

Supplemental material

Table S1. Key network topology property functions planted in Cytoscape and CentiBin.

Feature	Function	Description
Degree	k_i	The number of links to node i
Clustering coefficient	$2n_i / [k_i(k_i - 1)]$	n_i is the number of connected pairs between all neighbors of node i
Neighborhood connectivity	c_i	The average number of second neighbors of node i
Radiality	$\sum_{j \in V} (\Delta G + 1 - \text{dis}(i, j)) / n - 1$	ΔG is the maximal distance amongst all distance calculated between each couple of nodes, $\text{dis}(i, j)$ denotes the length of the shortest path between node i and node j
Topological coefficient	$\text{avg}(J(i, j)) / k_i$	$J(i, j)$ denotes the number of sharing nodes between node i and node j
Eccentricity	$1 / \max\{\text{dis}(i, j) : j \in V\}$	The longest shortest path of node i .
Stress	$\sum_{s \neq i \in V} \sum_{t \neq i \in V} \sigma_{st}(i)$	$\sigma_{st}(i)$ denotes the number of shortest paths from s to t that i lies on.
Betweenness centrality	$\sum_{s \neq i \in V} \sum_{t \neq i \in V} \sigma_{st}(i) / \sigma_{st}$	σ_{st} denotes the number of shortest paths from s to t
Closeness centrality	$1 / \text{avg}(\text{dis}(i, j))$	$\text{dis}(i, j)$ denotes the length of the shortest path between node i and node j
Average shortest path length	d_i	The shortest path of node i

Table S2. Summary for the 66 withdrawn drugs from DrugBank.

Accession Number	Therapy areas	Withdrawal reasons	Withdrawal date
DB00197	antihyperglycemic, treatment of Type II diabetes mellitus	Hepatotoxicity	2000
DB00323	potent, selective, and reversible inhibitor of catechol-O-methyltransferase, treatment of Parkinson's disease	Hepatotoxicity	1998 in UK.
DB00342	H1-receptor antagonist antihistamine,	cardiac arrhythmia	in the 1990s in

	the treatment of allergic rhinitis, hay fever, and allergic skin disorders	caused by QT interval prolongation	the USA
DB00365	antibacterial, treatment of adults with mild to moderate infections	cardiac events and sudden death, due to its side effect of lengthening the QT interval on the electrocardiogram	1999 in USA
DB00397	a sympathomimetic agent, the treatment of nasal congestion, control of urinary incontinence, priapism and obesity	hemorrhagic stroke	May 31, 2001 in Canada
DB00407	anticoagulant, prevention of deep vein thrombosis	excessive bleeding and bruising	March 2000 in the USA
DB00409	antipsychotic, the treatment of schizophrenia	incidence of aplastic anemia	1993 in UK
DB00439	Anticholesteremic, treatment of hypercholesterolemia and mixed dyslipidemia	Rhabdomyolysis,	August 8, 2001 in Canada
DB00533	anti-inflammatory, the treatment of osteoarthritis, rheumatoid arthritis, acute pain in adults, and primary dysmenorrhea, as well as acute treatment of migraine attacks with or without auras	increased risk of heart attack and stroke associated with long-term, high-dosage use	September 30, 2004 in USA
DB00574	the management of exogenous obesity, Anorexigenic agent	heart valve disease and pulmonary hypertension; cardiac fibrosis	1997 in USA
DB00580	anti-inflammatory, the treatment of osteoarthritis and dysmenorrhoea	possible increased risk of heart attack and stroke	in 2005 in Canada, USA and EUro
DB00604	treatment of adult patients with nocturnal heartburn due to gastroesophageal reflux disease	arrhythmias, long QT syndrome	28 July, 2000 in UK
DB00637	the treatment of allergy symptoms	cause arrhythmias at high doses, especially when taken with CYP inhibitors or grapefruit juice	1999
DB00664	Anti-Infective, used for respiratory and urinary tract infections and also for malaria	Agranulocytosis and anaemia	March 2000
DB00761	the treatment of hypokalemia	hyperkalemia, Late	

		manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest	
DB00897	Anti-anxiety, the short-term treatment of insomnia	risk of psychiatric adverse drug reactions.	withdrawn in UK
DB00901	the treatment of asthma and COPD	problems with dependence and abuse	in 2001 in USA
DB00914	the treatment of type II diabetes mellitus	high incidence of lactic acidosis	in 1977 in USA
DB00926	treat severe psoriasis; now used to treat T-cell lymphomas	the high risk of birth defects	in 1998 in USA
DB00969	the treatment of symptoms of severe diarrhea-predominant irritable bowel syndrome (IBS) in women with chronic symptoms	adverse effects including ischemic colitis, severely obstructed or ruptured bowel, and death	in November 2000 in USA
DB01041	the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL)	teratogenic effects	in 1961 in USA
DB01079	treatment of women with irritable bowel syndrome (IBS)	risks of heart attack or stroke	On March 30, 2007 in USA
DB01105	the treatment of obesity	the risk of heart attack and stroke in patients with a history of heart disease	In October 2010 in USA and Canada
DB01107	treating insomnia,	Side effects can include: Skin rash, fever, depression, ulcers or sores in mouth or throat, unusual bleeding or bruising, confusion, fast heartbeat, respiratory depression, swelling of feet or lower legs, dizziness, drowsiness, headache, double vision, clumsiness, constipation, diarrhea, nausea, vomiting, unusual weakness	in June 1965 in USA and in September 1990 in Canada

DB01108	the treatment of Cushing's syndrome	darkening of skin, drowsiness or tiredness, loss of appetite, mental depression, skin rash, and/or vomiting	in April 1994 in USA
DB01149	the treatment of depression	the small possibility of hepatic (liver) injury	On May 20, 2004 in USA
DB01178	Used in the management of anxiety and in the treatment of muscle spasm.	confirmed serious and rare cutaneous reactions (toxic epidermal necrolysis)	in 1996
DB01186	the treatment of Parkinson's Disease	the risk of cardiac valvulopathy	in 2007 in USA and Canada
DB01191	Antiobesity, the management of obesity	cardiovascular side-effects	in 1997 in USA
DB01228	management of irregular heartbeats	frequent proarrhythmic side effects	on December 16, 1991 in USA
DB01230	treatment of Attention Deficit Hyperactivity Disorder	Side effects include insomnia, anorexia, stomach ache, skin rashes, increased irritability, mild depression, nausea, dizziness, headache, drowsiness, and hallucinations	In March 2005 in USA
DB01388	the treatment of angina and high blood pressure	potentially harmful interactions with other drugs	in 1998
DB01405	Anti-Bacterial, the treatment of lower respiratory tract infections, genital and urinary infections like prostatitis, and skin infections	temafloxacin syndrome-- hemolysis	in USA in 1992
DB01424	anti-inflammatory, and antipyretic properties	risk of agranulocytosis	in 1999
DB01463	the treatment of depressive fatigue	due to problems with dependence and abuse	
DB01556	Used as an appetite suppressant	pulmonary hypertension and cardiac fibrosis	
DB03585		bone marrow suppression	in March, 1985 in Canada

DB03783	analgesic, NSAID and fever reducer	nephropathy (damage to or disease of the kidney)	in June 1973 in Canada
DB04812	Dermatologic Agent	cholestatic jaundic	on August 5, 1982
DB04813	Anti-Infective Agent	serious skin disorders	on October 24, 1967
DB04814		nephropathy	in 1963, in Canada, USA and UK
DB04815	used as a topical antifungal treatment, a broad-spectrum antibacterial with antifungal properties	neurotoxicity	in 1983
DB04816	Cathartics	genotoxicity	Withdrawn from the Canadian, US, and UK markets in 1998
DB04817	used a powerful painkiller and fever reducer; NSAID	potentially fatal agranulocytosis	on June 27, 1977
DB04818	the treatment of depression (originally intended to treat tuberculosis)	interactions with food products containing tyrosine	in July 1964 in Canada
DB04819	a antihistamine and anticholinergic drug	carcinogen	in May and June 1979
DB04820	MAOI (monoamine oxidase inhibitor) antidepressants	interactions with food products containing tyrosine	in 1963 in Canada, USA and UK
DB04821	dopamine reuptake inhibitor	increased incidence of hemolytic anemia	on March 20, 1992 in USA and Canada, UK
DB04822	treat all types of cough of various etiologies	carcinogenicity	in 1976 in Canada, USA and UK
DB04823	laxative	jaundice	in 1970s
DB04824	laxative	carcinogenicity	in 1997 in Canada
DB04825	Vasodilator Agent, treat angina pectoris	cardiac arrhythmias	in 1988 in Canada, USA and UK
DB04826	an antihistamine with anticholinergic properties used as an antipruritic	neutropenia	in 1963 in Canada, USA and UK

