A NETWORK PHARMACOLOGY APPROACH TO EXPLORE *CLINACANTHUS NUTANS* ON COLORECTAL CANCER

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Abstract
Network pharmacology is a discipline that investigates traditional herbal medications using bioinformatic tools like chemical, protein, gene, and disease databases, and cytoscape, by visualizing the complex network of interactions between the chemical constituents in the medications and their targets. *Clinacanthus nutans* (CN) is a traditionally used medicinal herb that has been suggested for its role in cancer treatment. The current study investigated the network pharmacology of CN bioactives as a prospect for the treatment of colorectal cancer. A series of database mining steps were performed to create lists of bioactives, their targets, and target-related diseases. The network was constructed using cytoscape. In this study, 8 bioactives, i.e. β-amyrin, betulin, isovitexin, linolenyl alcohol, lupeol, orientin, palmitic acid, vitexin) were identified which interacted with 46 different targets. β-amyrin was identified as the most potent bioactive with 29 targets.

Keywords: Network Pharmacology, *Clinacanthus nutans*, Colorectal Cancer, Anticancer Therapy, Bioactives

Introduction

The traditional approach for drug discovery has been a single gene-drug approach, which limits the usage of drugs being discovered, as a majority of diseases can involve multiple genetic and environmental complexities. Even though a single drug is being used to target a single protein of interest, it is often not the case as the drug may be able to interact with multiple target proteins. Network pharmacology is an approach that studies multi-drug multi-target interactions. This is a discipline that is extremely useful when studying herbal and natural drugs and formulations, like Traditional Chinese medicine (TCM), Ayurveda, or single plant extracts (1).

Clinacanthus nutans (*C. nutans,* CN), more commonly known as Sabah snake grass belongs to the Acanthaceae family. This particular plant has been quite popular for use in traditional herbal medicine in South-East Asia (2, 3). Its pharmacological abilities include treatment for herpes simplex virus (HSV), diabetes, skin rashes, and snakes and insect bites. Many bioactive phytochemicals have been identified in its extracts that have been studied for different pharmacological properties, including cancer treatment (4, 5). The chemical classes of these compounds are namely flavonoids, glycosides, glycerolipids, cerebrosides, etc (6, 7).

Colorectal cancer (CRC) is currently the second most common form of neoplasm worldwide. In the year 2020 itself, an estimated 1.9 million new CRC cases were reported and the disease consumed 0.9 million lives (8). CRCs are cancers that originate from the colon and rectum. Adenomatous polyps, sessile serrated polyps (SSP), and traditional serrated adenomas (TSA) are some of the polyps that have the potential to become cancerous (9). Chemotherapeutic agents administered in CRC patients include fluoropyrimidine(5-FU)-based drugs, and multiple-agent administrations that contain oxaliplatin (OX), irinotecan (IRI), and capecitabine. Targeted therapy for CRCs has also been under development, which uses antibodies to target specific proteins associated with CRCs (10).

A number of research articles have highlighted the use of CN in the treatment of CRC. In an experimental study conducted in 2019, CN ethyl-acetate fractions (CNEAF) were found to induce reactive oxygen species (ROS)-dependent autophagy and apoptosis of HCT116 human colorectal cancer cells (11). Similar observations were made where CNEAF induced autophagy and apoptosis, increased ROS levels, dissipated mitochondrial membrane potential, increased expression of Bax, and decreased the expression of Bcl-2 and Bcl-X2 in HCT116 cell lines (12). In an *in vitro* investigation of the potential

of CN against cancer, the chloroform extracts of CN were shown to inhibit the proliferation of 7 cancer cell lines including the human colon adenocarcinoma cell line (LS-174T) (13).

Given the potential of CN extracts, the current study aims to identify the bioactive phytochemicals present in CN that play key roles in CRC treatment and investigate their targets, using network pharmacology. The purpose of this research is to create a network of CN bioactives representing their interactions with the target proteins/genes that are important in CRC.

Materials and Methods

Identifying the anticancer bioactives of CN

The initial phase of the study involved database mining to create a list of bioactives found in CN. Using a list of articles gathered using the NCBI database a comprehensive list of phytochemicals found in CN extracts was generated, followed by trimming of the list only to include the bioactives relevant in cancer therapy.

Identifying targets or the bioactives

The selected phytochemicals were then queried into the PubChem database in order to collect their PubChem IDs and structure data files (SDFs). PubChem is an online database with a vast list of chemicals, with resources like information on their structure, chemistry, and related publications (14). Subsequently, the SDF files were used to identify protein targets of the bioactive ligands with 70% similarity, using BindingDB. BindingBD is a multifunctional web tool that can be used to search ligands and targets, gather information on targets, out-link to other databases, and so on. UniProt is one of the websites that BindingDB target profiles provide links to. The information on gene names of the target proteins and their UniProt IDs were collected from the UniProt database (15, 16).

Identifying target-associated diseases and pathways

The list of target genes was then searched on DisGeNet to obtain the list of all diseases associated with each gene (17). The DisGeNet results were filtered to only include CRC and a list of genes/targets associated with CRC was created. This list of targets was subsequently utilized to trim out the list of bioactives to include only those interacting with the specific targets.

The target genes were also queried into the KEGG Mapper in order to identify the cellular pathways in which the genes play important roles (19). The pathways were reviewed in order to select those relevant in cancers. Other than referenced carcinogenic pathways, those pathways that are involved in cell-cycle regulation, DNA repair, and metabolic and immune regulation are also relevant when it comes to carcinogenesis (20).

Creating the network

Using the information gathered, a network was created in cytoscape (version 3.9.1). It is an open-source bioinformatic tool that can be used to create, visualize, and analyze biological networks, available at cytoscape.org (18).

Results

Bioactives search

A list of 131 bioactives found in CN was created following the initial literature search, out of which 19 compounds were referenced to play a role in anticancer therapy (Table 1). The PubChem search landed hits for 11 of these compounds as 8 of them were quite novel and not documented in any available databases. Two more compounds were left out of the list due to a lack of results from the BindingDB database. Following the selection criteria for bioactives interacting with genes/targets involved in CRC, a total of 8 bioactives remained. Table 1 shows a list of bioactives found in CN extracts that have been studied and suggested to play important roles in cancer treatment, according to several published articles. Table 2 shows the list of 8 bioactives with their PubChem IDs.

