

LC-MS/MS Analysis

LC-MS/MS analysis was performed on a Thermo Scientific UHPLC-Q Exactive HF-X system (Shanghai Meiji Bio-Pharmaceutical Technology Co., Ltd.). The chromatography conditions were as follows: 3 μ L of the sample was separated on an HSS T3 column (100 mm $\times$ 2.1 mm i.d., 1.8 μ m) and subsequently introduced into the mass spectrometer. The mobile phase A consisted of 95% water and 5% acetonitrile (containing 0.1% formic acid), while mobile phase B comprised 47.5% acetonitrile, 47.5% isopropanol, and 5% water (containing 0.1% formic acid). The flow rate was set at 0.40 mL/min, and the column temperature was maintained at 40°C.

Mass Spectrometry Conditions:

The mass spectrometry signals were collected in both positive and negative ion scanning modes, with the mass scan range set from 70 to 1050 m/z. The sheath gas flow was 50 psi, the auxiliary gas flow was 13 psi, and the auxiliary gas heater temperature was 425°C. The positive ion spray voltage was set at 3500 V, while the negative ion spray voltage was set at -3500 V. The ion transfer tube temperature was 325°C, and the normalized collision energy was set to 20-40-60 V for cycle collision energy. The resolution of the first-order mass spectrometry was 60,000, while the second-order resolution was 7,500. Data acquisition was performed in DDA mode.

Supplementary Table 1 The primer sequences

The primer sequences	
b-ACTIN-F	ATAGAGGCTCTTGTGCGTACTGTC
b-ACTIN-R	TTGGTGTCTGGCTGGTCAGATG
BAX-F	ACCAAGAAGCTGAGCGAGTGTC
BAX-R	TGTCCACGGCGGCAATCATC
Caspase-3-F	GACTGGAAAGCCGAAACTCTTCATC
Caspase-3-R	AGTCCCCTGTCTGTCTCAATGC
TGF- β 1-F	CCTGGCGATACCTCAGCAACC
TGF- β 1-R	CCTCCACGGCTCAACCACTG
α -SMA-F	AGAAGAGTTACGAGTTGCCTGATGG
α -SMA-R	GCTGTTGTAGGTGGTTTCATGGATG
E-cadherin-F	ATTCTGCTGCTCTTGCTGTTTCTTC
E-cadherin-R	CTCTTCTCCGCCTCCTTCTTCATC
GPX4-F	CGCTGTGGAAGTGGATGAAGATC
GPX4-R	TGTCGATGAGGAACTGTGGAGAG
SLC7A11-F	ACGGTGGTGTGTTTGCTGTCTC
SLC7A11-R	GCTGGTAGAGGAGTGTGCTTGC
IL-6-F	GGTGTGCTGCTGCTGCCTTCC
IL-6-R	GTTCTGAAGAGGTGAGTGGCTGTC
TNF- α -F	AAGGACACCATGAGCACTGAAAGC
TNF- α -R	AGGAAGGAGAAGAGGCTGAGGAAC
ATG7-F	ATCCCACAGCCAACAGATTGAAGG
ATG7-R	TGCCTCCACCAAACCTGATTGAAG
NCOA4-F	CTGGAATGTCTTAGAAGCCGTGAG
NCOA4-R	GCTGAGCCTGCTGTTGAAGTG
SQSTM1-F	CGTTAGCAGCCCAGCACATAGC
SQSTM1-R	CCAGCAGGAAGCCCACAACAC
FTH1-F	TTCAACAGTGCTTGGACGGAACC

FTH1-R	ATGGCGGCGACTAAGGAGAGG
LC3-F	GCCTTCTTCCTGCTGGTGAACC
LC3-R	TCCTCGTCTTTCTCCTGCTCGTAG
HERC2-F	AGCAGAGGATTCGGACACAGAGG
HERC2-R	CAGCATGAACTCCAGCAGACAGAC