DB04827	Antineoplastic Agent	carcinogenic	in 1963 in Canada, USA and UK
DB04828	the management of mild to severe pain.	fatal and near-fatal anaphylactoid reactions	in March 1983 in Canada, USA and UK
DB04829	an agent in psychedelic therapy,	withdrawn after it became widely used recreationally	in 1950s-1960s
DB04830	anti-diabetic drug	lactic acidosis	in 1978
DB04831	treatment of hypertension	hepatitis	in 1982
DB04832	the treatment of depression	risk of Guillain-Barré syndrome	in 1983
DB04833	sedative-hypnotic drug, the treatment of insomnia, and as a sedative and muscle relaxant	Withdrawn because of risk of addiction and overdose	in 1984
DB04834	Used in anaesthesia, to aid and enable endotracheal intubation	fatal bronchospasm	in 2001 in many countries
DB04836	the treatment of depression	hepatotoxicity, dermatological side effects, and abuse potential.	in 1999
DB04898	anticoagulant, the treatment of acute deep vein thrombosis	hepatotoxicity (liver damage)	in 2006
DB06144	antipsychotic, the treatment of schizophrenia	numerous cardiac adverse effects	in 1998
DB06804	used as a vaginal spermicide, contraception	a higher incidence of vaginal lesions, increase the risk of infection with sexually transmitted human papillomaviruses (HPVs) that can cause cervical cancer	
DB06810	the treatment of testicular cancer, Paget's disease of bone, and, rarely, the management of hypercalcemia	a dose-related bleeding syndrom	in 2000

Table S3. Decisions and side effect records on approved drugs with similarity measurements more than 0.7 to withdrawn ones by same targets.

Withdrawn Drugs^a	Similar approved drugs by the same target^b	Side effect records^c
wd_DB00197, hepatotoxicity	app_DB00412, withdrawn in Euro, 2010, 9 and in New	Rosiglitazone, respiratory tract infection, 7.3%-9.9%

	Zealand in 2011, 4 for heart disease risks, but in USA is still allowed	
	app_DB01132, withdrawn in some countries in 2011,7, for an increased risk of bladder tumors	Pioglitazone, disease progression, 13.4%
wd_DB00342, cardiac arrhythmia	app_DB00376,	Trihexyphenidyl, no records
	app_DB00387,	Procyclidine, no records
	app_DB00505, many patients discontinued it for unwanted side effects.	Tridihexethyl, no records
	app_DB00950, adverse cardiac events including cardiac arrhythmias, discontinued only in France in 2004	Fexofenadine, vomiting, 4.2%-12%
	app_DB01146,	Diphenylpyraline, no records
	app_DB01231, currently not marketed in USA or Canada	Diphenidol, no records
wd_DB00365, cardiac arrhythmia	app_DB00218, FDA has issued many warnings about the adverse effects. last resort, discontinued in USA for some therapy areas in 2004	Moxifloxacin, nervous system disorder, 4.2%
	app_DB00467, no longer available in USA	Enoxacin, no records
	app_DB00487, extensively prescribed in France and not been approved for use in USA.	Pefloxacin, no records
	app_DB00537, FDA has issued many warnings about the adverse effects, discontinued in USA for some therapy areas in 2004	Ciprofloxacin, abdominal pain
	app_DB00685, withdrawn in Euro in 1999 for hepatotoxicity, but available in USA for very restricted indications	Trovafloxacin, dizziness, 2%-11%
	app_DB00978, banned in USA in 2008	Lomefloxacin, acidosis
	app_DB01044, banned in USA in 2006, in India in 2011	Gatifloxacin, anaphylactic shock

