Table SI. Multiple biological activities of Nuciferine.

A, Anti-inflammatory effects					
First author, year	Models	Doses	Biological activities	Molecular targets	(Refs.)
Wang, 2016	Fructose-fed rats HK-2 cells	7, 14 and 28 mg/kg 2.5-40 μM	Attenuates fructose-induced hyperuricemia, dyslipidemia and systemic inflammation Inhibits TLR4/PI3K/ NF-κB signaling and NLRP3 inflammasome activation	TLR4 ↓, MyD88 ↓, PI3K ↓, ILK ↓, p-Akt ↓, p-p65 ↓, NLRP3 ↓, IL-1β ↓, TNF-α ↓, IL-6 ↓, MCP-1 ↓	(33)
Wu, 2017	LPS-induced RAW264.7 cells BALB/c mice	10 and 20 μg/ml 10 and 20 mg/kg	Reduces the lung wet/dry ratio and myeloperoxidase activity Improves alveolar hyperemia, alveolar wall thickening and inflammatory cell infiltration	IL-6 ↓, IL-1β ↓, IL-10↑, TLR4 ↓, NF- κ B ↓ p-p65 ↓, TNF-α ↓, IκBα ↓	(10)
Yang, 2017	Mouse tracheal rings	100 and 300 μM	Inhibits Ca^{2+} influx and VDLCCs, NSCCs; relaxes high K^{+}-precontracted TRs	NA	(128)

Chen, 2018	LPS-induced mouse mastitis model Mouse mammary epithelial cells	10, 15 and 20 mg/kg 10, 15 and 20 μg/ml	Alleviates mammary gland floccules injury and inflammatory cell infiltration	TLR4 ↓, NF-κB ↓ p-p65 ↓, p-IκBα ↓, IL-1β ↓, TNF-α ↓	(35)
Zhang, 2018	LPS-stimulated BV2 microglial cells	5, 10 and 20 μM	Attenuates LPS-induced inflammation	PGE_2↓, NO ↓, PPARγ↑, TNF-α ↓, p-p65 ↓, p-IκBα ↓, IL-1β ↓	(68)
Zhang, 2018	LPS-induced RAW264.7 cells	1, 10, 30 and 50 μM	Attenuates LPS-induced inflammation	PPARα↑, PPARγ↑, TNF-α ↓, NF-κB ↓, IκBα ↓, IL-6 ↓	(130)
Cui, 2020	HFD-induced NAFLD rat model	20 mg/kg	Decreases the expression of inflammatory factors	IL-6 ↓, IL-1β ↓, TNF-α ↓	(34)
Li, 2021	Folic acid-induced mice acute kidney injury HK-2 cells and 293T cells	30 mg/kg 5, 10, 20 and 40 μM	Alleviates renal fibrosis, promotes renal regeneration, prevents iron accumulation and lipid peroxidation, mitigates RSL3-induced ferroptosis,	MCP-1 ↓, Fn14 ↓, TWEAK ↓, GSH↑, PCNA↑, ROS ↓, TNF-α ↓, MDA ↓, fibronectin ↓, COL1A1 ↓,	(34)

			suppresses ROS generation	IL-6 ↓, FTL ↓, FTH ↓, FDN1↑, TfR1↑, GPX4↑, SLC7A11↑, FSP1↑	
Xiong, 2021	Obese model mice	20 mg/kg	Decreases body weight of obese mice, Lee's index and adipocyte volume, and improves dysbacteriosis	TNF-α ↓, IL-1β ↓, IL-6 ↓, ZO-1↑, occludin↑	(129)
Kim, 2022	LPS-induced RAW264.7 cells	6.25, 12.5, 25 and 50 μM	Prevents inflammatory response	NO ↓, PGE_2 ↓, NF-κB p65 ↓, iNOS ↓, COX-2 ↓, AP-1 ↓, ATF2 ↓, p-IKK ↓, MKK3 ↓, MKK6 ↓, p38 AMPK ↓, p-p38 ↓, p-AFT2 ↓, TNF-α ↓, IL-1β ↓, IL-6 ↓	(39)

Zhu, 2022	DSS-induced ulcerative colitis mouse model	10 and 20 mg/kg	Improves histological injury and colon shortening, promotes T-cell proliferation and differentiation, restores the Th1/Th2 and Th17/Treg balance	ZO-1↑, occludin↑	(9)
Kulhari, 2023	LPS-stimulated RAW 264.7 cells DSS-induced ulcerative colitis in mice	0.31, 0.63 and 1.25 μg/ml 20 and 40 mg/kg	Inhibits oxidative stress-mediated ROS generation and inflammatory responses Improves the DAI and histological alterations	iNOS ↓, IL-1β ↓, IL-18 ↓, TNF-α ↓, NF-κB ↓, MAPK ↓, NLRP3 ↓, claudin-1↑, ZO-1↑	(36)
Li, 2024	OGD/R-induced PC12 cells MCAO/R-induced rats	6.25, 12.5 and 25 μM 20, 40 and 80 mg/kg	Reduces the inflammatory level of cerebral ischemia-reperfusion injury	TNF-α ↓, IL-6 ↓, PI3K ↓, Akt ↓, NF-κB ↓, NLRP3 ↓	(37)
B, Anti-lipogenic effects					
First author, year	Models	Doses	Biological activities	Molecular targets	(Refs.)

