Table SI. Effect of synthetic drugs against metabolic reprogramming in different cancer models.

A, Glucose metabolism					
First author/s, year	Target	Drugs	Cancer model	Clinical phase	(Refs.)
Liu, 2012	GLUT1	WZB115	*In vitro* analysis	Preclinical	(1)
Liu *et al*, 2012		WZB117	Lung cancer	Preclinical	(2)
Gunnink *et al*, 2016		Curcumin	Fibroblast cells	Preclinical	(3)
Wood *et al*, 2008		Fesentin	Prostate cancer cells, leukemia cells	Preclinical	(4)
Gunnink *et al*, 2016		Cytochalasin B	Enzymatic assay	Preclinical	(3)
Chan *et al*, 2011		STF-31	Renal cell carcinoma	Preclinical	(5)
Wu *et al*, 2018, Lin *et al*, 2016	GLUT2	Phloretin	Breast cancer, colorectal cancer	Preclinical	(6,7)
Flaig *et al*, 2007	GLUT4	Silybin	Prostate cancer	Phase I	(8)
Dalva-Aydemir *et al*, 2015		Ritonavir	Myeloma cells	Preclinical	(9)
Yang *et al*, 2023	GLUT5	2,5-AM	Lung cancer cell	Preclinical	(10)
B, Glycolysis					
First author/s, year	Target	Drugs	Cancer model	Clinical phase	(Refs.)
De Marinis *et al*, 1999; Berruti *et al*, 2002	HK1	Lonidamine	Lung cancer, breast cancer	Phase III	(11,12)
Dai *et al*, 2015; Boocock *et al*, 2007	HK2	Resveratrol	Liver cell	Phase I	(13,14)
Mohanti *et al*, 1996; Stein *et al*, 2010		2-Deoxyglucose	Human cerebral gliomas, prostate cancer	Phase II	(15,16)
Ko *et al*, 2012; El Sayed *et al*, 2014		3-Bromopyruvate	Melanoma cell	Preclinical	(17,18)

Xu *et al*, 2017		Chrysin	Hepatocellular carcinoma cells	Preclinical	(19)
Li *et al*, 2017		Benserazide	*In vitro* analysis	Preclinical	(20)
Li *et al*, 2017		Astragalin	Hepatocellular carcinoma cells	Preclinical	(21)
Tao *et al*, 2017		Genistein-27	Breast cancer cells	Preclinical	(22)
Huang *et al*, 2012	PKM2	Orlistat	Ovarian cancer	Preclinical	(23)
Zhang *et al*, 2021		Shikonin	Esophageal squamous cell carcinomas	Preclinical	(24)
Chesney *et al*, 2015	PFKFB4	5MPN	Lung cancer, breast cancer, prostatic cancer and adenocarcinoma cell lines	Preclinical	(25)
De Oliveira *et al*, 2021	PFKFB3	KAN0438757	Colorectal cancer cells	Preclinical	(26)
Wang *et al*, 2020		Compounds 26	Enzymatic assay	Preclinical	(27)
Lea *et al*, 2016		PQP	Colon cancer cells, bladder cancer cells	Preclinical	(28)
Jiang *et al*, 2022		3PO/PFK158	Ovarian cancer	Phase I	(29)
Mateo *et al*, 2013	PDK-1	AR-12	Advanced solid tumors	Phase I	(30)
Powell *et al*, 2022	Pan-PDK	DCA	Head and neck squamous cell carcinoma	Phase II	(31)
Dhar *et al*, 2009		Mitaplatin (cisplatin and DCA fusion)	Advanced solid tumor	Phase I	(32)
Liberti *et al*, 2017; Liberti *et al*, 2018	GAPDH	Koningic acid	Enzymatic assay	Preclinical	(33,34)
Ganapathy-Kanniappan *et al*, 2018		Iodoacetate	Enzymatic assay	Preclinical	(35)
Ganapathy-Kanniappan *et al*, 2010		3-bromopyruvate	Enzymatic assay	Preclinical	(36)

