

**Table S1 The Pharmacokinetics of ARs and its endogenous metabolites.**

<b>Molecule</b>	<b>CYP1A2 inhibitor</b>	<b>CYP2C19 inhibitor</b>	<b>CYP2C9 inhibitor</b>	<b>CYP2D6 inhibitor</b>	<b>CYP3A4 inhibitor</b>
AR-C25	No	No	No	No	No
AR-C23	No	Yes	No	No	No
AR-C21	No	Yes	No	No	No
AR-C19	Yes	Yes	No	No	No
AR-C17	Yes	Yes	No	No	No
AR-C15	Yes	Yes	No	Yes	No
3,5-DHPHTA	No	No	No	No	No
3,5-DHPHTA-G	No	No	No	No	No
3,5-DHPHTA-S	No	No	No	No	No
3,5-DHPPTA	No	No	No	No	No
3,5-DHPPTA-G	No	No	No	No	No
3,5-DHPPTA-S	No	No	No	No	No
3,5-DHPPTA-Gly	No	No	No	No	No
3,5-DHPPA	No	No	No	No	No
3,5-DHPPA-G	No	No	No	No	No
3,5-DHPPA-S	No	No	No	No	No
3,5-DHPPA-Glu	No	No	No	No	No
3,5-DHPPA-Gly	No	No	No	No	No
3,5-DHBA	No	No	No	No	No
3,5-DHBA-G	No	No	No	No	No
3,5-DHBA-S	No	No	No	No	No
3,5-DHBA-Gly	No	No	No	No	No
3,5-DHBA-G,S	No	No	No	No	No

**Table S2. Common target information of compound targets and different disease targets**

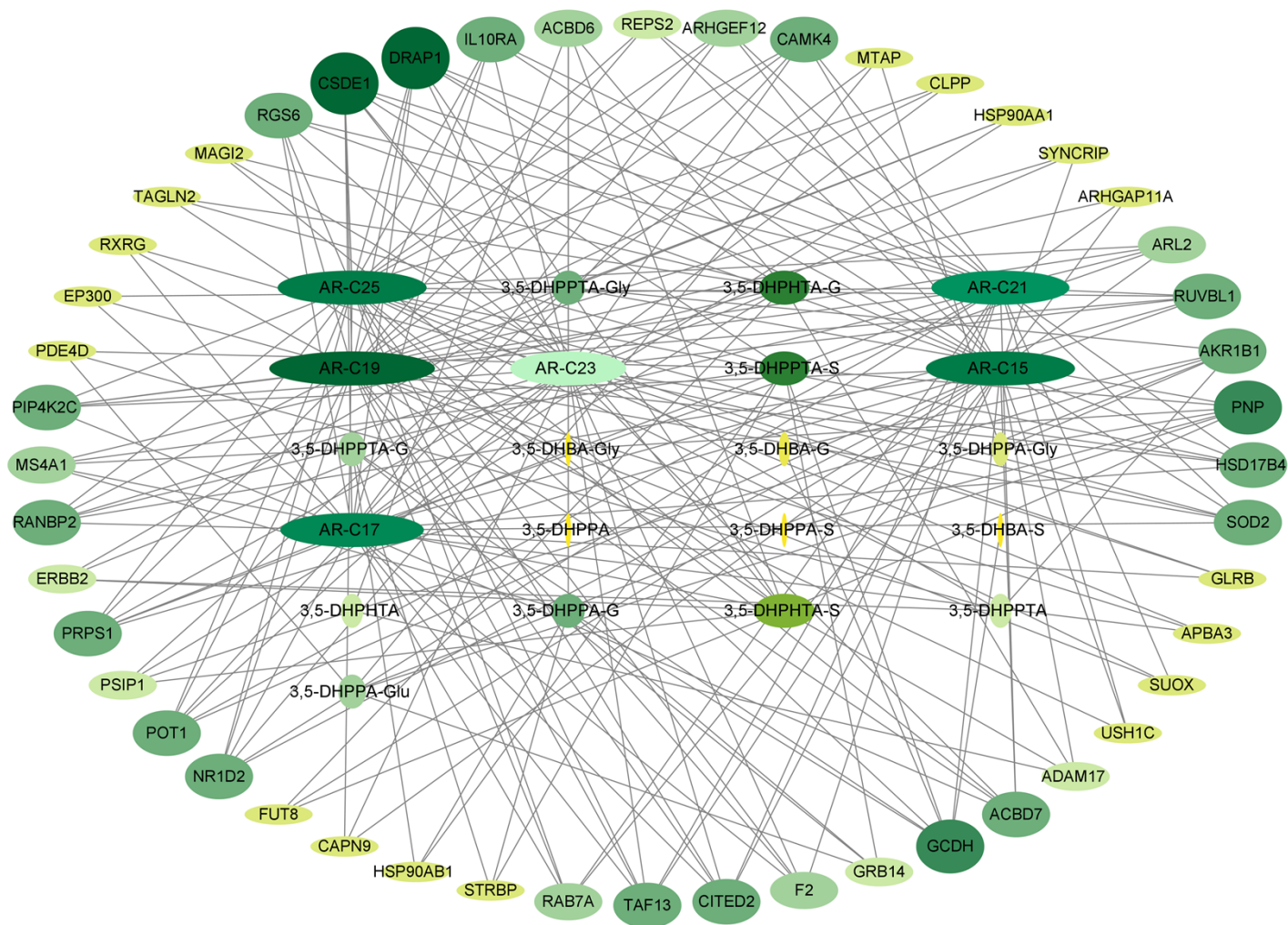
Disease target type	Intersection target <sup>a</sup>	Common target <sup>b</sup>	Top 20 target <sup>c</sup>
Cancer	161	AKR1C3 CYP11A1 CHEK1 IDE PDE4D RXRG KIF11 ITK MAPK14 NR1D2 GC AZGP1 HMOX1 CSDE1 CITED2 EP300 PPP2R1A RPA1	
Disorders of metabolism	143	HSD17B11 HSD17B4 LCK ALOX12 RGS6 SOD2 ADORA2A PTPN1 ARL2 ACVR1 RNASE2 RANBP2 MTAP PPARA ARSA NR4A2 HLA-B	HSP90AA1 MAPK14 MMP9 EP300 PPARG
Cardiovascular disease	135	ADAM17 AR MAOB AKR1B1 HEXA UNC45A CA2 LTF ESR2 HSP90AB1 MMUT ABL2 JAK2 FGF1 PPARG EHMT1 FBP1 CUL5 FUT8	HMOX1 ERBB2 PARP1 SOD2 PPARA CHEK1
Nervous system diseases	117	AMD1 NPC1 F2 ARHGEF12 NQO2 CA9 USH1C PRKG1 CAMK4 RET B2M MID1 PAX6 POLB PIK3CG KAT2B TAGLN2 PRPS1 PDE10A	JAK2 AR HSP90AB1 RPA1 RPA3 POLB B2M KAT2B ESR2
Immune system diseases	155	METAP2 BST1 MTRR GCDH HIF1AN BMPR1B REN PNP FOLH1 RUNX1T1 HSP90AA1 FOXM1 TNKS RPA3 RAB7A PIM1 PDE3B CUL1 MMP9 PARP1 CHKB ERBB2	