Guo, 2013	High-fat diet-fed hamsters	10 and 15 mg/kg	Ameliorates HFD-induced dyslipidemia, liver steatosis and injury	PPARα↑, FAS ↓, CD36 ↓, SREBP-1 ↓, β-HBA↑, CPT-1↑, MTP↑, ApoB↑, MDA ↓, CYP2E1 ↓, TNF-α ↓	(65)
Zhang, 2015	Oleic acid-induced HepG2 cells	4, 8, 16 and 32 μg/ml	Inhibits lipid accumulation and inflammation, and decreases fatty acids	TNF-α ↓, IL-6 ↓, IL-8 ↓, MDA ↓, T-AOC↑, IL-10↑, SOD↑, PASK ↓, SREBP-1c ↓, FAS ↓, ACC ↓, SCD1, PPARα ↓, PPARγ ↓, AMPK↑, Akt↑, p-AMPK↑, NF-κB ↓	(67)
Ma, 2015	Insulin-resistant 3T3-L1 mature adipocytes	2 mg/l	Decreases lipid accumulation, increases glucose uptake and	GLUT4↑, p-AMPK↑	(20)

			ameliorates insulin resistance		
Zhan, 2018	HFD/STZ-induced diabetic mice HepG2 cells	NA 10 μM	Improves lipid profile and attenuates hepatic steatosis	PPAR-α↑, ACOX1↑, Ehhadh↑, Fgf21↑, PGC1α↑	(68)
Ning, 2019	STZ-induced diabetic rat model	200 mg/kg	Decreases liver steatosis and injury	SREBP-1c ↓, LXP-α ↓, ACC1 ↓, SCD-1 ↓, FAS ↓, ACC2↑, PPARα↑, CPT-1α↑	(69)
Zhou, 2020	1-day-old Broiler chickens	25, 100 and 400 mg/kg	Reduces fat deposition, decreases hepatic triglyceride and total cholesterol concentrations	HMGCR ↓, SREBP-2 ↓, ACC ↓, SREBP-1c ↓, LXR-α↑, CYP7A1 ↑, CPT-1↑	(19)
Wang, 2020	HFD-fed rats	10 mg/kg	Improves the lipid profile and liver function, prevents hepatic fatty deposition and reduces lipid accumulation	TC ↓, TG ↓, LDLC ↓, ALT ↓, ALP ↓	(133)

Yu, 2021	HFD-fed mice	7.5, 15 and 30 mg/kg	Alleviates liver steatosis, and enriches *Akkermansia muciniphila* and *Bacteroides uniformis*	NA	(21)
Xu, 2021	3T3-L1 preadipocytes	0-20 μM	Inhibits 3T3-L1 preadipocyte proliferation and differentiation, attenuates lipid accumulation and reduces intracellular TG contents	PPARγ ↓, C/EBPα ↓, C/EBP β ↓, FAS ↓, ACC ↓, HSL ↓, ATGL ↓, SREBP-1 ↓, FGF21↑, ZAG↑	(70)
C, Antioxidative effects					
First author, year	Models	Doses	Biological activities	Molecular targets	(Refs.)
Liu, 2014	AGS cells and DU-145 cells	IC_{50}, 21±0.5 μM	Displays antioxidative activity	NA	(131)
Harishkumar, 2020	H9c2 cells	0-200 μM; IC_{50}, 33.28 μM	Mitigates DOX-mediated free radicals	SOD↑, CAT↑, GSH↑, MDA ↓, ROS ↓	(45)
Cui, 2020	HFD-induced NAFLD rat model	20 mg/kg	Inhibits oxidative stress	SOD↑, GSH-Px↑, MDA↓	(130)
Harishkumar, 2022	Isoproterenol-induced myocardial	10 and 20 mg/kg	Reduces lipid peroxidation,	SOD↑, CAT↑, MDA ↓,	(85)

	infarction rat model		prevents ISO-mediated lipid bilayer damage and mitigates ISO-induced oxidative stress	ROS ↓	
D, Cardiovascular protective effects					
First author, year	Models	Doses	Biological activities	Molecular targets	(Refs.)
Wang, 2015	SD rats, HUVECs and vascular smooth muscle cells	1, 3 and 10 μM	Induces relaxation of mesenteric arteries and suppresses Ca^{2+} influx	p-eNOS↑, NO↑	(81)
Harishkumar, 2021	Zebrafish embryo and H9c2 cardiomyocytes	10, 20, 50, 100 and 200 μM	Reduces doxorubicin-mediated cardiotoxicity	Caspase 8↓, Caspase 3/7↓, Caspase 9↓, Bax↓, Bcl-2↑, Cyto-c↓	(84)
Harishkumar, 2022	Isoproterenol-induced myocardial infarction rats	10 and 20 mg/kg	Reduces levels of serum biomarkers and maintains cardiac rhythm	LDH↓, CK-B↓, CK-MB↓, caspase 9↓, caspase 3↓, Bax↓, Bcl-2↑	(85)
Deng, 2022	SD rat thoracic aorta HUVECs	0.3-2.4 μM; EC_{50}, 0.36±	Promotes vasodilation and inhibits ROCCs and SR Ca^{2+}	ICAM-1↓, cGMP↓	(82)

