

Supplementary Materials

Table S1. In vitro induction of ferroptosis by natural products used in association.

Compound	Compound source	Cell line(s)	Concentration range (where specified)	Time (where specified)	Ferroptosis markers	Supplementary effects	Reference
Albiziabioside A (AlbA) conjugated with dichloroacetate (DCA)	<i>Albizia inundata</i> Mart.	MCF-7	2 µM	24h	↑ Cytotoxicity	↑ after Fe ²⁺ treatment ↓ after Ferr-1 treatment ↓ after DFO treatment ↓ after vitamin E treatment	[24]
				/	↑ ROS		
				24h	↓ GSH/GSSG ratio		
				48h	↓ GPX4 expression		
				/	↑ MDA ↑ Lipid peroxides		
Gallic Acid (GA) + low level of laser irradiation		A375, MDA-MB-231	10, 25, 50, 100 and 200 µg/mL	/	↓ Cell viability	[44]	
		MDA-MB-231	25 µg/mL	24h	↑ ROS		
		A375	50 µg/mL				
		A375, MDA-MB-231	/	/	↑ MDA ↓ GPX4 activity		
Phenethyl isothiocyanate (PEITC) + cotylenin-A (CN-A)	Cruciferous vegetables	MIAPaCa-2	PEITC (5 µM) ± CN-A (10 µg/mL)	12 days	↓ Anchorage-independent growth	[243]	
		MIAPaCa-2, Panc-1	PEITC (6 µM) ± CN-A (15 µg/mL)	16h	↓ Cell viability		↑ after NAC treatment ↑ after Trolox treatment

			PEITC (5 μ M) \pm CN-A (20 μ g/mL)	24h	\uparrow Cell death		
		Panc-1	PEITC (2, 4, 6 and 8 μ M) \pm CN- A (15 μ g/mL)	16h	\uparrow Cell death	\downarrow after Ferr-1 treatment \downarrow after Lip-1 treatment \uparrow after diferric holotransferrin treatment	
		MIAPaCa-2, Panc-1	PEITC (4 μ M) \pm CN-A (20 μ g/mL)	4h	\uparrow ROS		
		Panc-1, MIAPaCa-2, CFPAC-1	PL (2, 4, 6, 8 and 10 μ M) + CN-A (15 μ g/mL)	16h	\downarrow Cell viability		
		MIAPaCa-2	PL (6 μ M) + CN- A (15 μ g/mL)	16h	\downarrow Cell viability	\uparrow after NAC treatment \uparrow after Ferr-1 treatment \uparrow after Lip-1 treatment \uparrow after DFO treatment	
Piperlongumine (PL) + cotylenin A (CN-A)	<i>Piper Longum</i> L.	Panc-1	PL (6 μ M) + CN- A (15 μ g/mL)	16h	\downarrow Cell viability	\uparrow after NAC treatment \uparrow after Ferr-1 treatment \uparrow after Lip-1 treatment \uparrow after DFO treatment	[46]
		MIAPaCa-2	PL (7.5 and 15 μ M) \pm CN-A (15 μ g/mL)	4h	\uparrow ROS		
Piperlongumine (PL) + sulfasalazine (SSZ)	<i>Piper Longum</i> L.	Panc-1, MIAPaCa-2, CFPAC-1, BxPC-3	PL (2.5, 5 and 7.5 μ M) \pm SSZ (200 μ M)	16h	\downarrow Cell viability		[46]
				16h	\downarrow Cell viability	\uparrow after NAC treatment	

		Panc-1, MIAPaCa-2	PL (5 μ M) + SSZ (250 μ M)			<u>↑ after Ferr-1 treatment</u> <u>↑ after DFO treatment</u>	
		MIAPaCa-2	PL (7.5 and 15 μ M) + SSZ (200 μ M)	4h	↑ ROS		
Piperlongumine (PL) + cotylenin A (CN-A) + sulfasalazine (SSZ)	<i>Piper Longum</i> L.	PANC-1, MIAPaCa-2	PL (2, 4, 6 and 8 μ M) + CN-A (15 μ g/mL) + SSZ (250 μ M)	16h	↓ Cell viability	↑ after Ferr-1 treatment	[46]

Abbreviations.