a: The intersections number of compound targets and different disease targets; b: The common targets of compound targets and different disease targets. c: The cytoHubba plug-in screens out the top 20 targets in the comment target.

**Table S3. The top 20 target information of compound targets and different disease targets**

Disease target type	Top 20 target <sup>a</sup>		The association of target and compound					
	Special target <sup>b</sup>	Common target <sup>c</sup>	Target	Compound	Target	Compound	Target	Compound
Cancer	KIF11			AR-C17		3,5-DHPHTA-G		
	RXRG	EP300	EP300	AR-C19	ERBB2	3,5-DHPHTA-S	CHEK1	3,5-DHPPTA-G
	RXRB	HSP90AA1		AR-C21		3,5-DHPPTA		
Disorders of metabolism		MAPK14				3,5-DHPPTA-G		
	KIF11	PPARA		AR-C17		3,5-DHPPTA-Gly		
	RXRG	AR	HSP90AA1	AR-C19	KAT2B		FOXM1	AR-C19
Cardiovascular disease	RXRB	HSD17B4		3,5-DHPPTA-Gly	CUL1	AR-C15		AR-C21
	SRM	ERBB2	MAPK14					
	RXRG	KAT2B	PPARG	AR-C19	HSP90AB1	3,5-DHPPTA-S	RPA1	3,5-DHPHTA-S
Nervous system diseases	RXRB	HSP90AB1	RXRB			3,5-DHPPA-G		
		LCK			LCK			
	CUL1	JAK2	PPARA		PPP2R1A	AR-C17	SRM	3,5-DHPPA-G
Immune system diseases	B2M	CITED2	B2M	AR-C15				
	UNC45A	CHEK1			KIF11			
		FOXM1	AR	AR-C25	JAK2	AR-C17	UNC45A	3,5-DHPHTA-S
	RPA1				3,5-DHPPTA-G		3,5-DHPHTA-G	
	CUL5	PPP2R1A		AR-C15 AR-C17		3,5-DHPPTA-Gly		
	RXRG	PPARG				AR-C15 AR-C17		
	RXRB		HSD17B4	AR-C19 AR-C21	CITED2	AR-C19 AR-C21	CUL5	3,5-DHPPTA-S
				AR-C23 AR-C25		AR-C23 AR-C25		