Table 1: List of bioactives found in CN that have anticancer properties, according to literature.

Bioactives	References
Beta-amyrin	(28)
Betulin	(28)
Entadamide C	(29)
Iso-orientin	(30,31)
Iso-vitexin	(30–32)
Linolenyl alcohol	(26)
Lupeol	(28)
Orientin	(30,31,33)
Palmitic acid	(26)
Phaeophorbide a	(34)
Vitexin	(30–33)
13^2- hydroxy-(13^2-R)-phaeophytin a	(34)
13^2- hydroxy-(13^2-S)-phaeophytin b	(34)
13^2-hydroxy-(13^2-R)-phaeophytin b	(34)
13^2-hydroxy-(13^2-S)-chlorophyll b	(34)
13^2-hydroxy-(13^2-S)-phaeophytin a	(34)
Clinamide D	(33)
P18PE - Purpurin-18 phytyl ester	(34)
Polysaccharide–peptide complex CNP-1-2	(34)

Table 2: List of bioactives from CN that interacts with targets involved in CRC.

Bioactive	[a]PubChemID
Beta-amyrin	73145
Betulin	72326
Iso-Vitexin	162350
Linolenyl Alcohol	6436081
Lupeol	259846
Orientin	5281675
Palmitic acid	985
Vitexin	5280441

[a] – Corresponding unique PubChem identification numbers for the bioactives, collected from the PubChem database.

CRC – CN bioactive network

In the visualized network of CRC and CN, the 8 bioactives were shown to interact with 46 different targets for CRC (Table 3), involving 84 possible interactions (Table 4). Orientin, linolenyl alcohol, and isovitexin each had a degree of 4, indicating that they interact with 4 targets. Vitexin was found to be able to target 6 CRC-related proteins, whereas palmitate could only target 5 genes. Both betulin and lupeol were observed in the network to target 16 different proteins related to CRC. The highest degree was observed in β-amyrin with a total of 29 targets. The highest number of ligands binding to a single target was recorded at 3 and the genes being targeted were: *ALK, ALPI, AR, CA7, CES1, CRYAB, ESR2, F3, GRIN2A, GRIN2B, GSK3B, HSD11B1, NR1H3, RORC,* and *SHBG*.

Table 3: Disease-Target, (list of genes associated with CRC).

	Disease	Gene		Disease	Gene
1	Colorectal Carcinoma	ACHE	24	Colorectal Carcinoma	FFAR1
2	Colorectal Carcinoma	AKR1B10	25	Colorectal Carcinoma	FXR1
3	Colorectal Carcinoma	ALB	26	Colorectal Carcinoma	GPBAR1
4	Colorectal Carcinoma	ALK	27	Colorectal Carcinoma	GRIN2A
5	Colorectal Carcinoma	ALOX15	28	Colorectal Carcinoma	GRIN2B
6	Colorectal Carcinoma	ALPI	29	Colorectal Carcinoma	GSK3B
7	Colorectal Carcinoma	AR	30	Colorectal Carcinoma	HMGCR
8	Colorectal Carcinoma	CA7	31	Colorectal Carcinoma	HSD11B1
9	Colorectal Carcinoma	CDC25B	32	Colorectal Carcinoma	ITGAV
10	Colorectal Carcinoma	CDK2	33	Colorectal Carcinoma	KDM2A
11	Colorectal Carcinoma	CDK9	34	Colorectal Carcinoma	LIG1
12	Colorectal Carcinoma	CES1	35	Colorectal Carcinoma	NR1H2
13	Colorectal Carcinoma	CRYAB	36	Colorectal Carcinoma	NR1H3
14	Colorectal Carcinoma	CYP17A1	37	Colorectal Carcinoma	NR1I2
15	Colorectal Carcinoma	CYP19A1	38	Colorectal Carcinoma	PPARA
16	Colorectal Carcinoma	ELANE	39	Colorectal Carcinoma	PTPN1
17	Colorectal Carcinoma	ESR1	40	Colorectal Carcinoma	PTPRC
18	Colorectal Carcinoma	ESR2	41	Colorectal Carcinoma	RELA
19	Colorectal Carcinoma	F2	42	Colorectal Carcinoma	RORC
20	Colorectal Carcinoma	F3	43	Colorectal Carcinoma	SHBG
21	Colorectal Carcinoma	FABP1	44	Colorectal Carcinoma	SLCO1B3
22	Colorectal Carcinoma	FABP4	45	Colorectal Carcinoma	SREBF2
23	Colorectal Carcinoma	FABP5	46	Colorectal Carcinoma	UGT2B7

Table 4: List of ligands with their target data.

