SUPPLEMENTARY TABLES

Resveratrol and Clinical Trials: The Crossroad from *In Vitro* Studies to Human Evidence

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IN VITRO ASSAYS:

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Supplementary Table 2. Neuroprotective effects of resveratrol in *in vitro* models.

Supplementary Table 3. Effects of resveratrol on human cells involved in the vascular milieu.

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ANIMAL MODEL ASSAYS:

Supplementary Table 5. Cancer chemopreventive effects of resveratrol and related mechanisms in animal models.

Supplementary Table 6. Effects of exposure to resveratrol on animal models of cardiovascular disease.

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REGISTERED HUMAN TRIALS

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Supplementary Table 1. Effects of resveratrol and related mechanisms on human cancer cells.

Cancer Model	Human Cell Line	Treatment	Effects and Mechanisms	Reference
Colon	HT-29	100-150 μM / 24-72h	↑apoptosis; G_0/G_1 cell cycle arrest; ↓PPP; ↓cyclin-D1	[1]
		100-150 μM / 24-72h	↑apoptosis; G_0/G_1 cell cycle arrest; ↓Wnt pathway; ↑p27	[2]
		IC_{50}=78.9 μM / 24h	↓cell proliferation	[3]
		IC_{50}=276 μM / 24h	↑apoptosis; ↑caspase 3	[4]
		50-400 μM / 24h	↑apoptosis; ↑AMPK	[5]
		50-100 μM / 24-48h	↓cell proliferation; G_2 cell cycle arrest; ↓ cdk7, p34cdc2 kinase	
	RK2	2.5-40 μM / 48h	↓cell proliferation; ↓Wnt pathway	[6]
	Caco-2	10-50 μM / 24-48h	↓cell proliferation; S and G_2/M cell cycle arrest; ↓ODC activity	[7]
	Caco-2,	50-200 μM / 24-48h	↓cell proliferation; S and G_2/M cell cycle arrest; ↓cyclin-D1, cdk4; ↑cyclin-E,-A; ↑apoptosis; ↑caspase 3	[8]
	HCT-116	30-200 μM / 24-72h	↓cell proliferation; ↑p38 ↑sirt1; ↑PPARγ coactivator PGC-1α	[9]
	HCT-116	10-100 μM / 24-72h	↑apoptosis; ↑caspase 2, 8	[10]
	SW480, SW620, HT-29	$IC_{50} \approx$ 30 μM / 48h	↑apoptosis; ↑ERK, JNK, Akt	[11]
	DLD1	100 μM / 48h	↑apoptosis; ↑caspase 3	[12]
Prostate	LNCaP, PC-3	1-150 μM / 12-72h	↓cell proliferation; ↑apoptosis; ↑caspase 3, 9; change in the ratio of Bax/Bcl-2; G_0/G_1 cell cycle arrest; ↓cyclin-B, cdk1, cyclin-B/cdk1 kinase activity;	[13]