↑: Increase; ↓: Decrease; 3-MA: 3-Methyl-adenine; DFO: Deferoxamine; Fe²⁺: Ferrous ion; Ferr-1: Ferrostatin 1; GPX4: Glutathione peroxidase 4; GSH: Glutathione; GSSG: Oxidized glutathione; Lip-1: Liproxastatin-1; MDA: Malondialdehyde; NAC: N-acetylcysteine; ROS: Reactive oxygen species.

Table S2. Natural products as *in vivo* inducers of ferroptosis.

Compound	Compound source	Experimental model(s)	Treatment doses	Antitumor effects and ferroptosis markers	Reference
Amentoflavone	<i>Selaginella</i> spp. and other plants	BALB/c nude mice inoculated with U251 cells	40 and 80 mg/kg/day (for 28 days)	↓ Tumor volume	[25]
				↓ Tumor weight	
↓ GSH					
↑ MDA					
↓ FTH					
↑ LC3B, ↑ Beclin1, ↑ ATG5, ↑ ATG7					
Artenusate (artemisin semi-synthetic derivative)	<i>Artemisia annua</i> L.	NOD/SCID mice inoculated with CA-46 cells	200 mg/kg/day (30 days)	↓ Tumor volume	[29]
				↓ Tumor weight	
				↑ MDA	
				↑ CHAC1 expression	
		BALB/c nude mice inoculated with AsPC-1 cells transfected with control (CTRL) or GRP78 shRNA	30 mg/kg every 2 days (35 days)	↓ Tumor growth (> than CTRL shRNA)	[32]
				↓ Tumor volume (> than CTRL shRNA)	
				↓ Tumor weight (> than CTRL shRNA)	
Dihydroartemisinin (artemisin semi-synthetic derivative) (DAT)	<i>Artemisia annua</i> L.	Foxn1nu/ Foxn1+ athymic mice inoculated with GPX4 iKO H292 cells	DAT 5 mg/kg/day, normal diet/DAT 5 mg/kg/day, DOX diet / DAT 5 mg/kg/day + DOX and Lip-1 10 mg/kg (14 days)	↓ Tumor growth (partially restored after Lip-1 treatment)	[63]
Withaferin A	<i>Withania somnifera</i> L. Dunal	BALB/c nude mice inoculated with IMR-32 cells	Bi-sequential treatment (4 days treatment with 4 mg/kg/day + 6 days of recovery + 3 days treatment with 4 mg/kg/day);	↓ Tumor growth	[52]
				↓ Tumor relapse rates	
CD45-positive immune cells infiltration in tumor tissue					
↓ GPX4 expression					

continuous treatment (4 mg/kg/day, for 20 days)	↑ LOOH
	↑ phospholipids (phosphatidylglycerol/phosphatidylinositol)
WA-NPs (days 1 and 5, 14 days)	↓ Tumor growth

Abbreviations.

↑: Increase; ↓: Decrease ATG5: Autophagy related 5; ATG7: Autophagy related 7; CHAC1: Glutathione-specific gamma-glutamylcyclotransferase 1; DOX: Doxorubicin; FTH: Ferritin heavy chain; GPX4: Glutathione peroxidase IV; GSH: Glutathione; LC3B: Microtubule-associated protein 1 (MAP1) light chain 3B; Lip-1: Liproxastatin-1; LOOH: Lipid hydroperoxides; MDA: Malondialdehyde; Spp.: species; WA-NPs: Withaferin A nanoparticles

Table S3. *In vitro* induction of necroptosis by natural products used in association.