Ligand Name	Uniprot ID	Universal name of target	Gene name
Palmitic acid	P15090	Fatty acid-binding protein, adipocyte	FABP4
Palmitic acid	Q01469	Fatty acid-binding protein 5	FABP5
Palmitic acid	O14842	Free fatty acid receptor 1	FFAR1
Palmitic acid	Q9Y2K7	Lysine-specific demethylase 2A	KDM2A
Palmitic acid	P07148	Fatty acid-binding protein, liver	FABP1
Betulin	P28845	Corticosteroid 11-beta-dehydrogenase isozyme 1	HSD11B1
Betulin	P23141	Liver carboxylesterase 1	CES1
Betulin	P02511	Alpha-crystallin B chain	CRYAB
Betulin	P10275	Androgen receptor	AR
Betulin	P13726	Tissue factor	F3
Betulin	P11511	Aromatase	CYP19A1
Betulin	Q92731	Estrogen receptor beta	ESR2
Betulin	P51114	Fragile X mental retardation syndrome-related protein 1	FXR1
Betulin	Q13224	Glutamate receptor ionotropic, NMDA 2B	GRIN2B
Betulin	Q8TDU6	G-protein coupled bile acid receptor 1	GPBAR1
Betulin	Q12879	Glutamate receptor ionotropic, NMDA 2A	GRIN2A
Betulin	P51449	Nuclear receptor ROR-gamma	RORC
Betulin	Q13133	Oxysterols receptor LXR-alpha	NR1H3
Betulin	P02768	Albumin	ALB
Betulin	P04278	Sex hormone-binding globulin	SHBG
Betulin	P16662	UDP-glucuronosyltransferase 2B7	UGT2B7
Beta-amyrin	P28845	Corticosteroid 11-beta-dehydrogenase isozyme 1	HSD11B1
Beta-amyrin	P04035	3-hydroxy-3-methylglutaryl-coenzyme A reductase	HMGCR
Beta-amyrin	P22303	Acetylcholinesterase	ACHE
Beta-amyrin	P23141	Liver carboxylesterase 1	CES1
Beta-amyrin	O60218	Aldo-keto reductase family 1 member B10	AKR1B10
Beta-amyrin	P02511	Alpha-crystallin B chain	CRYAB
Beta-amyrin	P10275	Androgen receptor	AR
Beta-amyrin	P16050	Polyunsaturated fatty acid lipoxygenase ALOX15	ALOX15
Beta-amyrin	P13726	Tissue factor	F3
Beta-amyrin	P05093	Steroid 17-alpha-hydroxylase/17,20 lyase	CYP17A1
Beta-amyrin	P11511	Aromatase	CYP19A1
Beta-amyrin	P18858	DNA ligase 1	LIG1
Beta-amyrin	P30305	M-phase inducer phosphatase 2	CDC25B
Beta-amyrin	Q92731	Estrogen receptor beta	ESR2
Beta-amyrin	P03372	Estrogen receptor	ESR1
Beta-amyrin	Q13224	Glutamate receptor ionotropic, NMDA 2B	GRIN2B
Beta-amyrin	P06756	Integrin alpha-V	ITGAV
Beta-amyrin	P08575	Receptor-type tyrosine-protein phosphatase C	PTPRC
Beta-amyrin	P08246	Neutrophil elastase	ELANE

Beta-amyrin	Q12879	Glutamate receptor ionotropic, NMDA 2A	GRIN2A
Beta-amyrin	Q04206	Transcription factor p65	RELA
Beta-amyrin	P51449	Nuclear receptor ROR-gamma	RORC
Beta-amyrin	Q13133	Oxysterols receptor LXR-alpha	NR1H3
Beta-amyrin	P55055	Oxysterols receptor LXR-beta	NR1H2
Beta-amyrin	P18031	Tyrosine-protein phosphatase non-receptor type 1	PTPN1
Beta-amyrin	P00734	Prothrombin	F2
Beta-amyrin	Q9NPD5	Solute carrier organic anion transporter family member 1B3	SLCO1B3
Beta-amyrin	Q12772	Sterol regulatory element-binding protein 2	SREBF2
Beta-amyrin	P04278	Sex hormone-binding globulin	SHBG
Iso-Vitexin	Q9UM73	ALK tyrosine kinase receptor	ALK
Iso-Vitexin	P43166	Carbonic anhydrase 7	CA7
Iso-Vitexin	P49841	Glycogen synthase kinase-3 beta	GSK3B
Iso-Vitexin	P09923	Intestinal-type alkaline phosphatase	ALPI
Lupeol	P28845	Corticosteroid 11-beta-dehydrogenase isozyme 1	HSD11B1
Lupeol	P23141	Liver carboxylesterase 1	CES1
Lupeol	P02511	Alpha-crystallin B chain	CRYAB
Lupeol	P10275	Androgen receptor	AR
Lupeol	P13726	Tissue factor	F3
Lupeol	P11511	Aromatase	CYP19A1
Lupeol	Q92731	Estrogen receptor beta	ESR2
Lupeol	P51114	Fragile X mental retardation syndrome-related protein 1	FXR1
Lupeol	Q13224	Glutamate receptor ionotropic, NMDA 2B	GRIN2B
Lupeol	Q8TDU6	G-protein coupled bile acid receptor 1	GPBAR1
Lupeol	Q12879	Glutamate receptor ionotropic, NMDA 2A	GRIN2A
Lupeol	P51449	Nuclear receptor ROR-gamma	RORC
Lupeol	Q13133	Oxysterols receptor LXR-alpha	NR1H3
Lupeol	P02768	Albumin	ALB
Lupeol	P04278	Sex hormone-binding globulin	SHBG
Lupeol	P16662	UDP-glucuronosyltransferase 2B7	UGT2B7
Vitexin	Q9UM73	ALK tyrosine kinase receptor	ALK
Vitexin	P43166	Carbonic anhydrase 7	CA7
Vitexin	P24941	Cyclin-dependent kinase 2	CDK2
Vitexin	P50750	Cyclin-dependent kinase 9	CDK9
Vitexin	P49841	Glycogen synthase kinase-3 beta	GSK3B
Vitexin	P09923	Intestinal-type alkaline phosphatase	ALPI
Orientin	Q9UM73	ALK tyrosine kinase receptor	ALK
Orientin	P43166	Carbonic anhydrase 7	CA7
Orientin	P49841	Glycogen synthase kinase-3 beta	GSK3B
Orientin	P09923	Intestinal-type alkaline phosphatase	ALPI
Linolenyl Alcohol	P15090	Fatty acid-binding protein, adipocyte	FABP4
Linolenyl Alcohol	O14842	Free fatty acid receptor 1	FFAR1

Linolenyl Alcohol	Q07869	Peroxisome proliferator-activated receptor alpha	PPARA
Linolenyl Alcohol	O75469	Nuclear receptor subfamily 1 group I member 2	NR1I2

The KEGG mapper yielded up to 179 distinct pathways associated with the 46 genes queried (Table 4). Some of the notable pathways identified using the KEGG mapper, relevant in cancers, involving the genes included: hsa03320 PPAR signaling pathway, hsa04014 Ras signaling pathway, hsa04110 cell cycle, hsa05200 pathways in cancer, hsa05210 colorectal cancer, and hsa05226 gastric cancer, among several others (Table 5). Figure 1 shows the visualized network of interactions between CN bioactives and CRC-relevant targets.

Table 5: KEGG pathways for genes in this study.

