Supplementary Tables

Table S1. TaqMan gene expression assays used for the quantitative real time PCR analysis.

GENE	DESCRIPTION	Gene Expression Assay reference
Pparg	Peroxisome proliferator activated receptor gamma	Mm00440940_m1*
Cebpa	CCAAT/enhancer binding protein (C/EBP), alpha	Mm00514283_s1*
Fasn	Fatty acid synthase	Mm00662319_m1*
Scd1	Stearoyl-Coenzyme A desaturase 1	Mm00772290_m1*
Lpl	Lipoprotein lipase	Mm00434764_m1*
Tbp	TATA box binding protein. Housekeeping gene control	Mm00446973_m1*
Adipoq	Adiponectin	Mm.PT.58.9719546 **
Plin1	Perilipin 1	Mm.PT.58.10000337 **
Fabp4	Fatty acid binding protein 4, adipocyte	Mm.PT.58.43866459**

* TaqMan® Gene Expression Assays (Thermo Fisher Scientific).

** PrimeTime qPCR Probe Assays (Integrated DNA Technologies, Inc).

Table S2. Quantification of the toxicity induced by phenolic compounds in 3T3-L1 preadipocytes. Results are expressed as the mean cell viability in percentage (±SD) relative to DMSO-treated control cells. Shadowed are the concentrations at which a significant decrease in cell viability is observed.

	1 µM	**10 µM**	**50 µM**	**100 µM**	**250 µM**
Hesperidin	102.89 ± 1.59	95.70 ± 4.59	92.55 ± 9.84	102.09 ± 1.95	54.02 ± 9.34 ***
Naringin	89.00 ± 17.40	59.58 ± 4.65 **	55.19 ± 11.73 **	64.13 ± 10.05 **	39.25 ± 25.57 ***
Apigenin	104.39 ± 5.57	104.32 ± 2.37	102.66 ± 1.84	86.67 ± 7.54 **	33.28 ± 2.74 ***
Luteolin	78.41 ± 19.61 *	68.62 ± 16.32 **	60.70 ± 15.04 **	32.60 ± 8.57 ***	24.77 ± 10.02 ***
Myricetin	111.67 ± 3.91	104.18 ± 5.61	98.38 ± 13.19	54.92 ± 1.46 ***	59.92 ± 10.64 ***
Kaempferol	75.64 ± 4.38 *	28.64 ± 5.63 ***	48.69 ± 11.31 ***	64.91 ± 20.57 **	68.38 ± 1.98 **
Quercetin	111.33 ± 0.43	112.99 ± 1.07	118.76 ± 3.92 *	122.36 ± 2.42 *	116.21 ± 15.59
Resveratrol	92.64 ± 10.53	106.55 ± 6.08	92.12 ± 5.42	64.16 ± 6.16 ***	47.36 ± 9.64 ***
Curcumin	93.07 ± 2.39	94.87 ± 1.93	47.82 ± 19.41 #	36.35 ± 3.99 *	37.39 ± 0.47 **
p-Coumaric acid	99.49 ± 1.18	100.27 ± 2.37	99.61 ± 4.18	101.37 ± 2.49	101.02 ± 5.48
Ellagic acid	102.16 ± 4.99	103.65 ± 1.27	96.00 ± 0.1	99.25 ± 2.61	107.88 ± 2.16
Ferulic acid	103.24 ± 5.63	100.27 ± 3.52	106.83 ± 4.18	101.89 ± 1.57	97.66 ± 3.82
Gallic acid	102.29 ± 4.59	106.02 ± 4.08	99.82 ± 1.91	101.35 ± 2.49	104.09 ± 3.74
Vanillic acid	95.37 ± 2.71	99.25 ± 4.52	107.18 ± 4.61 *	97.88 ± 7.36	93.55 ± 1.23

Table S3. Cohen's D effect size of the anti-adipogenic activity (quantified by Nile Red) for each phenolic compound during S1, S2 and S3 stages.

