

# Multiscale Modeling of Drug-induced Effects of RDN Injection on Human Disease: From Drug Molecules to Clinical Symptoms of Disease

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Supplementary information

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**Supplementary Table S0: Impact of the RDN ingredients on the pathway.**

High Degree (31-62)		Middle degree (11-30)		Low degree (1-10)	
Pathway Name	Score	Pathway Name	Score	Pathway Name	Score
Metabolism of xenobiotics by cytochrome P450	15	Drug metabolism - cytochrome P450	10	Metabolism of xenobiotics by cytochrome P450	16
Drug metabolism - cytochrome P450	13	Serotonergic synapse	9	Drug metabolism - cytochrome P450	15
Insulin signaling pathway	11	Metabolism of xenobiotics by cytochrome P450	8	Neurotrophin signaling pathway	12
Serotonergic synapse	11	Dopaminergic synapse	7	Drug metabolism - other enzymes	12
PI3K-Akt signaling pathway	11	Glycine_ serine and threonine metabolism	6	Retinol metabolism	12
Regulation of actin cytoskeleton	10	Tryptophan metabolism	6	Colorectal cancer	11
Tuberculosis	10	Arginine and proline metabolism	5	MAPK signaling pathway	10
Peroxisome	9	Histidine metabolism	5	Steroid hormone biosynthesis	10
Steroid hormone biosynthesis	9	Toxoplasmosis	5	Focal adhesion	10
Focal adhesion	9	VEGF signaling pathway	5	FoxO signaling pathway	10
Chemokine signaling pathway	9	mTOR signaling pathway	5	Pancreatic cancer	9
Axon guidance	9	Gastric acid secretion	5	Insulin signaling pathway	9
Vascular smooth muscle contraction	9	PI3K-Akt signaling pathway	5	Cysteine and methionine metabolism	9
Endocytosis	8	Inflammatory mediator regulation of TRP channels	5	PI3K-Akt signaling pathway	9
Neurotrophin signaling pathway	8	MicroRNAs in cancer	5	Transcriptional misregulation in cancer	9
Toll-like receptor signaling pathway	8	Glioma	4	Glycine_ serine and threonine metabolism	8
Arginine and proline metabolism	8	Neurotrophin signaling pathway	4	Regulation of actin cytoskeleton	8
Tryptophan metabolism	8	MAPK signaling pathway	4	Axon guidance	8
T cell receptor signaling pathway	8	Fc gamma R-mediated phagocytosis	4	Amyotrophic lateral sclerosis (ALS)	7
Calcium signaling pathway	8	Cysteine and methionine metabolism	4	Natural killer cell mediated cytotoxicity	7

**Supplementary Table S1: Network parameters of several key target proteins.**

UNIPROT ID	Degree	Betweenness	UNIPROT Name
P11509	12	0.14543929	Cytochrome P450 2A6
Q6VVX0	7	0.08930768	Vitamin D 25-hydroxylase
P19801	5	0.04696212	Amiloride-sensitive amine oxidase [copper-containing]
P26358	5	0.02598916	DNA (cytosine-5)-methyltransferase 1
P27338	5	0.04885527	Amine oxidase [flavin-containing] B
P52848	5	0.04287594	Bifunctional heparan sulfate N-deacetylase/N-sulfotransferase 1
P00558	4	0.0157713	Phosphoglycerate kinase 1
P06132	4	0.03534159	Uroporphyrinogen decarboxylase
P08254	4	0.00928838	Stromelysin-1
P10635	4	0.08820364	Cytochrome P450 2D6
Q96EB6	4	0.01634897	NAD-dependent protein deacetylase sirtuin-1
Q96GA7	4	0.01556111	Serine dehydratase-like
Q9Y2Q3	4	0.03170179	Glutathione S-transferase kappa 1
O43157	3	0.01454842	Plexin-B1
O43741	3	0.00851393	5'-AMP-activated protein kinase subunit beta-2
O95749	3	0.01313714	Geranylgeranyl pyrophosphate synthase
P04040	3	0.01779917	Catalase
P05108	3	0.0227335	Cholesterol side-chain cleavage enzyme, mitochondrial
P09960	3	0.01620902	Leukotriene A-4 hydrolase
P11511	3	0.01627829	Aromatase
P12277	3	0.00610903	Creatine kinase B-type
P13569	3	0.01734233	Cystic fibrosis transmembrane conductance regulator
P21695	3	0.007109	Glycerol-3-phosphate dehydrogenase [NAD(+)], cytoplasmic
P29965	3	0.0219155	CD40 ligand
P35520	3	0.00977714	Cystathionine beta-synthase
P50336	3	0.01099991	Protoporphyrinogen oxidase
P51149	3	0.014247	Ras-related protein Rab-7a
P51449	3	0.00649119	Nuclear receptor ROR-gamma
P51857	3	0.01829734	3-oxo-5-beta-steroid 4-dehydrogenase
P60763	3	0.01975373	Ras-related C3 botulinum toxin substrate 3