		0.02 μM 1-100 μM	release to relax thoracic aorta Mediates the NO/cGMP signaling pathway and activates the KIR channel to HUVECs		
Xiao, 2023	HFD-fed ApoE(-/-) mice Mouse aortic vascular smooth muscle cells	5, 10 and 40 mg/kg 1, 5 and 10 μM	Ameliorates the aortic lesion and vascular plaque, attenuates the migration and proliferation of VSMCs and suppresses Calm4/MMP12/Akt signaling	Calm4↓, MMP12↓, p-Akt↓	(87)
E, Neuroprotective effects					
First author, year	Models	Doses	Biological activities	Molecular targets	(Refs.)
Wu, 2020	MCAO-induced stroke rat model	10, 20 and 40 mg/kg	Improves neurological deficit scores, and ameliorates cerebral edema and infarction	S1P↑, oxoglutaric acid ↓, TUDCA↑, PLA2↑, 12/15-LOX↑, SPHK↑, IDH↑, GOT1↑, CYP2B↑, FADS↑, GPT↑	(72)

Chen C, 2022	Acute ischemic stroke rat model	10, 20 and 40 mg/kg	Reduces cerebral infarction, and improves survival rates and neurological deficits	MDA ↓, SOD↑, T-AOC↑, GSH/GSSG↑, TNF-α ↓, IL-1β ↓	(11)
Khan, 2022	Alloxan-induced diabetic albino rats	10 mg/kg	Reduces blood glucose, restores body weight, recovers acetylcholinesterase activity, and displays potent inhibitory effects against α-glucosidase and α-amylase	SOD↑, CAT↑, GSH↑, GPx↑	(73)
Chen C, 2022	MCAO rat model	40 mg/kg	Alleviates brain damage	PPARγ↑, S1P↑, Rac1 ↓, PGH_2 ↓, PGE_2 ↓	(74)
F, Musculoskeletal protective effects					
First author, year	Models	Doses	Biological activities	Molecular targets	(Refs.)
Kang, 2017	BMMs	0-40 μM; IC_{50}, 17.9 μM	Inhibits RANKL-induced osteoclast genesis and osteoclast-mediated bone resorption	Cathepsin K ↓, MMP-9 ↓	(98)
Song, 2020	Bone marrow-derived macrophages	0-30 μM	Decreases multinucleated osteoclast formation,	p-ERK1/2 ↓, p-JNK ↓, p-p38 ↓,	(76)

	Ovariectomized mice	40 mg/kg	promotes type H vessel formation, increases the quantity of $Trap^+$ preosteoclasts and increases the PDGF-BB concentration	p-IκBα ↓, c-FOS ↓, NFATc1 ↓, Trap ↓, MMP-9 ↓, DC-STAMP ↓, ATP6V0D2 ↓, p-p65 ↓, p-IKKα/β ↓, CTX-I ↓, OCN↑	
Wen, 2021	Primary rat chondrocytes Rat OA model	0, 10, 20, 40 and 100 μM 30 mg/kg	Ameliorates the progression of OA, alleviates ECM degradation, inhibits the production of inflammatory mediators and inhibits the PI3K/Akt/NF-κB signaling pathway	MMP13 ↓, Col-II↑, ADAMTS5 ↓, iNOS ↓, COX-2 ↓, p-PI3K ↓, p65 ↓	(77)
Guo, 2024	Raw264.7 cells	30 μM	Inhibits osteoclast formation, inhibits glycolysis metabolism and ROS production, inactivates NF-κB and	c-Fos ↓, NFATc1 ↓, HK2 ↓, PKM2 ↓, LDHA ↓, Nox1 ↓, TRF6 ↓,	(12)

			MAPK signaling pathways	GTP-Rac1 ↓, HO-1↑, GSR↑	
Peng, 2024	Mouse chondrocytes DMM surgery-induced OA mouse model	0, 6.25, 12.5 and 25 μM 40 mg/kg	Ameliorates osteoarthritis, activates the PTEN/SIRT1/NF-κB pathway, exerts anti-inflammatory effects and improves ECM degradation	iNOS ↓, PEG2 ↓, IL-6 ↓, ADAMTS-5 ↓, MMP-13 ↓, PTEN↑, p-Akt ↓, p65 ↓	(78)
Wang, 2024	MH7A FLS cells CIA rat model	0, 20, 40 and 80 μmol/l 20 and 60 mg/kg	Decreases the proliferation and invasiveness of FLS cells and corrects Th17/Treg cell imbalance	Cyclin D1 ↓, Cyclin E1 ↓, CDK2 ↓, CDK4 ↓, Caspase 3↑, Bcl-2 ↓, Bax↑, IL-17↑, IL-10 ↓	(79)
Kulhari, 2024	CFA-mediated arthritis rat model	5 and 10 mg/kg	Inhibits the TLR4/NF-κB/MAPK signaling axis and alleviates adjuvant-induced arthritis	iNOS ↓, COX-2 ↓, TLR4 ↓, MAPK ↓, p65 ↓, IκB-α ↓	(80)
G, Metabolic regulatory effects					
First author, year	Models	Doses	Biological activities	Molecular targets	(Refs.)

