Table S1. Effect of screened compounds on DRAK2 activity at a concentration of 20 μM

No.	Concentration	Result Type	Result
JY-01519(Luteolin)	20 μM	%Activity	7.74 +/- 1.75
JY-01522	20 μM	%Activity	94.17 +/- 6.84
JY-01523	20 μM	%Activity	66.57 +/- 5.02
JY-01524	20 μM	%Activity	90.62 +/- 14.87
JY-01526	20 μM	%Activity	54.19 +/- 1.74
JY-01527	20 μM	%Activity	66.35 +/- 6.03
JY-01529	20 μM	%Activity	68.73 +/- 7.78
JY-01530	20 μM	%Activity	79.49 +/- 4.96
JY-01531	20 μM	%Activity	64.85 +/- 1.14
JY-01532	20 μM	%Activity	71.04 +/- 6.00
JY-01536	20 μM	%Activity	89.42 +/- 5.85
JY-01540	20 μM	%Activity	37.86 +/- 6.00
JY-01541	20 μM	%Activity	57.94 +/- 4.99
JY-01542	20 μM	%Activity	62.09 +/- 4.02
JY-01543	20 μM	%Activity	82.72 +/- 3.50
JY-01545	20 μM	%Activity	58.23 +/- 0.59
JY-01546	20 μM	%Activity	50.13 +/- 8.84
JY-01547	20 μM	%Activity	42.79 +/- 1.24
JY-01548	20 μM	%Activity	67.75 +/- 2.59
JY-01549	20 μM	%Activity	39.83 +/- 3.97
JY-01550	20 μM	%Activity	41.67 +/- 0.74
JY-01551	20 μM	%Activity	46.50 +/- 0.31
JY-01552	20 μM	%Activity	70.31 +/- 0.46
JY-01553	20 μM	%Activity	56.54 +/- 1.82
JY-01554	20 μM	%Activity	64.38 +/- 10.76
JY-01555	20 μM	%Activity	62.46 +/- 10.21
JY-01556	20 μM	%Activity	75.10 +/- 7.60
JY-01558	20 μM	%Activity	35.54 +/- 5.27
JY-02089	20 μM	%Activity	132.98 +/- 8.06
JY-02090	20 μM	%Activity	99.30 +/- 17.26
JY-02091	20 μM	%Activity	114.00 +/- 3.33
JY-02092	20 μM	%Activity	100.80 +/- 3.01
JY-02093	20 μM	%Activity	100.85 +/- 3.11
JY-02094	20 μM	%Activity	94.30 +/- 8.89
JY-02095	20 μM	%Activity	96.97 +/- 12.62
JY-02096	20 μM	%Activity	87.74 +/- 4.46
JY-02097	20 μM	%Activity	87.24 +/- 3.42
JY-02098	20 μM	%Activity	101.29 +/- 9.46
JY-02099	20 μM	%Activity	121.20 +/- 4.76
JY-02100	20 μM	%Activity	107.05 +/- 14.73
JY-02101	20 μM	%Activity	124.97 +/- 1.60
JY-02102	20 μM	%Activity	117.22 +/- 1.77
JY-02103	20 μM	%Activity	120.93 +/- 1.52
JY-02104	20 μM	%Activity	90.94 +/- 5.62
JY-02105	20 μM	%Activity	115.96 +/- 2.70
JY-02106	20 μM	%Activity	91.04 +/- 10.28
JY-02107	20 μM	%Activity	84.23 +/- 5.15
JY-02108	20 μM	%Activity	77.85 +/- 8.63

Table S1 ***Related to Figure 1.*** **Effect of screened natural products on DRAK2 activity**

The kinase activity of DRAK2 after treatment with natural product at a concentration of 20 μM.