Compound	Compound source	Cell line(s)	Concentrations (where specified)	Time (where specified)	Necroptosis markers	Supplementary effects	Reference
Arctigenin (A) + desamethasone (D)	<i>Arctium lappa</i> L., <i>Saussurea heteromalla</i>	RPMI-2650	A (5 μ M) + D (12.5 μ M)	48h	\uparrow Necrotic cells	\downarrow after NAC treatment	[114]
					\uparrow ROS	\downarrow after NAC treatment	
					\downarrow $\Delta\Psi_m$	\uparrow after NAC treatment	
					\downarrow ATP levels	\downarrow after Nec-1 treatment	
						\downarrow after Nec-1 treatment	
					\uparrow RIP3, \uparrow p-RIP3 protein expression	\downarrow after ATP treatment	
						\downarrow after NAC treatment	
					\uparrow MLKL, \uparrow p-MLKL protein expression	\downarrow after Nec-1 treatment	
						\downarrow after ATP treatment	
						\downarrow after NAC treatment	
	\uparrow p-ATM, \uparrow p-ATR, \uparrow p-CHK1/2 protein expression	\downarrow after NAC treatment					
	24, 48 and 72h	\downarrow Cell viability	\uparrow after Nec-1 treatment				
			\uparrow after ATP treatment				
			\uparrow after NAC treatment				
	RPMI-2650 spheroid cells	A (5 μ M) + D (12.5 μ M)	48h	\uparrow Cytotoxicity	\downarrow after NAC treatment		
				\downarrow Spheroid viability	\uparrow after NAC treatment		
				\uparrow RIP3, \uparrow p-RIP3 protein expression	\downarrow after NAC treatment		
				\uparrow MLKL, \uparrow p-MLKL protein expression	\downarrow after NAC treatment		
Berberine (B) + cisplatin (Cis)	Huang Lian Chinese herb (<i>Coptis chinensis</i>) and others plant spp.	OVCAR3	B (100 μ M) + Cis (5 mg/mL)	24h	Extensive vacuolation	[116]	
					Rupture of plasma membrane		
					\uparrow RIP3, \uparrow MLKL mRNA levels		
		OVCAR3, POCCLs			\uparrow RIP3, p-RIP3 protein expression		
					\uparrow MLKL, p-MLKL protein expression		

Goniothalamins + Z-VAD-FMK 10 μM	Plants of <i>Goniothalamus</i> genus	MDA-MB-231	33.82 μM	24h	↑ PI positive cells	
					Loss of membrane integrity	
					No caspase-3/-8/-9 activation	
				1, 2, 4 and 6h	↑ Calpain activity	↓ after Z-LLY-FMK treatment
					↑ ROS	↓ after NAC treatment
			13.53 and 33.82 μM	24h	↑ Ca ²⁺ levels	
					↑ RIP3 protein expression	
					↑ Cleaved AIF	

[244]

Abbreviations.

↑: Increase; ↓: Decrease; AIF: Apoptosis-inducing factor; ATP: Adenosine triphosphate; Ca²⁺: Calcium; MLKL: Mixed lineage kinase domain like pseudokinase; NAC: N-acetyl-L-cysteine; Nec-1: Necrostatin-1; p-ATM: Phospho-ataxia telangiectasia mutated kinase; p-ATR: Phospho-ataxia telangiectasia and Rad3-related kinase; p-CHK1/2: Phospho-checkpoint kinase 1/2; p-MKLK: Phospho-mixed lineage kinase domain like pseudokinase; p-RIP3: Phospho-receptor-interacting serine/threonine-protein kinase 3; PI: Propidium iodide; RIP3: Receptor-interacting serine/threonine-protein kinase 3; ROS: Reactive oxygen species; Spp.: species; Z-LLY-FMK: Calpain inhibitor; ΔΨ_m: Mitochondrial membrane potential.

Table S4: Natural products as *in vivo* inducers of necroptosis.

