Supplementary Table S1. Kinase profiling of 4HD and XAG.

Kinase profiler screening was performed with 10 μM 4HD or XAG and 10 μM ATP according to Millipore's protocol. Scores are represented as percent (%) of activity remaining after treatment. The letter h represents human.

Kinases	Activity (4HD 10 μM)	Activity (XAG 10 μM)
Abl(h)	109	101
B-Raf(h)	96	103
B-Raf(V600E)(h)	70	68
CDK1/cyclinB(h)	117	116
CDK2/cyclinA(h)	90	93
CDK2/cyclinE(h)	104	114
cKit(h)	82	86
c-RAF(h)	91	94
DAPK1(h)	89	94
EGFR(h)	96	89
FAK(h)	85	82
FGFR2(h)	91	100
IGF-1R(h), activated	92	98
JAK2(h)	92	101
JNK1α1(h)	108	112
JNK2α2(h)	81	90
JNK3(h)	82	73
MAPK1(h)	96	88
MAPK2(h)	95	104
MEK1(h)	106	118
mTOR(h)	94	90
PKBα(h)	88	93
PKCα(h)	97	101
PKCβI(h)	88	88
PI3 Kinase (p110β/p85α)(h)	89	59
PI3 Kinase (p110δ/p85α)(h)	72	48
PI3 Kinase (p110α/p85α)(h)	94	78
Rsk2(h)	118	107
SAPK2a(h)	91	92
SAPK2b(h)	83	88

Supplementary Figure Legends

Supplementary Figure 1. ^{1}H NMR (400 MHz, CDCl3) spectrum of 4-hydroxyderricin (4-HD) and xanthoangelol (XAG)

Supplementary Figure 2. Ligand interaction diagram (LID) for 4HD and XAG binding with BRAFV600E (A) and PI3-K (B). The interaction of the 4HD and XAG with BRAF and PI3-K is shown in the binding models.

Supplementary Figure 3. The effects of 4HD or XAG on CDK4 (A) and CDK6 (B) kinase activity. The effect of 4HD or XAG on CDK4 and CDK6 kinase activity was conducted by *in vitro* kinase assay using an Rb-C fusion protein (701-928 amino acids), [γ^{32}P] ATP and a ^{32}P-labled Rb protein and was visualized by autoradiography.

Supplementary Figure 4. 4HD or XAG has no cytotoxicity at concentrations less than 20 μM against normal melanocytes. Normal human epidermal melanocytes, NHEM cells were seeded into 96-well plates. After overnight incubation, cells were treated with different concentrations of (A) 4HD or (B) XAG and incubated for 1 or 2 days. (C) SK-MEL-31 cells were seeded into 96-well plates. The cells were treated with 4HD or XAG. After incubation for 1, 2, 3 or 4 days, 20 μL of the CellTiter 96 Aqueous One Solution (Promega, Madison, WI) were added to each well and cells were incubated for an additional 1 h at 37°C. Viability was estimated using the MTS assay as described in Materials and Methods. Data are represented as mean values ±

S.D. as determined from 3 independent experiments. The asterisks indicate a significant decrease compared with untreated control cells (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$).