Nguyen, 2012	INS-1E cells	0-40 μM	Stimulates insulin secretion and closes K-ATP channels	Calcium channels↑, PKA↑, PKC↑	(51)
Ma, 2015	Insulin-resistant 3T3-L1 adipocytes	0.5-50 μg/ml	Enhances glucose consumption	AMPK↑	(20)
Wang, 2015	Potassium oxonate-induced hyperuricemic mice HK-2 cells	10, 20 and 40 mg/kg 10,20 and 40 μM	Reduces serum uric acid levels, improves renal function, promotes intestinal urate excretion, suppresses TLR4/MyD88/NF-κB signaling and NLRP3 inflammasome activation	URAT1↓, GLUT9↓, ABCG2↑, OAT1↑, OCT1↑, OCTN1↑, OCTN2↑, IL-1β↓, TLR4↓, MyD88↓, p-NF-κB↓, p-IKKβ↓, p-IκBα↓, NLRP3↓, ASC↓, Caspase 1↓	(52)
Li, 2018	ICR mice MDCK-hOCT1 cells and MDCK-hMATE1 cells	40 mg/kg 0.01-100 μM	Decreases the transcellular transport and intracellular accumulation of metformin and	MATE1↓, OCT1↓	(56)

			attenuates the glucose-lowering effect of metformin		
Cui, 2020	NAFLD rat model	20 mg/kg	Reduces body weight, lipid levels and liver enzymes, improves hepatic steatosis and metabolic disorder	PLA2↓, PTDSS2↓, FADS2↓, CYP2E1↓, CYP3A4↓, PEMT↑, LCAT↑	(130)
Liu, 2020	BMMSCs	10^{-7}-10^{-4} mol/l	Inhibits adipocyte differentiation	cAMP↑, PKA↑	(132)
Wang, 2020	HFD-fed rats	10 mg/kg	Prevents HFD-induced obesity, changes the diversity and composition of gut microbiota, reduces body weight and fat accumulation, ameliorates lipid metabolic disorders, improves HFD-induced disorders of endogenous metabolism, promotes SCFA production, enhances intestinal	TNF-α↓, IL-6↓, IL-1β↓, LPS↓, IL-10↑, SREBP-1↓, FAS↓, ZO-1↑, occludin↑, PPARα↑, PPARγ↓	(133)

			barrier integrity and reduces inflammation		
Shi, 2021	HFD-induced obese mice, Caco-2 cells and HT-29 cells	0-200 μM	Reduces weight gain, fat accumulation and intestinal permeability, alters the composition of the gut microbiota and promotes the formation of autophagosomes	ZO-1↑, JAM-1↑, occludin↑, LPS ↓, TNF-α ↓, IL-6 ↓, IL-1 β ↓, P62 ↓, LC3II↑, Atg5↑	(134)
Xu, 2022	HFD-fed obese mice, 3T3-L1 preadipocytes, HepG2 hepatocytes and eWAT/adipocytes	0-20 μM	Prevents HFD-induced obesity, attenuates hepatic steatosis, reduces lipid accumulation, improves dyslipidemia, glucose tolerance and insulin resistance	p-AMPK↑, SREBP-1 ↓, FAS ↓, ACC ↓, HSL↑, ATGL↑, FGF21↑, ZAG↑, PPARα↑, CPT1α↑	(58)
Tang, 2022	Gestational diabetes mellitus mouse model	30 mg/kg	Improves glucose intolerance, reduces lipid accumulation, elevates glycogen content within hepatocytes,	SREBP-1c ↓, FASN ↓, ACC ↓, ACOX1 ↓, PPAR α ↓, G-6-Pase ↓,	(59)

			diminishes placental lipid and glycogen depositions, ameliorates glycolipid disorders and corrects intestinal dysbacteriosis	PEPCK ↓	
Du, 2022	NAFLD mouse model Primary hepatocytes and AML-12 cells	10 and 30 mg/kg 0-200 μmol/l	Ameliorates hepatic steatosis and insulin resistance, regulates the mTORC1-TFEB-ALP axis and activates hepatic autophagy lysosomal pathway	IR↑, Akt↑, MDA ↓, p-NK-κB ↓, SOD↑, GSH-Px↑, IκBα↑, TFEB↑, P62 ↓, LC3II↑, LAMP1↑, CTSD↑, p-mTORC1 ↓	(60)
Sun, 2022	HFD-induced NAFLD rat model	10 and 25 mg/kg	Elevates conjugated BA and non-12OH BA levels, regulates the gut microbiota, inhibits ileal FXR signaling, promotes BA synthesis, suppresses BA reabsorption	FXR ↓, FGF15 ↓, FGFR4 ↓, ASBT ↓, CYP7A1↑, CYP27A1↑, Fgfr4 ↓	(61)