**Supplementary Table S2: The possible interaction network of tuberculosis.**

Molecular ID	Autodock Score	Uniprot ID	Uniprot Name	Protein ID in Pathway	Pathway ID	Disease Name	Disease Symptom
UNPD149880	6.23	O60603	Toll-like receptor 2	TLR2	hsa05152	Tuberculosis	Breathing difficulty Chest pain Cough with mucus Coughing up blood Excessive sweating especially at night Fatigue Fever Weight loss Wheezing
UNPD189689	6.22	O60603	Toll-like receptor 2	TLR2			
UNPD60650	6.26	P04049	RAF proto-oncogene serine/threonine-protein kinase	Raf1			
UNPD189689	6.23	P07339	Cathepsin D	CathepsinD			
UNPD189689	6.23	P25774	Cathepsin S	CathepsinS			
RDN15	6.33	P28482	Mitogen-activated protein kinase 1	ERK1/2			
RDN1	6.5	P29460	Interleukin-12 subunit beta	IL-12			
RDN56	6.12	P51149	Ras-related protein Rab-7a	Rab7			
UNPD164733	7.14	P51149	Ras-related protein Rab-7a	Rab7			
UNPD189689	6.01	P51149	Ras-related protein Rab-7a	Rab7			
RDN47	6.08	P99999	Cytochrome c	CytC			
UNPD60430	6.08	P99999	Cytochrome c	CytC			
UNPD49205	6.29	Q13555	Calcium/calmodulin-dependent protein kinase type II subunit gamma	CAMKII			
UNPD149880	6.4	Q15399	Toll-like receptor 1	TLR1/6			
UNPD189689	6.26	Q15399	Toll-like receptor 1	TLR1/6			
UNPD51223	6.05	Q15399	Toll-like receptor 1	TLR1/6			
RDN56	6.23	Q16539	Mitogen-activated protein kinase 14	p38			
UNPD130563	6.51	Q8NEB9	Phosphatidylinositol 3-kinase catalytic subunit type 3	VPS34			
RDN20	6.24	Q9UQM7	Calcium/calmodulin-dependent protein kinase type II subunit alpha	CAMKII			
UNPD189689	6.59	Q9UQM7	Calcium/calmodulin-dependent protein kinase type II subunit alpha	CAMKII			

The red color protein ID is also in the interaction network of influenza.

**Supplementary Table S3: The possible interaction network of influenza.**

Molecular ID	Autodock Score	Uniprot ID	Uniprot Name	Protein ID in Pathway	Pathway ID	Disease Name	Disease Symptom
UNPD60650	6.26	P04049	RAF proto-oncogene serine/threonine-protein kinase	Raf1	hsa05164	Influenza	Body aches Chills Dizziness Dry cough Flushed face Headache Increased breathing symptoms Lack of energy Nausea and vomiting Runny nose Sneezing Sore throat
RDN56	6.89	P05771	Protein kinase C beta type	PKC $\beta$ II			
UNPD29278	6.18	P17252	Protein kinase C alpha type	PKC $\alpha$			
RDN15	6.33	P28482	Mitogen-activated protein kinase 1	ERK1/2			
RDN1	6.5	P29460	Interleukin-12 subunit beta	IL-12			
UNPD130563	6.32	P29597	Non-receptor tyrosine-protein kinase TYK2	Tyk2/Jtk1			
RDNB23	6.16	P42336	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform	PI3K			
UNPD29278	7.03	P48736	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit gamma isoform	PI3K			
RDN47	6.08	P99999	Cytochrome c	CytC			
UNPD60430	6.08	P99999	Cytochrome c	CytC			
UNPD149880	6	Q02750	Dual specificity mitogen-activated protein kinase kinase 1	MEK1/2	Avian influenza	Cough Diarrhea Fever greater than 100.4°F (38°C) General ill feeling(malaise) Headache Muscle aches Runny nose Sore throat Trouble breathing	
UNPD51223	6.92	Q02750	Dual specificity mitogen-activated protein kinase kinase 1	MEK1/2			
RDN56	6.23	Q16539	Mitogen-activated protein kinase 14	p38			
RDN21	6.69	Q9NZJ5	Eukaryotic translation initiation factor 2-alpha kinase 3	PKR			

The red color protein ID is also in the interaction network of tuberculosis.