a: The intersections number of compound targets and different disease targets; b: The common targets of compound targets and different disease targets. c: The cytoHubba plug-in screens out the top 20 targets in the comment target.



**Fig. S1. The degree of association between different compounds and the target (degree $\geq$ 3) .**

**Table S4. Enrichment analysis results of biological processes**

Term ID	Description	P value	Count	Symbols
GO:0007167	enzyme linked receptor protein signaling pathway	1.35495E-10	14	PARP1 MAPK14 ERBB2 FUT8 GRB14 JAK2 LCK MMP9 PPARG ADAM17 CUL5 REPS2 MAGI2 CITED2
GO:0009725	response to hormone	1.95819E-10	15	PARP1 AR MAPK14 EP300 ESR2 GRB14 HMOX1 JAK2 PPARA PPARG RXRB RXRG KAT2B NR1D2 CITED2
GO:0048534	hematopoietic or lymphoid organ development	3.26448E-10	14	PARP1 B2M CAMK4 MS4A1 MAPK14 EP300 JAK2 LCK MMP9 POLB PPARG SOD2 ADAM17 CITED2
GO:0009755	hormone-mediated signaling pathway	6.15739E-10	8	AR ESR2 JAK2 PPARA PPARG RXRB RXRG NR1D2
GO:0002520	immune system development	7.1248E-10	14	PARP1 B2M CAMK4 MS4A1 MAPK14 EP300 JAK2 LCK MMP9 POLB PPARG SOD2 ADAM17 CITED2
GO:0002521	leukocyte differentiation	8.05703E-10	11	PARP1 B2M CAMK4 MS4A1 MAPK14 EP300 LCK MMP9 PPARG ADAM17 CITED2
GO:0030097	hemopoiesis	1.41399E-09	13	PARP1 B2M CAMK4 MS4A1 MAPK14 EP300 JAK2 LCK MMP9 PPARG SOD2 ADAM17 CITED2
GO:0030522	intracellular receptor signaling pathway	1.62028E-09	8	AR ESR2 JAK2 PPARA PPARG RXRB RXRG NR1D2
GO:0034654	nucleobase-containing compound biosynthetic process	1.35429E-08	13	PARP1 GCDH HSP90AA1 HSP90AB1 MTAP PNP POLB PPARG PRPS1 RPA1 TAF13 DRAP1 POT1
GO:0032870	cellular response to hormone stimulus	1.48016E-08	11	PARP1 AR ESR2 GRB14 JAK2 PPARA PPARG RXRB RXRG KAT2B NR1D2
GO:0090092	regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	1.50523E-08	9	PARP1 EP300 HSP90AB1 JAK2 PPARA PPARG ADAM17 MAGI2 CITED2
GO:0090100	positive regulation of transmembrane receptor protein serine/threonine kinase signaling pathway	1.55506E-08	7	PARP1 EP300 HSP90AB1 JAK2 PPARG ADAM17 CITED2
GO:0043401	steroid hormone mediated signaling pathway	2.22256E-08	6	AR ESR2 JAK2 PPARA RXRB RXRG
GO:0000723	telomere maintenance	3.58858E-08	6	PARP1 HSP90AA1 HSP90AB1 RPA1 RPA3 POT1
GO:0018130	heterocycle biosynthetic process	4.14893E-08	13	PARP1 GCDH HSP90AA1 HSP90AB1 MTAP PNP POLB PPARG PRPS1 RPA1 TAF13 DRAP1 POT1
GO:0019438	aromatic compound biosynthetic process	4.73333E-08	13	PARP1 GCDH HSP90AA1 HSP90AB1 MTAP PNP POLB PPARG PRPS1 RPA1 TAF13 DRAP1 POT1
GO:0097193	intrinsic apoptotic signaling pathway	6.32464E-08	7	EP300 HMOX1 JAK2 POLB SOD2 CUL5 CUL1
GO:0030099	myeloid cell differentiation	8.13044E-08	8	PARP1 CAMK4 MAPK14 EP300 JAK2 MMP9 PPARG CITED2
GO:0051099	positive regulation of binding	1.77869E-07	7	PARP1 B2M EP300 HSP90AB1 JAK2 MMP9 PPARG
GO:0007004	telomere maintenance via telomerase	2.09939E-07	4	HSP90AA1 HSP90AB1 RPA1 POT1

