



Figure S1 Quality control and normalization of scRNA-seq data (GSE134520). (A) nCount and nFeature of RNA expression range and percentages of mitochondria and ribosomes in NAG and EGC groups. (B) Violin plots of cutoff value of nCount and nFeature of RNA expression and percentage of mitochondria in NAG and EGC groups. (C) Highly variable genes in EGC and NAG groups. (D) Between-group and phase (G1, G2M, and S) batch effect removal for EGC and NAG in UMAP, tSNE, and PCA plots. NAG, nonatrophic gastritis; EGC, early gastric cancer; PC, principal component; tSNE, t-distributed stochastic neighbor embedding; UMAP, uniform manifold approximation and projection; scRNA-seq, single-cell RNA sequencing; PCA, principal component analysis.

Table S1 DeepPK predicted molecule properties of cimifugin

PK and toxicity category	Property name	Predicted value	Property unit	Predictive confidence	Is prediction within training range?	Is MW within training range?
Absorption	Caco-2 (logPaap)	-4.85	LogPaap	-	Yes	Yes
	Human oral bioavailability 20%	Bioavailable	Category (bioavailable/non-bioavailable)	0.685	-	Yes
	Human intestinal absorption	Absorbed	Category (absorbed/non-absorbed)	0.988	-	Yes
	Madin-Darby canine kidney	-4.35	cm/s	-	Yes	Yes
	Human oral bioavailability 50%	Bioavailable	Category (bioavailable/non-bioavailable)	0.554	-	Yes
	P-glycoprotein inhibitor	Non-inhibitor	Category (inhibitor/non-inhibitor)	0.217	-	Yes
	P-glycoprotein substrate	Non-substrate	Category (substrate/non-substrate)	0.239	-	Yes
	Skin permeability	-2.08	Log Kp	-	Yes	Yes
Distribution	Blood-brain barrier (central nervous system)	-3.19	Log BB	-	Yes	Yes
	Blood-brain barrier	Penetrable	Category (penetrating/non-penetrating)	0.943	-	Yes
	Fraction unbound (human)	0.86	Free proportion	-	Yes	Yes
	Plasma protein binding	47.53	Therapeutic index	-	Yes	Yes
	Steady state volume of distribution	0.74	Log VDss	-	Yes	Yes
Metabolism	Breast cancer resistance protein	Non-inhibitor	Category (inhibitor/non-inhibitor)	0.233	-	Yes
	CYP 1A2 inhibitor	Inhibitor	Category (inhibitor/non-inhibitor)	0.884	-	Yes
	CYP 1A2 substrate	Substrate	Category (substrate/non-substrate)	0.527	-	Yes
	CYP 2C19 inhibitor	Non-inhibitor	Category (inhibitor/non-inhibitor)	0.048	-	Yes
	CYP 2C19 substrate	Non-substrate	CYP 2C19 substrate	0.404	-	Yes
	CYP 2C9 inhibitor	Non-inhibitor	Category (inhibitor/non-inhibitor)	0.013	-	Yes
	CYP 2C9 substrate	Non-substrate	Category (substrate/non-substrate)	0.309	-	Yes
	CYP 2D6 inhibitor	Non-inhibitor	Category (inhibitor/non-inhibitor)	0	-	Yes
	CYP 2D6 substrate	Non-substrate	Category (substrate/non-substrate)	0.454	-	Yes
	CYP 3A4 inhibitor	Non-inhibitor	Category (inhibitor/non-inhibitor)	0.028	-	Yes