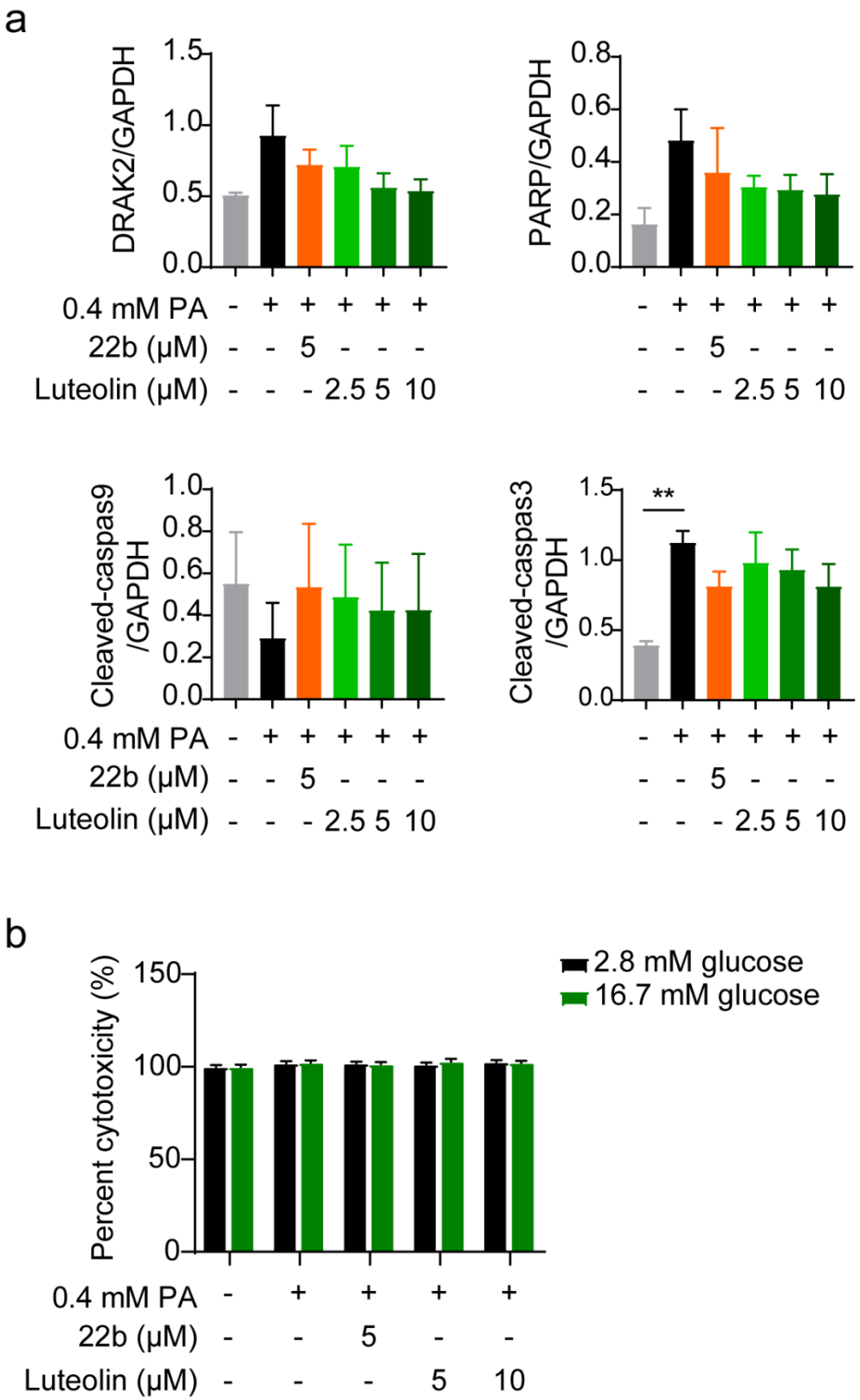

Figure S1. ***Related to Figure 2.*** **Contents of LDH in KRBH solution after therapy**

(**a**). Grayscale analysis of Figure 2c, n= 3. (**b**). LDH levels in KRBH solution measured by CytoTox-ONE™ Homogeneous Membrane Integrity Assay, n= 3.