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			↓cyclin-D1, -E, cdk 4, cyclin-D1/cdk4 kinase activity; ↑p53, p21, and p27 (only LNCaP cells)	
	LNCaP	1-50 μM / 24h	↓cell proliferation; ↑apoptosis; ↑caspase 3, 9; change in the ratio of Bax/Bcl-2; G_0/G_1 cell cycle arrest; ↓PI3K, p-Akt, Bcl-2; ↑Bax, Bak, Bid, and Bad	[14]
	LNCaP, DU145	1-100 μM / 24-72h	↑apoptosis; ↓MTA1/NuRD; ↑p53, p21, Bax	[15]
	LNCaP	1- 25 μM / 24-72h	G_0/G_1 cell cycle arrest; ↑cdk inhibitor 1A and B	[16]
	PC-3 cells	1-50 μM / 24h	↑XRT-induced apoptosis and proliferation inhibition; ↑p15, p21, p53; ↓cyclin-B, -D and cdk2; ↑p-H2A.X	[17]
	PC3, CWR22rv1	2.5-10 μM / 7-10 days	↑IR-induced apoptosis and proliferation inhibition; G_0/G_1 and S cell cycle arrest; ↑p27, p21, p53; ↓caspase 3; ↓p-Akt	[18]
	LNCaP	1-50 μM / 24-72h 20 μM / 1-48h	↑p53R2, p21; ↓PSA expression ↑apoptosis; ↓p-PI3K, p-Akt and mTOR; ↓p-FOXO; ↑Bim, TRAIL, p27/KIP1, DR4 and DR5; ↓cyclin-D1	[19] [20]
	LNCaP, DU-145, CWR22rv1	1–50 μM / 1-5 days	↓cell proliferation; ↓PTEN; ↑AR; ↓EGFR; ↓PI3K/Akt	[21]
Liver	HepG2	10^{-6}-1 μM / 6 days 50, 100 μM / 24h 1-100 μM / 24-72h 10-300 μM / 24h 2.5-320 μM / 1-48h	↓cell proliferation; G_0/G_1 and G_2/M cell cycle arrest; ↑apoptosis; ↓ROS; ↑iNOS ↓cell invasion; ↓MMP-9, NF-κB ↓cell proliferation; ↑NADPH; ↑iNOS ↓cell proliferation; G_0/G_1 cell cycle arrest; ↓Cyclin-D1; ↓p-p38, Akt, Pak1; ↑p-ERK ↓cell proliferation; G_0/G_1 and S cell cycle arrest; ↑apoptosis	[22] [23] [24] [25] [26]
	Huh-7	IC_{50}=22.4 μM	↓cell proliferation; G_0/G_1 cell cycle arrest; ↓cyclin -A, -E and cdk 2; ↑apoptosis; ↑p53, p21/WAF1; ↓p-ERK, p-p38; ↑autophagy-related Atg5, Atg7, Atg9, and Atg12 proteins	[27]
	SK-HEP-1	50-250 μM / 24-48h	↓cell proliferation; ↑apoptosis/caspase 3; ↓ROS	[28]
	HepG2, Hep3B	1−100 μM / 24-48h 10, 20 μM / 24-48h	↓cell proliferation; ↑ TIMP-1, -2; ↓MMP-2, -9 ↓cell proliferation; G_0/G_1 cell cycle arrest; ↑apoptosis; ↑p21, Bax, p53	[29] [30]
Breast	MCF-7, MDA-MB-231	10-200 μM / 12-60h 1-100 μM / 48h 1-50 μM / 48h 1-50 μM / 72h IC_{50}=120, 370 μM / 24h, respectively	↓cell proliferation; G_0/G_1 cell (MDA-MB-231) and S (MCF-7) cycle arrest; ↑apoptosis (MCF-7); ↑p21, p27, p53 ↓cell proliferation; ↑apoptosis; ↑Bax, p21 ↓cell proliferation; ↓PI3K/Akt pathway; ↓mTOR/p70S6K pathway; ↓rapamycin-induced Akt activation ↓colonies formation; G_0/G_1 cell cycle arrest (MDA-MB-231); S and G2/M cell cycle arrest (in MCF-7); ↓cyclin-B,-D1; ↓Rb, E2F; ↑p53, p21; ↑p-ERK, p-p38 ↑melphalan-induced cytotoxic and apoptosis; ↑p53, caspase 7, 9, p-Chk2; ↓procaspase 8; S cell cycle arrest; ↓cyclin-A, p-CDK2	[31] [32] [33] [34] [35]
	MCF-7	10, 50 μM / 2-6 days 1-150 μM / 36h 5- 40 μM / 24-72h 5-20 μM / 90 min 16-64 μM / 24-72h 25 μM / 24h 50-100 μM / 24-48h	↓cell proliferation; ↓TNFα-induced NF-κB activation ↑apoptosis; ↓Bcl-2; ↑ROS, NO; ↓NF-κB; ↓MMP-9; ↓activity and cell migration ↓cell proliferation; S cell cycle arrest; ↑apoptosis; ↓telomerase activity ↑accumulation of DNA strand; ↑AhR; ↓BRCA-1 ↓cell proliferation; ↓colonies formation; ↑apoptosis; ↑caspase 3; ↓p-Akt/PKB and mTOR ↓EGF-induced epithelial mesenchymal transition (EMT) ↓cell proliferation; G_0/G_1 cell cycle arrest (MCF-7); ↑apoptosis; ↑NHE-1 and NHE-3; ↑uptake of NaCl; ↓pH	[36] [37] [38] [39] [40] [41] [42]