			and facilitates fecal BA excretion		
Zhang, 2022	Uric acid-induced HK-2 cell model Hyperuricemic mice	10, 20 and 40 μM 10, 20 and 40 mg/kg	Suppresses PI3K/Akt and TLR4/IκBα/NF-κB signaling pathways, inhibits URAT1 activity, reduces uric acid levels and ameliorates kidney damage	URAT1 ↓, GLUT9 ↓, p-Akt ↓, TLR4 ↓, p-IκBα ↓, p-p65 ↓, TNF-α ↓, IL-6 ↓, IL-1β ↓	(119)
H, Antipsychotic effects					
First author, year	Models	Doses	Biological activities	Molecular targets	(Refs.)
Farrell, 2016	293T cells C57BL/6J mice	0-100 μM 1-10 mg/kg	Blocks head-twitch responses, enhances amphetamine-induced locomotor activity and inhibits phencyclidine-induced locomotor activity	5-HT_{2A} ↓, 5-HT_{2C} ↓, 5-HT_{2B} ↓, 5-HT_7, D_2, D_5 ↓, 5-HT_6, ↓ 5-HT_{1A}, D_4 ↓	(22)
I, Anti-microbial effects					
First author, year	Models	Doses	Biological activities	Molecular targets	(Refs.)
Kashiwada, 2005	H9 T-cell line	EC_{50}, 0.8 μg/ml; TI, 36.3	Anti-HIV activity	NA	(40)
Chan, 2016	*Schistosoma mansoni*	IC_{50}, 0.62±	Inhibits both basal and 5-HT evoked	Sm.5HTRL ↓	(135)

		0.22 μM	motility of adult schistosomes		
Yang, 2025	lung adenocarcinoma hACE2-A549 cell line	EC_{50}, 30.59 ±13.58 μM	Anti-SARS-CoV-2 activity	NA	(41)

TLR4, Toll-like receptor 4; PI3K, phosphatidylinositol 3-kinase; AKT, AKT serine/threonine kinase; MCP-1, monocyte chemoattractant protein-1; PGE2, prostaglandin E2; PPARγ, peroxisome proliferator-activated receptor γ; TWEAK, tumor necrosis factor-related weak inducer of apoptosis; GSH, glutathione; PCNA, proliferating cell nuclear antigen; ROS, reactive oxygen species; GPX4, glutathione peroxidase 4; SLC7A11, solute carrier family 7 member 11; FSP1, ferroptosis suppressor protein 1; NO, nitric oxide; ATF2, activating transcription factor 2; AMPK, AMP-activated protein kinase; SREBP-1, sterol regulatory element-binding protein-1; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; IC_{50}, half maximal inhibitory concentration; EC_{50}, half maximal effective concentration; 5-HT, 5-hydroxytryptamine; URAT1, urate transporter 1; NAFLD, non-alcoholic fatty liver disease; HFD, high-fat diet; mTORC1, mechanistic target of rapamycin complex 1; TFEB, transcription factor EB; ALP, alkaline phosphatase; MDA, malondialdehyde; ACOX1, Acyl-CoA oxidase 1; PEPCK, phosphoenolpyruvate carboxykinase; IR, insulin receptor; CPT1α, carnitine palmitoyltransferase 1α; LC3, microtubule-associated protein 1 light chain 3; LPS, lipopolysaccharide; PLA2, phospholipase A2; PTDSS2, phosphatidylserine synthase 2; FADS2, fatty acid desaturase 2; PEMT, phosphatidylethanolamine N-methyltransferase; LCAT, lecithin-cholesterol acyltransferase; CYP2E1, cytochrome P450 2E1; ZO-1, Zonula occludens-1; FAS, fatty acid synthase; PKA, protein kinase A; cAMP, cyclic adenosine monophosphate; GLUT9, glucose transporter 9; ABCG2, ATP-binding cassette sub-family G member 2; iNOS, inducible nitric oxide synthase; HK2, hexokinase 2; COX-2, cyclooxygenase-2; NFATc1, nuclear factor of activated T-cells 1; TRF6, TNF receptor-associated factor 6; PKM2, pyruvate kinase M2; LDHA, lactate dehydrogenase A; HO-1, heme

oxygenase-1; ADAMTS-5, A disintegrin and metalloproteinase with thrombospondin motifs 5; MMP-13, matrix metalloproteinase-13; CDK2, cyclin-dependent kinase 2; ATP6V0D2, ATPase H+ transporting V0 subunit d2; OCN, osteocalcin; JNK, c-Jun N-terminal kinase; SOD, superoxide dismutase; SPHK, sphingosine kinase; FADS, fatty acid desaturase; GPT, glutamic-pyruvic transaminase; TUDCA, tauroursodeoxycholic acid; ICAM-1, intercellular adhesion molecule 1; Calm4, Calmodulin 4; LDH, lactate dehydrogenase; CAT, Catalase; C/EBPα, CCAAT/enhancer-binding protein α; ACC, acetyl-CoA carboxylase; MKK3, mitogen-activated protein kinase kinase 3; ILK, integrin-linked kinase.

Table SII. Nuciferine and its mechanisms against different types of cancer.