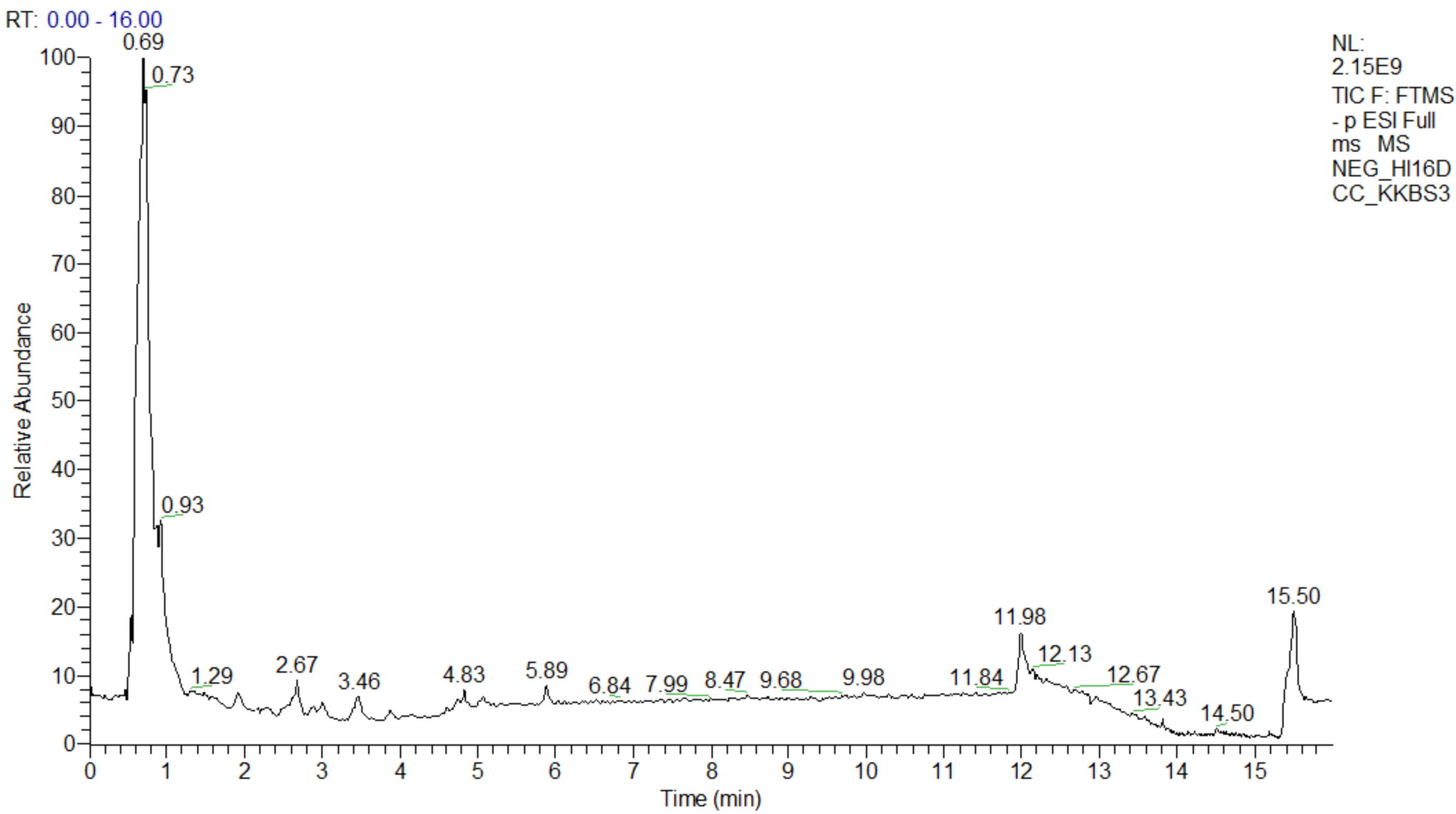
Supplementary Table 2 Compound quantification of KKBS

Metabolite	M/Z	Formula	CAS ID
Sweroside	359.1343	C16H22O9	14215-86-2;_
Isoquercetin	465.1039	C21H20O12	482-35-9
L-tyrosine	182.0817	C9H11NO3	60-18-4
Kaempferol 3-o-galactoside	449.1088	C21H20O11	23627-87-4
Ononin	431.1343	C22H22O9	486-62-4;
Calycosin	285.0763	C16H12O5	20575-57-9; ;
Formononetin	269.0813	C16H12O4	485-72-3;
Quercetin	303.0505	C15H10O7	117-39-5;
Kaempferol	287.0557	C15H10O6	520-18-3;80714-53-0;
Quercetin 3-o-malonylglucoside	551.1045	C24H22O15	96862-01-0

M/Z: The mass-to-charge ratio, denoted as m/z , refers to the ratio of the mass of an ion to its charge; Metabolite: The metabolites identified in this study are listed as follows; Formula: chemical formula of metabolite; CAS ID: CAS number of the compound.