Uniprot ID	Gene Name	KEGG Gene ID	KEGG Pathways
P23141	CES1	hsa:10062	hsa03320 PPAR signaling pathway - Homo sapiens (human) (1)
P23142	CES2	hsa:10062	hsa04931 Insulin resistance - Homo sapiens (human) (1)
P23143	CES3	hsa:10062	hsa04932 Non-alcoholic fatty liver disease - Homo sapiens (human) (1)
P23144	CES4	hsa:10062	hsa05160 Hepatitis C - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa04068 FoxO signaling pathway - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa04110 Cell cycle - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa04114 Oocyte meiosis - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa04115 p53 signaling pathway - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa04151 PI3K-Akt signaling pathway - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa04218 Cellular senescence - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa04914 Progesterone-mediated oocyte maturation - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa04934 Cushing syndrome - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa05160 Hepatitis C - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa05161 Hepatitis B - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa05162 Measles - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa05165 Human papillomavirus infection - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa05166 Human T-cell leukemia virus 1 infection - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa05169 Epstein-Barr virus infection - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa05200 Pathways in cancer - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa05203 Viral carcinogenesis - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa05215 Prostate cancer - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa05222 Small cell lung cancer - Homo sapiens (human) (1)
P24941	CDK2	hsa:1017	hsa05226 Gastric cancer - Homo sapiens (human) (1)
P50750	CDK8	hsa:1025	hsa03250 Viral life cycle - HIV-1 - Homo sapiens (human) (1)
P50750	CDK9	hsa:1025	hsa05202 Transcriptional misregulation in cancer - Homo sapiens (human) (1)
P23141	CES1	hsa:1066	hsa00983 Drug metabolism - other enzymes - Homo sapiens (human) (1)
P02511	CRYAB	hsa:1410	hsa04213 Longevity regulating pathway - multiple species - Homo sapiens (human) (1)
P02511	CRYAB	hsa:1410	hsa04141 Protein processing in endoplasmic reticulum - Homo sapiens (human) (1)
Q8TDU6	GPBAR1	hsa:151306	-
P05093	CYP17A1	hsa:1586	hsa00140 Steroid hormone biosynthesis - Homo sapiens (human) (1)

P05093	CYP17A1	hsa:1586	hsa01100 Metabolic pathways - Homo sapiens (human) (1)
P05093	CYP17A1	hsa:1586	hsa04913 Ovarian steroidogenesis - Homo sapiens (human) (1)
P05093	CYP17A1	hsa:1586	hsa04917 Prolactin signaling pathway - Homo sapiens (human) (1)
P05093	CYP17A1	hsa:1586	hsa04927 Cortisol synthesis and secretion - Homo sapiens (human) (1)
P05093	CYP17A1	hsa:1586	hsa04934 Cushing syndrome - Homo sapiens (human) (1)
P11511	CYP19A1	hsa:1588	hsa00140 Steroid hormone biosynthesis - Homo sapiens (human) (1)
P11511	CYP19A1	hsa:1588	hsa01100 Metabolic pathways - Homo sapiens (human) (1)
P11511	CYP19A1	hsa:1588	hsa04913 Ovarian steroidogenesis - Homo sapiens (human) (1)
P08246	ELANE	hsa:1991	hsa05322 Systemic lupus erythematosus - Homo sapiens (human) (1)
P08246	ELANE	hsa:1991	hsa05202 Transcriptional misregulation in cancer - Homo sapiens (human) (1)
P08246	ELANE	hsa:1991	hsa04613 Neutrophil extracellular trap formation - Homo sapiens (human) (1)
P03372	ESR1	hsa:2099	hsa01522 Endocrine resistance - Homo sapiens (human) (1)
P03372	ESR1	hsa:2099	hsa04915 Estrogen signaling pathway - Homo sapiens (human) (1)
P03372	ESR1	hsa:2099	hsa04917 Prolactin signaling pathway - Homo sapiens (human) (1)
P03372	ESR1	hsa:2099	hsa04919 Thyroid hormone signaling pathway - Homo sapiens (human) (1)
P03372	ESR1	hsa:2099	hsa04961 Endocrine and other factor-regulated calcium reabsorption - Homo sapiens (human) (1)
P03372	ESR1	hsa:2099	hsa05200 Pathways in cancer - Homo sapiens (human) (1)
P03372	ESR1	hsa:2099	hsa05205 Proteoglycans in cancer - Homo sapiens (human) (1)
P03372	ESR1	hsa:2099	hsa05207 Chemical carcinogenesis - receptor activation - Homo sapiens (human) (1)
P03372	ESR1	hsa:2099	hsa05224 Breast cancer - Homo sapiens (human) (1)
Q92731	ESR2	hsa:2100	hsa01522 Endocrine resistance - Homo sapiens (human) (1)
Q92731	ESR2	hsa:2100	hsa04915 Estrogen signaling pathway - Homo sapiens (human) (1)
Q92731	ESR2	hsa:2100	hsa04917 Prolactin signaling pathway - Homo sapiens (human) (1)
Q92731	ESR2	hsa:2100	hsa04929 GnRH secretion - Homo sapiens (human) (1)
Q92731	ESR2	hsa:2100	hsa05200 Pathways in cancer - Homo sapiens (human) (1)
Q92731	ESR2	hsa:2100	hsa05207 Chemical carcinogenesis - receptor activation - Homo sapiens (human) (1)
Q92731	ESR2	hsa:2100	hsa05224 Breast cancer - Homo sapiens (human) (1)
P02768	ALB	hsa:213	hsa04918 Thyroid hormone synthesis - Homo sapiens (human) (1)
P00734	F2	hsa:2147	hsa04072 Phospholipase D signaling pathway - Homo sapiens (human) (1)
P00734	F2	hsa:2147	hsa04080 Neuroactive ligand-receptor interaction - Homo sapiens (human) (1)
P00734	F2	hsa:2147	hsa04610 Complement and coagulation cascades - Homo sapiens (human) (1)
P00734	F2	hsa:2147	hsa04611 Platelet activation - Homo sapiens (human) (1)
P00734	F2	hsa:2147	hsa04810 Regulation of actin cytoskeleton - Homo sapiens (human) (1)
P00734	F2	hsa:2147	hsa05130 Pathogenic Escherichia coli infection - Homo sapiens (human) (1)
P00734	F2	hsa:2147	hsa05171 Coronavirus disease - COVID-19 - Homo sapiens (human) (1)
P00734	F2	hsa:2147	hsa05200 Pathways in cancer - Homo sapiens (human) (1)
P13726	F3	hsa:2152	hsa04610 Complement and coagulation cascades - Homo sapiens (human) (1)
P13726	F3	hsa:2152	hsa04933 AGE-RAGE signaling pathway in diabetic complications - Homo sapiens (human) (1)
P15090	FABP4	hsa:2167	hsa03320 PPAR signaling pathway - Homo sapiens (human) (1)