**Table S5. Enrichment analysis results of molecular functions**

Term	Description	P value	Count	Symbols
GO:0004879	nuclear receptor activity	3.97542E-11	7	AR ESR2 PPARA PPARG RXR RXRG NR1D2
GO:0098531	ligand-activated transcription factor activity	3.97542E-11	7	AR ESR2 PPARA PPARG RXR RXRG NR1D2
GO:0008134	transcription factor binding	1.58114E-07	11	PARP1 AR MAPK14 EP300 PPARA PPARG TAF13 RUVBL1 KAT2B CITED2 DRAP1
GO:0003707	steroid hormone receptor activity	3.03867E-07	4	ESR2 PPARA RXR RXRG
GO:0023026	MHC class II protein complex binding	4.99166E-07	4	B2M MS4A1 HSP90AA1 HSP90AB1
GO:0003684	damaged DNA binding	6.1919E-07	5	EP300 POLB RPA1 RPA3 POT1
GO:0019904	protein domain specific binding	6.66387E-07	11	AR CHEK1 FUT8 HSP90AA1 HSP90AB1 JAK2 LCK PPARA PPARG ADAM17 CITED2
GO:0051117	ATPase binding	1.57937E-06	5	AR LCK PDE4D CLPP RUVBL1
GO:0023023	MHC protein complex binding	1.64848E-06	4	B2M MS4A1 HSP90AA1 HSP90AB1
GO:0019901	protein kinase binding	4.2426E-06	10	PARP1 MAPK14 FOXM1 GRB14 HSP90AA1 HSP90AB1 JAK2 KIF11 LCK KAT2B
GO:0008022	protein C-terminus binding	4.49414E-06	6	EP300 ERBB2 JAK2 LCK PPARG TAF13
GO:0140296	general transcription initiation factor binding	7.36138E-06	4	AR TAF13 RUVBL1 DRAP1
GO:0019900	kinase binding	1.15993E-05	10	PARP1 MAPK14 FOXM1 GRB14 HSP90AA1 HSP90AB1 JAK2 KIF11 LCK KAT2B
GO:0140297	DNA-binding transcription factor binding	1.59435E-05	8	PARP1 AR MAPK14 EP300 PPARA PPARG KAT2B CITED2
GO:0061629	RNA polymerase II-specific DNA-binding transcription factor binding	1.92763E-05	7	PARP1 AR MAPK14 EP300 PPARA PPARG CITED2
GO:0000062	fatty-acyl-CoA binding	1.93473E-05	3	GCDH ACBD6 ACBD7
GO:1901567	fatty acid derivative binding	2.22114E-05	3	GCDH ACBD6 ACBD7
GO:0001091	RNA polymerase II general transcription initiation factor binding	2.5341E-05	3	AR RUVBL1 DRAP1
GO:0017025	TBP-class protein binding	2.87473E-05	3	TAF13 RUVBL1 DRAP1
GO:0120227	acyl-CoA binding	2.87473E-05	3	GCDH ACBD6 ACBD7