	NR S1	**NR S2**	**NR S3**
3T3-L1 preadipocytes	12.52	11.57	17.02
3T3-L1 DMSO control	0.00	0.00	0.00
Hesperidin	-0.20	1.00	0.48
Myricetin	1.95	0.32	1.87
Quercetin	5.32	5.27	4.34
Apigenin	2.44	0.38	2.57
Resveratrol	3.29	4.34	1.76
Curcumin	0.78	0.00	1.05
***p*-Coumaric Acid**	1.48	0.57	1.53
Ellagic acid	2.34	2.10	-0.50
Ferulic acid	2.14	0.76	-0.21
Galic acid	3.16	0.00	0.66
Vanillic acid	4.35	1.02	-0.08

Table S4. Interactions of each phenolic compound with the specific amino acids of the PPARγ LBD, predicted by DockingServer (H for hydrogen, C for carbon and O for oxygen). Troglitazone and aglycones from naringin and hesperidin (naringenin and hesperetin, respectively) are shown shadowed for comparative purposes.

	Hydrogen bonds	Polar	Cation-pi	Hydrophobic	pi-pi	Other
Troglitazone	O-LYS265 (N)[3.38]			C-HIS266 (CD2) [3.51] C-LEU228 (CD2) [3.74] C-LEU333 (CD1) [3.89] C-PHE287 (CD1) [3.75]		O-LEU228 (CB,CD2) [3.39] N-LEU228 (CD2) [3.43] H-LEU228 (CD2) [2.89] C-HIS266 (NE2) [3.49] O-PHE287 (CD1) [3.89] C-ARG288 (CG) [3.78] C-GLU291 (CD,OE1,OE2) [2.85] S-GLU291 (OE2) [3.62] H-LEU333 (CD1) [3.84] O-LEU333 (CD1) [3.76]
Hesperetin		O-GLU291 (OE1) [3.62] H-GLU291 (OE1, OE2) [3.29]	H-PHE264 (CB, CD1, CG) [3.49] H-HIS266 (CD2, CG) [2.87]	C-HIS266 (CD2) [3.64] C-LEU333 (CD1) [3.60] C-ILE341 (CB,CG2) [3.56]		O-PHE264 (CB, CD1, CG) [3.65] O-HIS266 (CD2) [3.35] H-GLU291 (CG) [3.67] O-LEU330 (CD1) [3.78] O-LEU333 (CD1) [3.39] H-LEU333 (CD1) [3.47] O-VAL339 (CG2) [3.67] H-VAL339 (CG2) [2.95] O-ILE341 (CB,CG2) [3.60]
Luteolin	O-ARG280 (*CB, NH2*) [3.42] O-CYS285 (*SG*) [3.29]	O-GLU259 (OE2) [3.25] H-GLU259 (OE2) [2.29] H-ARG280 (CZ, NE, NH2) [3.36] O-ARG288 (CB) [3.53]		C-LEU255 (CD1) [3.80] C-CYS285 (SG) [3.82] C-ILE341 (CG2) [3.86]	C-PHE264 (CB, CD2, CG) [3.31] C-HIS266 (CB, CD2, CG) [3.06]	H-LEU255 (CD1, CD2, CG) [2.94] O-LEU255 (CD1, CD2) [3.37] H -GLU259 (CD) [3.33] C-GLU259 (OE2) [3.67] O-HIS266 (CB) [3.88] O-ILE281 (CG1) [3.60] H-CYS285 (SG) [2.57] C-ARG288 (CB) [3.87] O-ILE341 (CG2) [3.50]