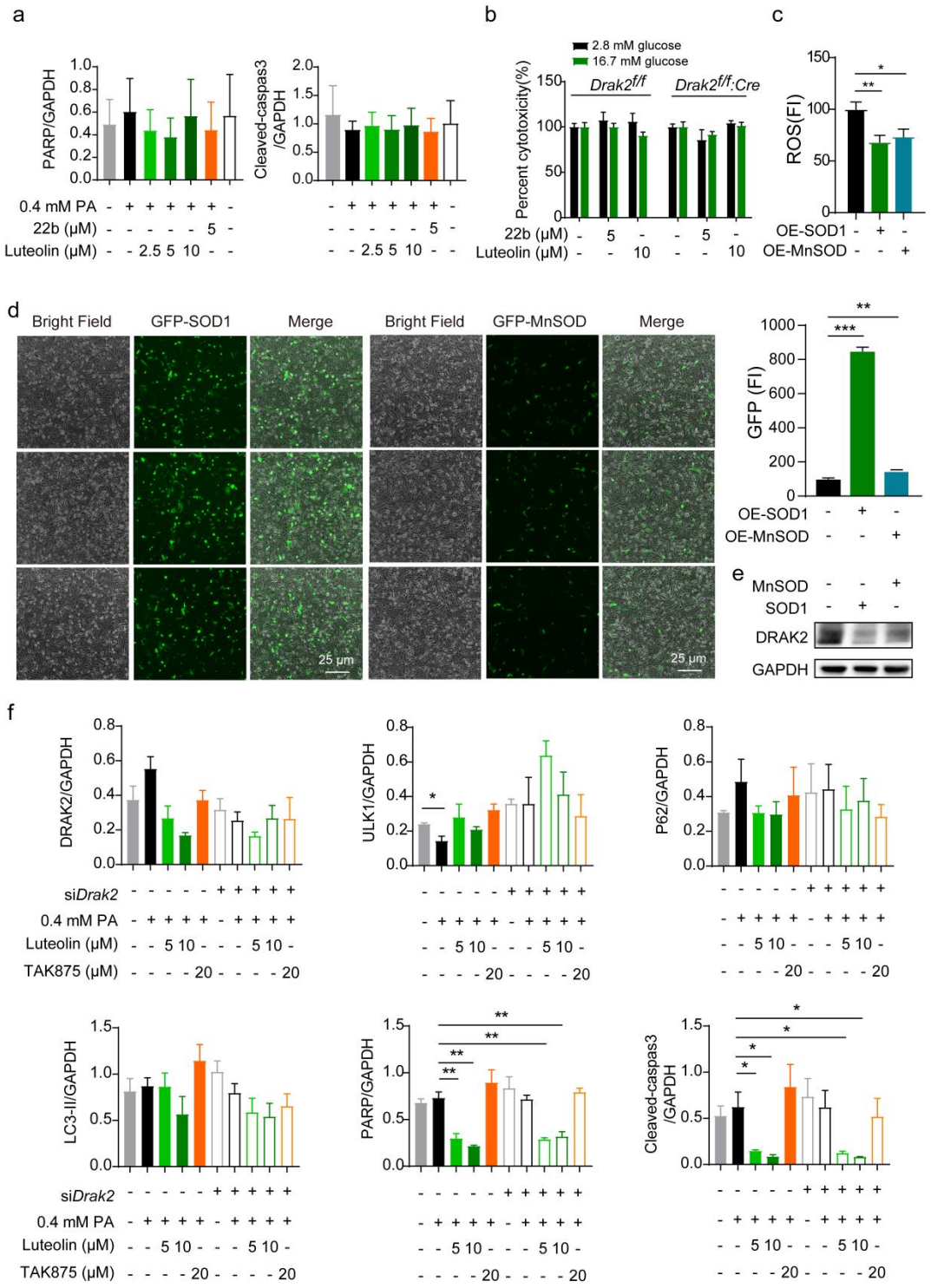

Figure S2. ***Related to Figure 3.*** **Content of LDH in KRBH solution after therapy and SOD fluorescence intensity in CHO cells**

(**a**). Grayscale analysis of Figure 3a, n= 3. (**b**). LDH levels in KRBH solution measured by CytoTox-ONE™ Homogeneous Membrane Integrity Assay, n= 3. (**c**)-(**d**). Overexpressing SOD1 or MnSOD in CHO cells. (c) The ROS levels in CHO cells, n= 4. (d) Fluorescence intensity and quantification of SOD in CHO cells after overexpressing SOD, n= 6. (**e**). Western-blot analysis of DRAK2 protein levels in response to overexpression of SOD and MnSOD. (**f**). Grayscale analysis of Figure 3d, n= 3. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