	app_DB01059, very strict indications, last resort	Norfloxacin, arthralgia
	app_DB01137, FDA has issued many warnings about the adverse effects, discontinued in Singapore, Romania and South Africa in 2011	Levofloxacin, application site reaction, 0.6%-16.8%
	app_DB01155, withdrawn in 2009 in Euro	Gemifloxacin, anaphylactic shock
	app_DB01165, FDA has issued many warnings about the adverse effects, discontinued only in USA in 2012 for bacterial infection	Ofloxacin, application site reaction, 0.6%-16.8%
	app_DB01208, banned in USA in 2000	Sparfloxacin, no records
wd_DB00397, hemorrhagic, stroke	app_DB00368,	Norepinephrine, acidosis
	app_DB00610, discontinued by Manufacturer in 2003 in USA	Metaraminol, no records
	app_DB00852, banned or strict prescription in some countries like Australia	Pseudoephedrine, anorexia
	app_DB01364, limited used in USA and UK	Ephedrine, anorexia
	app_DB01576, discontinued by GSK, but not withdrawn	Dextroamphetamine, abdominal cramps
	app_DB06707, discontinued in USA	Levonordefrin, no records
wd_DB00574, heart valve disease	app_DB01577, scheduled drug in most countries due to its high potential for addiction and abuse, discontinued in USA	Methamphetamine, constipation
wd_DB00897, psychiatric	app_DB00404, discontinued in USA	Alprazolam, drowsiness, 41%-76.8%
	app_DB00546, discontinued in USA and Euro	Adinazolam, no records
	app_DB00683, discontinued by Roche in UK	Midazolam, vomiting, 0.75%-11%
	app_DB01215, discontinued by Abbott	Estazolam, anxiety, frequent
wd_DB00901,	app_DB00449, discontinued	Dipivefrin, arrhythmia

addiction and abuse	app_DB01408,	Bambuterol, no records
wd_DB00926, birth defects	app_DB00459, discontinued for a narrow TI and a long elimination half life	Acitretin, abdominal pain
wd_DB01041, teratogenic effects	app_DB00480, discontinued in Phase III	Lenalidomide, angioedema
wd_DB01107, bleeding depression and vomit	app_DB00237, discontinued	Butabarbital, no records
	app_DB00312, discontinued	Pentobarbital, anaemia
	app_DB01351, discontinued in UK	Amobarbital, no records
	app_DB01353, discontinued in UK	Butethal, no records
wd_DB01186, heart valve disease	app_DB00216, only by prescription in USA and Canada	Eletriptan, asthenia, 4%-10%
	app_DB00248, discontinued in Euro	Cabergoline, aggression
wd_DB01191	app_DB01577, scheduled drug in most countries due to its high potential for addiction and abuse, discontinued in USA	Methamphetamine, constipation
wd_DB01405, hemolysis	app_DB00218, FDA has issued many warnings about the adverse effects. last resort, discontinued in USA for some therapy areas in 2004	Moxifloxacin, nervous system disorder, 4.2%
	app_DB00467, no longer available in USA	Enoxacin, no records
	app_DB00487, extensively prescribed in France and not been approved for use in USA. last resort	Pefloxacin, no records
	app_DB00537, FDA has issued many warnings about the adverse effects, discontinued in USA for some therapy areas in 2004	Ciprofloxacin, abdominal pain
	app_DB00685, withdrawn in Euro in 1999 for hepatotoxicity, but available in USA for very restricted indications	Trovafloxacin, dizziness, 2%-11%
	app_DB00978, banned in USA	Lomefloxacin, acidosis