Supplementary Figure 1

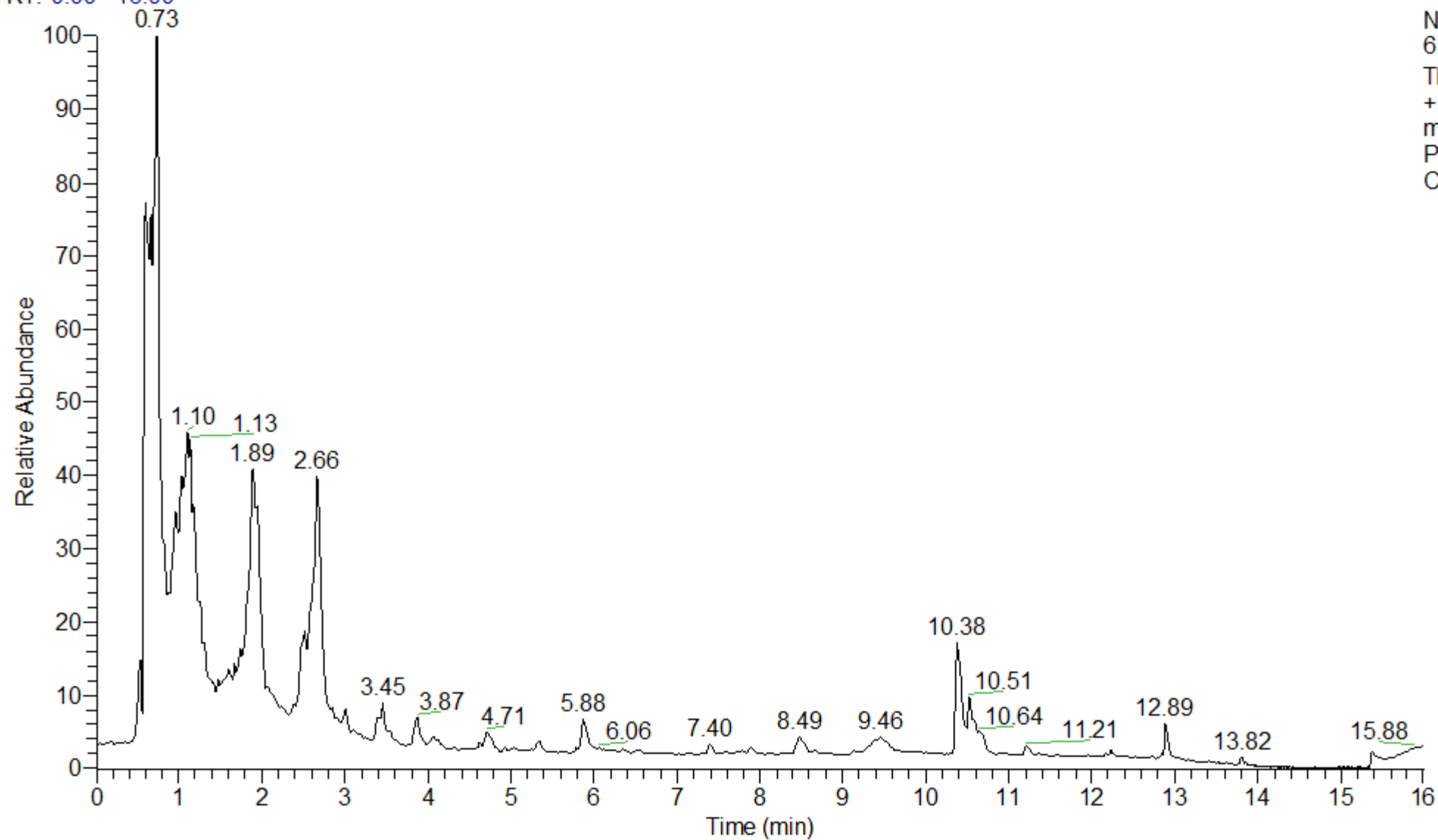
A



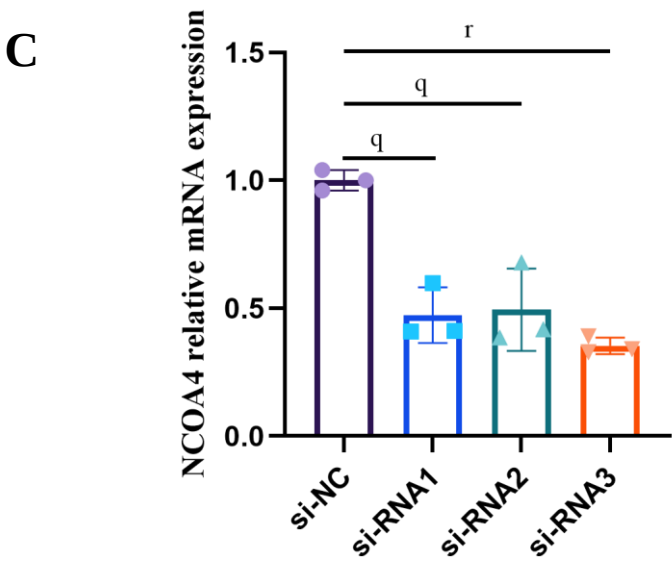
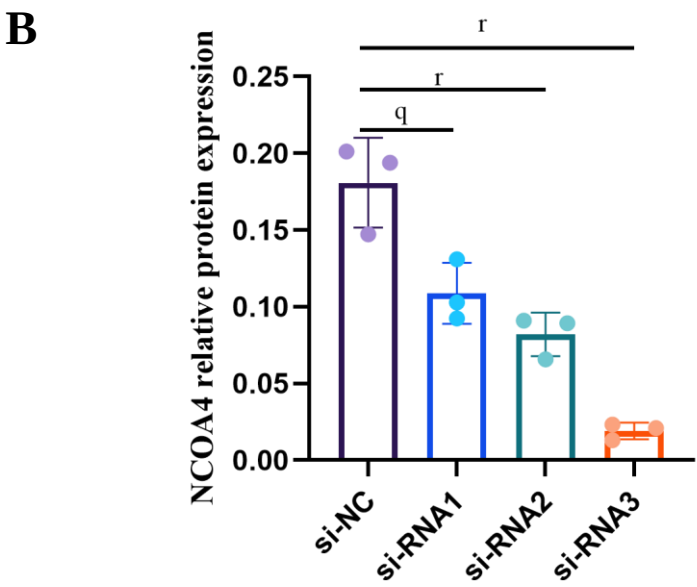
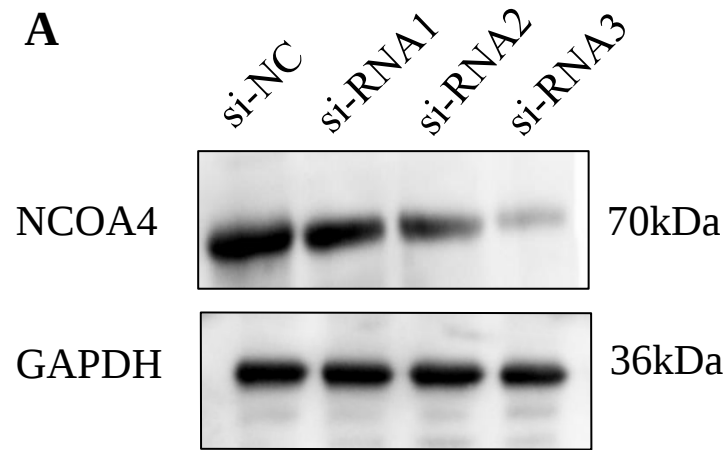
B