	CYP 3A4 substrate	Non-substrate	Category (substrate/non-substrate)	0.436	-	Yes
	OATP1B1	Non-inhibitor	Category (inhibitor/non-inhibitor)	0.047	-	Yes
	OATP1B3	Non-inhibitor	Category (inhibitor/non-inhibitor)	0.065	-	Yes
	Excretion	Clearance	4.03	Log (mL/min/kg)	-	Yes
Organic cation transporter 2		Non-inhibitor	Category (inhibitor/non-inhibitor)	0.1	-	Yes
Half-life of drug		Half-life <3 h	Category (half-life ≥3 h/half-life <3 h)	0.148	-	Yes
Toxicity	AMES mutagenesis	Toxic	Category (toxic/safe)	0.606	-	Yes
	Avian	Safe	Category (toxic/safe)	0.242	-	Yes
	Bee	Toxic	Category (toxic/safe)	0.711	-	Yes
	Bioconcentration factor	1.28	Log ₁₀ (L/kg)	-	Yes	Yes
	Biodegradation	Safe	Category (toxic/safe)	0.062	-	Yes
	Carcinogenesis	Safe	Category (toxic/safe)	0.209	-	Yes
	Crustacean	Toxic	Category (toxic/safe)	0.732	-	Yes
	Liver injury I	Safe	Category (toxic/safe)	0.28	-	Yes
	Eye corrosion	Safe	Category (toxic/safe)	0	-	Yes
	Eye irritation	Safe	Category (toxic/safe)	0.194	-	Yes
	Maximum tolerated dose	0.59	Log mg/kg/day	-	Yes	Yes
	Liver injury II	Toxic	Category (toxic/safe)	0.756	-	Yes
	hERG blockers	Safe	Category (toxic/safe)	0.001	-	Yes
	Daphnia Maga	5.76	-Log ₁₀ [(mg/L)/(1,000 × MW)]	-	Yes	Yes
	Micronucleos	Toxic	Category (toxic/safe)	0.783	-	Yes
	NR-AhR	Safe	Category (toxic/safe)	0.471	-	Yes
	NR-AR	Safe	Category (toxic/safe)	0.03	-	Yes
	NR-AR-LBD	Safe	Category (toxic/safe)	0.002	-	Yes
	NR-aromatase	Safe	Category (toxic/safe)	0.069	-	Yes
	NR-ER	Safe	Category (toxic/safe)	0.089	-	Yes
	NR-ER-LBD	Safe	Category (toxic/safe)	0.01	-	Yes
	NR-GR	Safe	Category (toxic/safe)	0.425	-	Yes
	NR-PPAR-gamma	Safe	Category (toxic/safe)	0.029	-	Yes
	NR-TR	Safe	Category (toxic/safe)	0.014	-	Yes
	T. pyriformis	2.91	-Log ₁₀ [(mg/L)/(1,000 × MW)]	-	Yes	Yes
	Rat (acute)	2.72	mol/kg	-	Yes	Yes
	Rat (chronic oral)	1.76	LOAEL	-	Yes	Yes
	Fathead minnow	4.24	-Log ₁₀ [(mg/L)/(1,000 × MW)]	-	Yes	Yes
	Respiratory disease	Toxic	Category (toxic/safe)	0.887	-	Yes
Skin sensitization	Safe	Category (toxic/safe)	0.436	-	Yes	
SR-ARE	Safe	Category (toxic/safe)	0.097	-	Yes	
SR-ATAD5	Safe	Category (toxic/safe)	0.012	-	Yes	
SR-HSE	Safe	Category (toxic/safe)	0.015	-	Yes	
SR-MMP	Safe	Category (toxic/safe)	0.037	-	Yes	
SR-p53	Safe	Category (toxic/safe)	0.078	-	Yes	
General properties	Boiling point	418.16	Degree Celsius (°C)	-	Yes	Yes
	Hydration free energy	-11.71	kcal/mol	-	Yes	Yes
	Log(D) at pH =7.4	1.09	Log mol/L	-	Yes	Yes
	Log(P)	1.08	Log mol/L	-	Yes	Yes
	Log S	-2.36	Log mol/L	-	Yes	Yes
	Log(vapor pressure)	-7.48	Log(vapor pressure)	-	Yes	Yes
	Melting point	199.22	Degree Celsius (°C)	-	Yes	Yes
	pKa acid	10.23	-Log Ka	-	Yes	Yes
pKa basic	4.85	-Log Ka	-	Yes	Yes	