Compound	Compound source	Experimental model(s)	Treatment doses	Necroptosis markers	Reference
2-methoxy-6-acetyl-7-methyljuglone	<i>Polygonum cuspidatum</i> Sieb. et Zucc	U251-derived xenograft zebrafish model	50 nM (3 days)	No caspase- 3/-7/-8 cleavage ↑ p-JNK1/2 ↑ HMGB1	[108]
		BALB/c nude mice inoculated with A549 cells	1 and 2 mg/kg/day (18 days)	↓ Tumor growth ↓ Tumor volume ↓ Tumor weight ↑ RIP1 protein expression ↑ p-RIP3 protein expression Intact cell nuclei Damaged mitochondria	[109]
Emodin	<i>Rheum palmatum</i> L.	BALB/c nude mice inoculated with U251 cells	20, 40 and 80 mg/kg/day (28 days)	↓ Tumor growth ↓ Tumor volume ↓ Tumor weight ↑ RIP1 protein expression ↑ RIP3 protein expression ↑ MLKL protein expression ↑ TNF- α protein expression ↑ Tumor necrosis	[121]
Pristimerin	Various plant spp. of <i>Celastraceae</i> and <i>Hippocrateaceae</i> families	BALB/c nude mice inoculated with C6 cells	1 and 3 mg/kg every 2 days (8 days)	↓ Tumor volume ↓ Tumor weight ↑ JNK protein expression ↑ p-JNK protein expression ↑ AIF nuclear translocation	[127]
Resibufogenin	Asiatic toad (<i>Bufo gargarizans</i>)	BALB/c nude mice inoculated with eGFP-SW480 cells	5 and 10 mg/kg/day (21 days)	↓ Tumor volume (partially restored after RIP3 knockdown) ↓ Tumor weight	[129]

			(partially restored after RIP3 knockdown)	
			↑ RIP3 protein expression	
			↑ PYGL, ↑ GLUL, ↑ GLUD1 protein expression	
		C57BL6/j mice inoculated with eGFP-MC38 cells	↓ Number of liver metastatic foci	
			↓ Size of liver metastatic foci	
		Nude mice inoculated with CNE-2Z cells	0.5 and 1 mg/kg every 3 days (21 days)	↓ Tumor growth ↓ Tumor weight ↑ Tumor necrosis [133]
		BALB/c athymic nude mice inoculated with A549 cells	2 mg/kg/day (14 days)	↓ Tumor growth ↓ Tumor volume ↓ Tumor weight ↑ Tumor necrosis [134]
			↑ RIP1 protein expression	
		BALB/c nude mice inoculated with K7 cells	2 mg/kg/day (7 days)	↓ Tumor growth ↓ Tumor volume ↓ Tumor weight ↑ RIP1 protein expression ↑ RIP3 protein expression ↓ Number of lung metastasis ↓ Lung weight ↑ Tumor necrosis in lung metastasis [136]
			↓ Tumor volume	
			↓ Tumor weight	
		BALB/c nude mice inoculated with C6 cells	2 mg/kg every 2 days for 4 times	↑ RIP1 protein expression ↑ RIP3 protein expression ↑ γ -H2AX protein expression ↑ p-ATM protein expression [140]
Shikonin	<i>Lithospermum erythrorhizon</i> Siebold & Zucc., <i>Arnebia euchroma</i> (Royle) Johnst, or <i>Arnebia guttata</i> Bunge			

		RIP1-RIP3 interaction	
		↑ HMGB1 protein expression	
		↑ HSP70 protein expression	
		↑ Calreticulin protein expression	
		Macrophages infiltration in tumor tissue	
		↓ Tumor volume	
		↑ Cytoplasmatic/mitochondrial p-MLKL protein expression	[141]
		↓ Mitochondrial AIF protein expression	
		↑ Cytoplasmatic/nuclear AIF protein expression	
		↓ Tumor growth	
BALB/c nude mice inoculated with 5-8F cells	0.5 mg/kg every 3 days (21 days)	↓ Tumor weight	[142]
		↑ Tumor necrosis	

Abbreviations.