P15090	FABP4	hsa:2167	hsa04923 Regulation of lipolysis in adipocytes - Homo sapiens (human) (1)
P07148	FABP1	hsa:2168	hsa04936 Alcoholic liver disease - Homo sapiens (human) (1)
P07148	FABP1	hsa:2168	hsa03320 PPAR signaling pathway - Homo sapiens (human) (1)
P07148	FABP1	hsa:2168	hsa04975 Fat digestion and absorption - Homo sapiens (human) (1)
Q01469	FABP5	hsa:2171	hsa03320 PPAR signaling pathway - Homo sapiens (human) (1)
Q9Y2K7	KDM2A	hsa:22992	-
Q9UM73	ALK	hsa:238	hsa05200 Pathways in cancer - Homo sapiens (human) (1)
Q9UM73	ALK	hsa:238	hsa05223 Non-small cell lung cancer - Homo sapiens (human) (1)
Q9UM73	ALK	hsa:238	hsa05235 PD-L1 expression and PD-1 checkpoint pathway in cancer - Homo sapiens (human) (1)
P16050	ALOX15	hsa:246	hsa00590 Arachidonic acid metabolism - Homo sapiens (human) (1)
P16050	ALOX15	hsa:246	hsa00591 Linoleic acid metabolism - Homo sapiens (human) (1)
P16050	ALOX15	hsa:246	hsa01100 Metabolic pathways - Homo sapiens (human) (1)
P16050	ALOX15	hsa:246	hsa04216 Ferroptosis - Homo sapiens (human) (1)
P16050	ALOX15	hsa:246	hsa04217 Necroptosis - Homo sapiens (human) (1)
P16050	ALOX15	hsa:246	hsa04726 Serotonergic synapse - Homo sapiens (human) (1)
P09923	ALPI	hsa:248	hsa00730 Thiamine metabolism - Homo sapiens (human) (1)
P09923	ALPI	hsa:248	hsa00790 Folate biosynthesis - Homo sapiens (human) (1)
P09923	ALPI	hsa:248	hsa01100 Metabolic pathways - Homo sapiens (human) (1)
P09923	ALPI	hsa:248	hsa01240 Biosynthesis of cofactors - Homo sapiens (human) (1)
Q9NPD5	SLCO1B3	hsa:28234	hsa04976 Bile secretion - Homo sapiens (human) (1)
O14842	FFAR1	hsa:2864	hsa04911 Insulin secretion - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa04014 Ras signaling pathway - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa04015 Rap1 signaling pathway - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa04020 Calcium signaling pathway - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa04024 cAMP signaling pathway - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa04080 Neuroactive ligand-receptor interaction - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa04713 Circadian entrainment - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa04720 Long-term potentiation - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa04724 Glutamatergic synapse - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa04728 Dopaminergic synapse - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa05010 Alzheimer disease - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa05014 Amyotrophic lateral sclerosis - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa05017 Spinocerebellar ataxia - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa05020 Prion disease - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa05022 Pathways of neurodegeneration - multiple diseases - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa05030 Cocaine addiction - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa05031 Amphetamine addiction - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa05033 Nicotine addiction - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa05034 Alcoholism - Homo sapiens (human) (1)
Q12879	GRIN2A	hsa:2903	hsa05322 Systemic lupus erythematosus - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa04014 Ras signaling pathway - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa04015 Rap1 signaling pathway - Homo sapiens (human) (1)

Q13224	GRIN2B	hsa:2904	hsa04024 cAMP signaling pathway - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa04080 Neuroactive ligand-receptor interaction - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa04713 Circadian entrainment - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa04720 Long-term potentiation - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa04724 Glutamatergic synapse - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa04728 Dopaminergic synapse - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa05010 Alzheimer disease - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa05014 Amyotrophic lateral sclerosis - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa05016 Huntington disease - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa05017 Spinocerebellar ataxia - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa05020 Prion disease - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa05022 Pathways of neurodegeneration - multiple diseases - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa05030 Cocaine addiction - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa05031 Amphetamine addiction - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa05033 Nicotine addiction - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa05034 Alcoholism - Homo sapiens (human) (1)
Q13224	GRIN2B	hsa:2904	hsa05322 Systemic lupus erythematosus - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa01521 EGFR tyrosine kinase inhibitor resistance - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04012 ErbB signaling pathway - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04062 Chemokine signaling pathway - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04110 Cell cycle - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04150 mTOR signaling pathway - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04151 PI3K-Akt signaling pathway - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04310 Wnt signaling pathway - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04340 Hedgehog signaling pathway - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04360 Axon guidance - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04390 Hippo signaling pathway - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04510 Focal adhesion - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04550 Signaling pathways regulating pluripotency of stem cells - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04657 IL-17 signaling pathway - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04660 T cell receptor signaling pathway - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04662 B cell receptor signaling pathway - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04722 Neurotrophin signaling pathway - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04728 Dopaminergic synapse - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04910 Insulin signaling pathway - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04916 Melanogenesis - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04917 Prolactin signaling pathway - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04919 Thyroid hormone signaling pathway - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04931 Insulin resistance - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04932 Non-alcoholic fatty liver disease - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04934 Cushing syndrome - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa04935 Growth hormone synthesis, secretion and action - Homo sapiens