	MCF-7, MDA-MB-231, MDA-MB-468	10 μM / 1-7 days	↓growth tumors; ↓STAT-3 acetylation	[43]
	MDA-MB-231	5–50 μM / 12h	↓EGF-induced migration; ↓MED28, MMP-9; ↓EGFR/PI3K; ↓NF-κB activity	[44]
Leukemia-Lymphoma	K562	40 μM / 1-12h	↑apoptosis; ↓p-Akt; ↓PI3K/Akt activity; ↑ERK1/2 activity	[45]
	K562/IMA-3,	1-100 μM / 24h	↓cell proliferation; G_0/G_1 cell cycle arrest; ↑apoptosis; ↑UPR markers	[46]
	K562	50 μM / 48h	↑autophagy; ↑JNK-p62, AMPK; ↓mTOR pathway	[47
	K562, U937, KCL22, HL-60, THP1,	1-100 μM / 24h	↓cell proliferation; ↑apoptosis; ↑caspase 3	[48
	WSU-CLL	1-100 μM / 72h	↓cell proliferation; G_2/M and S cell cycle arrest; ↑cyclins-A, -B; ↑apoptosis; ↑caspases activity; ↓colonies formation	[49
	HL-60	2.5-320 μM / 1-48h	↓cell proliferation; G_0/G_1 and S cell cycle arrest; ↑apoptosis	[36]
		1-200 μM / 24-48h	↓cell proliferation; G_0/G_1 cell cycle arrest; ↑apoptosis; ↓Bcl-2; ↑caspase 3; ↑Bax, Annexin A1; ↑DNA damage	[50]
	OCI-LY8	25 μM / 24h	↓cell proliferation; G_0/G_1 cell cycle arrest; ↑apoptosis; ↓Bcl-6; ↑p27, p53 and CD69; ↓c-myc	[51]
	OCI-LY8, OCI-LY1	25, 50 μM / 24h	↓cell proliferation; G_0/G_1 cell cycle arrest; ↑apoptosis; ↓p-Akt, p-p70 S6K, S6 and FOXO; ↓PI3K; ↓glucose metabolism	[52]
	AML-2	1-100 μM / 24-72h	↓cell proliferation; ↑apoptosis; ↓MRP1	[53]
	U937, MV-4-11	25-50 μM / 24-48h	↑ vorinostat and LBH-589-induced citotoxicity; ↑apoptosis; ↑DNA damage; ↑DR5, caspase-8; ↑ROS	[54]
Melanoma	B16/DOX	1-500 μM / 24-72h	↓cell proliferation; G_0/G_1 cell cycle arrest; ↑apoptosis; ↓cyclin-D1/cdk4; ↑p53	[55]
	B16F10, B16BL6	100 μM / 4-24h	↓cell migratory and invasion; ↓Akt	[56]
	DM443, DM738	1-100 μM / 1-4 days	↓cell proliferation; ↑TMZ-induced cytotoxicity	[57]
Myeloma	RPMI8226, OPM-2	1-100 μM / 1-3 days	↓cell proliferation; ↑apoptosis; ↓NF-κB	[58]
	U266, RPMI8226, MM.1R	50 μM / 1-6 days	↓cell proliferation; ↑apoptosis; ↑ bortezomib and thalidomide-induced cytotoxicity; G_0/G_1 cell cycle arrest; ↓cyclin-D1, cIAP-2, XIAP, survivin, Bcl-2, Bcl-xL, Bfl-1/A1, and TRAF2; ↑Bax, caspase 3; ↓NF-κB; ↓IκBα kinase; ↑p-IκBα, p-p65; ↓IL-6; ↑STAT-3	[59]
Glioma	U251	25 μM / 1-15 days	↓cell proliferation; ↓cell migration; ↓p-Akt; ↓cyclin-D1/caspase 3; ↓colonies formation	[60]
		1-100 μM / 24-48h	↓cell proliferation; ↓SULTs	[61]
	U-87MG	20–80 μM / 48h	↓cell proliferation; S cell cycle arrest	[62]
		10–200 μM / 24-96h	↓cell proliferation; S cell cycle arrest; ↑Bax; ↓cell migration and invasion	[63]
	U-87MG, GBM8401, GBM-SKH	30 μM / 24-48h	↓cell proliferation; ↑apoptosis; ↑autophagy; S and G_2/M cell cycle arrest; ↑Atg5, beclin-1 and LC3-II; ↑Bax, Caspase 3; ↑pCdc2(Y15), cyclin-A, -E ,-B, and Rb; ↓cyclin-D1	[64]
		1-20 μM /1h	↓cell proliferation; ↑TMZ-induced cytotoxicity	[65]
Bladder	T24	1–200 μM / 24h	↓cell proliferation; G_0/G_1 cell cycle arrest; ↑apoptosis; ↑p21; ↓p-Akt, p-Rb; ↓cyclin-D1, cdk4; ↑p-p38; ↓VEGF, FGF-2	[66]
		50–100 μM / 24-48h	↓cell proliferation; ↑apoptosis; ↑ROS; ↑caspase 3, 9; ↓ATP; ↑Cyt-c	[67]

	ECV304	1–100 μM / 24-48h	↑apoptosis; ↑Bad/Bcl-2 ratio; ↑NO; ↓oxidative damage; ↓neutrophils activation	[68]
Medullo-blastoma	UW228-3	100 μM / 1-48h	↓cell proliferation; G_0/G_1 cell cycle arrest; ↑apoptosis; ↓SULTs	[69]
	UW228-3, UW228-2	100 μM / 1-48h	↑apoptosis; ↓NF-κB, Bcl-2; ↓IkBα	[70]
		100 μM / 1-48h	↓cell proliferation; S cell cycle arrest; ↓c-myc; ↑apoptosis	[71]
Endometrial	HEC1B	1-100 μM / 24-48h	↓cell proliferation; ↑apoptosis; ↓beta-arrestin 2; ↑caspase 3; ↓Akt/GSK3ß	[72]
Gastric	SGC7901	50-200 μM / 48h	↓cell proliferation; ↑apoptosis; ↑ROS; ↑DNA damage	[73]
	AGS	500 nM / 1-24h	↓H_2O_2-induced cell proliferation; ↓MEK1/2-ERK1/2-c-Jun	[74]
	HGC-27	50 μM / 24h	↑apoptosis; ↑autophagy; ↓dihydroceramide desaturase	[75]
Thyroid	MTC	1-100 μM / 4-6 days	↓cell proliferation; ↑apoptosis; ↑Notch2; ↑caspase 3, PARP; ↓ASCL1, CgA	[76]
	BHP 2–7, BHP 18–21, FTC 236, FTC 238	0.1-100 μM / 4-24h	↓cell proliferation; ↑apoptosis; ↑p-ERK1/2; ↑p-p53, c-fos, c-jun, p21; ↓ASCL1, CgA	[77]
Osteo-sarcoma	HOS, MG-63 Saos-2, U-2 OS,	1-100 μM / 3-7 days	↓cell proliferation; ↑apoptosis	[78]
	SJSA1	1-100 μM / 1-3 days	↓cell proliferation; ↑apoptosis; ↑p-ERK1/2; ↑p-p53, c-fos, c-jun, p21; ↓ASCL1, CgA	[79]
Retino-blastoma	Y79	1-100 μM / 24-96h	↓cell proliferation; S cell cycle arrest; ↓Membrane Mitochondrial Potential; ↑Cyt-c, caspase 3, 9	[80]