C, Tricarboxylic acid cycle

First author/s, year	Target	Drugs	Cancer model	Clinical phase	(Refs.)
Megias-Vericat *et al*, 2019	Mutant IDH1	IDH305	Leukemia cell lines	Phase IV	(37)
Norsworthy *et al*, 2019		Olutasidenib (FT-2102)	Brain tumor	Phase II	(38)
Heuser *et al*, 2020		Ivosidenib (AG-120)	Acute myeloid leukemia	Phase IV	(39)
Konteatis *et al*, 2020		BAY1436032	Leukemia cell lines	Phase I	(40)
Philip *et al*, 2019	Mutant IDH2	Enasidenib (AG-221)	Acute myeloid leukemia	Phase IV	(41)
Nyce, 2017	Mutant IDH1/2	Vorasidenib (AG-881)	Brain tumor	Phase III	(42)
Fang *et al*, 2016	PDH	CPI-613	Metastatic adenocarcinoma	Phase III	(43)

D, Oxidative phosphorylation

First author/s, year	Target	Drugs	Cancer model	Clinical phase	(Refs.)
Arrieta *et al*, 2019	Complex I	Metformin	Lung adenocarcinoma	Clinical and preclinical	(44)
Dalton *et al*, 2021		Phenformin	Neuroblastoma cells	Clinical and preclinical	(45)
Guo *et al*, 2016	Complex II	Lonidamine	Human melanoma cells, colon cancer cells	Phase III	(46)
Fiorillo *et al*, 2016	Complex III	Atovaquone	Cancer stem cells	Early phase I	(47)
Sun *et al*, 2011	Complex IV	Arsenic trioxide	Breast cancer cells	Phase III	(48)
Moncada, 2015		Nitric oxide	Colon cancer cells	Clinical and preclinical	(49)

E, Pentose phosphate pathway

First author/s, year	Target	Drugs	Cancer model	Clinical phase	(Refs.)
Nyce, 2017	G6PD	Polydatin	Skin cancer	Preclinical	(42)

Fang *et al*, 2016		Dehydroepiandrosterone	Cervical cancer cells	Phase I	(43)
Oronsky *et al*, 2016		RRx-001	Hepatocellular carcinoma, colorectal cancer	Phase II	(50)
Daneshmandi *et al*, 2021	6PGD	6-aminonicotinamide	T-cell metabolism	Preclinical	(51)
F, Lactate metabolism					
First author/s, year	Target	Drugs	Cancer model	Clinical phase	(Refs.)
Le *et al*, 2010	LDHA	Oxamate	Pancreatic cancer cells	Preclinical	(52)
Zhou *et al*, 2010		FX11	Breast cancer cells	Preclinical	(53)
Colen *et al*, 2011		Galloflavin	Brain tumor	Preclinical	(54)
Guan *et al*, 2020	MCTs	α-cyano-4-hydroxycinnamic acid	Breast tumor	Preclinical	(55)
Guan *et al*, 2019	MCTs-1	AR-C155858	Breast tumor cancer cells	Preclinical	(56)
Noble *et al*, 2017		AZD3965	B-cell lymphoma	Phase I	(57)
G, Lipid metabolism					
First author/s, year	Target	Drugs	Cancer model	Clinical phase	(Refs.)
Alwarawrah *et al*, 2016	FAS	Fasnall	Breast cancer	Preclinical	(58)
Sadowski *et al*, 2014		Triclosan	Prostate cancer	Preclinical	(59)
Zhou *et al*, 2003		C75	Breast cancer cells	Preclinical	(60)
Zhou *et al*, 2003; Flavin *et al*, 2010		C93	Breast cancer cells, prostate cancer	Preclinical	(60,61)
Hardwicke *et al*, 2014		GSK2194069	Gastric cell lines, non-small cell lung cancer cell lines	Preclinical	(62)
Vázquez *et al*, 2008		GSK837149A	Enzymatic assay	Preclinical	(63)
Kridel *et al*, 2004		Orlistat	Adenocarcinoma cell lines, prostate carcinoma cell lines	Preclinical	(64)
Shiragami *et al*, 2013		Cerulenin	Human colon cancer cells	Preclinical	(65)

