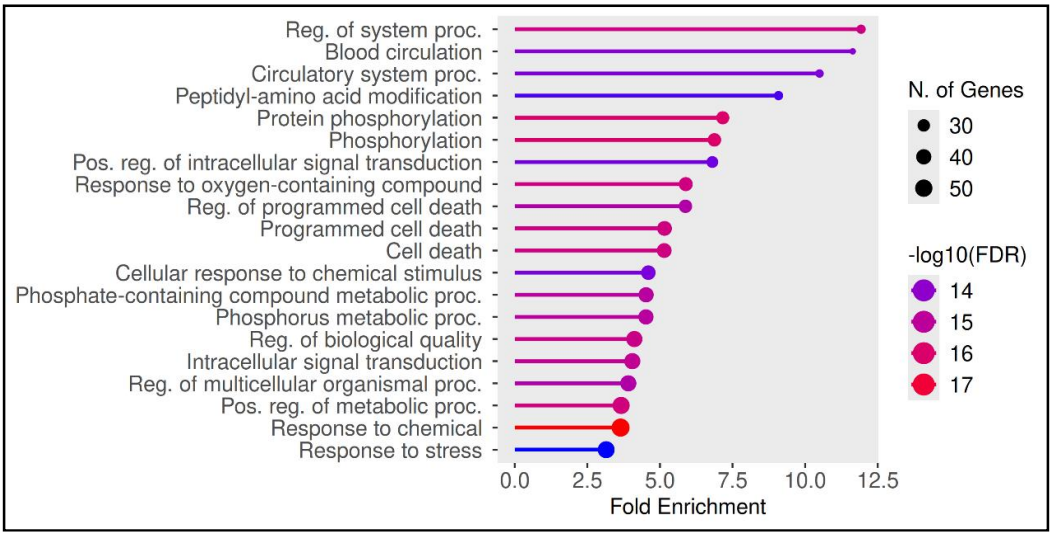

Fig 6: GO CELLULAR

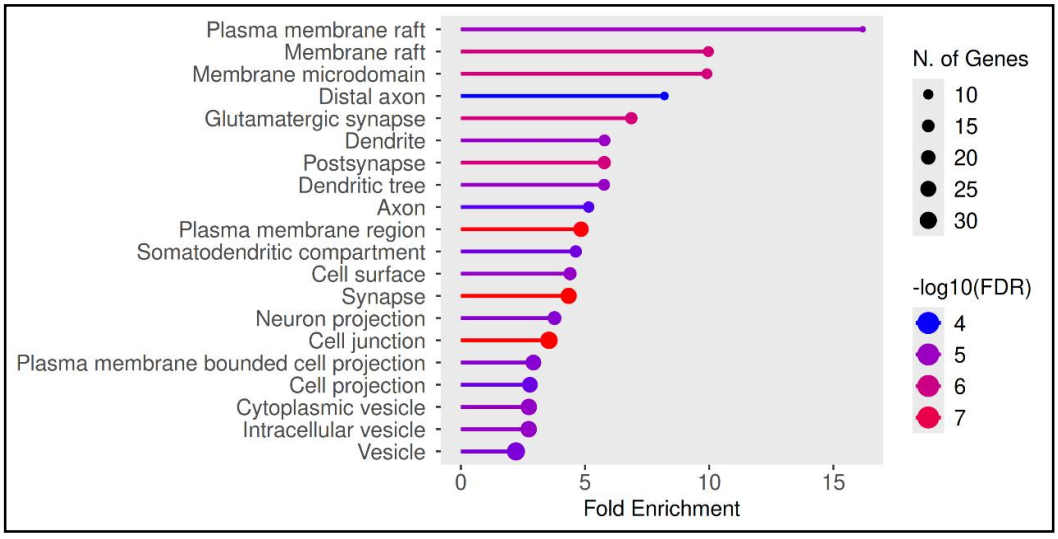

Fig 7: GO BIOLOGICAL

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GO CELLULAR