**Table S6. Enrichment analysis results of cellular components**

Term	Description	P value	Count	Symbols
GO:1904813	ficolin-1-rich granule lumen	1.20605E-05	5	MAPK14 HSP90AA1 HSP90AB1 MMP9 PNP
GO:0032993	protein-DNA complex	1.42061E-05	6	PARP1 EP300 RPA1 RPA3 RUVBL1 POT1
GO:0101002	ficolin-1-rich granule	8.1862E-05	5	MAPK14 HSP90AA1 HSP90AB1 MMP9 PNP
GO:0090734	site of DNA damage	8.68975E-05	4	PARP1 RPA1 RPA3 CUL5
GO:0005667	transcription regulator complex	0.000153693	7	PARP1 EP300 PPARG RXRB RXRG TAF13 DRAP1
GO:0090575	RNA polymerase II transcription regulator complex	0.000226238	5	PPARG RXRB RXRG TAF13 DRAP1
GO:0098687	chromosomal region	0.000241861	6	PARP1 CHEK1 PPP2R1A RPA1 KAT2B POT1
GO:0048471	perinuclear region of cytoplasm	0.000309778	8	ERBB2 HMOX1 HSP90AA1 HSP90AB1 PDE4D APBA3 MAGI2 UNC45A
GO:0140535	intracellular protein-containing complex	0.000378639	8	EP300 HSP90AB1 PPP2R1A TAF13 CUL5 CUL1 RUVBL1 KAT2B
GO:0005657	replication fork	0.000402882	3	CHEK1 RPA1 RPA3
GO:1990234	transferase complex	0.000577474	8	EP300 PRPS1 RANBP2 TAF13 CUL5 CUL1 RUVBL1 KAT2B
GO:0000781	chromosome, telomeric region	0.000676185	4	PARP1 CHEK1 RPA1 POT1
GO:0034774	secretory granule lumen	0.00104065	5	B2M MAPK14 HSP90AA1 HSP90AB1 PNP
GO:0060205	cytoplasmic vesicle lumen	0.001084375	5	B2M MAPK14 HSP90AA1 HSP90AB1 PNP
GO:0045121	membrane raft	0.001099249	5	MS4A1 HMOX1 JAK2 LCK ADAM17
GO:0031983	vesicle lumen	0.001114274	5	B2M MAPK14 HSP90AA1 HSP90AB1 PNP
GO:0098857	membrane microdomain	0.001114274	5	MS4A1 HMOX1 JAK2 LCK ADAM17
GO:0000123	histone acetyltransferase complex	0.001191805	3	EP300 RUVBL1 KAT2B
GO:0031248	protein acetyltransferase complex	0.001629853	3	EP300 RUVBL1 KAT2B
GO:1902493	acetyltransferase complex	0.001629853	3	EP300 RUVBL1 KAT2B

**Table S7. Enrichment analysis results of KEGG pathway.**

Term	Description	P value	Count	Symbols
hsa05200	Pathways in cancer	1.78705E-12	15	AR EP300 ERBB2 ESR2 F2 HMOX1 HSP90AA1 HSP90AB1 JAK2 MMP9 PPARG RXR RXRG CUL1 ARHGFE12
hsa05417	Lipid and atherosclerosis	2.28549E-09	9	MAPK14 HSP90AA1 HSP90AB1 JAK2 MMP9 PPARG RXR RXRG SOD2
hsa04659	Th17 cell differentiation	7.45563E-09	7	MAPK14 HSP90AA1 HSP90AB1 JAK2 LCK RXR RXRG
hsa05207	Chemical carcinogenesis-receptor activation	4.19423E-08	8	AR ESR2 HSP90AA1 HSP90AB1 JAK2 PPARA RXR RXRG
hsa05215	Prostate cancer	1.23346E-07	6	AR EP300 ERBB2 HSP90AA1 HSP90AB1 MMP9
hsa05152	Tuberculosis	4.64042E-06	6	MAPK14 EP300 IL10RA JAK2 RAB7A ARHGFE12
hsa05166	Human T-cell leukemia virus 1 infection	1.53427E-05	6	B2M CHEK1 EP300 LCK POLB KAT2B
hsa05418	Fluid shear stress and atherosclerosis	2.09501E-05	5	MAPK14 HMOX1 HSP90AA1 HSP90AB1 MMP9
hsa04920	Adipocytokine signaling pathway	2.27994E-05	4	JAK2 PPARA RXR RXRG
hsa03320	PPAR signaling pathway	3.17113E-05	4	PPARA PPARG RXR RXRG
hsa04657	IL-17 signaling pathway	7.68937E-05	4	MAPK14 HSP90AA1 HSP90AB1 MMP9
hsa01522	Endocrine resistance	9.04329E-05	4	MAPK14 ERBB2 ESR2 MMP9
hsa05216	Thyroid cancer	9.51431E-05	3	PPARG RXR RXRG
hsa05202	Transcriptional misregulation in cancer	9.74997E-05	5	FUT8 MMP9 PPARG RXR RXRG
hsa05170	Human immunodeficiency virus 1 infection	0.000155009	5	B2M CHEK1 MAPK14 CUL5 CUL1
hsa04151	PI3K-Akt signaling pathway	0.000202215	6	ERBB2 HSP90AA1 HSP90AB1 JAK2 PPP2R1A MAGI2
hsa04919	Thyroid hormone signaling pathway	0.000204088	4	EP300 RXR RXRG KAT2B
hsa04380	Osteoclast differentiation	0.000253087	4	CAMK4 MAPK14 LCK PPARG
hsa04114	Oocyte meiosis	0.000276475	4	AR MAPK14 PPP2R1A CUL1
hsa04915	Estrogen signaling pathway	0.000337031	4	ESR2 HSP90AA1 HSP90AB1 MMP9