Loomba *et al*, 2021		TVB-2640	Non-alcoholic steatohepatitis	Phase II	(66)
Lally *et al*, 2019	ACC	ND-654	Hepatocellular carcinoma	Preclinical	(67)
Li *et al*, 2019		ND-646	Non-small cell lung cancer	Preclinical	(68)
Beckers *et al*, 2007		Soraphen-A	Prostate cancer cells	Preclinical	(69)
Wang *et al*, 2009		5-(tetradecyloxy)-2-furoic acid	Breast cancer, prostate cancer	Preclinical	(70)
Bauer *et al*, 2005; Hatzivassiliou *et al*, 2005	ACLY	SB0204990	Hematopoietic cells	Preclinical	(71,72)
Shrypek *et al*, 2021	SCD	A939572	Pancreatic tumor	Preclinical	(73)
Fritz *et al*, 2010		BZ36	Prostate cancer	Preclinical	(74)
Li *et al*, 2014	SREBP	Fatostatin	Prostate cancer	Preclinical	(75)
Król *et al*, 2015		Betulin	Ovarian carcinoma, cervical carcinoma, glioblastoma multiforme	Preclinical	(76)

H, Amino acid metabolism

First author/s, year	Target	Drugs	Cancer model	Clinical phase	(Refs.)
Ju *et al*, 2019	MTHFD2	LY345899	Colorectal cancer	Preclinical	(77)
Fu *et al*, 2017	MTHFD1/2	Carolacton	Colon cancer cells	Preclinical	(78)
Okimoto *et al*, 2020	TS, DHFR, GARFT	Pemetrexed/MTA/LY231514	Lung cancer cells	Phase IV	(79)
Rana *et al*, 2020; Neradil *et al*, 2015	TS, DHFR	Amethopterin/MTX/methotrexate	Medulloblastoma and osteosarcoma cells	Phase IV	(80,81)
Sharma *et al*, 2008; Siddiqui *et al*, 2019	TS	Capecitabine/xeloda	Colorectal cancer, pancreatic cancer	Phase IV	(82,83)
Kim *et al*, 2022		5-Fluorouracil/Adrucil	Colon cancer	Phase IV	(84)
Atkinson *et al*, 1965;	PPAT	6-mercaptopurine	Ehrlich ascites tumor cells, malignant neoplasm	Phase III	(85,86)

Kodama *et al*, 2020					
Munshi *et al*, 2014		6-thioguanine	Colon cancer, gastric cancer, pancreatic cancer, head and neck cancer, renal cell cancer, breast cancer	Phase III	(87)
Elgogary *et al*, 2016	GLS	BPTES	Pancreatic cancer	Preclinical	(88)
Tannir *et al*, 2018		CB-839	Metastatic renal cell carcinoma	Phase II	(89)
Yamashita *et al*, 2021		JHU-083	Malignant glioma cells	Preclinical	(90)
Wang *et al*, 2010		969	Mesothelioma, pancreatic cancer, sarcoma, glioblastoma, gastrointestinal tumors	Preclinical	(91)

6PGD, 6-phosphogluconate dehydrogenase; ACC, acetyl CoA carboxylase; ACLY, ATP citrate lyase; DCA, dichloroacetate; DHFR, dihydrofolate reductase; FAS, fatty acid synthase; G6PD, glucose-6-phosphate dehydrogenase; GARFT, glycinamide ribonucleotide formyl transferase; GLS, glutaminase; GLUT, glucose transporter; HK, hexokinase; IDH, isocitrate dehydrogenase; LDHA, lactate dehydrogenase; MCT, monocarboxylate transporter; MTHFD, methylene tetrahydrofolate dehydrogenase; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PFKFB, fructose-2,6-bisphosphatase; PK, pyruvate kinase; PPAT, phosphoribosyl pyrophosphate aminotransferase; SCD, stearoyl CoA desaturase; SREBP, sterol regulatory element binding protein; TS, thymidylate synthase.

Table SII. Effect of flavonoids against metabolic reprogramming in different cancer models.