PPP, pentose phosphate pathway; cdk, cyclin-dependent kinase; IC50, half maximal inhibitory concentration; AMPK, adenosine monophosphate activated protein kinase; ODC, ornithine decarboxylase; PPARγ, coactivator 1 proliferator-activated receptor-gamma; p53, tumour protein 53; p21Waf1/Cip1, cyclin-dependent kinase inhibitor 1A; p27, cyclin dependant kinase inhibitor 27; E2F,transcription factor E2F; Rb, retinoblastoma tumour suppressor gene; ERK, extracellular signal regulated kinase; JNK-1, c-Jun N-terminal kinases; MEK1/2, mitogen-activated protein kinase kinase 1/2; Akt, serine/threonine protein kinase; PI3K, phosphoinositide 3 kinases; FOXO, forkhead transcription factor; TRAIL, TNF-related apoptosis inducing ligand; DR4/5, tumour necrosis factor receptor superfamily,member 10a/10b; PTEN, phosphatase and tensin homolog; AR, andogen receptor; EGFR, endothelial growth factor receptor; ROS, reactive oxygen species; iNOS, inducible nitric oxide synthase; MRP1, motility-related protein 1; NO, nitric oxide; MMP, matrix metalloproteinase; NFkB, nuclear factor kappa B; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; TNFα, tumour necrosis factor alpha; STAT-3, signal transducer and activator of transcription 3; Bcl-2, B-cell lymphoma 2; Sirt1, sirtuin 1; mTOR, mammalian target of rapamycin; MTA1, Metastasis-associated protein MTA1; XRT, X-ray telescope; IR, Ionizing radiation; Atg, autophagy proteins; NADPH, nicotinamide adenine dinucleotide phosphate; TIMP, tissue inhibitors of metalloproteinases; ASPP1, Apoptosis-stimulating of p53 protein 1; cIAPs, inhibitor of apoptosis proteins; MED28, mediator of RNA polymerase II transcription subunit 28; AhR, Aryl hydrocarbon receptor; BRCA-1, breast cancer type 1 protein; NHE, sodium-hydrogen exchanger protein; ATP, Adenosine triphosphate; UPR, unfolded protein response; Cyt-c, cytochrome C; TMZ, temozolomide; SULTs, sulfotransferases. Effect is indicated by ↓: reduction; ↑: induction; p-: phosphorylate status.

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Supplementary Table 2. Neuroprotective effects of resveratrol in *in vitro* models.

Effect	Cell Model	Treatment	Effects and Mechanisms	Reference
Antiinflammatory	Primary rat cortical neuron-glia cultures stimulated with LPS (100 ng/mL)	Pretreatment 15-60 μM / 30 min	↓TNF-α, iNOS, IL-1β, NO	[1]
	murine microglial BV-2 cells stimulated with LPS (1μg/mL)	Pretreatment 25-100 μM / 1h	↓TNFα, IL-1β, NO, PGE2; ↓Akt/mTOR, NF-κB, CREB, MAPKs	[2]
	Coculture Neuronal PC12 cells and N9 microglia stimulated with LPS (1μg/mL)	Pretreatment 0.1 μM / 3h	↓TNFα, IL-1α; ↑Cell survival	[3]
	Primary microglial cell cultures stimulated with LPS 10 ng/mL	1-50 μM / 24h	↓PGE2, 8iso-PGF2; ↓mPGES-1	[4]
Anti-amylodogenic	rat astroglioma C6 cells treated with β-amiloid	Pretreatment 2.5-20 μM / 40 min	↓iNOS, NO; ↓ PGE2, COX-2 ; ↓NF-κB	[5]
	SK-N-BE cells	7.5 μM / 6-43h	↓ROS; ↓Cell toxicity α-syn and Aβ; ↑SIRT1	[6]
	HEK293 and N2a cells stably transfected with human APP695 and primary neuronal culture male APP/PS1 transgenic mice	10-40 μM / 24h	↓Aβ-40, Aβ-42; ↑AMPK, CREB, ATF-1, ACC phosphorylation; ↑c-FOS; AMPK/CREB/c-FOS	[7]
	Primary hippocampal cell cultures	Pretreatment, cotreatment and post-treatment 5-40 μM / 2h	↑Cell survival, PKC	[8]
	APP665-HEk293; APP695-N2a	10-40 μM / 26h	↓Aβ intracellular, Proteosome activation	[9]
Antioxidant	Rat primary astrocyte culture	Pretreatment 0.1-100 μM / 1h	↓DNA damage; ↑Cell survival	[10]
	HT22 murine hippocampal neuronal cells treated with glutamate 4mM	1-20 μM / 24h	↑Cell survival; ↓ROS; ↑SOD2 ; PI3K/Akt and GSK-3β/β-catenin	[11]
	primary neuronal cultures treated with 30 μM glutamate	25 μM 24h / 6-8h	↑HO-1	[12]
	Primary midbrain slice cultures treated with 30 μM MPP+	10-100 μM / 48h	↑Cell survival; ↓ROS; ↓DNA damage	[13]
	Primary cortical neuronal cells	5-50 μM / 6h	↑Cell survival; HO-1 induction	[14]
	Primary rat hippocampal cells co-treated with SNP (100μM)	5-25 μM / 2h	↑Cell survival; ↓ROS	[15]
Antiapoptotic	Human neuroblastoma cell lines (SH-SY5Y and SK-N-SH) treated with prion protein peptide PrP	Pretreatment 1-2 μM / 12h	↓Bax translocation; ↓Cytochrome C release; Autophagy regulation	[16]
	hSOD1G93A-bearing VSC4.1 cells	0.5-20 μM / 24h	↑Cell survival; ↑Intercellular ATP, SIRT1/PGC1-α	[17]
	mesencephalic dopaminergic neuronal cell culture treated with methamphetamine	Pretreatment 10 μM / 1h	↓Caspase 3; ↓DNA fragmentation	[18]
	SH-SY5Y cells treated with rotenone/ α-synuclein PC12 cells	12-50 μM / 24-72h	↑Cell survival; ↓DNA fragmentation; ↓Caspase 3, PARP, AMPK/SIRT1/Autophagy	[19]
	PC12 cells treated with MPP+	Pretreatment 0.1 μM / 3h	↓Bax/Bcl-2, AIF and Cytochrome C release	[20]
	Primary culture of neurons from SAMP8 & SAMR1 mice strains	50 μM / 2h	↑Cell survival; ↓acetylp53, SIRT1	[21]