**Table S8. List of ARs-related targets reported in the literature.**

Compound	Testing object	Related targets	Result	References
ARs	human adrenocortical cell line H295R	CYP17A1, CYP21A2, HSD3B2, CYP19A1, CYP11A1	The suppressed synthesis of testosterone and estradiol by ARs suggest a novel mechanism for ARs in the chemoprevention of prostate and breast cancer.	[46]
ARs	RAW264.7 macrophage cells	IL-1 $\beta$ , IL-6, TNF- $\alpha$ , NF- $\kappa$ B(NFKB1), JNK(MAPK8), IKBA(NFKBIA)	ARs treatment notably decreased NF- $\kappa$ B p65 nuclear translocation and inhibitor $\kappa$ B (I $\kappa$ B $\alpha$ ) kinase and JNK phosphorylation	[52]
ARs	Human ColonCancer Cells	p53(TP53), PUMA(BBC3), p21(TCEAL1), Mdm2	AR C15 and AR C17 can specifically activate the mitochondrial pathway of apoptosis and cause cell-cycle arrest and that inhibition of p53 greatly reduces the activation of this pathway.	[49]
ARs	human retinal pigment epithelium cells (ARPE-19)	Nrf2(GABPA), HO-1(HMOX1)	ARs could protect ARPE-19 cells from oxidative stress induced cell damage possibly through Akt dependent Nrf2/HO-1 signaling	[19]
ARs	HepG2 Cells	LC3-II (ATG16L1), RhoA, MMP-7, PI3K, Akt mTOR	ARs can activate autophagy and suppresses the biological behaviors of HepG2 cells by inhibiting the activation of MMP-7, Rho/Rho-associated protein kinase, and activation of the phosphatidylinositol 3-kinase/Akt signaling pathway.	[47]
AR-C17	Human breast cancer MDA-MB-231 cells	Bax, Bcl-2(BAD), LC3-II(ATG16L1)	AR-C17 could inhibit proliferation of human triple-negative breast cancer MDA-MB-231 cells through increasing cell apoptosis and autophagy .	[50]
ARs	Mouse hippocampal HT22 cells	Nrf2(GABPA), HO-1(HMOX1), NQO1, GCLC, GCLM	Potential neuroprotection of wheat alkylresorcinols in hippocampal neurons via Nrf2/ARE pathway	[21]
AR-C17	human MCF-7 breast cancer cells	Atg7, Beclin-1(BECN1), LC3-II, SQSTM1, p62, PI3K, Akt, mTOR	AR-C17 exerted anti-cancer activity through modulating PI3K/Akt/mTOR signaling pathway which was evidenced by decreasing the protein expression of PI3K, p-Akt and p-mTOR.	[48]
AR-C17	Rat pheochromocytoma (PC-12) cells	SIRT3, FOXO3a	5-Heptadecylresorcinol attenuates oxidative damage and mitochondria-mediated apoptosis through activation of the SIRT3/FOXO3a signaling pathway in neurocytes	[22]
ARs	3T3-L1 adipocytes cell	p-Akt, GLUT4(SLC2A4)	ARs ameliorated adipocyte insulin resistance by specifically activating the p-Akt/GLUT4signaling pathway.	[51]
ARs	Male mice	Srebf2, Hmgcs1	Alkylresorcinols significantly increased fecal cholesterol excretion by 39.6% and reduced blood cholesterol concentrations by 30.4%, while upregulating the expression of hepatic cholesterol synthetic genes such as Srebf2 and Hmgcs1.	[7]
AR-C17	APP/PS1 transgenic mice	ADAM10, PSD-95(DLG4), NLRP3, IL1B, SIRT3, SOD2	AR-C17 can be applied as a potential functional food ingredient to ameliorate cognitive impairments and prevent Alzheimer's disease	[23]
AR-C17	C57 BL/6J mice	Sirt3, LC3B-II/I, Beclin1, Atg5, PINK1, Parkin	Sirt3-mediated autophagy plays an essential role in alleviating adipocyte mitochondrial dysfunction by AR-C17	[53]
ARs	Drosophila melanogaster	SIRT1	Alkylresorcinols activate SIRT1 and delay ageing in <i>Drosophila melanogaster</i>	[45]