RT: 0.00 - 16.00

NL:
6.29E9
TIC F: FTMS
+ p ESI Full
ms MS
POS_HI16D
CC_KKBS3

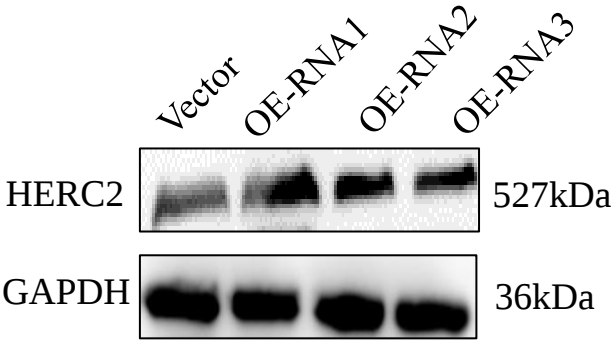


Supplementary Figure 2

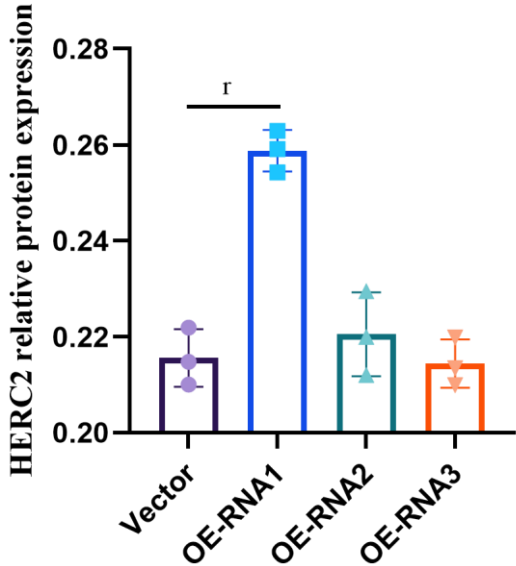


Supplementary Figure 3

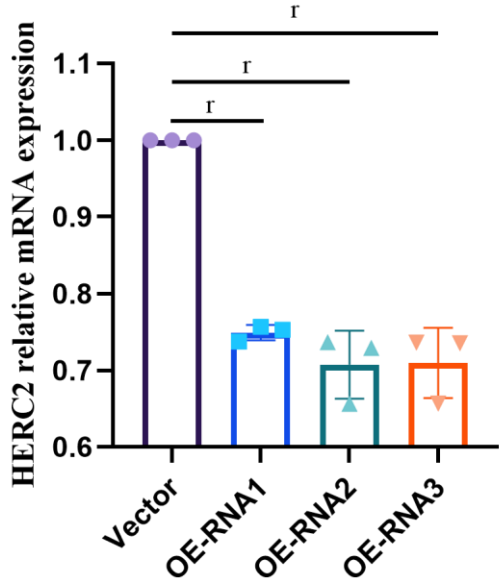
A



B

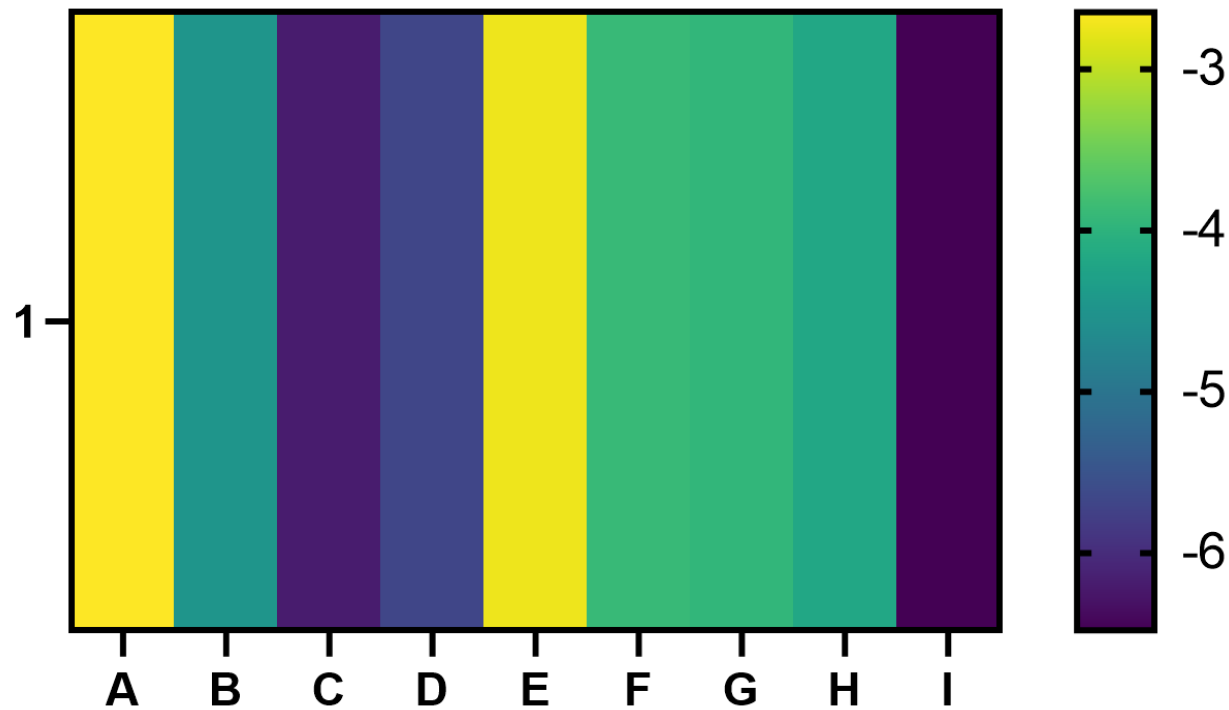


C



Supplementary Figure 4