	PC12 cells with oxygen-glucose deprivation	Pretreatment, cotreatment and post-treatment 5-25 μM / 6-24h	↓ROS; ↑GSH; ↓HIF-α; ↓Caspase 3, Bax, Bcl-2	[22]
	Human neuroblastoma SH-SY5Y cells treated with paclitaxel 1 μM	1-100 μM / 24h	↑Cell survival; ↓caspase 7 and PPAR activation	[23]
	Organotypic hippocampal slice cultures with oxygen-glucose deprivation	10-50 μM / 24h	↑Cell survival; PI3K	[24]
	Neuro2a cells/mouse dorsal root ganglia (DRG) sensory and cortical neuron cultures	10 μM / 2-72h	↑AMPK phosphorylation; ↑ACC phosphorylation; ↑Differentiation; ↑Mitochondrial biogenesis	[25]

8-iso-PGF2α, 8-iso-prostaglandin-F2α; ACC, acetyl-CoA carboxylase; AIF, apoptosis inducing factor; Akt, protein kinase B; α-syn, alpha-synuclein; AMPK, adenosine monophosphate activated protein kinase; Aβ, amyloid beta peptide; ATF1, activating transcription factor 1; Bax, Bcl2-associated X protein; Bcl-2, B-cell lymphoma 2; Casp3, caspase 3; COX-2, cyclooxigenase 2; CREB, cAMP response element-binding; GPx, glutathione peroxidase; GSH, glutathione; GSK-3β, glycogen synthase kinase 3beta; HIF-α, hypoxia inducible factor; HO-1, heme oxygenase-1; IL-1α, interleukin 1-alpha; IL-1β, interleukin 1-beta; MAPKs, Mitogen-activated protein kinases; mPGES-1, membrane-associated PGE synthase-; mTOR, mammalian target of rapamycin; iNOS, inducible nitric oxide synthase; NFkB, nuclear factor kappa B; NO, nitric oxide; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PGE_2, prostaglandin E_2; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SIRT1, sirtuin 1; SOD2, superoxide dismutase 2; TNFα, tumour necrosis factor alpha; XO, xanthine oxidase. Effect is indicated by ↓: reduction; ↑: induction; p-: phosphorylate status.

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Supplementary Table 3. Effects of resveratrol on human cells involved in the vascular milieu.

Effect	Mechanisms	Human Cell Line	Tested dose	Reference
Endothelial function improvement	↑eNOS	HUVEC	50 nM - 100 μM	[1-4]
		HCAEC	1-10 μM	[5]
		EA.hy 926	1-100 μM	[1]
	↑NO release	HUVEC	50 nM – 60 μM	[6-9]
Anti-oxidant	↑SOD	HUVEC	1-100 μM	[10]
		HCAEC	3-30 μM	[11]
		EA.hy 926	1-100 μM	[10, 12]
	↑GPx1	HUVEC	1-100 μM	[10]
		EA.hy 926	1-100 μM	[10, 12]
	↑HO-1	HCAEC	0.1-50 μM	[13, 14]
		HASMC	1-40 μM	[15]
	↑NQO-1; ↑GCLC; ↑Nrf-2	HCAEC	0.1-50 μM	[13]
	↑Catalase; ↑GCH1	EA.hy 926	100 μM	[12]
	↓Mitochondrial O_2^- and H_2O_2; ↑GSH	HCAEC	3-30 μM	[11]
	↑Trx-1; ↑VEGF	HCAEC	1-50 μM	[14]
	↑Mitochondrial biogenesis; ↑PGC-1α; ↑Nrf-1; ↑Tfam; ↑SIRT1	HCAEC	1-10 μM	[5]
	↑NQO-1; ↑NQO-2; ↑p53; ↑HSP27	HASMC	10-50 μM	[17]
	↓ROS	HCAEC	10-100 μM	[18, 19]
	↓NOX activity	HUVEC	5-10 μM	[20]
	↓NOX4-mRNA	HUVEC & EA.hy 926	1-100 μM	[2]
Anti-inflammation	↓IL-6; ↓TNFα; ↓iNOS	HCAEC	10 μM	[21]
	↓IL-6; ↓IL-8	SGBS preadipocytes and adipocytes	10-100 μM	[22]
	↓ICAM-1; ↓VCAM	HUVEC	0.1- 10 μM	[23, 24]
		HSVEC	0.1&1 μM	[23]
		HCAEC	0.1-10 μM	[18]
	↓Monocyte adhesion to EC	HUVEC	1-10 μM	[25]
		HCAEC	0.1-10 μM	[21]
	↓EC migration	HUVEC	1-20 μM	[26]
	↓MCP-1	THP-1	1-20 μM	[26]
	↓NF-κB	HUVEC	1-10 μM	[25]
		HCAEC	0.1-10 μM	[18, 21]
		HASMC	10-50 μM	[17]
		THP-1& U937	30 μM	[27]
	↓MMP-9; ↓COX-2	HBMEC	5-100 μM	[16]
	↓PGE_2; ↓LB_4; ↓MMP	Chondrocytes	1-10 μM	[28]