	in 2008	
	app_DB01044, banned in USA in 2006, in India in 2011	Gatifloxacin, anaphylactic shock
	app_DB01059, very strict indications, last resort	Norfloxacin, arthralgia
	app_DB01137, FDA has issued many warnings about the adverse effects, discontinued in Singapore, Romania and South Africa in 2011	Levofloxacin, application site reaction, 0.6%-16.8%
	app_DB01165, FDA has issued many warnings about the adverse effects, discontinued only in USA in 2012 for bacterial infection	Ofloxacin, application site reaction, 0.6%-16.8%
	app_DB01208, banned in USA in 2000	Sparfloxacin, no records
wd_DB01463, addiction and abuse	app_DB00182, used under severe restriction, withdrawn only in Canada in 2005	Amphetamine, no records
	app_DB00191,	Phentermine, constipation
	app_DB00865, discontinued but not withdrawn	Benzphetamine, no records
	app_DB01576, discontinued by GSK, but not withdrawn	Dextroamphetamine, abdominal cramps
	app_DB01577, scheduled drug in most countries due to its high potential for addiction and abuse, discontinued in USA	Methamphetamine, constipation
wd_DB03783, nephropathy	app_DB00316, discontinued	Acetaminophen, abdominal pain
wd_DB04817, agranulocytosis	app_DB01435,	Antipyrine, no records
wd_DB04821, hemolysis	app_DB06148,	Mianserin, no records

^aThe abbreviation of “wd” represents “withdrawn”, and the drug numbers are from the Drugbank database.

^bThe abbreviation of “app” represents “approved”, and the drug numbers are from the Drugbank database.

^cThe side effect event and frequency records are from the SIDER database.

Table S4. Natural Products from the in-house TCM database with similarity values more

than 0.7 to withdrawn drugs.

withdrawn drugs	targets	therapy intentions	withdrawn reasons	Compounds from TCM database ^a	Notes
DB04816	Cytochrome P450 1A2	Cathartics	Withdrawn from the Canadian, US, and UK markets in 1998 due to genotoxicity.	NPD41	3,4-dihydroxycetophenone
				NPD44	2,4-dihydroxycetophenone
				NPD90	Physcion
				NPD140	2,6-Dihydroxycetophenone
				NPD153	3,4-Dihydroxycetophenone
				NPD330	(+)-6-hydroxy-1-methyl-2,3-dihydro-1H-Indene-4-carboxaldehyde
			NPD408	Sugiol	
DB00926	Retinoic acid receptor alpha; Retinoic acid receptor RXR-alpha; Retinoic acid receptor beta; Retinoic acid receptor RXR-gamma; Retinoic acid receptor RXR-beta; Retinoic acid receptor gamma-1; Cytochrome P450 19A1; Cytochrome P450 26A1; Cellular retinoic acid-binding protein 1	to treat severe psoriasis, now used to treat T-cell lymphomas. It also appears to inhibit NADH oxidase activity	It was removed from the United States market in 1998 and the Canadian market in 1996 as a psoriasis medication, due to the high risk of birth defects	NPD882	Difengpin-A
DB04824	UDP-glucuronosyltransferase 1-9	Used for over a century as a laxative	withdrawn in Canada due to concerns with carcinogenicity in 1997	NPD264	ethyl-4-hydroxybenzoate ^b
				NPD881	Ethyl p-hydroxybenzoate ^b
DB06804	Prostaglandin G/H synthase 2	vaginal spermicide	an increased risk of	NPD283	(-)-Secoisolariciresinol

			opportunistic infections	NPD291	5-O-methylafzelechin
				NPD292	(-)-afzelechin
				NPD562	Secoisolariciresinol ^b
				NPD676	1-(4-Hydroxy-3-methoxyphenyl)-2-[2-methoxy-4-(3-hydroxypropyl)phenoxy]-3-propanol
				NPD685	(-)-Epiafzelechin
				NPD689	Afzelechin
				NPD876	4,4'-Dihydroxy-3,3'-dimethoxy-9,9'-epoxylicnan
				NPD1150	epiafzelechin
				NPD1159	secoisolariciresinol ^b
				NPD1395	Bisphenol A diglycidyl ether
				NPD1625	4-(4-hydroxy-3-methoxyphenyl)-2-butanol
				NPD1702	3-methoxy-8,4'-oxyneolign-3',4,9,9'-tetraol
				NPD1871	2-[4-(3-hydroxypropyl)-2-methoxyphenoxy]-propan-1,3-diol
DB06810	DNA	Treatment of testicular cancer, Paget's disease of bone, and, rarely, the management of hypercalcemia		a dose-related bleeding syndrome	NPD4
			NPD2197		Wistin
			NPD358		Myzodendrone
			NPD203		(2R,3S)-dihydratomyricetin
			NPD207		(2R,3S)-taxifolin-3-O-arabinoside
			NPD208		(2S,3R)-taxifolin-3-O-arabinoside