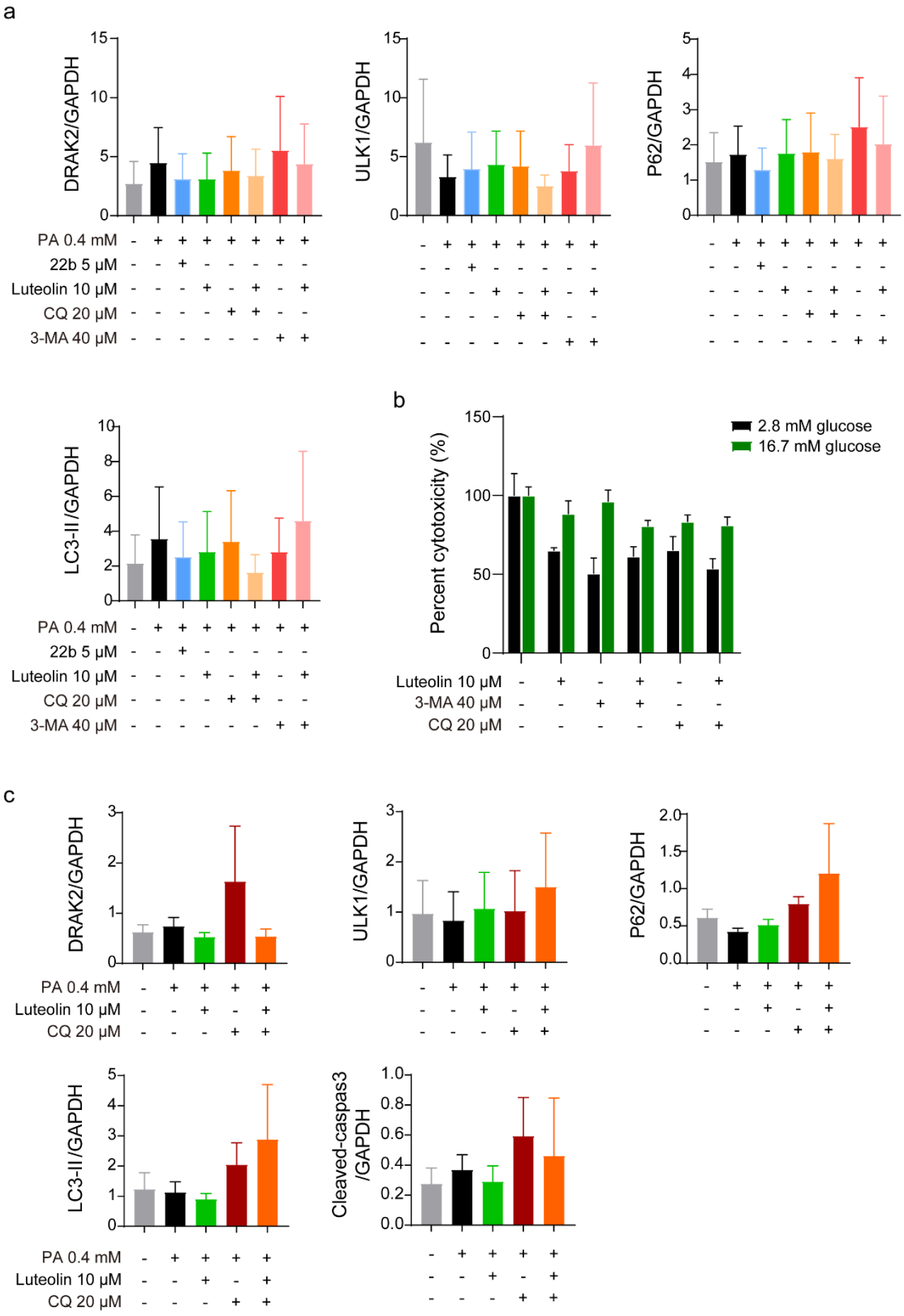

Figure S3. ***Related to Figure 4.*** **Content of LDH in KRBH solution after therapy**

(**a**). Grayscale analysis of Figure 4b, n= 3. (**b**). LDH levels in KRBH solution measured by CytoTox-ONE™ Homogeneous Membrane Integrity Assay, n= 3. (**c**). Grayscale analysis of Figure 4d, n= 3.