Lipidic modulation	↓Preadipocyte proliferation; ↓Adipogenic differentiation; ↓De novo lipogenesis; ↓Lipogenic gene expression	SGBS preadipocytes and adipocytes	10-100 μM	[22]
Platelet interaction	↓Aggregation	Washed platelets	0.05-0.25 μM	[29]
	↑Platelet apoptosis		5-25 μM	[30]

COX, cyclooxygenase; EA.hy 926, human umbilical vein cell line; EC, endothelial cells; eNOS, endothelial nitric oxide synthase; GCH1, GTP cyclohydrolase 1; GCLC, glutamate-cysteine ligase catalytic subunit; GPx, glutathione peroxidase; GSH, glutathione; HASMC, human aortic smooth muscle cells; HBMEC, human brain microvascular endothelial cells, HCAEC, human coronary artery endothelial cells; HSVEC, human saphenous vein endothelial cell; HUVEC, human umbilical vein endothelial cells; HO-1, heme oxygenase-1; HSP, heat shock protein; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; iNOS, inducible nitric oxide synthase; LB_4, leukotriene B4; MCP, monocyte chemotactic protein; MMP, matrix metallopeptidase; MPO, myeloperoxidase; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-κB-binding; NO, nitric oxide; NOX, NADPH oxidase; NQO, NADPH: quinone oxidoreductase; Nrf, nuclear factor-E_2-related factor; PGC, peroxisome proliferator-activated receptor-γ coactivator; PGE2, prostaglandin E2; ROS, reactive oxygen species; SGBS, human Simpson-Golabi-Behmel syndrome; SIRT1, sirtuin (silent mating type information regulation 2 homolog) 1; SOD, superoxide dismutase; Tfam, transcription factor A, mitochondrial; THP-1, human acute monocytic leukemia cell line; TNF, tumor necrosis factor; Trx, thioredoxin; U937, human macrophage cell line; VCAM-1, vascular cell adhesion protein 1; VEGF, vascular endothelial growth factor; ↓, reduction; ↑, induction.

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Supplementary Table 4. Anti-aging effects of resveratrol in *in vitro* models.

Cell Model	Treatment	Effects and Mechanisms	Reference
Presenescent cultures human MRC5 fibroblasts	5 μM from presenescent until senescence (44-55 PDL)	↓SASP development; ↓IL-1α, IL-1β, IL-8, IL-6, GRO-α, VEGF; ↑Type I collagen; ↑adhesion capacity	[1]
C2C12 myoblast cells HeLa cells	50 μM / 4 days	↑cAMP via Epac1; ↑NAD^+ levels; ↑oxygen consumption rate; ↑fat oxidation; ↑Mitochondrial Biogenesis; Inhibits PDEs; Epac1-SIRT1; PLC-Ryr2	[2]
BAECs	0.01-1 μM / 24h	↓aorta senescence (SA-β-gal); ↓ROS; ↓NADPH oxidase p47phox; ↑SIRT1; SIRT1/NADPH oxidase	[3]
Primary vascular smooth muscle cells (VSMCs) from Macaca mulatta13 and 21 years old	1 μM / 48h	↓IL-1β, TNFα, IFN-γ; ↓IL-8, MCP-1, VEGF; ↓IL-2, IL-4, IL-5, IL-10, IL-12/23; ↓MIP-β, sCD40L; ↓mitochondrial O2 – generation; ↓NF-κB activation; ↑Nrf-2	[4]
Young and senesce endothelial cells	10 μM / 1h	↓Akt; ↓S6k1; ↓SOD; ↑NO; mTOR/S6K1	[5]
VLCAD- and CPT2- deficient human skin fibroblasts	10-125 μM / 48h	↑palmitate oxidation rate; ↑FAO flux; ↑VLCAD, CPT2 expression; ↑SIRT1; ↑PGC1-α	[6]
Endothelial cells of cardiac coronary vessels from patients receiving coronary artery CABG surgery and SD aged rats	10-100 μM / 48h	↑SIRT1 expression and activity; ↓ROS	[7]
SaOS2 & RGCcells incubated in reduced glucose levels	20-160 μM / 48h	↓SIRT1 expression; ↑TXNIP (20-40 μM); ↓TXNIP (80-160 μM)	[8]
Retinal Stem Cells	5-20 μM / 48h	↑SIRT1 mRNA and activity; ↑Cell survival; ↓ROS	[9]
human WI-38 fibroblasts/ HT-1080 cells/ Retina pigment epithelial cells	3-200 μM / 72 h	↓Senescence morphology; ↑proliferation; ↓S6 phosphorylation; mTOR	[10]
Mortal human diploid foreskin fibroblasts	0.2-1 μM / 24h	↓INK4a mRNA; ↓α-macroglobulin mRNA; ↓UBE2D3	[11]