↑: Increase; ↓: Decrease; AIF: Apoptosis-inducing factor; GLUD1: Glutamate dehydrogenase; GLUL: Glutamine synthetase; HMGB1: High-mobility group box 1; HSP70: Heat shock protein 70; JNK: c-Jun-N-terminal kinase; MLKL: Mixed lineage kinase domain like pseudokinase; p-ATM: Phospho-ataxia telangiectasia mutated kinase; p-JNK1/2: Phospho-c-Jun N-terminal kinase 1/2; p-MLKL: Phospho-mixed lineage kinase domain like pseudokinase; p-RIP3: Phospho-receptor-interacting serine/threonine-protein kinase 3; PYGL: Glycogen phosphorylase; RIP1: Receptor-interacting serine/threonine-protein kinase 1; RIP3: Receptor-interacting serine/threonine-protein kinase 3; TNF- α : Tumor necrosis factor- α ; γ -H2AX: Phospho-H2A histone family member X.

Table S5. Natural products as *in vivo* inducers of pyroptosis

Compound	Compound source	Experimental model(s)	Treatment doses	Antitumor effects and pyroptosis markers	Reference
Alpinumisoflavone	<i>Derris eriocarpa</i> F.C	BALB/c nude mice inoculated with KYSE30 cells	40 and 80 mg/kg/day (30 days)	↓ Tumor volume ↓ Tumor weight ↑ GSDME, ↑ cleaved caspase-3, ↑ Bax expression	[198]
		BALB/c nude mice inoculated with TPC-1 cells	20 and 40 mg/kg/day (30 days)	↓ Tumor volume ↓ Tumor weight ↑ NLRP3, ↑ cleaved caspase-1, ↑ cleaved IL-1 β , ↑ cleaved IL-18, ↑ cleaved GSDMD protein expression	[199]
Berberine	Huang Lian Chinese herb (<i>Coptis chinensis</i>) and others plant spp.	BALB/c-nude mice inoculated with HepG2 cells	20 mg/kg/day (21 days)	↓ Tumor volume (partially restored after AC-YVAD-CMK treatment) ↑ Caspase-1 mRNA and protein expression (↓ after AC-YVAD-CMK treatment)	[201]
Dioscin	<i>Polygonatum zanzlanscianense</i> Pamp., <i>Dioscorea nipponica</i> Makino, and <i>Dioscorea zingiberensis</i> C. H. Wright	BALB/c mice inoculated with MNNG/HOS cells	12 and 24 mg/kg, every 3 days (15 days)	↓ Tumor volume ↓ Tumor weight ↑ GSDME-NT expression ↑ Cleaved caspase-3 expression	[203]
Huaier extract	<i>Trametes robiniophila</i> murr (Huaier)	BALB/c nude mice inoculated with H520 cells	50 mg/mL/day (28 days)	↓ Tumor volume ↑ NLRP3, ↑ cleaved-caspase-1, ↑ IL-1 β , ↑ IL-18 protein levels in tumor tissue	[205]
Polyphyllin VI	<i>Trillium tschonoskii</i> Maxim	Athymic nude mice inoculated with A549 cells	2.5, 5 and 10 mg/kg/day (10 days)	↑ NLRP3, ↑ cleaved caspase-1, ↑ cleaved IL-1 β , ↑ cleaved GSDMD protein levels ↑ NLRP3, ↑ caspase-1, ↑ IL-1 β , ↑ GSDMD protein levels in tumor tissue	[195]

Abbreviations.

↑: Increase; ↓: Decrease; AC-YVAD-CMK: Caspase-1 inhibitor; GSDMD: Gasdermin D; GSDME: Gasdermin E; GSDME-NT: N terminal fragment of Gasdermin E; IL-18: Interleukin-18; IL-1 β : Interleukin 1 beta; NLRP3: NLR (nucleotide-binding oligomerization domain (NOD)-like receptor) family pyrin domain-containing 3; Spp.: species