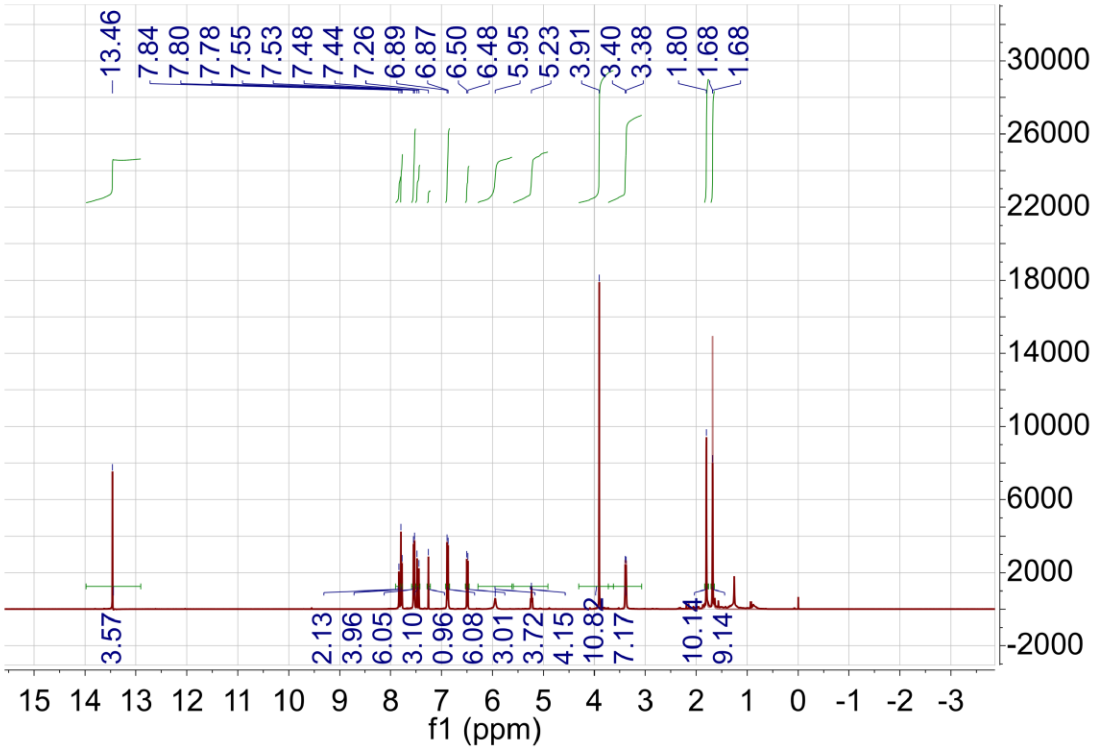
Supplementary Figure 5. Statistical analysis for Figure 3A and B: the effects of 4HD and XAG on melanoma cell cycle. SK-MEL-28 melanoma cells (2.5 $\times 10^4$/well) were cultured in 60-mm plates and then synchronized in the G0-phase by serum deprivation. (A) The cells were treated with 15 μM 4HD, XAG or vehicle control for 6, 12, 18, 24 or 48 h. (B) The cells were treated with various concentrations of 4HD, XAG or vehicle control for 18 h. Data are represented as mean values ± S.D. as determined from 3 independent experiments. The asterisks indicate a significant decrease compared with control cells (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$).

Supplementary Figure 6. Prevention of BRAF [600E]/ PTEN-null induced melanoma by 4HD or XAG. Images of solvent control, 4HD- or XAG-treated mice are shown at day 47.

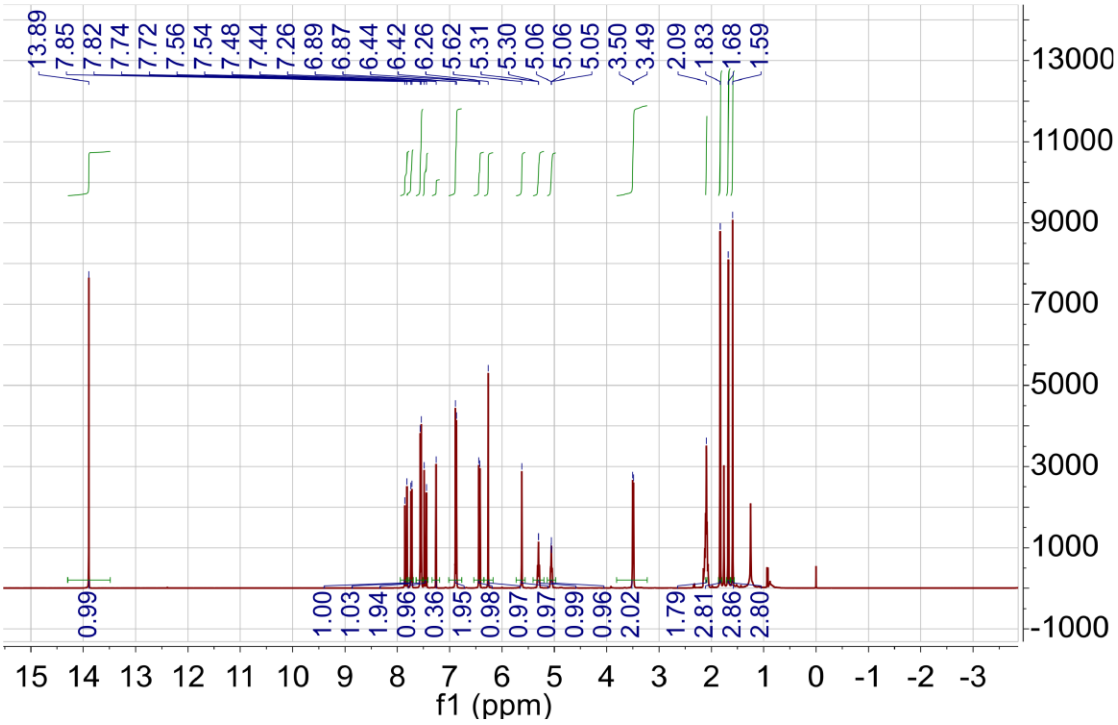
Supplementary Figure 7. The inhibitory effects of 4HD or XAG on tumor growth in BRAF [600E]/PTEN-null mice. Images of solvent control, 4HD- or XAG-treated mice are shown at day 50.