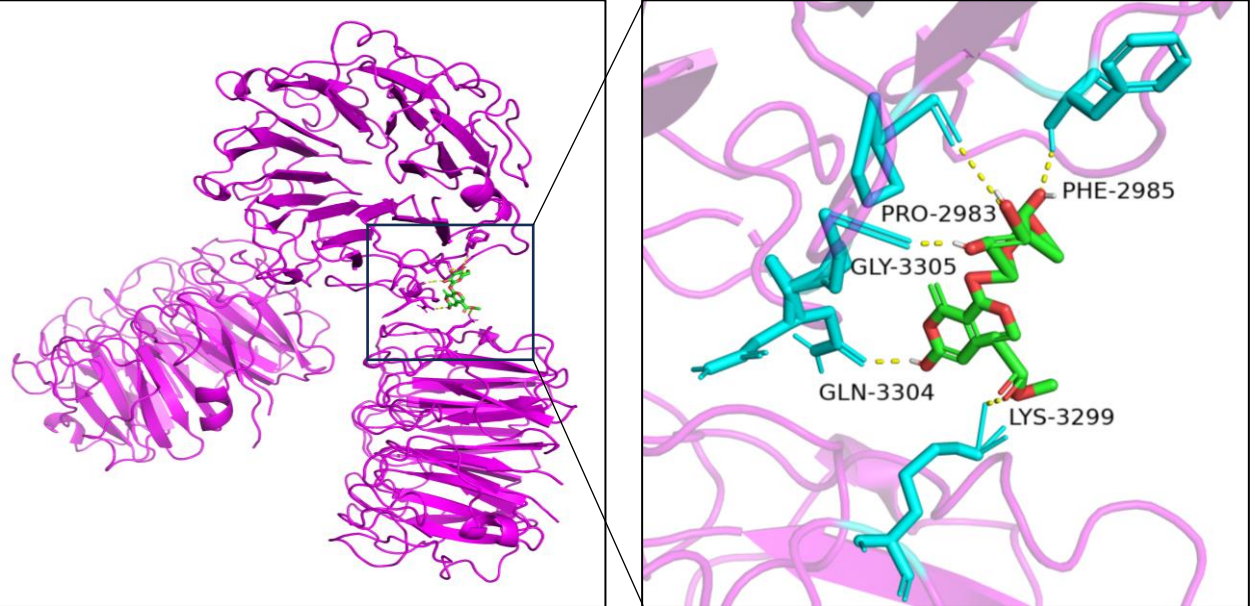
A



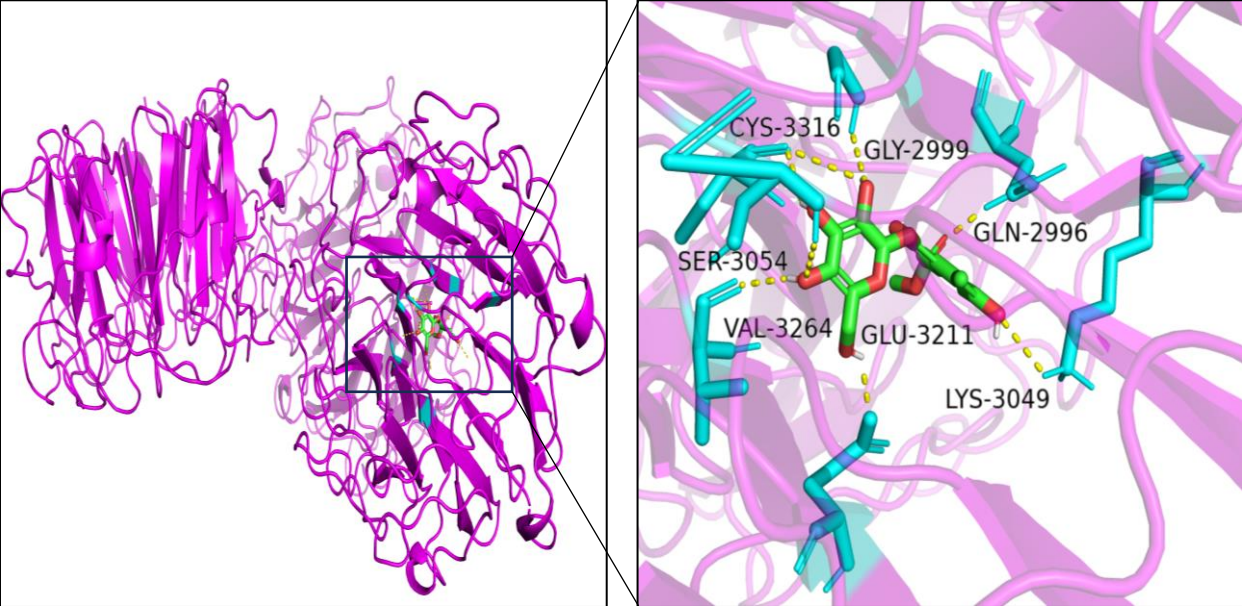
1 represented HERC2; The compounds represented by A to I are as follows: (A) Secologanin, (B) Sweroside, (C) Calycosin 7-O-beta-D-glucoside, (D) Isoquercetin, (E) Quercetin, (F) Myricetin, (G) Kaempferol, (H) Ononinn, and (I) Formononetin, respectively.