Apigenin	O-TYR327 (CE1,CZ,OH) [3.06]	O-ARG288 (CB, NH2) [3.56] O-GLU291 (CE1) [3.90] H-GLU291 (CE1) [3.58] H-TYR327 (OH) [2.22] O-HIS449 (NE2) [3.44] H-HIS449 (NE2) [3.26]	H-TYR327 (CE1, CZ) [2.73] H- HIS449 (CD2) [3.42]	C-CYS285 (CB, SG) [3.51] C-ILE326 (CG2) [3.32] C-LEU330 (CG) [3.90] C-LEU333 (CD1) [3.83] C-MET364 (SD) [3.69]	C-TYR327 (CE1) [3.40] C- PHE363 (CZ) [3.83]	C-ARG288 (CB, NE, NH2) [3.23] H-GLU291 (CB) [3.29] H-ALA292 (CB) [3.82] O-LEU333 (CD1) [3.33] H-LEU333 (CD1) [3.48] O-VAL339 (CG2) [3.78] O-PHE363 (CE1,CZ) [3.37] O-HIS449 (CD2) [3.66]

Table S4 (cont). Interactions of each phenolic compound with the specific amino acids of the PPARγ LBD, predicted by DockingServer (H for hydrogen, C for carbon and O for oxygen). Troglitazone and aglycones from naringin and hesperidin (naringenin and hesperetin, respectively) are shown shadowed for comparative purposes.

	Hydrogen bonds	**Polar**	**Cation-pi**	**Hydrophobic**	**pi-pi**	**Other**
Naringenin		H-ARG280 (CB) [3.88] O-GLU291 (OE1,OE2) [3.51] H-GLU291 (OE1,OE2) [2.95]		C-ILE341 (CB,CG2) [3.52]		H-ILE281 (CG1) [3.89] C-ARG288 (CG) [3.78] H-GLU291 (CD) [3.72] O-LEU333 (CD1) [3.76] H-LEU333 (CD1) [3.47]
Ellagic acid		O-ARG288 (CB,CG) [3.58] O-GLU291 (CE1,CE2) [3.17] H-GLU291 (CE1,CE2) [2.26]				O-PHE264 (CD1) [3.77] H-ILE281 (CB, CG1, CG2) [3.39] O-ILE281 (CG2) [3.39] O-CYS285 (SG) [3.80] H-CYS285 (SG) [3.04] C-ARG288 (CB,CG) [3.43] O-GLU291 (CD) [3.78] H-GLU291 (CD) [2.95] O-MET348 (CE) [3.63]

Kaempferol	O-CYS285 (SG) [3.62]	O-ARG288 (CB, NH2) [3.49] H-SER289 (OG) [3.68] H-GLU295 (CE1,CE2) [1.93] O-GLU295 (OE2) [2.89]	C-CYS285 (CB,SG) [3.73] C-LEU333 (CD1) [3.68]	O-PRO227 (CB, CD, CG) [3.25] H-PRO227 (CB, CD, CG) [2.93] H-CYS285 (CB) [3.72] O-ARG288 (CB, NH2) [3.26] O-SER289 (CB) [3.40] H-SER289 (CB) [2.96] O-GLU295 (CD) [3.79] H-GLU295 (CD) [2.87] C-GLU295 (OE2) [3.61] O-LEU333 (CD1) [3.68] H-LEU333 (CD1) [3.86] O-ILE341 (CD1,CG1) [3.39] H-ILE341 (CD1,CG1) [3.27]

Table S4 (cont). Interactions of each phenolic compound with the specific amino acids of the PPARγ LBD, predicted by DockingServer (H for hydrogen, C for carbon and O for oxygen).