Supplementary Figure S1

A, ^{1}H NMR (400 MHz, CDCl3) spectrum of 4-hydroxyderricin

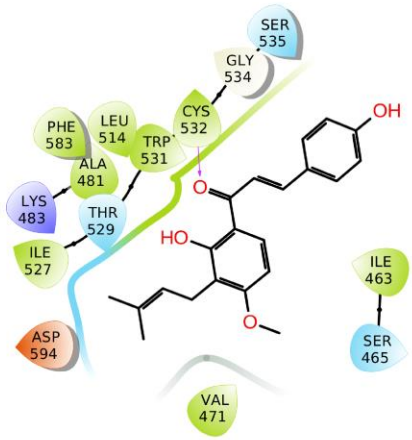


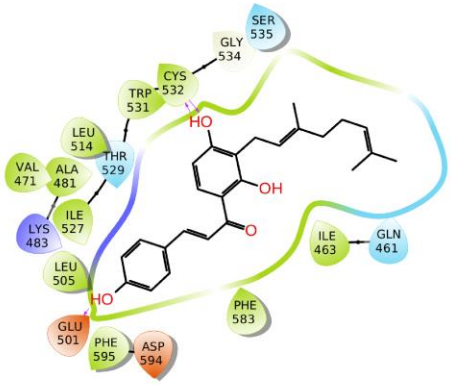
B, ^{1}H NMR (400 MHz, CDCl3) spectrum of xanthoangelol



Supplementary Figure S2

A





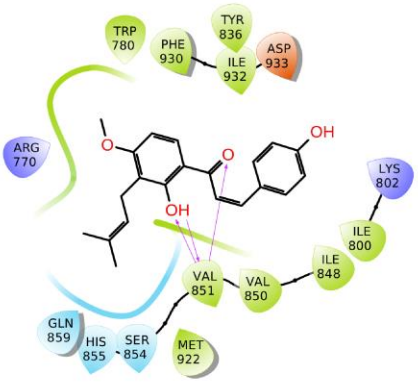
4HD binding with BRAFV600E

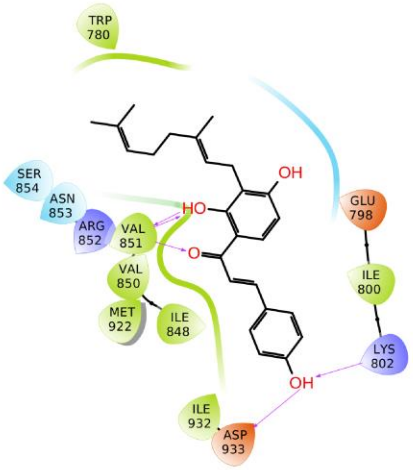
BRAFV600E Binding area	4HD Binding area	Distance (Angstrom)
Residue CYS532 H	carbonyl O	2.06

XAG binding with BRAFV600E

BRAFV600E Binding area	XAG Binding area	Distance (Angstrom)
Residue CYS532 H	4'-hydroxy O	1.78
Residue CYS532 O	4'-hydroxy H	1.90
Side chain GLU501 O	4-hydroxy H	2.84

B





4HD binding with PI3-K

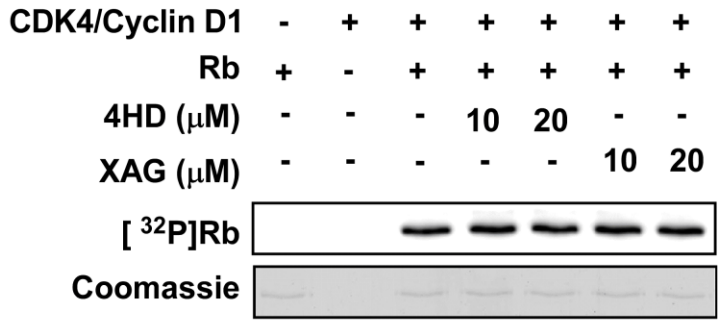
PI3-K Binding area	4HD Binding area	Distance (Angstrom)
Residue VAL851 O	2'-hydroxy H	2.19
Residue VAL851 H	2'-hydroxy O	2.10
Residue VAL851 H	carbonyl O	2.63