B

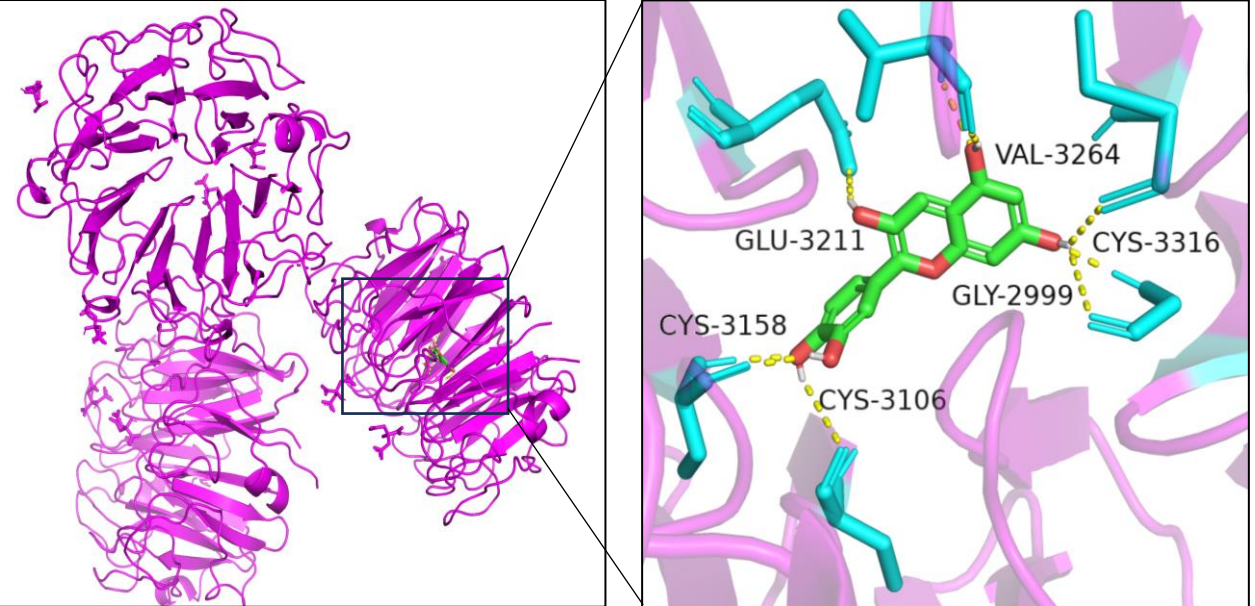
HERC2-Secologanin



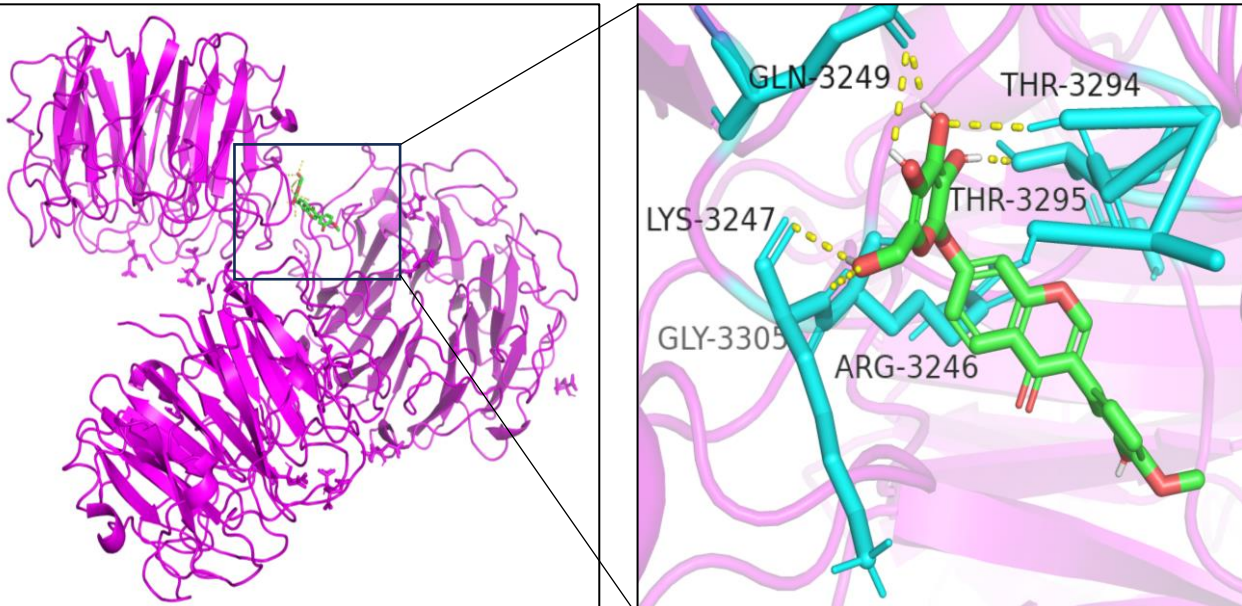
HERC2-Sweroside



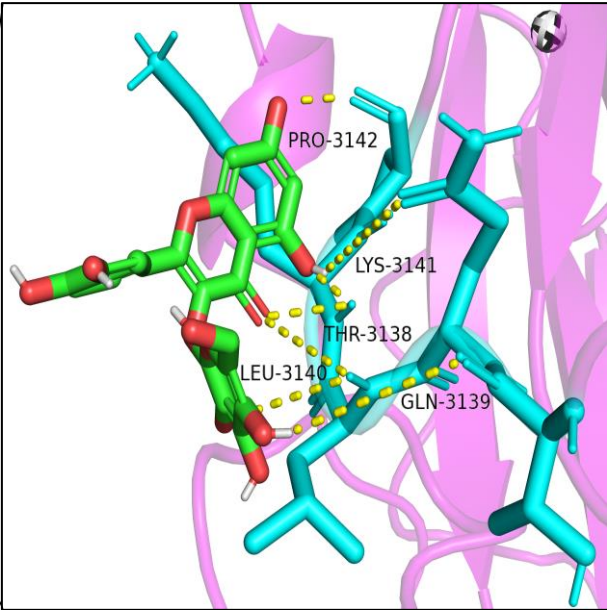