PK, pharmacokinetics; MW, molecular weight; Caco-2, colorectal adenocarcinoma cell line; logPaap, logarithm of apparent permeability; P-glycoprotein, permeability glycoprotein; log Kp, logarithm of permeability coefficient; therapeutic index, plasma protein binding index; log BB, logarithm of blood-brain barrier permeability; log VDss, logarithm of the volume of distribution at steady state; CYP, cytochrome P450; OATP1B1, organic anion transporting polypeptide 1B1; OATP1B3, organic anion transporting polypeptide 1B3; AMES, ames test; hERG, human ether-à-go-go-related gene; NR, nuclear receptor; LOAEL, lowest observed adverse effect level; SR, stress response; log(D), logarithm of distribution coefficient at a specific pH; log mol/L, logarithm of molarity; log(P), logarithm of octanol-water partition coefficient; log S, logarithm of solubility; log(vapor pressure), logarithm of vapor pressure; pKa acid, acid dissociation constant; pKa basic, basic dissociation constant.

Table S2 Predictive analysis of cimifugin-anticancer drug interactions in multiple cancer cells

Drug A	Drug B	Drug A SMILES	Drug B SMILES	MolWt drug A	MolWt drug B	Heavy Atom Count drug A	Heavy Atom Count drug B	Ring Count drug A	Ring Count drug B	Num Rotatable Bonds drug A	Num Rotatable Bonds drug B	Donor Count drug A	Donor Count drug B	Acceptor Count drug A	Acceptor Count drug B	MolLogP drug A	MolLogP drug B	MELANOMA prediction	OVARIAN prediction	GENERAL prediction	LUNG prediction	BREAST prediction	COLON prediction	PROSTATE prediction
Cimifugin	Capecitabine	<chem>CC(C)(C1CC2=C(O1)C=C3C(=C2OC)C(=O)C=C(O3)CO)O</chem>	<chem>CCCCCOC(=O)NC1=NC(=O)N(C=C1F)C2C(C(C(O2)C)O)O</chem>	306.314	359.354	22	25	3	2	3	6	2	3	5	8	1.3683	0.7602	Antagonistic	Antagonistic	Antagonistic	Synergistic	Synergistic	Synergistic	Synergistic
Cimifugin	Cisplatin	<chem>CC(C)(C1CC2=C(O1)C=C3C(=C2OC)C(=O)C=C(O3)CO)O</chem>	<chem>N.N.Cl[Pt]Cl</chem>	306.314	300.046	22	5	3	0	3	0	2	2	5	0	1.3683	1.7005	Synergistic	Synergistic	Synergistic	Antagonistic	Synergistic	Synergistic	Synergistic
Cimifugin	5-FU	<chem>CC(C)(C1CC2=C(O1)C=C3C(=C2OC)C(=O)C=C(O3)CO)O</chem>	<chem>C1=C(C(=O)NC(=O)N1)F</chem>	306.314	130.078	22	9	3	1	3	0	2	2	5	3	1.3683	-0.7977	Antagonistic	Antagonistic	Synergistic	Antagonistic	Synergistic	Synergistic	Synergistic
Cimifugin	Irinotecan	<chem>CC(C)(C1CC2=C(O1)C=C3C(=C2OC)C(=O)C=C(O3)CO)O</chem>	<chem>CCC1=C2CN3C(=CC4=C(C3=O)COC(=O)C4(CC)O)C2=NC5=C1C=C(C=C5)OC(=O)N6CCC(CC6)N7CCCC7</chem>	306.314	586.689	22	43	3	7	3	4	2	3	5	7	1.3683	4.0911	Antagonistic	Antagonistic	Synergistic	Synergistic	Antagonistic	Antagonistic	Antagonistic
Cimifugin	Oxaliplatin	<chem>CC(C)(C1CC2=C(O1)C=C3C(=C2OC)C(=O)C=C(O3)CO)O</chem>	<chem>C1CCC(C(C1)[NH-])[NH-].C(=O)(C(=O)O)O.[Pt+2]</chem>	306.314	397.288	22	15	3	1	3	0	2	2	5	4	1.3683	1.5551	Synergistic	Synergistic	Antagonistic	Synergistic	Synergistic	Antagonistic	Synergistic
Cimifugin	Paclitaxel	<chem>CC(C)(C1CC2=C(O1)C=C3C(=C2OC)C(=O)C=C(O3)CO)O</chem>	<chem>CC1=C2C(C(=O)C3(C(CC4C(C3C(C2(C)C)(CC1OC(=O)C(C5=CC=CC=C5)NC(=O)C6=CC=CC=C6)O)OC(=O)C7=CC=CC=C7)(CO4)OC(=O)C)O)C(=O)C</chem>	306.314	853.918	22	62	3	7	3	10	2	4	5	14	1.3683	3.7357	Antagonistic	Synergistic	Antagonistic	Antagonistic	Antagonistic	Antagonistic	Synergistic