			(human) (1)
P49841	GSK3B	hsa:2932	hsa04936 Alcoholic liver disease - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05010 Alzheimer disease - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05020 Prion disease - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05022 Pathways of neurodegeneration - multiple diseases - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05131 Shigellosis - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05135 Yersinia infection - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05160 Hepatitis C - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05162 Measles - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05163 Human cytomegalovirus infection - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05165 Human papillomavirus infection - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05167 Kaposi sarcoma-associated herpesvirus infection - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05200 Pathways in cancer - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05210 Colorectal cancer - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05213 Endometrial cancer - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05215 Prostate cancer - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05217 Basal cell carcinoma - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05224 Breast cancer - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05225 Hepatocellular carcinoma - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05226 Gastric cancer - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05415 Diabetic cardiomyopathy - Homo sapiens (human) (1)
P49841	GSK3B	hsa:2932	hsa05417 Lipid and atherosclerosis - Homo sapiens (human) (1)
P04035	HMGCR	hsa:3156	hsa00900 Terpenoid backbone biosynthesis - Homo sapiens (human) (1)
P04035	HMGCR	hsa:3156	hsa01100 Metabolic pathways - Homo sapiens (human) (1)
P04035	HMGCR	hsa:3156	hsa04152 AMPK signaling pathway - Homo sapiens (human) (1)
P04035	HMGCR	hsa:3156	hsa04976 Bile secretion - Homo sapiens (human) (1)
P28845	HSD11B1	hsa:3290	hsa00140 Steroid hormone biosynthesis - Homo sapiens (human) (1)
P28845	HSD11B1	hsa:3290	hsa00980 Metabolism of xenobiotics by cytochrome P450 - Homo sapiens (human) (1)
P28845	HSD11B1	hsa:3290	hsa01100 Metabolic pathways - Homo sapiens (human) (1)
P28845	HSD11B1	hsa:3290	hsa05204 Chemical carcinogenesis - DNA adducts - Homo sapiens (human) (1)
P10275	AR	hsa:367	hsa04114 Oocyte meiosis - Homo sapiens (human) (1)
P10275	AR	hsa:367	hsa05200 Pathways in cancer - Homo sapiens (human) (1)
P10275	AR	hsa:367	hsa05207 Chemical carcinogenesis - receptor activation - Homo sapiens (human) (1)
P10275	AR	hsa:367	hsa05215 Prostate cancer - Homo sapiens (human) (1)
P06756	ITGAV	hsa:3685	hsa04145 Phagosome - Homo sapiens (human) (1)
P06756	ITGAV	hsa:3685	hsa04151 PI3K-Akt signaling pathway - Homo sapiens (human) (1)
P06756	ITGAV	hsa:3685	hsa04510 Focal adhesion - Homo sapiens (human) (1)
P06756	ITGAV	hsa:3685	hsa04512 ECM-receptor interaction - Homo sapiens (human) (1)
P06756	ITGAV	hsa:3685	hsa04514 Cell adhesion molecules - Homo sapiens (human) (1)
P06756	ITGAV	hsa:3685	hsa04810 Regulation of actin cytoskeleton - Homo sapiens (human) (1)
P06756	ITGAV	hsa:3685	hsa04919 Thyroid hormone signaling pathway - Homo sapiens (human) (1)

P06756	ITGAV	hsa:3685	hsa05163 Human cytomegalovirus infection - Homo sapiens (human) (1)
P06756	ITGAV	hsa:3685	hsa05165 Human papillomavirus infection - Homo sapiens (human) (1)
P06756	ITGAV	hsa:3685	hsa05200 Pathways in cancer - Homo sapiens (human) (1)
P06756	ITGAV	hsa:3685	hsa05205 Proteoglycans in cancer - Homo sapiens (human) (1)
P06756	ITGAV	hsa:3685	hsa05222 Small cell lung cancer - Homo sapiens (human) (1)
P06756	ITGAV	hsa:3685	hsa05410 Hypertrophic cardiomyopathy - Homo sapiens (human) (1)
P06756	ITGAV	hsa:3685	hsa05412 Arrhythmogenic right ventricular cardiomyopathy - Homo sapiens (human) (1)
P06756	ITGAV	hsa:3685	hsa05414 Dilated cardiomyopathy - Homo sapiens (human) (1)
P06756	ITGAV	hsa:3685	hsa05418 Fluid shear stress and atherosclerosis - Homo sapiens (human) (1)
P18858	LIG1	hsa:3978	hsa03030 DNA replication - Homo sapiens (human) (1)
P18858	LIG1	hsa:3978	hsa03410 Base excision repair - Homo sapiens (human) (1)
P18858	LIG1	hsa:3978	hsa03420 Nucleotide excision repair - Homo sapiens (human) (1)
P18858	LIG1	hsa:3978	hsa03430 Mismatch repair - Homo sapiens (human) (1)
P22303	ACHE	hsa:43	hsa04725 Cholinergic synapse - Homo sapiens (human) (1)
P22303	ACHE	hsa:43	hsa00564 Glycerophospholipid metabolism - Homo sapiens (human) (1)
Q07869	PPARA	hsa:5465	hsa03320 PPAR signaling pathway - Homo sapiens (human) (1)
Q07869	PPARA	hsa:5465	hsa04024 cAMP signaling pathway - Homo sapiens (human) (1)
Q07869	PPARA	hsa:5465	hsa04920 Adipocytokine signaling pathway - Homo sapiens (human) (1)
Q07869	PPARA	hsa:5465	hsa04922 Glucagon signaling pathway - Homo sapiens (human) (1)
Q07869	PPARA	hsa:5465	hsa04931 Insulin resistance - Homo sapiens (human) (1)
Q07869	PPARA	hsa:5465	hsa04932 Non-alcoholic fatty liver disease - Homo sapiens (human) (1)
Q07869	PPARA	hsa:5465	hsa04936 Alcoholic liver disease - Homo sapiens (human) (1)
Q07869	PPARA	hsa:5465	hsa05160 Hepatitis C - Homo sapiens (human) (1)
Q07869	PPARA	hsa:5465	hsa05207 Chemical carcinogenesis - receptor activation - Homo sapiens (human) (1)
Q07869	PPARA	hsa:5465	hsa05415 Diabetic cardiomyopathy - Homo sapiens (human) (1)
O60218	AKR1B10	hsa:57016	hsa00040 Pentose and glucuronate interconversions - Homo sapiens (human) (1)
O60218	AKR1B10	hsa:57016	hsa00051 Fructose and mannose metabolism - Homo sapiens (human) (1)
O60218	AKR1B10	hsa:57016	hsa00052 Galactose metabolism - Homo sapiens (human) (1)
O60218	AKR1B10	hsa:57016	hsa00561 Glycerolipid metabolism - Homo sapiens (human) (1)
O60218	AKR1B10	hsa:57016	hsa00790 Folate biosynthesis - Homo sapiens (human) (1)
O60218	AKR1B10	hsa:57016	hsa01100 Metabolic pathways - Homo sapiens (human) (1)
P18031	PTPN1	hsa:5770	hsa04520 Adherens junction - Homo sapiens (human) (1)
P18031	PTPN1	hsa:5770	hsa04910 Insulin signaling pathway - Homo sapiens (human) (1)
P18031	PTPN1	hsa:5770	hsa04931 Insulin resistance - Homo sapiens (human) (1)
P18031	PTPN1	hsa:5770	hsa05208 Chemical carcinogenesis - reactive oxygen species - Homo sapiens (human) (1)
P08575	PTPRC	hsa:5788	hsa04514 Cell adhesion molecules - Homo sapiens (human) (1)
P08575	PTPRC	hsa:5788	hsa04660 T cell receptor signaling pathway - Homo sapiens (human) (1)
P08575	PTPRC	hsa:5788	hsa04666 Fc gamma R-mediated phagocytosis - Homo sapiens (human) (1)
P08575	PTPRC	hsa:5788	hsa05132 Salmonella infection - Homo sapiens (human) (1)
P08575	PTPRC	hsa:5788	hsa05340 Primary immunodeficiency - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa01523 Antifolate resistance - Homo sapiens (human) (1)