	Hydrogen bonds	Polar	Cation-pi	Hydrophobic	pi-pi	Other
Quercetin	O-ARG280 (NE,NH2) [3.40]	O-GLU259 (OE2) [3.56] H-GLU259 (OE2) [2.93] H-ARG280 (NE,NH2) [3.68]	H-PHE264 (CB) [3.61] H-HIS266 (CB, CD2, CG) [3.07]	C-ILE281 (CG1) [3.67] C-CYS285 (SG) [3.27] C-ILE341 (CB,CG2) [3.21] C-MET348 (CE,SD) [3.19]	C-PHE264 (CD2) [3.66] C-HIS266 (CB) [3.78]	O-GLU259 (CD) [3.89] H-GLU259 (CD) [3.43] O-PHE264 (CB,CD2,CG) [3.21] O-HIS266 (CB) [3.61] C-ARG280 (CB) [3.64] O-CYS285 (SG) [3.43] H-CYS285 (SG) [3.19] H-ILE341 (CB) [3.61] O-MET348 (CE) [3.32] H-LEU353 (CD1,CD2) [3.75]
Curcumin		O-ARG288 (CB, NH2) [3.40] O-GLU343 (OE1) [3.69]		C-LEU333 (CD1) [3.51]		O-LEU228 (CB) [3.41] O-CYS285 (SG) [3.81] H-CYS285 (SG) [3.39] C-ARG288 (CB,NE,NH2) [3.44] C-GLU291 (CB,CD,CG,OE2) [3.23] C-GLN294 (CB) [3.84] C-GLU295 (CD,CG,OE1,OE2) [3.07] C-GLU343 (OE1) [3.61]
Resveratrol	O-ARG280 (NE,NH2) [3.30]	O-GLU259 (OE2) [3.04] H-GLU259 (OE1,OE2) [2.10] O-ARG288 (CB) [3.48] H-ARG288 (CB) [3.05]	H-HIS266 (CB) [3.70]	C-LEU255 (CD1) [3.54] C-ILE281 (CG1) [3.81] C-CYS285 (SG) [3.66] C-ILE341 (CG2) [3.49] C-MET348 (CE) [3.09]	C-PHE264 (CD2) [3.52] C-HIS266 (CB) [3.48]	C-GLU259 (OE2) [3.90] H-GLU259 (CD) [3.11] O- HIS266 (CB) [3.54] C-ARG280 (CB,NE) [3.51] O-CYS285 (SG) [3.47] H-CYS285 (SG) [2.66]

					O-ILE341 (CG2) [3.60] O-MET348 (CE,SD) [3.63]
p-Coumaric acid	O-GLU259 (OE2) [3.00] H-GLU259 (OE2) [2.18] O-ARG280 (NH2) [3.46]		C-LEU255 (CD1,CD2) [3.50] C-PHE264 (CB,CD2,CG) [3.48] C-HIS266 (CB) [3.73] C-ILE281 (CG1) [3.75] C-MET348 (CE) [3.49]		O-LEU255 (CD1) [3.79] H-LEU255 (CD1) [3.77] H-GLU259 (CD,CG) [3.18] H-ILE281 (CB,CG2) [3.24] O-CYS285 (SG) [3.88] H-CYS285 (SG) [3.84] O-CYS285 (SG) [3.47] O-ILE341 (CG2) [3.69] O-MET348 (CE) [3.71]

Table S4 (cont). Interactions of each phenolic compound with the specific amino acids of the PPARγ LBD, predicted by DockingServer (H for hydrogen, C for carbon and O for oxygen).

	Hydrogen bonds	**Polar**	**Cation-pi**	**Hydrophobic**	**pi-pi**	**Other**
Vanillic acid		O-GLU418 (OE2) [3.07] H-GLU418 (OE1,OE2) [2.11]		C-LEU421 (CB) [3.56] C-PHE432 (CB) [3.20]		O-GLU418 (CD, CG) [3.58] O-LEU421 (CB) [3.81] O-LYS422 (CE) [3.63] H-SER428 (CB) [3.75] O-LEU431 (CB) [3.21] H-LEU431 (CB) [3.45] H-GLU418 (CD) [3.10] C-GLU418 (OE2) [3.76]
Myricetin	O-LYS263 (CD,CE,CG,NZ) [3.07]	H-LYS263 (NZ) [2.64] O-GLN345 (NE2) [3.40] H-GLN345 (NE2) [3.19]		C-MET348 (CE) [3.60]	C-PHE264 (CD1,CE1) [3.46]	O-LEU255 (CD1) [3.82] H-LEU255 (CD1,CD2) [2.88] H-LYS263 (CD,CG) [3.49] O-PHE264 (CD1,CE1,CG) [3.48]