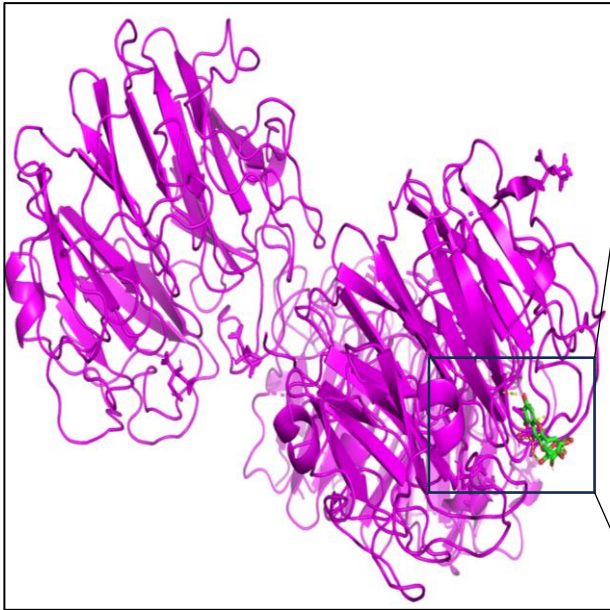
HERC2-Calycosin 7-O-beta-D-glucoside



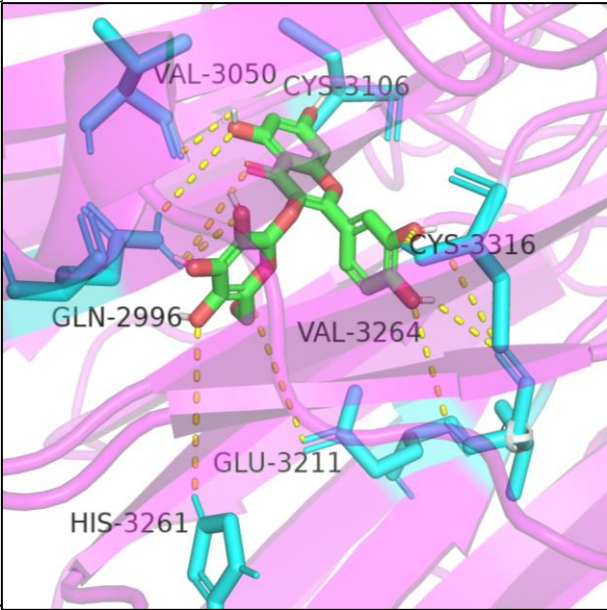
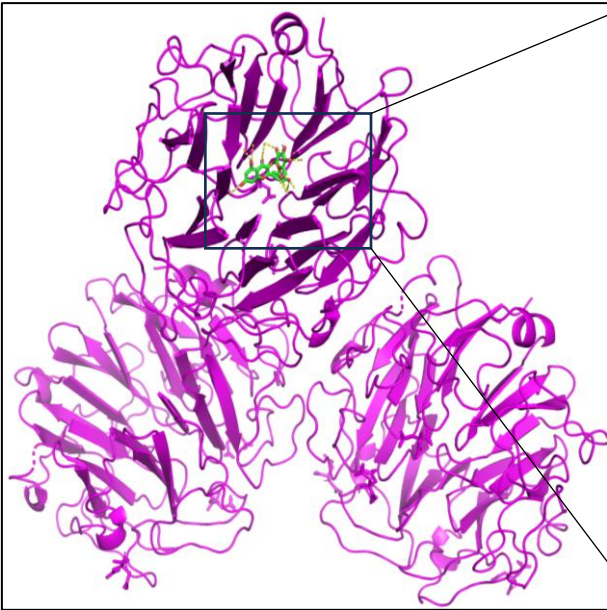
HERC2-Isoquercetin