Q04206	RELA	hsa:5970	hsa04010 MAPK signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04014 Ras signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04024 cAMP signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04062 Chemokine signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04064 NF-kappa B signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04066 HIF-1 signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04071 Sphingolipid signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04137 Mitophagy - animal - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04151 PI3K-Akt signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04210 Apoptosis - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04211 Longevity regulating pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04218 Cellular senescence - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04380 Osteoclast differentiation - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04613 Neutrophil extracellular trap formation - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04620 Toll-like receptor signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04621 NOD-like receptor signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04622 RIG-I-like receptor signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04623 Cytosolic DNA-sensing pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04625 C-type lectin receptor signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04657 IL-17 signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04658 Th1 and Th2 cell differentiation - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04659 Th17 cell differentiation - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04660 T cell receptor signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04662 B cell receptor signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04668 TNF signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04722 Neurotrophin signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04917 Prolactin signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04920 Adipocytokine signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04926 Relaxin signaling pathway - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04931 Insulin resistance - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04932 Non-alcoholic fatty liver disease - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04933 AGE-RAGE signaling pathway in diabetic complications - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa04936 Alcoholic liver disease - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05010 Alzheimer disease - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05022 Pathways of neurodegeneration - multiple diseases - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05030 Cocaine addiction - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05120 Epithelial cell signaling in Helicobacter pylori infection - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05130 Pathogenic Escherichia coli infection - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05131 Shigellosis - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05132 Salmonella infection - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05133 Pertussis - Homo sapiens (human) (1)

Q04206	RELA	hsa:5970	hsa05134 Legionellosis - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05135 Yersinia infection - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05140 Leishmaniasis - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05142 Chagas disease - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05145 Toxoplasmosis - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05146 Amoebiasis - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05152 Tuberculosis - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05160 Hepatitis C - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05161 Hepatitis B - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05162 Measles - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05163 Human cytomegalovirus infection - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05164 Influenza A - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05165 Human papillomavirus infection - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05166 Human T-cell leukemia virus 1 infection - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05167 Kaposi sarcoma-associated herpesvirus infection - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05168 Herpes simplex virus 1 infection - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05169 Epstein-Barr virus infection - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05170 Human immunodeficiency virus 1 infection - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05171 Coronavirus disease - COVID-19 - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05200 Pathways in cancer - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05202 Transcriptional misregulation in cancer - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05203 Viral carcinogenesis - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05207 Chemical carcinogenesis - receptor activation - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05208 Chemical carcinogenesis - reactive oxygen species - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05212 Pancreatic cancer - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05215 Prostate cancer - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05220 Chronic myeloid leukemia - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05221 Acute myeloid leukemia - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05222 Small cell lung cancer - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05235 PD-L1 expression and PD-1 checkpoint pathway in cancer - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05321 Inflammatory bowel disease - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05415 Diabetic cardiomyopathy - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05417 Lipid and atherosclerosis - Homo sapiens (human) (1)
Q04206	RELA	hsa:5970	hsa05418 Fluid shear stress and atherosclerosis - Homo sapiens (human) (1)
P51449	RORC	hsa:6097	hsa04710 Circadian rhythm - Homo sapiens (human) (1)
P51449	RORC	hsa:6097	hsa05321 Inflammatory bowel disease - Homo sapiens (human) (1)
P51449	RORC	hsa:6097	hsa04659 Th17 cell differentiation - Homo sapiens (human) (1)
P04278	SHBG	hsa:6462	-
Q12772	SREBF2	hsa:6721	-