A, Glucose metabolism					
First author/s, year	Target	Flavonoids	Mode of action	Cancer model	(Refs.)
Melstrom *et al*, 2008; Gonzalez-Menendez *et al*, 2014	GLUTs	Apigenin	↓GLUT1 expression	Prostate cancer	(92,93)
Farhan, 2022		Catechin	↓GLUT1 expression	Prostate cancer	(94)
Li *et al*, 2017		Genistein	↓GLUT1 expression	Hepatocellular carcinoma	(95)
Melstrom *et al*, 2008		Phloretin	↓GLUT4 expression	Prostate cancer	(92)
Yang *et al*, 2013		Hesperitin	↓GLUT1 level; ↓GLUT4 translocation	Breast cancer	(96)
Azevedo *et al*, 2015		Kaempferol	↓GLUT1 level	Breast cancer	(97)
Moreira *et al*, 2013		Quercetin	↓GLUT1 activity	Breast cancer	(98)
Moreira *et al*, 2013; Wei *et al*, 2018		EGCG	↓GLUT1 expression	Breast cancer	(98,99)
Zhan *et al*, 2011		Silibinin	↓GLUT4 activity	Non-tumor CHO	(100)
B, Glycolysis					
First author/s, year	Target	Flavonoids	Mode of action	Cancer model	(Refs.)
Liu *et al*, 2019	HK2	Xanthohumol	↓HK2 expression	Colon cancer	(101)
Wu *et al*, 2019		Quercetin	↓HK2 level	Hepatocellular cancer	(102)
Wei *et al*, 2018		EGCG	↓HK2 activity	Breast cancer	(99)
Deng *et al*, 2019		*Chalcones* (10v)	↓HK2 level	Colon cancer	(103)
Guo *et al*, 2020		*Wogonin* (Gl-v9)	↓HK2 expression	Breast cancer	(104)
Zhou *et al*, 2016		*Wogonin* (Fv-429)	↓HK2 activity	Breast cancer	(105)

Tao *et al*, 2017		Genistein *27*	↓HK2 expression	Breast cancer	(22)
Li *et al*, 2017		Astralangin	↓HK2 expression	Hepatocellular cancer	(21)
Li *et al*, 2017		Hesperitin	↓HK2 expression	Hepatocellular cancer	(95)
Shan *et al*, 2017	PKM2	Apigenin	↓PKM2 expression	Colon cancer	(106)
Feng *et al*, 2019		Proanthocyanidin B2	↓PKM2 expression	Hepatocellular cancer	(107)
Wei *et al*, 2018		EGCG	↓PKM2 expression	Breast cancer	(99)
Aslan *et al*, 2016		Taxifolin	↓PKM2 activity	Breast cancer	(108)
		Neoeriocitrin	↓PKM2 activity	Breast cancer	
		Fisetin	↓PKM2 activity	Breast cancer	
		Catechin gallate	↓PKM2 activity	Breast cancer	
		Epicatechin	↓PKM2 activity	Breast cancer	
Jia *et al*, 2018		Quercetin	↓PKM2 activity	Breast cancer	(109)
Chen *et al*, 2011		Shikonin	↓PKM2 activity	Breast cancer, lung cancer, melanoma	(110)
Mazlaghaninia *et al*, 2019	LDH	Morin	↓LDH activity	*In vitro* study	(111)
Wu *et al*, 2021		Kaempferol	↓LDH activity	Colon cancer	(112)
Jia *et al*, 2018		Quercetin	↓LDH activity	Breast cancer	(109)
Bader *et al*, 2015		Luteolin-7-O-β-D-glucoside	↓LDH enzymatic activity	*In vitro* study	(113)
Wei *et al*, 2018		EGCG	↓LDH activity	Breast cancer	(99)
Li *et al*, 2016	PFK	EGCG	↓PFK activity	Breast cancer	(114)
Gomez *et al*, 2013		Resveratrol	↓PFK activity	Breast cancer	(115)
Dihal *et al*, 2008	Aldolase	Quercetin	↓ Aldolase level	Colon mucosa	(116)