A, Melanoma					
First author, year	Models	Treatment concentrations	Biological activities	Molecular mechanisms	(Refs.)
Nakamura, 2013	B16 melanoma 4A5 cells	0-100 μM; IC_{50}, 15.8 μM	Inhibits melanogenesis	Tyrosinase ↓, TRP-1 ↓, TRP-2 ↓	(91)
Wu, 2015	A375 cells, A375.S2 cells and A2058 cells BALB/c nude mice	0-100 μM 20 mg/kg	Induces autophagy, apoptosis and G_2/M arrest	Beclin-1↑, ATG-3, 5, 7, 10, 12, 16↑, LC3II/I↑, cytochrome *c*↑, Apaf-1↑, Caspase 3, 6, 7, 8, 9↑, PARP↑, Bax↑, Bcl-2 ↓, p53↑	(92)
Xu, 2020	A375 cells, COLO829 cells, Malme-3M cells, SK-MEL-1 cells and SK-MEL-5 cells Nude mice	0-80 μM 25-50 mg/kg	Suppresses melanoma growth, inhibits cell survival, and inhibits tumor size and weight	p-p65 ↓, TLR4 ↓, TLR4/NF-κB signaling ↓	(16)
B, Lung cancer					
First author, year	Models	Treatment concentrations	Biological activities	Molecular mechanisms	(Refs.)
Liu, 2015	A549 cells and H1299 cells	A549 cells (0-50 μmol/l);	Induces apoptosis; inhibits cell	β-catenin ↓, c-Myc ↓,	(18)

	BALB/c nude mice	H1299 cells (0-1μmol/l) 50 mg/kg	proliferation, migration, invasion and suppresses tumor growth	cyclin D1 ↓, VEGF-A ↓, Axin↑, Bax↑, Bcl-2 ↓	
Liu, 2020	A549 and ABCB1-overexpressing drug-resistant A549/T cell line A549/T xenograft mice	48, 24 and 4 μM 7.5 mg/kg	Overcomes drug resistance to chemotherapeutic agents, boosts apoptosis and arrests MDR cells in G_2/M-phase; modulates the P-gp ATPase activity; inhibits the PI3K/Akt and MAPK/ERK signaling pathways	P-gp ↓, BCRP ↓, p-ERK1/2 ↓, p-Akt ↓, Nrf2 ↓, HIF-1α ↓	(97)
Bai, 2022	LA795 cells BALB/c nude mice	0-50 μM; IC_{50}, 4.94±1.49 μM 30 μM	Inhibits cell proliferation, migration,	TMEM16A ↓, p-MEK1/2 ↓, p-ERK1/2 ↓, cyclin D1 ↓,	(93)

			promotes cell apoptosis and enhances cancer therapy effect of cisplatin	β-catenin ↓, E-cadherin↑, N- cadherin ↓, vimentin ↓, cleaved-caspase 3↑, cleaved-caspase 9↑	
Gautam, 2025	A549 cells C57BL/6 mice	10 and 20 μM 20 and 40 mg/kg	Restores oxidative balance, reduces inflammation and alleviates pulmonary fibrosis	α-SMA↓, CTGF↓, collagen I↓, fibronectin↓, E-cadherin↑, N-cadherin↓, vimentin↓	(94)
C, Neuroblastoma					
First author, year	Models	Treatment concentrations	Biological activities	Molecular mechanisms	(Refs.)
Qi, 2016	SY5Y cells Nude mice	0-200 μg/ml 9.5 mg/kg	Inhibits cell viability and invasion; decreases tumor weight	p-Akt ↓, PI3K ↓, IL-1 β ↓, PI3K-Akt signaling ↓	(95)
D, Colorectal cancer					
First author, year	Models	Treatment concentrations	Biological activities	Molecular mechanisms	(Refs.)
Qi, 2016	CT26 cells and HCT116 cells Nude mice	0-200 μg/ml 9.5 mg/kg	Inhibits cell invasion and viability, and	p-Akt ↓, PI3K ↓, IL-1 β ↓, PI3K-Akt signaling ↓	(95)

			decreases tumor weight		
Liu, 2020	HCT-8 and drug-resistant HCT-8/T cell line	48, 24 and 4 μM	Overcomes drug resistance to chemotherapeutic agents, boosts apoptosis and arrests MDR cells in G_2/M-phase, modulates the P-gp ATPase activity, inhibits PI3K/Akt and MAPK/ERK signaling pathways	P-gp ↓, BCRP ↓, p-ERK1/2 ↓, p-Akt ↓, Nrf2 ↓, HIF-1α ↓	(97)
Okayama, 2024	HT-29 human colon cancer cell line and its cancer stem cells	0-50 μM	Anti-proliferative activity, cytotoxic activity via inhibition of Wnt/β-catenin pathway	c-Myc ↓, survivin ↓, active-β-catenin ↓	(96)
E, Breast cancer					