XAG binding with PI3-K

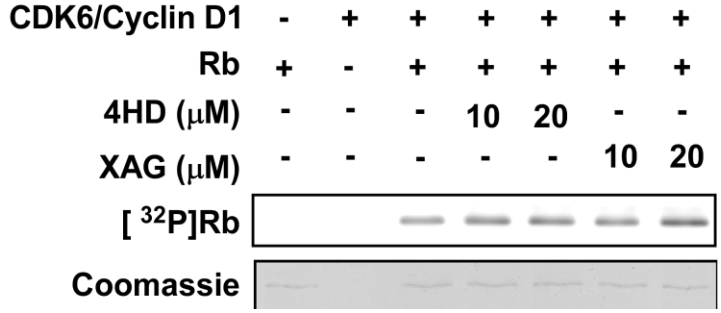
PI3-K Binding area	XAG Binding area	Distance (Angstrom)
Residue VAL851 O	2'-hydroxy H	2.03
Residue VAL851 H	2'-hydroxy O	1.97
Residue VAL851 H	carbonyl O	2.80
Side chain LYS802 H	4-hydroxy O	3.03
Side chain ASP O	4-hydroxy H	2.82

Supplementary Figure S3

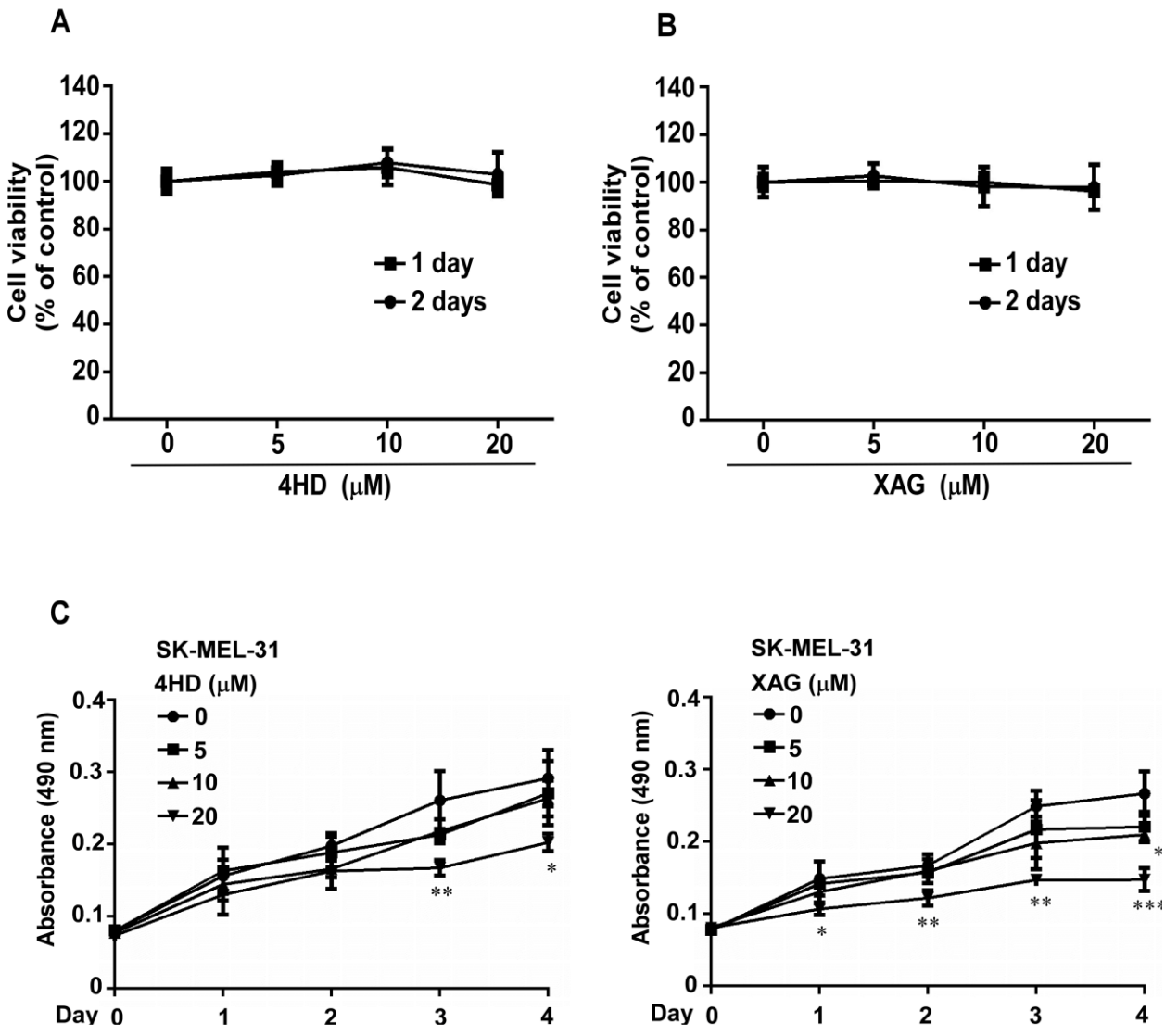
A