P16662	UGT2B7	hsa:7364	hsa00040 Pentose and glucuronate interconversions - Homo sapiens (human) (1)
P16662	UGT2B7	hsa:7364	hsa00053 Ascorbate and aldarate metabolism - Homo sapiens (human) (1)
P16662	UGT2B7	hsa:7364	hsa00140 Steroid hormone biosynthesis - Homo sapiens (human) (1)
P16662	UGT2B7	hsa:7364	hsa00830 Retinol metabolism - Homo sapiens (human) (1)
P16662	UGT2B7	hsa:7364	hsa00860 Porphyrin metabolism - Homo sapiens (human) (1)
P16662	UGT2B7	hsa:7364	hsa00980 Metabolism of xenobiotics by cytochrome P450 - Homo sapiens (human) (1)
P16662	UGT2B7	hsa:7364	hsa00982 Drug metabolism - cytochrome P450 - Homo sapiens (human) (1)
P16662	UGT2B7	hsa:7364	hsa00983 Drug metabolism - other enzymes - Homo sapiens (human) (1)
P16662	UGT2B7	hsa:7364	hsa01100 Metabolic pathways - Homo sapiens (human) (1)
P16662	UGT2B7	hsa:7364	hsa01240 Biosynthesis of cofactors - Homo sapiens (human) (1)
P16662	UGT2B7	hsa:7364	hsa04976 Bile secretion - Homo sapiens (human) (1)
P16662	UGT2B7	hsa:7364	hsa05204 Chemical carcinogenesis - DNA adducts - Homo sapiens (human) (1)
P16662	UGT2B7	hsa:7364	hsa05207 Chemical carcinogenesis - receptor activation - Homo sapiens (human) (1)
P55055	NR1H2	hsa:7376	-
P43166	CA7	hsa:766	hsa00910 Nitrogen metabolism - Homo sapiens (human) (1)
P43166	CA7	hsa:766	hsa01100 Metabolic pathways - Homo sapiens (human) (1)
P51114	FXR1	hsa:8087	-
O75469	NR1I2	hsa:8856	-
P30305	CDC25B	hsa:994	hsa04010 MAPK signaling pathway - Homo sapiens (human) (1)
P30305	CDC25B	hsa:994	hsa04110 Cell cycle - Homo sapiens (human) (1)
P30305	CDC25B	hsa:994	hsa04914 Progesterone-mediated oocyte maturation - Homo sapiens (human) (1)
P30305	CDC25B	hsa:994	hsa05206 MicroRNAs in cancer - Homo sapiens (human) (1)

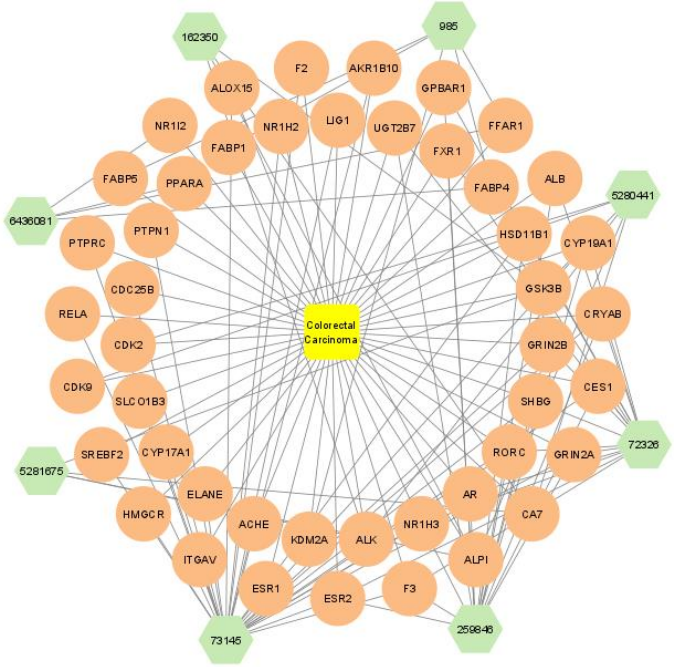

Figure 1: The visualized network of interactions between CN bioactives and CRC relevant targets

Ligands
Targets
Disease - CRC

Discussion

In the study, 8 bioactives were matched to 46 different genes involving CRC (according to the DisGeNet database), to create a network of colorectal cancer-CN bioactives. The observations made from the network support the multi-drug multi-target nature of network pharmacology. Given the abundance of targets and interactions between the phytochemical compounds and the proteins significant in CRC, CN extracts can be acknowledged as potent chemicals for targeting CRC.

β-amyrin was the most potent chemical identified from CN, according to the network. In a study of cytotoxicity in human cervical adenocarcinoma (HeLa) cell-line, β-amyrin induced apoptosis via an increase in reactive oxygen species (ROS) (21). In a study by Maiyo and colleagues, when β-amyrin extracted from *Prunus africana* was tested on colorectal carcinoma (Caco-2) cell lines, a significant cytotoxic activity was observed with an IC_{50} value of 81 µg/mL (22). Evidence suggests that β-amyrin can target cancer cells in order to induce apoptosis.

Betulin and lupeol were shown to target 16 different proteins making them drug candidates with great potential. In an experiment on metastatic CRC, betulin was shown to decrease the viability of the cells in CRC CT26 (Murine), HCT116 (Human), and SW620 (Human) cell lines. It was shown that betulin can induce AMPK-mediated G0/G1 phase arrest and autophagy in CT26 and HCT116 cell lines. Additionally, it is able to trigger caspase-dependent apoptosis in metastatic CRC (23). In another *in vitro* assay of oxaliplatin-resistant LoVo CRC cell-lines, lupeol was shown to downregulate cell viability via decreased expression of *ABCG2* and activating ER stress to induce apoptosis (24).

In experiments on azoxymethane and dextran sodium sulfate-induced mouse model of ulcerative colitis-associated CRC, vitexin significantly improved the clinical signs and symptoms when administered orally. There was an observed reduction of cytokine production and macrophage count with the M1 pro-inflammatory characteristics in neighboring non-cancerous tissue (25). In an investigation involving molecular docking of CN extract isolated compounds, palmitate, and linolenyl alcohol were found to strongly interact with p53 binding protein Mdm2, indicating that both chemicals possess anticancer potential (26). While iso-vitexin has shown antioxidant properties in studies, orientin has been known to act as an anti-inflammatory agent (27).

Conclusion

Network pharmacology is a powerful tool to identify bioactive constituents of herbal medications, their targets, and the interactions between them. While CRC has become the second leading cancer type worldwide, the demand for better alternative treatments has been quite high. CN extracts can be extremely beneficial in a number of disease treatments, including CRC. The current study showed 84 possible interactions between the bioactives and CRC-related targets, making the phytochemicals studied, excellent candidates for drug development. Although there is an understanding of the effects of individual chemicals, research needs to further highlight how the combinatorial effect of these bioactives can improve clinical signs and symptoms in CRC patients.

Conflicts of Interest

The authors declare no conflict of interest.

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