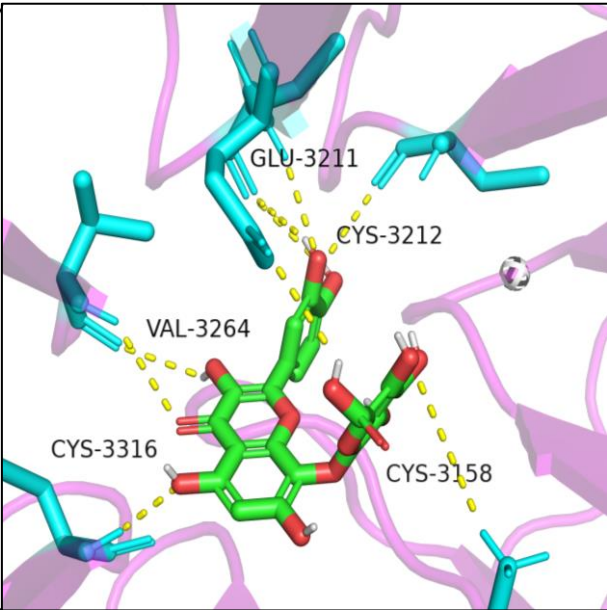
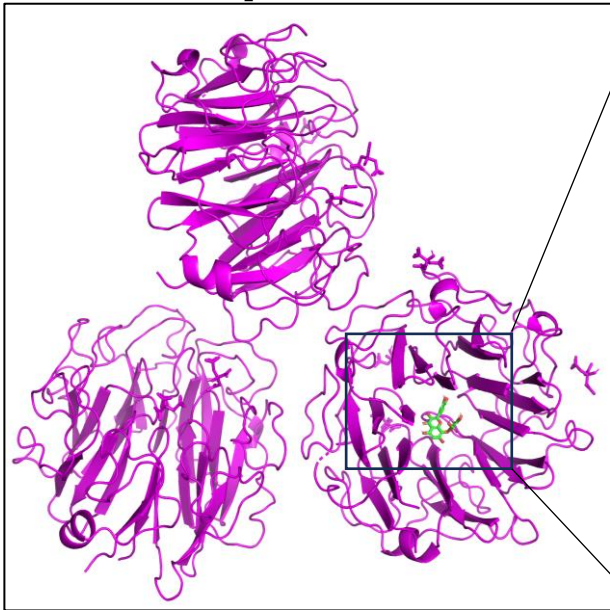
HERC2-Quercetin



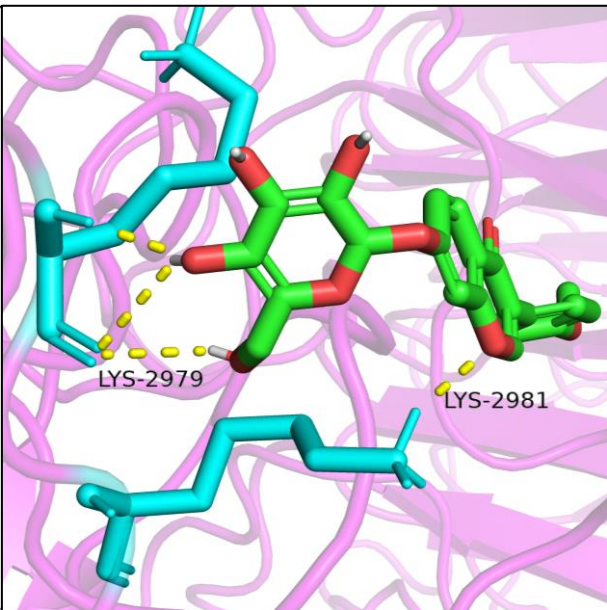
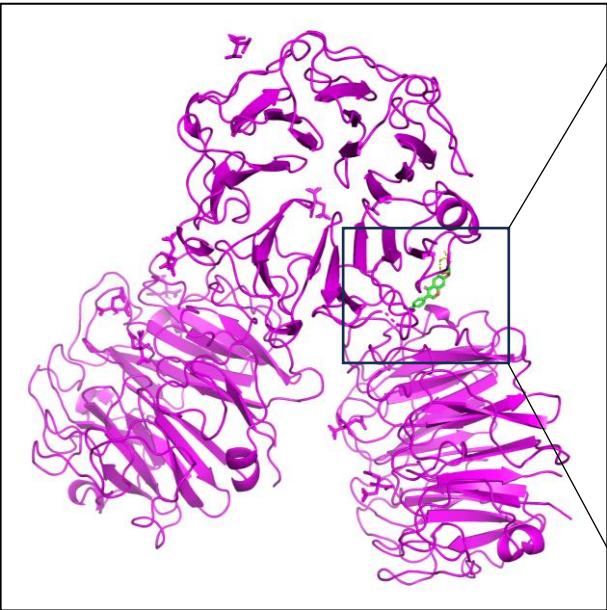
HERC2-Myricetin



HERC2-Kaempferol



HERC2-Ononin



HERC2-Formononetin