Akt, protein kinase B; cAMP, cyclic adenosine monophosphate; CPT2,carnitine palmitoyl transferase 2; Epac1, exchange protein activated by cyclic AMP; FAO, mitochondrial fatty acid β-oxidation; IFN-γ, interferon-gamma; IL-2, interleukin 2; IL-4, interleukin 4; IL-5, interleukin 5; IL-6, interleukin 6; IL-8, interleukin 8; IL-10, interleukin 10; IL-12/23, interleukin 12/23; IL-1β, interleukin 1-beta; IL-6, interleukin 6; MCP-1, monocyte chemotactic protein-1; MIP-1β, macrophage inflammatory protein-1-beta; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa B; NO, nitric oxide; Nrf-2, nuclear factor erythroid 2-related factor 2; PGC-β, peroxisome proliferator-activated receptor gamma coactivator 1 beta; PLC; phospholipase C; ROS, reactive oxygen species; Ryr2, ryanodine receptor 2; S6, ribosomal protein 6; S6k1, ribosomal protein S6 kinase beta-1; SA-β-Gal, senescence-associated beta-galactosidase; SASP, senescence-associated secretory phenotype; sCD40L, soluble CD40 ligand; SIRT1, sirtuin 1; SOD, superoxide dismutase; TXNIP, thioredoxin-interacting protein; TNFα, tumour necrosis factor alpha; UBE2D3, ubiquitin-conjugating enzyme E2D 3; VEGF, vascular endothelial growth factor; VLCAD, very-long-chain Acyl-CoA dehydrogenase. Effect is indicated by ↓: reduction; ↑: induction; p-: phosphorylate status.

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Suplementary Table 5. Cancer chemopreventive effects of resveratrol and related mechanisms in animal models.

Cancer Model	Animal Model	Treatment	Effects and Mechanisms	Reference
Colon	Apc^{Min} mice (male)	45 μg/kg bw (po) / 60 days	↓BaP-induced colon carcinogenesis in Apc^{Min} mouse model; ↓number of colon adenomas	[1]
	C57BL/6 mice	48 mg/kg bw/day (diet) / 62 days	↓colon cancer incidence	[2]
	C57BL/6J A-pcMin/+ mice (male)	60, 240 mg/kg bw/day (diet) / 3 weeks	↓adenoma load; ↓PGE-2 levels in the intestinal mucosa; ↓COX activity	[3]
	Wistar rats (male)	8 mg/kg/day (po) / 15, 30 weeks	↓DMH-induced colon carcinogenesis; ↓number of ACF	[4]
	CF-1 mice	2.4 mg/kg bw/day (diet) / 5 weeks	↓number of ACF/mouse	[5]
	F344 rats (male)	200 μg/kg bw/day (in water) / 100 days	↓AOM-induced colon carcinogenesis; ↓number and multiplicity of ACF colon; ↑Bax; ↓p21	[6]
Prostate	PTEN-KO mice (male)	50 mg/kg (po) / 7 weeks (3 times/week)	↓prostate cancer incidence	[7]
	SV-40 Tag rats (male)	25 mg/kg/day (diet) / 30 weeks	↓Incidence; ↓cell proliferation; ↓IGF-1	[8]
	TRAP rats (male heterozygous)	50, 100, 200 μg/mL/day (in water) / 7 weeks	↓prostate cancer growth; ↑apoptosis; ↓AR	[9]
	BALB/cAnNCr-nu/nu mice (male athymic nude)	50, 100 mg/kg (diet) / 2+7 weeks	↓cancer growth; ↑angiogenesis; ↓apoptosis	[10]
		30 mg/kg (po) /6 weeks (3 times/week)	↑apoptosis inducing potential of TRAIL in PC-3 xenografts in nude mice; ↓cell proliferation; ↓angiogenesis; ↑TRAIL-R1/DR4, TRAIL-R2/DR5, Bax and p27(/KIP1); ↓Bcl-2, cyclin-D1; ↓MMP-2, -9; ↓number of blood vessels in tumors; ↓EGFR2; ↓p-FOXO3a	[11]
Liver	Sprague–Dawley rats (female)	50, 100, 300 mg/kg bw/day (diet) / 4+20 weeks	↓Incidence, total number and multiplicity of visible hepatocyte nodules; ↓cell proliferation; ↑apoptosis; ↑Bax; ↓Bcl-2; ↓DENA-initiated and PB-promoted hepatocarcinogenesis; ↓DENA-induced increased expressions of hepatic HSP70, COX-2, NF-κB; ↓DENA-induced of the level and expression of hepatic TNFα, IL-1β and IL-6; ↓DENA-induced hepatic lipid peroxidation and protein oxidation; ↑Nrf-2	[12-15]
	BALB/C mice	15 mg/kg/ (ip) / 21 days (every 2 days)	↓growth of CAV1-expressing HepG2 cells transplanted in female mice; ↓cell proliferation; ↑apoptosis; ↑caspase 3; ↑p-p38, p-ERK	[16]
		5, 10, 15 mg/kg/day (ip) / 10 days	↓tumor growth and size in male mice implanted with H22 hepatoma cells; S arrest cell cycle; ↑enhanced 5-FU effect (synergy)	[17]
		5, 10, 15 mg/kg/day (ip) / 10 days	↓tumor growth and size in mice implanted with H22 hepatoma cells; ↓cyclin-B1; ↓p34cdc2	[18]
		500, 1000, 1500 mg/kg/day (ip) / 10 days	↓tumor weights in mice implanted with H22 hepatoma cells	[19]
	C57BL/6J mice	20 mg/kg b.i.d. (diet) or 23 mg/L in drinking water / 10 days	↓B16M carcinoma cell growth; S and G_2/M arrest cell cycle; ↑apoptosis; ↓ROS; ↓metastasis	[20]
	Wistar rats (male)	20 mg/kg (ip) / 7 days	↓DOX-induced cellular damage; ↓DOX-induced increased iNOS and eNOS expression; ↓p53	[21]
		1 mg/kg (ip) / 7 days	↓tumour cell content in male rats implanted with AH-130 hepatoma	[22]