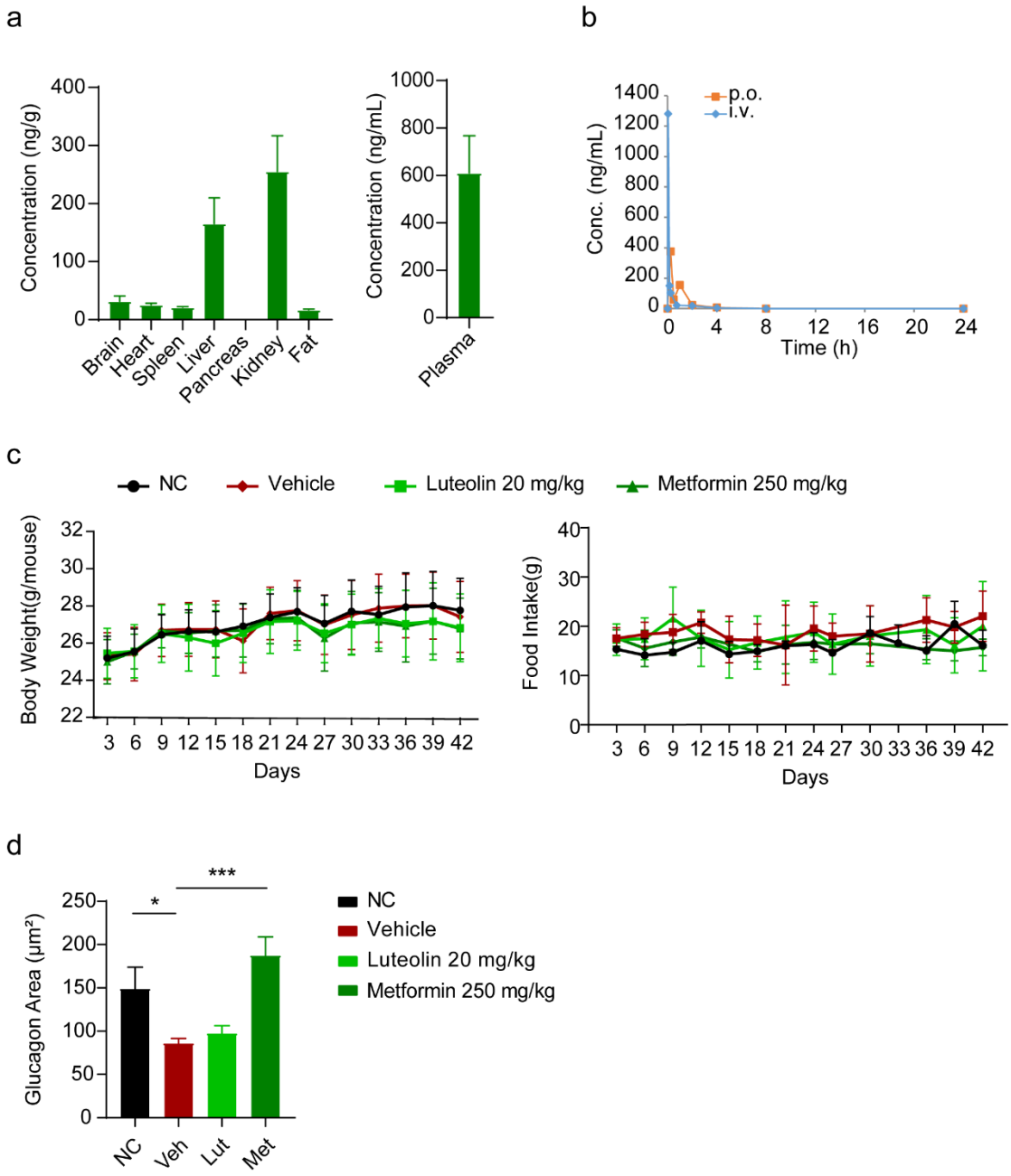

Figure S4. ***Related to Figure 5*****. Protective effect of luteolin on mice**

(**a**). Tissue distribution of luteolin by oral on ICR mice, n= 4. (**b**). Drug-time curve of luteolin *in vivo*. (**c**). Body weight on the last day of dosing and the average food intake during the 42 days treatment period, n= 8-13. (**d**). Area of glucagon assessed by immunofluorescence, n= 20.

Table S2. Pharmacokinetics parameters of Luteolin after p.o and i.v. administration in mouse

Administration	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{INF_obs} (h*ng/mL)	CL_obs mL/min/kg	MRT_{INF_obs} (h)	Vss_obs (mL/kg)	F (%)
p.o.	0.714	0.25	376	241	248	-	1.13	-	34.4
i.v.	1.36	-	-	175	184	453	0.879	23887	

Comment: N/A

Table S2. Related to Figure 5. Concentration-time Data

The pharmacokinetics parameters of luteolin after p.o. and i.v. administration in ICR mice