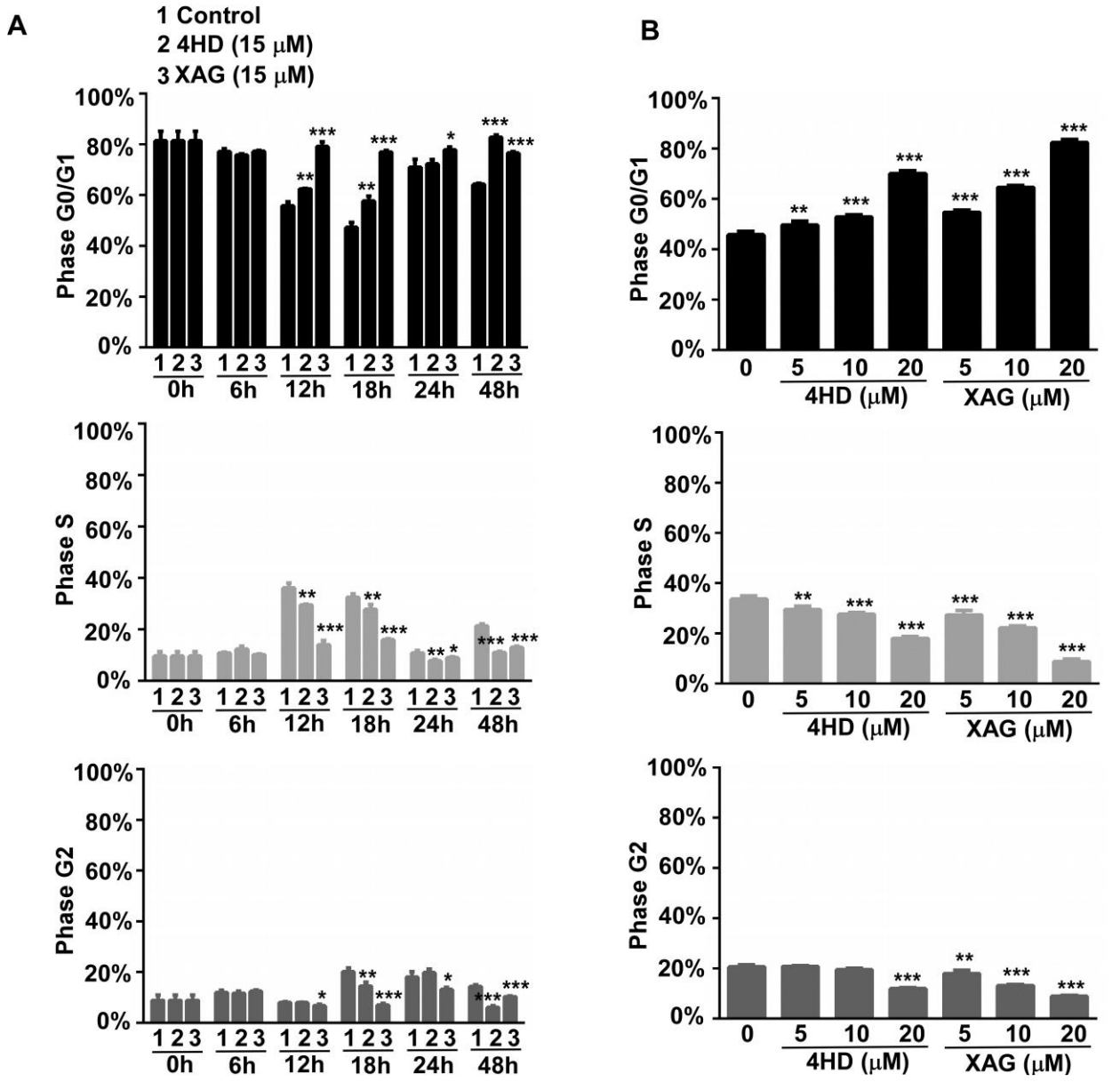
B



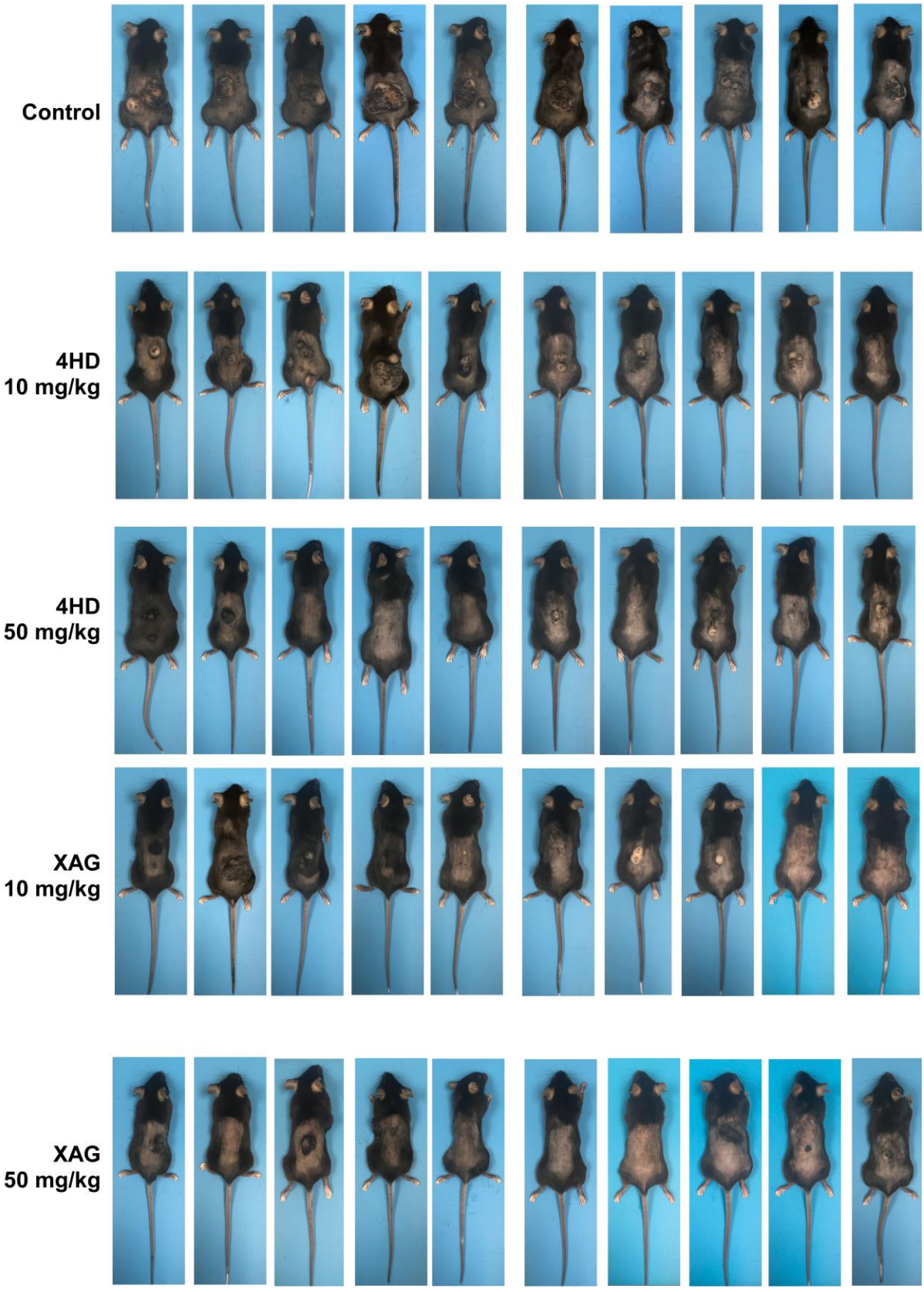
Supplementary Figure S4



Supplementary Figure S5



Supplementary Figure S6



Supplementary Figure S7