**Supplementary Table S4: The relation between several diseases and ZHENG.**

<b>Disease ID</b>	<b>Disease Name</b>	<b>Disease category</b>	<b>ZHENG</b>
H00630	Disease_Rheumatoid arthritis	Autoimmune disease	Hot ZHENG
H00912	Disease_Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)	Autoimmune disease	Hot ZHENG
H00001	Disease_Acute lymphoblastic leukemia (ALL) (precursor B lymphoblastic leukemia)	Cancer	Hot ZHENG
H00002	Disease_Acute lymphoblastic leukemia (ALL) (precursor T lymphoblastic leukemia)	Cancer	Hot ZHENG
H00003	Disease_Acute myeloid leukemia (AML)	Cancer	Hot ZHENG
H00004	Disease_Chronic myeloid leukemia (CML)	Cancer	Hot ZHENG
H00007	Disease_Hodgkin lymphoma	Cancer	Hot ZHENG
H00008	Disease_Burkitt lymphoma	Cancer	Hot ZHENG
H00010	Disease_Multiple myeloma	Cancer	Hot ZHENG
H00011	Disease_Lymphoplasmacytic lymphoma	Cancer	Hot ZHENG
H00013	Disease_Small cell lung cancer	Cancer	Hot ZHENG
H00020	Disease_Colorectal cancer	Cancer	Hot ZHENG
H00034	Disease_Carcinoid	Cancer	Hot ZHENG
H00295	Disease_Viral myocarditis	Cardiovascular disease	Hot ZHENG
H00465	Disease_Fragile X Syndrome	Chromosomal abnormality	Cold ZHENG
H00606	Disease_Early infantile epileptic encephalopathy	Congenital disorder; Epilepsy	Hot ZHENG
H00480	Disease_Non-syndromic X-linked mental retardation	Congenital disorder; Mental retardation	Hot ZHENG
H00577	Disease_Syndromic X-linked mental retardation with epilepsy or seizures	Congenital disorder; Mental retardation; Epilepsy	Hot ZHENG
H00478	Disease_Prader-Willi and Angelman syndromes	Developmental disorder	Hot ZHENG
H00570	Disease_Kabuki syndrome	Developmental disorder	Cold ZHENG
H00935	Disease_Cold-induced sweating syndrome (CISS) and Crisponi syndrome (CRISPS)	Developmental disorder	Hot ZHENG
H00992	Disease_Seckel syndrome	Developmental disorder	Cold ZHENG
H01288	Disease_Mosaic variegated aneuploidy (MVA) syndrome	Developmental disorder	Cold ZHENG

H00539	Disease_PTEN hamartoma tumor syndrome (PHTS)	Developmental disorder; Cancer	Cold and Hot ZHENG
H00523	Disease_Noonan syndrome and related disorders	Developmental disorder; Cardiovascular disease	Hot ZHENG
H00910	Disease_Hirschsprung disease (HD)	Developmental disorder; Digestive disease	Hot ZHENG
H00267	Disease_Holoprosencephaly (HPE)	Developmental disorder; Nervous system disease	Cold ZHENG
H00979	Disease_Caudal regression syndrome and Sirenomelia	Developmental disorder; Nervous system disease	Hot ZHENG
H00560	Disease_Pseudoxanthoma elasticum	Developmental disorder; Skin and connective tissue disease	Cold ZHENG
H00249	Disease_Thyroid hormone resistance syndrome	Endocrine disease	Hot ZHENG
H00251	Disease_Thyroid dysmorphogenesis	Endocrine disease	Cold and Hot ZHENG
H00258	Disease_Aldosterone synthase deficiency	Endocrine disease	Hot ZHENG
H00252	Disease_Congenital nephrogenic diabetes insipidus (NDI)	Endocrine disease; Kidney disease	Hot ZHENG
H00239	Disease_Bartter syndrome	Endocrine disease; Urinary system disease	Hot ZHENG
H01027	Disease_Anophthalmia and microphthalmia (A/M)	Eye disease	Cold ZHENG
H00238	Disease_Fanconi anemia	Hematologic disease	Cold ZHENG
H00081	Disease_Hashimoto's thyroiditis	Immune system disease	Hot ZHENG
H00083	Disease_Allograft rejection	Immune system disease	Hot ZHENG
H00282	Disease_Cryopyrin associated periodic syndrome (CAPS)	Immune system disease	Hot ZHENG
H00288	Disease_Familial Mediterranean fever (FMF)	Immune system disease	Hot ZHENG
H01109	Disease_Chronic mucocutaneous candidiasis (CMC)	Immune system disease	Cold ZHENG
H01232	Disease_Syndromic multisystem autoimmune disease	Immune system disease	Cold ZHENG
H00110	Disease_Cholera	Infectious disease	Hot ZHENG
H00111	Disease_Typhoid fever	Infectious disease	Hot ZHENG
H00277	Disease_Enterohemorrhagic Escherichia coli (EHEC) infection	Infectious disease	Hot ZHENG
H00299	Disease_Shigellosis	Infectious disease	Hot ZHENG
H00311	Disease_Legionellosis	Infectious disease	Hot ZHENG
H00319	Disease_Pertussis	Infectious disease	Hot ZHENG