					H-CYS285 (SG) [3.67] C-SER342 (CB) [3.19] O-SER342 (CB) [3.29] H-SER342 (CB) [2.73] O-MET348 (CE) [3.68]
Gallic acid		O-GLU418 (OE2) [3.49] H-GLU418 (OE2) [2.83] O-GLN430 (NE2) [3.16]	H-PHE432 (CD2) [3.79]	C-PHE432 (CB) [3.52]	O-GLU418 (CG) [3.63] H-GLU418 (CD,CG) [3.72] O-LEU421 (CB) [3.83] H-SER428 (CB) [3.58] O-LEU431 (CB) [3.23] H-LEU431 (CB) [3.28] O-PHE432 (CB) [3.44]
Ferullic acid	O-GLN286 (CD,NE2,OE1) [3.17] O-TYR327 (CE1,CZ,OH) [3.05]	H-TYR327 (OH) [2.14] O-HIS449 (NE2) [3.60] H-HIS449 (NE2) [3.26]	H-TYR327 (CE1,CZ) [2.99] H-HIS449 (CD2,CE1) [3.68]	C-CYS285 (CB,SG) [3.69] C-ILE326 (CG2) [3.71] C-LEU330 (CB,CG) [3.56]	C-SER289 (CB) [3.84] O-LEU330 (CD2,CG) [3.80] H-LEU330 (CD2) [3.90] H-LEU330 (CD1) [3.12] O-PHE363 (CZ) [3.78]

Table S4 (cont). Interactions of each phenolic compound with the specific amino acids of the PPARγ LBD, predicted by DockingServer (H for hydrogen, C for carbon and O for oxygen).

	Hydrogen bonds	Polar	Cation-pi	Hydrophobic	pi-pi	Other
Naringin	O-SER355 (OG) [2.96]	O-GLU272 (OE1) [3.65] H-GLU272 (OE1) [3.68] O-GLU276 (OE1) [3.49] H-GLU276 (OE1) [2.70] H-SER355 (OG) [2.02] O-ARG357 (NE) [3.84] H-ARG357 (CZ,NE,NH2) [3.24]	H-PHE352 (CD1,CE1) [3.20]	C-MET252 (CG) [3.40]		H-ASP251 (CB) [3.36] O-ASP251 (CB) [3.77] C-GLU272 (OE1,OE2) [3.43] H-GLU276 (CD) [3.65] C-GLU276 (OE1) [3.17] O-PHE352 (CD1,CE1) [3.19] H-SER355 (CB) [3.21] C-SER355 (OG) [3.13] C-ARG357 (CB, CG) [3.60] C-LYS358 (CD,CE,CG) [3.62] O-LYS358 (CD) [3.38]
Hesperidin	O-ASN412 (CB,ND2) [3.43]	ARG357 (*CZ, NE, NH2*)		C-LEU309 (CD2) [3.88] C-PRO405 (CB) [3.18] C-ILE409 (CD1,CG1) [3.18]		O-ASN308 (CB) [3.34] H-ASN308 (CB) [3.24] O-LEU309 (CD2) [3.54] O-PRO405 (CB) [3.88] C-ASP408 (CB) [3.68] H-ASN412 (CB,CG) [3.37] C-ASN412 (ND2) [3.79]

