Table S1 Sources of materials and reagents.

Material/reagent name	Brand	Address
High-fat diet (15% fat, 1% cholesterol, and 0.2% sodium cholate)	Keao Xieli	Beijing, China
Simvastatin (97%)	Aladdin	Shanghai, China
ALT reagent kit	Mindray	Shenzhen, China
AST reagent kit	Mindray	Shenzhen, China
MDA reagent kit	Nanjing Jiancheng	Nanjing, China
SOD reagent kit	Nanjing Jiancheng	Nanjing, China
TNFα reagent kit	Nanjing Jiancheng	Nanjing, China
IL-1β reagent kit	Nanjing Jiancheng	Nanjing, China
IL-6 reagent kit	Nanjing Jiancheng	Nanjing, China
Oil Red O solution	Solarbio	Beijing, China
H&E staining kits	Solarbio	Beijing, China
DMEM	Gibco	Guangzhou, China
FBS	Biological Industries	Berlin, Germany
Penicillin/streptomycin	Biosharp	Beijing, China
Sodium palmitate and sodium oleate	KunChuang	Xi'an, China
PMSF	Beyotime	Shanghai, China
RIPA	Beyotime	Shanghai, China
BCA assay kit	Beyotime	Shanghai, China
SDS-PAGE gel preparation kits	Beyotime	Shanghai, China
Enhanced chemiluminescence kit	Beyotime	Shanghai, China
PVDF membranes	Millipore	Burlington, USA
Anti-Hsp90 alpha (ET1605-57)	Huabio	Hangzhou, China
Anti-Hsp90 beta (ET1605-56)	Huabio	Hangzhou, China
Anti-AKT1 (ET1609-47)	Huabio	Hangzhou, China
Anti-phospho-AKT (S473) (HA722129)	Huabio	Hangzhou, China
Anti-phospho-GSK3 beta (Ser9) (ET1607-60)	Huabio	Hangzhou, China
Anti-GSK3 beta (ET1607-7)	Huabio	Hangzhou, China
Anti-ERK1/2 (ET1601-29)	Huabio	Hangzhou, China
Anti-phospho-Erk1 (T202+Y204) + Erk2 (T185+Y187) (ET1610-13)	Huabio	Hangzhou, China
Anti-beta Actin (EM21002)	Huabio	Hangzhou, China
Acetonitrile	J&K	Beijing, China
Methanol	J&K	Beijing, China
Formic acid	Macklin	Shanghai, China
LC-MS-grade water	Wahaha	Hangzhou, China

Table S2 Chromatographic and mass spectrometric conditions for component identification of HFE.

Chromatographic conditions	
Chromatographic column	Waters ACQUITY UPLC BEH C18 column (2.1 mm × 100 mm, 1.7 μm)
Column temperature	30℃
Sample injection volume	1 μL
Mobile phase A	water
Mobile phase B	acetonitrile
Flow rate	0.3 mL/min
Gradient elution method	0-15 min, 95% A; 15-25 min, 95%-70% A; 25-29 min, 25%-0% A; 29-34 min, 0% A; 34-35 min A; 0%-95% A; and 35-40 min, 95% A
Mass spectrometric conditions	
Ion source	Electrospray ionization (ESI)
MS range	20-1200 Da
Nebulizer pressure	40 psi
Nebulizer temperature	325°C
Drying gas temperature	350°C
Drying gas flow rate	11 L/min
Capillary voltage	4 kV
Fragmentation voltage	150 V

Table S3 Chromatographic and mass spectrometric conditions for untargeted metabolomics analysis.

Chromatographic conditions in positive mode (ESI^+)	
Chromatographic column	Agilent InfinityLab Poroshell 120 EC-C18 column
Column temperature	25°C
Sample injection volume	2 μL
Mobile phase A	0.1% carboxylic acid/water solution
Mobile phase B	100% acetonitrile
Flow rate	0.5 mL/min
Gradient elution method	0–1 min (5% B), 1–8 min (5-100% B), 8–10 min (100% B), 10–10.1 min (100-5% B); 10.1–12 min (5% B)
Chromatographic conditions in negative mode (ESI^-)	
Chromatographic column	Waters ACQUITY UPLC BEH Amide column
Column temperature	25°C
Sample injection volume	2 μL
Mobile phase A	25 mM ammonium acetate and 25 mM NH_4OH mixed solution
Mobile phase B	100% acetonitrile
Flow rate	0.5 mL/min
Gradient elution method	0–0.5 min (95% B), 0.5–7 min (95-65% B), 7–8 min (65-40% B) 8–9 min (40% B), 9–9.1 min (40-95% B) 9.1–12 min (95% B)
Mass spectrometric conditions	
Ion source	ESI
Ionization mode	Positive mode and negative mode
Mass range	50 to 1200 Da
Sheath gas temperature	275°C
Sheath gas flow rate	11 L/min
Dry gas temperature	225°C
Dry gas flow rate	13 L/min
Capillary voltage (ESI^+)	3500 V
Capillary voltage (ESI^-)	3000 V

Table S4 The detailed information on the identified compounds from HFE.