First author, year	Models	Treatment concentrations	Biological activities	Molecular mechanisms	(Refs.)
Kang, 2017	MDA-MB-231 cells and MCF-7 cells	0-80 μM; IC_{50}, 17.9 μM	Decreases cell viability, migration and invasion, induces cell apoptosis, inhibits RANKL-induced osteoclast formation and induces G_1 and G_2 arrest	Cleaved-caspase 3↑, cleaved PARP↑, Bcl-2 ↓, procaspase3 ↓	(98)
Tong, 2021	SKBR3 cells, HCC1806 cells and MDA-MB-231 cells	0-1.6925 μM	Does not inhibit migration and does not affect cell viability		(99)
F, Pancreatic cancer					
First author, year	Models	Treatment concentrations	Biological activities	Molecular mechanisms	(Refs.)
Zhou, 2019	PANC-1 cells and ASPC-1 cells BALB/c nude mice	0-80 μM 30 mg/kg	Enhances the sensitivity of PC cells to gemcitabine, attenuates	p-YAP (Ser127)↑, p-AMPK↑, HMGCR ↓, YAP ↓	(101)

			gemcitabine resistance of PC cells and inhibits PC proliferation		
G, Laryngeal squamous cell carcinoma					
First author, year	Models	Treatment concentrations	Biological activities	Molecular mechanisms	(Refs.)
Li, 2021	AMC-HN-8 cells and TU-212 cells	0-100 μM	Inhibits cell survival and displays antitumor activity	TRIM44 ↓, TLR4 ↓, p-Akt ↓	(102)
H, Oral squamous cell carcinoma					
First author, year	Models	Treatment concentrations	Biological activities	Molecular mechanisms	(Refs.)
Xie, 2023	SCC25 and CAL27 cells BALB/c nude mice	0, 40, 80 and 120 μM 20 mg/kg	Inhibits proliferation, promotes apoptosis, and inhibits migration and invasion	STAT3 ↓, p65 ↓, Bcl-2 ↓, Bax↑, caspase 3↑, E-cadherin↑, vimentin ↓	(17)
I, Hepatocellular carcinoma					
First author, year	Models	Treatment concentrations	Biological activities	Molecular mechanisms	(Refs.)
Li, 2025	HepG2 and HCCLM3 cells	0, 25, 50, 100 and 200	Suppresses proliferat	Cyclin B1 ↓, survivin ↓, HER2 ↓, p-	(103)

	BALB/c nude mice	μM 15 mg/kg	ion and cell cycle at G_2 phase, and accelerates apoptosis	Akt ↓ , p-ERK1/2 ↓ , PI3K ↓	

TRP-1, tyrosinase-related protein 1; ATG-3, autophagy related 3; Apaf-1, apoptotic protease activating factor 1; PARP, poly(ADP-ribose) polymerase; BAX, Bcl-2 associated X protein; Bcl-2, B-cell lymphoma 2; TLR4, Toll-like receptor 4; VEGF, vascular endothelial growth factor; TMEM16A, transmembrane protein 16A; MEK1/2, mitogen-activated protein kinase 1/2; BCRP, breast cancer resistance protein; Nrf2, nuclear factor erythroid 2-related factor 2; HIF-1α, hypoxia-inducible factor 1α; α-SMA, α-smooth muscle actin; CTGF, connective tissue growth factor; PI3K, phosphatidylinositol 3-kinase; Akt, serine/threonine kinase; IL-1β, interleukin 1β; YAP, Yes-associated protein; AMPK, AMP-activated protein kinase; HMGCR, 3-Hydroxy-3-methylglutaryl-CoA reductase; TRIM44, tripartite motif containing 44; STAT3, signal transducer and activator of transcription 3; HER2, human epidermal growth factor receptor 2.

Table SIII. Inhibitory effects of nuciferine on different enzymes (targets).

First author, year	Enzyme (target) source	IC_{50}	*Ki*	(Refs.)
Hu, 2010	CYP1A2	2.12 mmol/l		(28)
Ye, 2014	CYP2D6	3.78 μM	1.88 μM	(27)
	CYP2C9	94.88 μM		
	CYP2C19	29.00 μM		
Zhang, 2018	β_2-AR	15.8±2.6 μM	0.091 μM	(114)
	5-HT_{2A}	7.18±0.03 nM		
	5-HT_{2B}	7.51±0.21 nM		
	5-HT_{2C}	7.44±0.01 nM		
Heng, 2018	α_{1A}	7.42±0.07 nM		(115)
	α_{1B}	7.22±0.01 nM		
	α_{1D}	6.78±0.01 nM		
Liu, 2020	*Mucor miehei* lipase	0.194 mg/ml	0.16 mg/ml	(29)
Guan, 2023	TNF-α	61.19 μM		(116)

CYP, cytochrome P450; β_2-AR, β_2-adrenergic receptor.

Table SIV. Molecular docking proteins of Nuciferine through an *in silico* study.

First author, year	Proteins	Binging energy, kcal/mol	Interacting residues	(Refs.)
Liu, 2020	*Mucor miehei* lipase	-6.13	Arg169, Asp238, Tyr195, P194, Ile193, Gly219, Gly192, Ser237 and Glu220	(29)
Gao, 2020	CYP1A1	-2.1636	Arg106, Thr385, Ile386, Ala317, Ser122, Arg135, Arg455, His388	(55)
	CYP1A2	-2.7153	Thr321, Cys458, Leu382, Thr124, Leu144, Gly460, Ile314, Ile459, Ala317, Gly318	
	CYP2B6	-1.74	Thr302, Gly438, Ala298, Gly299, Ile114, Cys436, Leu363, Phe429, Leu362	
	CYP2C9	-1.3183	Thr301, Gly298, Ala297, Cys435, Val113, Ser429, Ser365, Leu391, Leu366, Leu362, Phe428, Pro427	
	CYP2D6	-2.2814	Thr309, Cys443, Ala305, Val374, Gly373, Pro435, Phe436, Val370, Gln364, Ile369	
	CYP3A4	-1.3802	Arg105, Arg130, Arg440, Ile118, Cys442, Gly444, Phe302, Ile443, Ile301, Ala305, Ser119	
Wen, 2021	PI3K	-7.29	Ser594, Asp632, Asn634, Pro563, Leu564, Leu567, Lys591, Gln629,	(77)