					de
				NPD356	Choerospondin
				NPD351	Narirutin
				NPD295	neochamaejasmin B
				NPD294	isochamaejasmin
				NPD274	Isonochamaejasmin A
				NPD906	11-O-vanilloylbergenin
				NPD754	3,5,3'-Trihydroxy-7,4'-dimethoxy-dihydroflavone
				NPD669	Dihydroquercetin
				NPD545	4-O- α -L-rhamnopyranosyl-(1 \rightarrow 6)- β -D-glucopyranosyl acetophenone
				NPD528	4-O- β -D-glucopyranoside-acetophenone
				NPD464	Prunin
				NPD448	ormocarpin
				NPD447	Pyrroside B
				NPD445	Hemiphloin
				NPD362	Scolymoside
				NPD905	11-O-(4'-O-methylgalloyl)-bergenin
				NPD838	taxifolin
				NPD818	L-Picein
				NPD763	Davidioside
				NPD756	3,5,7,3'-tetrahydroxy-4'-methoxy-dihydroflavone
				NPD907	11-O-(4'-hydroxybenzoyl)-bergenin

				NPD908	bergenin
				NPD1066	matairesinoside
				NPD1119	7-methoxy neo chamaejasmin A
				NPD1126	7-methoxy neo chamaejasmin B
				NPD1149	2,2'-bisteppoge nin-7-O- β -gluc opyranoside
				NPD1334	Osmanthuside G
				NPD1696	Dihydrosyringi n ^b
				NPD1335	Dihydrosyringi n ^b
				NPD1697	Pallasiin
				NPD1708	Cyanoneside A
				NPD1750	Gaultheroside A
				NPD1757	Gaultheroside G
				NPD1758	dihydrodehydro diconiferylalco hol-9-O- β -D-ox ylopyranoside
				NPD1940	1-(4-((2S,3S,4 R,5S)-tetrahydr o-3,4,5-trihydro xy-6-(hydroxy methyl)-2H-pyr an-2-yloxy)phe nyl)ethanone
				NPD2061	1-(4'-hydroxy- 3'-methoxyphe nyl)-2-[4''-(3-h ydroxypropyl)- 2''-hydroxyphe noxy]-1,3-prop andiol-4'-O- β - D-xylopyranosi de

				NPD1999	β -D-Glucopyranoside-4-phenylbutan-2-one
				NPD2141	(+)-lyoniresinol-3 α -O- β -D-glucopyranoside
				NPD2140	(-)-lyoniresinol-3 α -O-9-O-(6'-3,5-dimethoxy-4-hydroxybenzoyl)- β -D-glucopyranoside
				NPD2139	(+)-lyoniresinol-3 α -O- β -D-glucopyranoside
				NPD2105	Junipetrioloside A
				NPD2074	1-(4'-hydroxy-3'-methoxyphenyl)-2-[4''-(3-hydroxypropyl)-2''-hydroxyphenoxy]-1,3-propanediol-4''c-O- α -L-rhamnoside
				NPD2071	1-(4'-hydroxy-3'-methoxyphenyl)-2-[4''-(3-hydroxypropyl)-2''-methoxyphenoxy]-1,3-propanediol-4''c-O- α -L-rhamnoside
				NPD2069	1-(4'-hydroxy-3'-methoxyphenyl)-2-[4''-(3-hydroxypropyl)-2''-hydroxyphenoxy]-1,3-propanediol-4'-O- α -L-rhamno-2''-O- β -D-glucopyranoside

				NPD2068	Styraxlignolide D
				NPD2065	1-(4'-hydroxy-3'-methoxyphenyl)-2-[2''-hydroxy-4''-(3-hydroxypropyl)phenoxy]-3-propano-1-3-O- α -L-rhamno-4''c- O- β -D-xylopyranoside

^a The “NPD” is the abbreviation of “Natural product database”, and the accession numbers are from the in-house TCM database as well.

^b They were extracted from different herbal sources.