Dihal *et al*, 2008	Enolase	Quercetin	↓ Enolase level	Colon mucosa	(116)
Dihal *et al*, 2008	GAPDH	Quercetin	↓GAPDH level	Colon mucosa	(116)
Sellam *et al*, 2020	PD-L1	Silibinin	↓PD-L1 level	Prostate cancer	(117)
C, Tricarboxylic acid cycle					
First author/s, year	Target	Flavonoids	Mode of action	Cancer model	(Refs.)
Coricovac *et al*, 2021	PDH	Betulinic acid	↓PDH level	*In vitro*	(118)
Peeters *et al*, 2019	IDH	EGCG	↓ IDH activity	Colorectal cancer	(119)
Icard *et al*, 2021		Curcumin		In vitro study	(120)
Wei *et al*, 2022		Silibinin		Ovarian cancer	(121)
Frattaruolo *et al*, 2020		Resveratrol		In vitro assay	(122)
Shuvalov *et al*, 2023		Kaempferol		Enzymatic assay	(123)
D, OXPHOS					
First author/s, year	Target	Flavonoids	Mode of action	Cancer model	(Refs.)
Bianchi *et al*, 2018	ATP synthase	Curcumin	⊥ATP synthase	Breast cancer	(124)
Zheng *et al*, 2022		Kaempferol		Melanoma metastasis	(125)
Brecht *et al*, 2017	Mitochondrial chain complexes II and IV	Arctigenin	⊥Mitochondrial chain complexes II and IV and selectively killed only the OXPHOS-dependent cancer cells	Pancreatic cancer	(126)
Abotaleb *et al*, 2018	Mitochondrial membrane potential	Hesperetin	↓ Mitochondrial membrane potential ($\Delta\Psi_M$)	Gastric cancer	(127)
Patel *et al*, 2018		Naringenin	↓ Mitochondrial membrane potential	*In vitro*	(128)
Kicinska and	Complex I	Luteolin	Complex I, lower H_2O_2	Rat heart mitochondria	(129)

Jarmuszkiewicz, 2020		Myricetin	production		
		Fisetin			
		Rhamnetin			
		Baicalein			
Kincinskaand Jarmuszkiewicz, 2020	Complex III	Hispidulin	⊥Complex III, lower H_2O_2 production	Rat heart mitochondria	(129)
E, Pentose phosphate pathway					
First author/s, year	Target	Flavonoids	Mode of action	Cancer model	(Refs.)
Adem *et al*, 2014	G6PD	Caffeic acid	↓Regulation of G6PD	*In vitro*, cultured rainbow trout gill cells	(130)
Patrício, 2022		Polydatin	↓ Regulation of G6PD	*In vitro*	(131)
Adem *et al*, 2014		Ellagic acid	↓Regulation of G6PD	*In vitro*, enzymatic assay	(130)
Gomez *et al*, 2013	TK	Resveratrol	↓ Regulation of TK	Colon cancer	(115)
Adem *et al*, 2014	6PGD	Caffeic acid	↓ Regulation of 6PGD	*In vitro*	(130)
		Ellagic acid		*In vitro*	
Khan *et al*, 2021		Genistein		*In vitro*	(132)
Lin *et al*, 2015		Physcion		Lung cancer, leukemia cells, breast cancer	(133)
G, Lactate metabolism					
First author/s, year	Target	Flavonoids	Mode of action	Cancer model	(Refs.)
Wei *et al*, 2018	LDHA	EGCG	↓LDHA activity	*In vitro* study	(99)
Jia *et al*, 2018		Quercetin	↓LDHA activity	*In vitro* study	(109)