Supplementary Figures

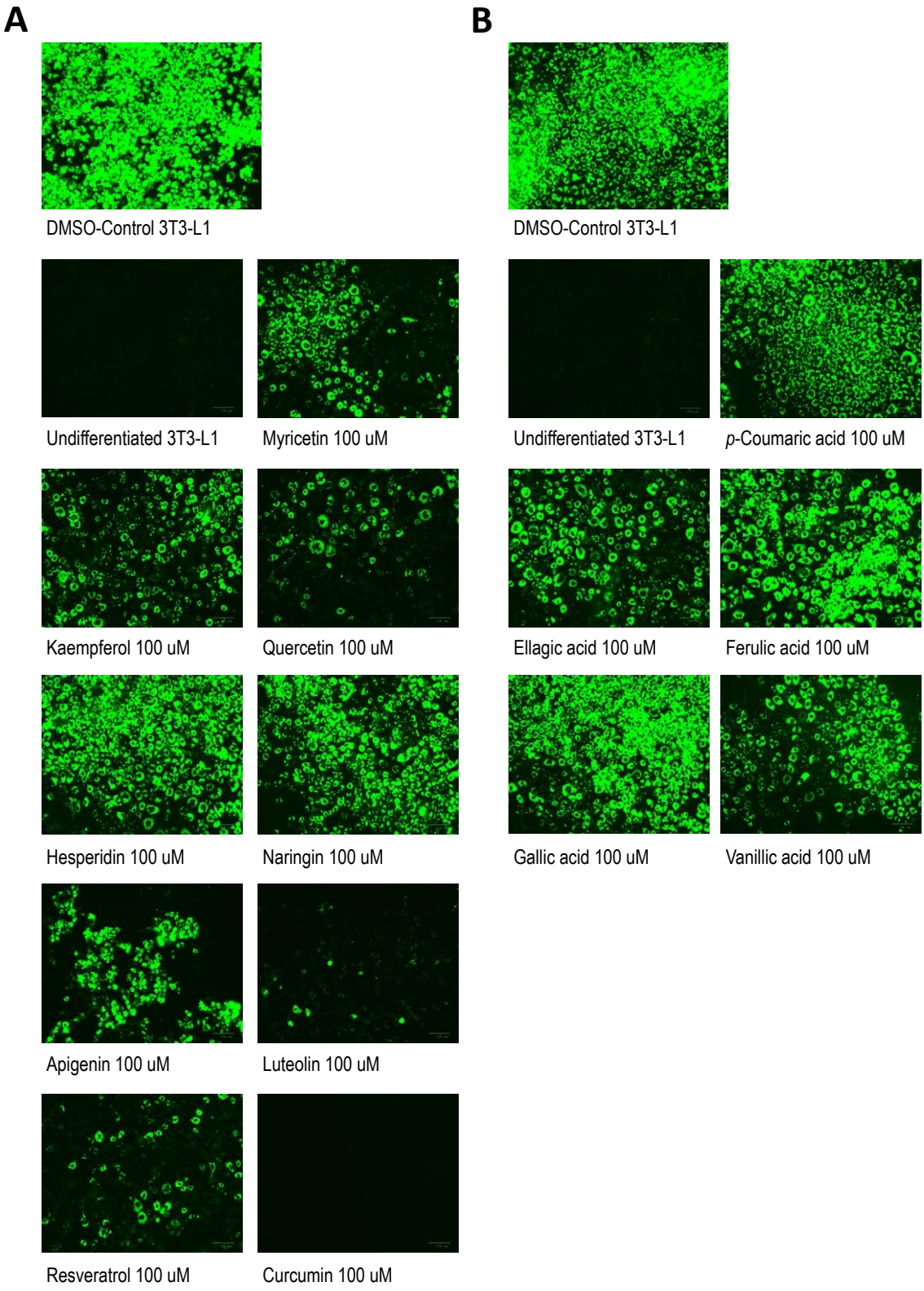

Figure S1. Images obtained from observation under a fluorescence microscope of the effect of the different treatments in 3T3-L1 after Nile Red staining. The figure corresponds to the effect of the treatments at the dose of 100 uM and the S1 test. A) Triglyceride content of 3T3-L1 adipocytes after

treatment with polyphenols. B) Triglyceride content of 3T3-L1 adipocytes after treatment with phenolic acids.