			Asn634, Ile1029, Ser1032	
Harishkumar, 2021	β2 adrenergic receptors	-5.02	Lys140, Gln229, Glu1005	(84)
	β1 adrenergic receptors	-8.46	Val122, Thr126, Ser211	
Du, 2022	HBXIP	NA	Thr36, Glu40, His41, Val44, Ile45, Gly72, Ile74, His87	(60)
Khan, 2022	α-amylase	NA	Lys35, Trp396	(73)
	α-glycosidase	NA	Trp484, Glu456, Glu173, Glu474, Glu480	
Zheng, 2022	DRD2	-7.92	Phe389, Trp386, Thr412, Tyr416, Cys118, Asp114, Val115, Phe189, Ile184, Ser193, Val190, Ser194, Phe390, His393, Ile122	(100)
Zhang, 2022	COX-2	-5.78	Lys328	(118)
Zhang, 2022	URAT1	-7.44	Lys393, Phe364	(119)
Xue, 2023	AMPK	-6.732	Glu94, Glu100, Glu143, Asp157, Met93, Tyr95, Val96, Leu22, Leu146, Ala156, Ala43, Ile77, Val30	(47)
Guan JW, 2023	TNF-α	-8.4	Tyr119, Ser60	(116)
Veerichetty, 2023	AbTYR	-7.0	Glu356, Thr308	(121)
	Human tyrosinase	–7.3	Glu241	
Zhao, 2023	5HT2A receptor	-5.86	NA	(122)
Zhou, 2023	Beclin 1	5.895	Thr267, Lys263	(123)
	ATG5	4.832	Leu157, Asn159, Lys51, Leu37,	

			Val48, Pro40, Leu47, Leu39, Asp160, Gln158	
	LC3-II	5.588	Asn84, Lys39, Arg37, Tyr38, Glu36, Val112, Ile34, Tyr110, Met111, Leu82, Gly85	
	p62	6.713	Gly62, Phe63, Gln64, Ser78, Glu45, Ser49, Leu48, Ala52, Pro60	
Ishrat, 2024	HPAA	-5.58	Trp58, Trp59, Tyr62, Gln63, Asp300, Asp356	(120)
Li, 2024	NF-κB	-5.71±0.09	Asp266, Thr304, Val303	(37)
	NLRP3	-6.35±0.07	Glu47, Glu15	
Peng, 2024	PTEN	-8.1	Tyr176, Arg172, Ile300, Ile303, Glu299	(78)
Li, 2025	PI3K	-6.33	Ser594, Asn634	(30)
Rapuru, 2025	PTGS2	-9.33	Gln203, His207, His388	(31)
	JUN	-7.05	Gln671	
Li, 2025	JAK2	-7.5903±0.7926	Gly993	(71)
Ding, 2025	TAS2R46	-8.20±0.28	Ser248	(117)
Li, 2025	FGF15	-7.58	NA	(124)
	FXR	-9.56	NA	

URAT1, urate transporter 1; HBXIP, hepatitis B X-interacting protein; COX-2, cyclooxygenase-2; PTGS2, prostaglandin-endoperoxide synthase 2; JAK2, Janus kinase 2; TAS2R46,Taste 2 receptor member 46; JUN, Jun proto-oncogene, AP-1 Subunit; PTEN, phosphatase and tensin homolog; NLRP3, NLR family pyrin domain containing 3; DRD2, dopamine receptor d2; AMPK, AMP-activated protein kinase; NF-κB, nuclear factor-kappa B; FGF15, fibroblast growth factor 15; FXR, farnesoid X receptor; HPAA, hypothalamic-pituitary-adrenal axis; ATG5, Autophagy related 5; AbTYR, abalone tyrosinase; CYP1A1, cytochrome P450 family 1 subfamily A member 1.

Table SV. Various drug delivery carriers containing nuciferine.

First author, year	Carrier	Model system	Inferences	(Refs.)
Liu, 2017	PLGA nanoparticles	HepG2 cells and SD rats	Sustains and controls drug delivery with improved bioavailability for alleviating lipogenesis	(24)
Zhu, 2022	NF-EGCG double-encapsulated microgel	HFD-fed rats	Improves the diversity of gut microbiota reducing harmful bacteria	(26)
Bharathi, 2023	3D-printed PLA scaffolds loaded with CS-NF hydrogel	Mouse MSCs (C3H10T1/2)	Promotes new bone formation	(25)
Lu, 2024	Nuciferine-liposomes	HFD-fed obese dogs	Improves relative bioavailability and exerts an anti-obesity effect in dogs	(125)

HFD, high-fat diet; PGLA, poly lactic-co-glycolic acid; PLA, polylactic acid; MSC, mesenchymal stem cells; EGCG, epigallocatechin-3-gallate; SD, Sprague-Dawley; CS-NF, Chitosan-Nuciferine.