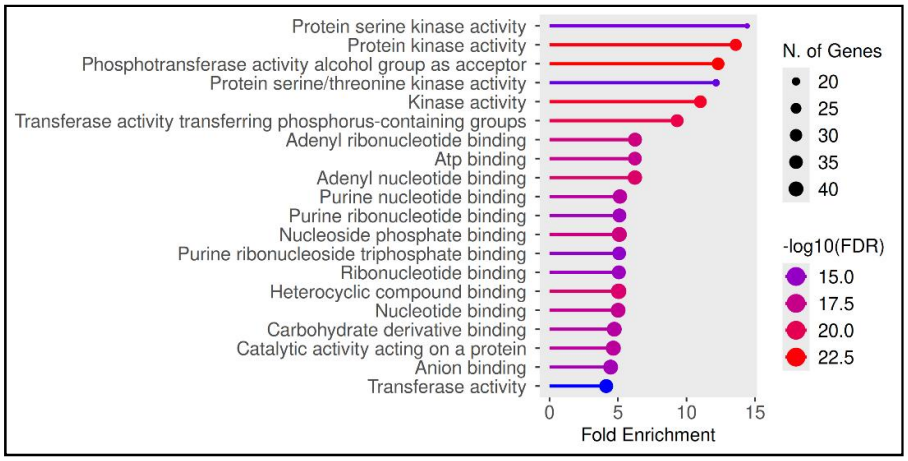

Fig 8: GO MOLECULAR FUNCTION

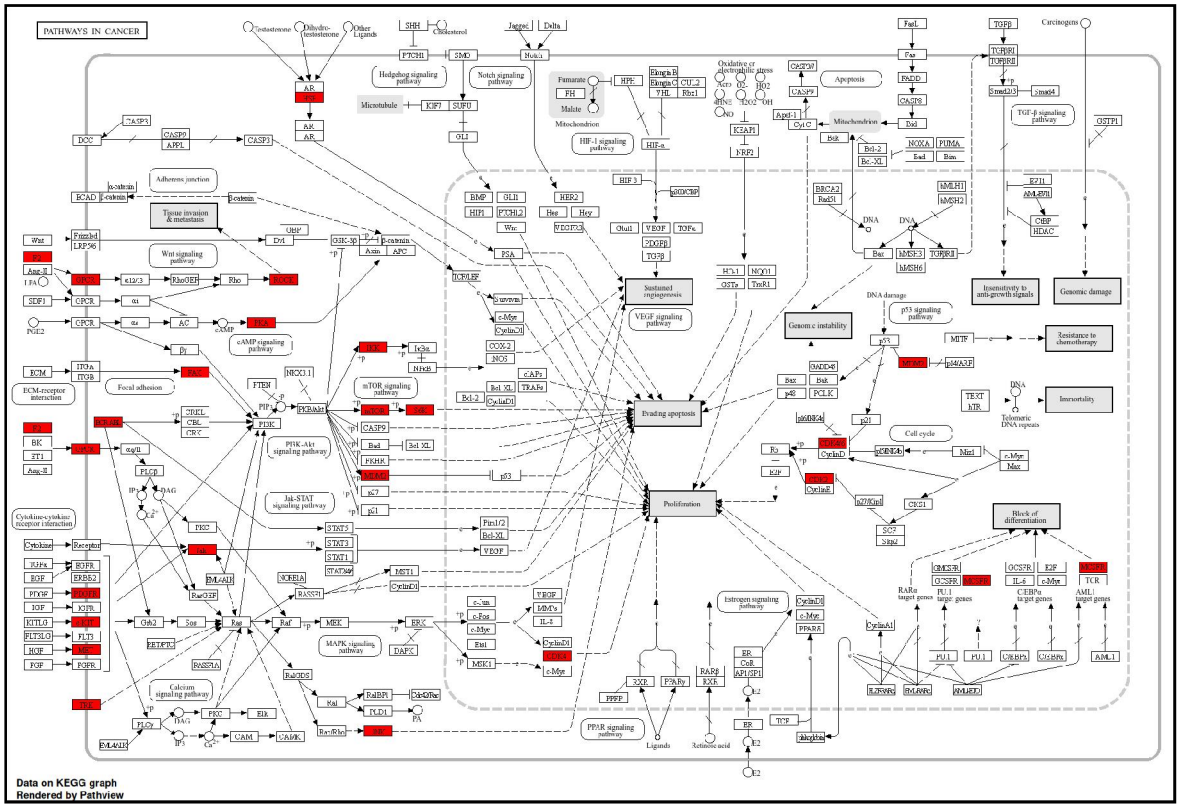

Fig 9: KEGG ANALYSIS

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Discussion:

The present study investigated the anti-colorectal cancer potential of Piperine through an integrated network pharmacology approach. SwissADME analysis demonstrated that Piperine possesses favorable drug-likeness characteristics with good gastrointestinal absorption, acceptable lipophilicity, high bioavailability score, and compliance with Lipinski's rule of five, indicating its suitability as a potential orally active therapeutic agent. SwissTargetPrediction identified several biologically relevant targets associated with cancer progression, cell proliferation, apoptosis, inflammation, and metastasis. Overlapping analysis between Piperine-associated targets and colorectal cancer-related genes revealed multiple common therapeutic targets including MTOR, SRC, JAK2, CDK4, TOP2A, and PARP1, suggesting the multitarget therapeutic potential of Piperine against colorectal cancer. The PPI network analysis highlighted strong interactions among hub proteins involved in tumor growth and signaling regulation. GO enrichment analysis revealed that the common targets were mainly associated with protein phosphorylation, regulation of apoptosis, inflammatory response, kinase activity, ATP binding, and membrane-associated cellular components. KEGG pathway analysis demonstrated significant enrichment in cancer-related pathways including PI3K-Akt signaling, MAPK signaling, focal adhesion, mTOR signaling, and pathways in cancer, indicating that Piperine may exert anticancer effects through modulation of multiple molecular pathways. Toxicity prediction analysis showed that Piperine possesses relatively acceptable toxicity characteristics, although some predictions indicated possible neurotoxicity, respiratory toxicity, and immunotoxicity, which require further experimental validation. Overall, the findings suggest that Piperine may inhibit colorectal cancer progression through multitarget and multipathway mechanisms and could serve as a promising phytochemical candidate for future anticancer drug development.

Limitation of the Study

The present study is primarily based on computational and bioinformatics approaches, and therefore several limitations should be considered. The predicted targets and signaling pathways were obtained from publicly available databases and may not fully represent the complex biological interactions occurring in vivo. Protein–protein interaction networks and enrichment analyses are dependent on database accuracy and may include false-positive associations. In addition, molecular mechanisms identified in the present study were not experimentally validated through in vitro or in vivo studies. Toxicity predictions generated using computational platforms require further confirmation through preclinical toxicological evaluation. Moreover, the pharmacokinetic behavior and bioavailability of Piperine under physiological conditions may differ from in silico predictions. Therefore, further experimental investigations are necessary to validate the anticancer efficacy and molecular targets of Piperine against colorectal cancer.

IV. CONCLUSION

The present network pharmacology study successfully explored the potential molecular mechanisms underlying the anti-colorectal cancer activity of Piperine. The study demonstrated that Piperine possesses favorable pharmacokinetic and drug-likeness properties and interacts with multiple therapeutic targets involved in cancer progression, inflammation, apoptosis, and cell proliferation. Key hub targets such as MTOR, SRC, JAK2, CDK4, and TOP2A were identified as major targets associated with the therapeutic effects of Piperine. GO and KEGG enrichment analyses revealed that Piperine may regulate multiple signaling pathways including PI3K-Akt, MAPK, mTOR, and focal adhesion pathways. Overall, the findings indicate that Piperine exhibits promising multitarget anticancer potential and may serve as a valuable phytochemical candidate for colorectal cancer therapy.

Way Forward

Future studies should focus on validating the identified targets and signaling pathways through experimental approaches such as molecular docking, molecular dynamics simulation, cell line studies, gene expression analysis, western blotting, and animal models of colorectal cancer. In vitro studies using human colorectal cancer cell lines may

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help confirm the antiproliferative and apoptotic effects of Piperine. Furthermore, in vivo pharmacokinetic and toxicity studies are required to establish the safety profile and therapeutic efficacy of Piperine. Development of Piperine-loaded nanoformulations, targeted drug delivery systems, or combination therapies with existing chemotherapeutic agents may improve its bioavailability and therapeutic effectiveness. Clinical studies are ultimately required to evaluate the translational potential of Piperine as a novel anticancer agent for colorectal cancer management.

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