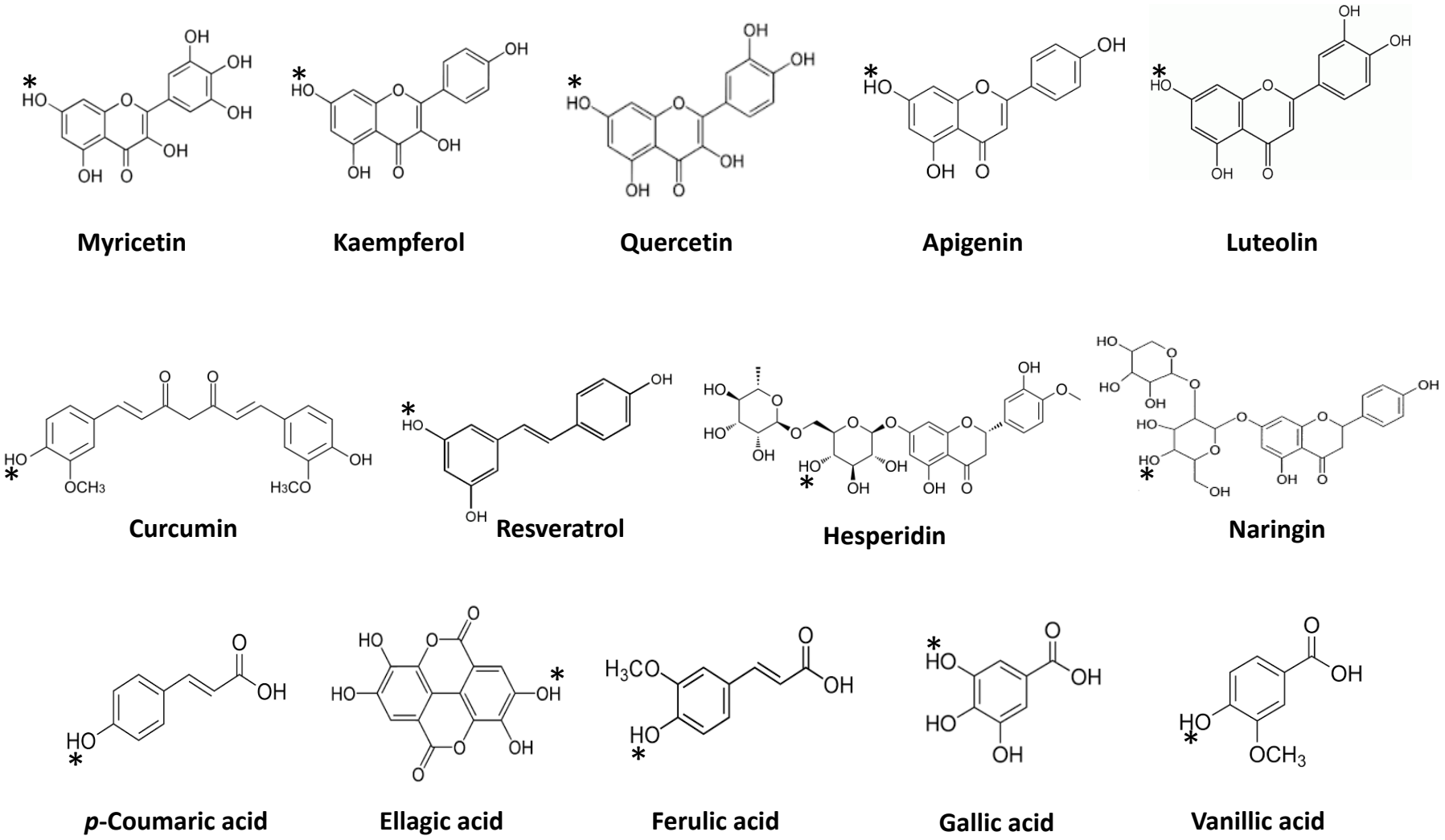

Figure S2. Structures of the phenolic compounds evaluated in this study. The hydrogens indicated with the symbol * are involved in the interactions with the

LBD of PPARγ.