Compound	RT (min)	Precursor m/z	Mass error (ppm)	Formula	Adduct
Aconitic acid	1.3	175.0238	0.2	$C_6H_6O_6$	$[M+H]^+$
Dianthoside	2.6	289.0926	2.6	$C_{12}H_{16}O_8$	$[M+H]^+$
Allo Maltol	3	127.0393	2.2	$C_6H_6O_3$	$[M+H]^+$
6-Hydroxycoumarin	4.3	163.0393	2	$C_9H_6O_3$	$[M+H]^+$
Homovanillyl alcohol 4-O-glucoside	6.5	353.1207	0	$C_{15}H_{22}O_8$	$[M+Na]^+$
Epicatechin	7.7	291.0858	-1.7	$C_{15}H_{14}O_6$	$[M+H]^+$
Isoquercetin	10.3	465.1035	1.5	$C_{21}H_{20}O_{12}$	$[M+H]^+$
Berberine	15.7	336.1233	0.6	$C_{20}H_{17}NO_4$	$[M+H]^+$
Quinic acid	1.1	191.0551	-5.4	$C_7H_{12}O_6$	$[M-H]^-$
2-Furoic acid	1.9	111.009	1.4	$C_5H_4O_3$	$[M-H]^-$
Adoxosidic acid	2	375.1297	0.1	$C_{16}H_{24}O_{10}$	$[M-H]^-$
Neochlorogenic acid	6	353.0893	4.3	$C_{16}H_{18}O_9$	$[M-H]^-$
3-O-Feruloylquinic acid	8.4	367.1035	0	$C_{17}H_{20}O_9$	$[M-H]^-$
Rutin	10.3	609.1487	4.1	$C_{27}H_{30}O_{16}$	$[M-H]^-$
Quercetin	16.1	301.0356	0.6	$C_{15}H_{10}O_7$	$[M-H]^-$
Isorhamnetin	18.5	315.0514	1.2	$C_{16}H_{12}O_7$	$[M-H]^-$
Gingerol	21.3	293.1764	2	$C_{17}H_{26}O_4$	$[M-H]^-$

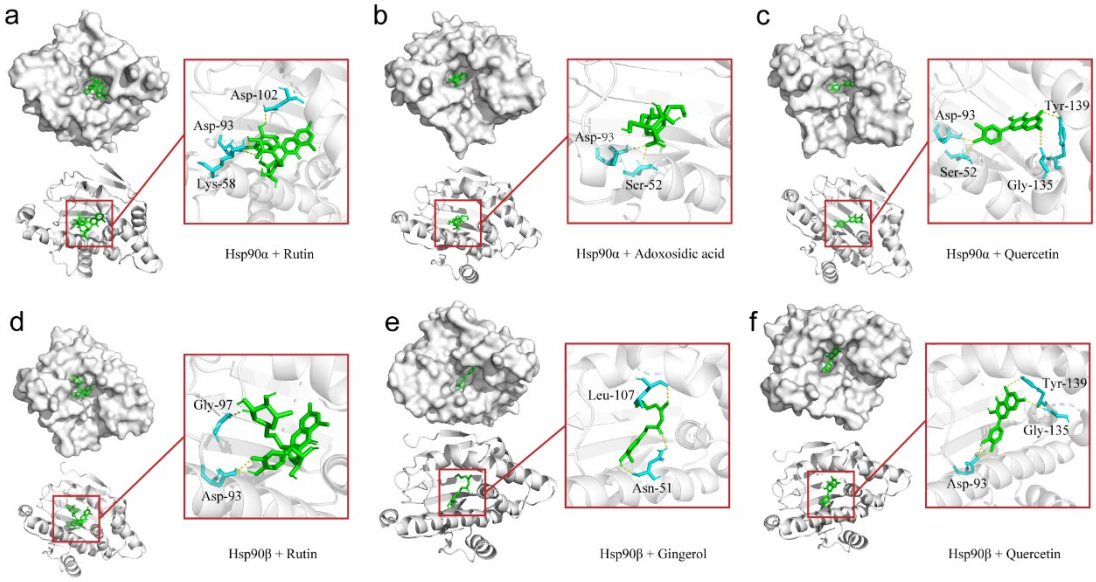

Figure S1 Molecular docking results between HFE compounds and Hsp90α/β. Molecular docking of Hsp90α with rutin (a), adoxosidic acid (c), and quercetin (d); molecular docking of Hsp90β with rutin (e), gingerol (f), and quercetin (g).