H00342	Disease_Tuberculosis	Infectious disease	Hot ZHENG
H00357	Disease_African trypanosomiasis	Infectious disease	Hot ZHENG
H00358	Disease_Chagas disease	Infectious disease	Hot ZHENG
H00359	Disease_Leishmaniasis	Infectious disease	Hot ZHENG
H00360	Disease_Amoebiasis	Infectious disease	Hot ZHENG
H00361	Disease_Malaria	Infectious disease	Hot ZHENG
H00367	Disease_Infectious mononucleosis	Infectious disease	Hot ZHENG
H00394	Disease_Measles	Infectious disease	Hot ZHENG
H00398	Disease_Influenza	Infectious disease	Hot ZHENG
H00399	Disease_Avian influenza	Infectious disease	Hot ZHENG
H00413	Disease_Hepatitis C	Infectious disease	Hot ZHENG
H00435	Disease_Toxoplasmosis	Infectious disease	Hot ZHENG
H00069	Disease_Glycogen storage diseases (GSD)	Inherited metabolic disease	Hot ZHENG
H00118	Disease_Congenital disorders of glycosylation (CDG) type I	Inherited metabolic disease	Cold ZHENG
H00161	Disease_Smith-Lemli-Opitz syndrome	Inherited metabolic disease	Hot ZHENG
H00179	Disease_3-Hydroxy-3-methylglutaryl-CoA lyase deficiency	Inherited metabolic disease	Hot ZHENG
H01071	Disease_Acute alcohol sensitivity	Inherited metabolic disease	Hot ZHENG
H01283	Disease_Malonyl-CoA decarboxylase deficiency	Inherited metabolic disease	Hot ZHENG
H01398	Disease_Primary hyperammonemic disorders	Inherited metabolic disease	Hot ZHENG
H01400	Disease_Secondary hyperammonemia	Inherited metabolic disease	Cold ZHENG
H00881	Disease_Li-Fraumeni syndrome	Inherited metabolic disease; Cancer	Hot ZHENG
H00802	Disease_Ehlers-Danlos syndrome (EDS)	Inherited metabolic disease; Connective tissue disease	Hot ZHENG
H00216	Disease_Congenital adrenal hyperplasia (CAH)	Inherited metabolic disease; Endocrine disease	Hot ZHENG
H01199	Disease_Hyperalphalipoproteinemia	Inherited metabolic disease; Hematologic disease	Cold ZHENG
H01117	Disease_Majeed syndrome	Inherited metabolic disease; Immune system disease	Hot ZHENG