SMILES, simplified molecular input line entry system; MolWt, molecular weight; NumRotatableBonds, number of rotatable bonds; MolLogP, molecular logarithm of partition coefficient; 5-FU, 5-fluorouracil.

Table S3 Eight core genes, cell types, and KEGG metabolic pathways mapping list

Gene name	Cell type	KEGG metabolic pathway	P value
<i>AKR1B10</i>	PMC	Folate biosynthesis	9.67E-08
	T cell	Folate biosynthesis	9.67E-08
	PMC	Fructose and mannose metabolism	0.057448
	T cell	Fructose and mannose metabolism	0.057448
	PMC	Galactose metabolism	0.001346
	T cell	Galactose metabolism	0.001346
	PMC	Glycerolipid metabolism	0.005303
	T cell	Glycerolipid metabolism	0.005303
	PMC	Pentose and glucuronate interconversions	0.060829
	T cell	Pentose and glucuronate interconversions	0.060829
<i>AKR1C2</i>	PMC	Chemical carcinogenesis—DNA adducts	0.000226
	PMC	Chemical carcinogenesis—reactive oxygen species	0.000527
	PMC	Steroid hormone biosynthesis	0.005303
<i>AKR1C3</i>	PMC	Arachidonic acid metabolism	0.005137
	PMC	Chemical carcinogenesis—reactive oxygen species	0.000527
	PMC	Folate biosynthesis	9.67E-08
	PMC	Ovarian steroidogenesis	0.08747
	PMC	Steroid hormone biosynthesis	0.005303
<i>CA2</i>	PMC	Collecting duct acid secretion	0.047238
	PMC	Nitrogen metabolism	0.029991
	PMC	Proximal tubule bicarbonate reclamation	0.040374
<i>CBR1</i>	PMC	Arachidonic acid metabolism	0.005137
	T cell	Arachidonic acid metabolism	0.005137
	PMC	Chemical carcinogenesis—DNA adducts	0.000226
	T cell	Chemical carcinogenesis—DNA adducts	0.000226
	PMC	Chemical carcinogenesis—reactive oxygen species	0.000527
	T cell	Chemical carcinogenesis—reactive oxygen species	0.000527
	PMC	Folate biosynthesis	9.67E-08
	T cell	Folate biosynthesis	9.67E-08
	PMC	Metabolism of xenobiotics by CYP	8.73E-06
	T cell	Metabolism of xenobiotics by CYP	8.73E-06
<i>GSTA1</i>	PMC	Chemical carcinogenesis—DNA adducts	0.000226
	PMC	Drug metabolism—CYP	0.000256
	PMC	Drug metabolism—other enzymes	0.008699
	PMC	Glutathione metabolism	0.004499
	PMC	Metabolism of xenobiotics by CYP	8.73E-06
<i>MAOB</i>	Endocrine cell	Drug metabolism—CYP	0.000256
	CMP	Drug metabolism—CYP	0.000256
	Endocrine cell	Glycine, serine and threonine metabolism	0.069232
	CMP	Glycine, serine and threonine metabolism	0.069232
	Endocrine cell	Histidine metabolism	0.000675
	CMP	Histidine metabolism	0.000675
	Endocrine cell	Phenylalanine metabolism	0.000353
	CMP	Phenylalanine metabolism	0.000353
	Endocrine cell	Tyrosine metabolism	0.001815
CMP	Tyrosine metabolism	0.001815	
<i>PDE2A</i>	Endocrine cell	Glycine, serine and threonine metabolism	0.069232

KEGG, Kyoto Encyclopedia of Genes and Genomes; CMP, common myeloid progenitor; CYP, cytochrome P450; PMC, pit mucous cell.