H, Lipid metabolism

First author/s, year	Target	Flavonoids	Mode of action	Cancer model	(Refs.)
Li *et al*, 2014	FAS	α-mangostin	↓Regulation of FAS	Breast cancer	(134)
Funabashi *et al*, 1989		Cerulenin	↓Regulation of FAS	*In vitro*	(135)
Lee *et al*, 2017		Emodin	↓Regulation of FAS	Colon cancer	(136)
Wangand Tian, 2001; Huang *et al*, 2009		EGCG	↓Regulation of FAS	Hepatocellular carcinoma	(137,138)
Liand Tian, 2004		Kaempferol	↓ Regulation of FAS	*In vitro*	(139)
Brusselmans *et al*, 2005		Luteolin	↓ Regulation of FAS	Breast cancer, prostate cancer	(140)
Li and Tian, 2004		Morin	↓ Regulation of FAS	*In vitro*	(139)
Lee and Sung, 2016		Platyphylloside	↓ Regulation of FAS	Preadipocytes	(141)
Brusselmans *et al*, 2005		Quercetin	↓ Regulation of FAS	Breast cancer, prostate cancer	(140)
Khan *et al*, 2014		Resveratrol	↓ Regulation of FAS	Breast cancer	(142)
Gao *et al*, 2014	ACLY	Cucurbitacins	⊥Xenograft growth in an ACLY-dependent manner	Prostate cancer	(143)
Wang and Tian, 2001; Huang *et al*, 2009	ACC	EGCG	⊥ACC	Hepatocellular carcinoma	(137,138)
Gnoni *et al*, 2009		Quercetin	⊥ACC	Rat hepatocytes	(144)
Vahlensieck *et al*, 1994; Weatherly *et al*, 2004		Soraphen A	⊥CC	*In vitro*	(145,146)
Potze *et al*, 2016	SCD	Betulinic acid	⊥SCD	Colon cancer, HeLa cells	(147)
Lee and Sung, 2016		Platyphylloside	⊥SCD	Preadipocytes	(141)

Wang and Tian, 2001	HIF-1	EGCG	⊥HIF-1 inducible pathways	Breast cancer	(137)
Wei *et al*, 2015		Oroxylin A		Breast cancer	(148)
Jung *et al*, 2013		Resveratrol		Breast cancer	(149)
Chen *et al*, 2015		Baicalein		Gastric cancer	(150)
Liu *et al*, 2009		Methylalpinumisoflavone		Breast cancer	(151)
Jiang *et al*, 2017		Eupafolin		Hepatocellular carcinoma	(152)
Ansó *et al*, 2010	HIF-1α	Quercetin	↓Protein expression	*In vitro*	(153)
Sun *et al*, 2015		Resveratrol			(154)
Wang *et al*, 2011		EGCG			(155)
I, Amino acid metabolism					
First author/s, year	Target	Flavonoids	Mode of action	Cancer model	(Refs.)
Nenkov *et al*, 2021	ASCT-2	Resveratrol	↓ Regulation of ASCT-2	Hepatoma	(156)
Fan *et al*, 2022	GLS	Curcumin	↓GLS	Renal cell carcinoma	(157)
Wang *et al*, 2020	GLS	Betulinic acid	↓GLS	*In vitro* study	(158)
Pournourmohammadi*et al*, 2017	GDH	EGCG	⊥GDH	*In vitro* study	(159)
Hay, 2016	PYCR1	Shikonin	↓PYCR1	T-cell leukemia/lymphoma	(160)

6PGD, 6-phosphogluconate dehydrogenase; ACC, acetyl CoA carboxylase; ACLY, ATP citrate lyase; ASCT2, alanine, serine, cysteine transporter 2; CHO, Chinese hamster ovary cells; EGCG, epigallocatechin-3-gallate; FAS, fatty acid synthase; G6PD, glucose-6-phosphate dehydrogenase; GDH, glutamine dehydrogenase; GLS, glutaminase; GLUT, glucose transporter; HIF, hypoxia-inducible factor; HK, hexokinase; IDH, isocitrate dehydrogenase; LDH, lactate dehydrogenase; LDHA, lactate dehydrogenase A; OXPHOS, oxidative phosphorylation; PD-L1, programmed death-ligand 1; PDH, pyruvate dehydrogenase; PFK, phosphofructokinase; PKM2, pyruvate kinase M2; PYCR1, pyrroline-5-carboxylate reductase 1; SCD, stearoyl CoA desaturase; TK, transketolase.

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