H00137	Disease_Niemann-Pick disease (NPD) typeA and B	Inherited metabolic disease; Lysosomal storage disease	Hot ZHENG
H00275	Disease_Cystinosis	Inherited metabolic disease; Lysosomal storage disease	Cold ZHENG
H00124	Disease_GM2 gangliosidoses	Inherited metabolic disease; Lysosomal storage disease; Nervous system disease	Cold ZHENG
H00424	Disease_Defects in the degradation of sphingomyelin	Inherited metabolic disease; Lysosomal storage disease; Nervous system disease	Hot ZHENG
H00426	Disease_Defects in the degradation of ganglioside	Inherited metabolic disease; Lysosomal storage disease; Nervous system disease	Cold ZHENG
H00849	Disease_Creatine deficiency syndrome	Inherited metabolic disease; Mental retardation	Hot ZHENG
H00469	Disease_Mitochondrial DNA depletion syndrome (MDS)	Inherited metabolic disease; Mitochondrial disease	Hot ZHENG
H00174	Disease_Methylmalonic aciduria (MMA)	Inherited metabolic disease; Nervous system disease	Cold ZHENG
H00692	Disease_Lowe syndrome	Inherited metabolic disease; Nervous system disease	Hot ZHENG
H00854	Disease_Wolfram syndrome (WFS)	Inherited metabolic disease; Neurodegenerative disease	Cold ZHENG
H01390	Disease_Mitochondrial neurogastrointestinal encephalomyopathy	Inherited metabolic disease; Neurodegenerative disease; Mitochondrial disease	Hot ZHENG
H00176	Disease_Adrenoleukodystrophy (ALD)	Inherited metabolic disease; Neurodegenerative disease; Peroxisomal disease	Cold ZHENG
H00202	Disease_Hepatic porphyria	Inherited metabolic disease; Skin and connective tissue disease; Liver disease	Hot ZHENG
H00756	Disease_Pitt-Hopkins syndrome	Mental retardation	Hot ZHENG
H00409	Disease_Type II diabetes mellitus	Metabolic disease; Endocrine disease	Hot ZHENG
H00410	Disease_Maturity onset diabetes of the young (MODY)	Metabolic disease; Endocrine disease	Cold ZHENG
H00937	Disease_Precocious puberty	Metabolic disease; Endocrine disease	Cold ZHENG
H00408	Disease_Type I diabetes mellitus	Metabolic disease; Immune system disease; Endocrine disease	Hot ZHENG
H00420	Disease_Familial partial lipodystrophy (FPL)	Metabolic disease; Skin and connective tissue disease	Hot ZHENG
H00652	Disease_Solitary median maxillary central incisor syndrome	Mouth and dental disease	Cold ZHENG
H00594	Disease_Distal muscular dystrophies	Musculoskeletal disease; Nervous system disease	Hot ZHENG
H00595	Disease_Myofibrillar myopathies (MFM)	Musculoskeletal disease; Nervous system disease	Hot ZHENG
H00265	Disease_Hereditary sensory and autonomic neuropathy	Nervous system disease	Hot ZHENG
H00775	Disease_Familial or sporadic hemiplegic migraine	Nervous system disease	Hot ZHENG
H00856	Disease_Distal hereditary motor neuropathies (dHMN)	Nervous system disease	Hot ZHENG

H00916	Disease_Congenital central hypoventilation syndrome (CCHS)	Nervous system disease	Hot ZHENG
H01161	Disease_Aromatic L-amino acid decarboxylase (AADC) deficiency	Nervous system disease	Hot ZHENG
H01391	Disease_Familial episodic pain syndrome (FEPS)	Nervous system disease	Hot ZHENG
H00845	Disease_Familial amyloidosis	Nervous system disease; Inherited metabolic disease	Hot ZHENG
H01118	Disease_Progressive external ophthalmoplegia (PEO)	Nervous system disease; Musculoskeletal disease; Eye disease; Inherited metabolic disease	Hot ZHENG
H00915	Disease_Tuberous sclerosis complex (TSC)	Nervous system disease; Skin and connective tissue disease	Cold ZHENG
H00057	Disease_Parkinson's disease (PD)	Neurodegenerative disease	Hot ZHENG
H00061	Disease_Prion diseases	Neurodegenerative disease	Hot ZHENG
H00455	Disease_Spinal muscular atrophy (SMA)	Neurodegenerative disease	Hot ZHENG
H00933	Disease_Hereditary pancreatitis	Pancreas disease	Hot ZHENG
H00093	Disease_Combined immunodeficiencies (CIDs)	Primary immunodeficiency	Hot ZHENG
H00107	Disease_Other well-defined immunodeficiency syndromes	Primary immunodeficiency	Cold and Hot ZHENG
H00540	Disease_Osteoporosis_lymphedema_anhydrotic ectodermal dysplasia with immunodeficiency (OLEDAID)	Primary immunodeficiency; Skeletal dysplasia	Hot ZHENG
H00599	Disease_46_XX disorders of sex development (Disorders related to androgen excess)	Reproductive system disease	Hot ZHENG
H00607	Disease_46_XY disorders of sex development (Disorders of gonadal development1)	Reproductive system disease	Cold and Hot ZHENG
H00608	Disease_46_XY disorders of sex development (Disorders in androgen synthesis or action)	Reproductive system disease	Cold and Hot ZHENG
H01122	Disease_Pulmonary alveolar proteinosis (PAP)	Respiratory disease	Hot ZHENG
H00894	Disease_FG syndrome (FGS)	Skeletal dysplasia; Nervous system disease	Hot ZHENG
H00651	Disease_Ectodermal dysplasia	Skin and connective tissue disease	Hot ZHENG