			cells; G_2/M arrest cell cycle; ↑apoptosis	
	Donryu rats (male)	10, 50 ppm (diet) / 20 days	↓tumor size in male rats implanted with AH109A hepatoma cells; ↓lipid peroxidation; ↓serum triglycerides; ↓VLDL; ↓LDL	[23]
Breast	BALB/c mice (female)	100, 200 mg/kg (po) / 21 days	↓metastasis of 4T1 cells in BALB/C mice; ↓plasma MMP-9 activity	[24]
	Athymic nu/nu mice (female)	16.5 mg/kg/ (ip) / 2 weeks (3 times/week)	↑paclitaxel-induced death of MDA-MB-435s cancer cells subc. injected in mice; ↓apoptosis	[25]
	FVB/N mice (female)	1 mg/L in drinking water / 10 weeks	↓latency; ↓number of mammary tumors; ↓metastasis; ↑apoptosis	[26]
	Swiss mice (female)	20, 40 mg/kg/day / 20 days	↓tumor size; ↑cisplatin-chemoprevention	[27]
	Sprague-Dawley rats (female)	50 mg/kg bw/day (diet) / 18 weeks	↓tumor multiplicity rates; ↓tumor latency; ↓DMBA-induced mammary tumorigenesis; ↓cell proliferation; ↑apoptosis	[28]
		0.5 mg/kg bw (diet) / 120 days	↓DMBA-induced mammary tumorigenesis; ↓tumor multiplicity; ↓tumor incidence; ↓COX-2; ↓MMP-9	[29]
Leukemia	BALB/c mice	12.5, 25, 50 mg/kg/day/3 weeks (ig) injection p. with L1210 cells	↑long-term survival of tumor (L1210 cells)-bearing mice; ↑CD4/CD8 ratios; ↑lymphocyte proliferation; ↑NK cell activity; ↓IL-6	[30]
Melanoma	C57BL/6 mice (female)	100 mg/kg bw (po) / 12 days	↓development of vascular leak syndrome (VLS) induced by IL-2; ↑tumor metastasis and growth; ↑endothelial cell integrity tumor incidence	[31]
	(male)	1 mg/kg (po) / 12 days	↓metastatic growth of melanoma; ↓IL-8, VCAM-1; ↓adhesion- and proliferation-stimulating effects of IL-18; ↓NFκB	[32]
	SENCAR mice	Applied topically / 4 weeks	↓DMBA-induced hyperplasia skin; ↓Bcl-2; ↓p2; ↓COX-2; ↓CYP1B1; ↓c-jun and c-fos	[33]
	C3H/HeN mice (female)	10 μmol/mouse (topically) / 25 weeks	↓melanoma incidence-induced by DMBA; ↓tumor size; ↓angiogenesis	[34]
	Swiss mice (female)	25-50 μM/mouse (applied topically) / 28 weeks	↓DMBA-induced hyperplasia skin; ↓Bcl-2, survivin; ↑p53, Bax DMBA-induced; ↑Cyt-c, caspases activation; ↑Apaf-1; ↓PI3K/Akt pathway	[35]
Neuroblastoma/glioma	A/J mice (female)	20 mg/twice a week (iv) / 20 days	↓tumor growth; ↑immunocytokine therapy; ↑necrosis	[36]
	(male)	40 mg/kg/day (sc) / 28 days	↓growth subcutaneous neuroblastomas; ↑long-term survival	[37]
	Fischer 344 rats	10 or 40 mg/kg/day(ip) / 4 weeks	↓tumor growth after subc. injection of RT-2 glioma cells; ↑long-term survival; ↓microvessels density in glioma tissues; ↑apoptosis	[38]
	BALB/cA nude mice	40 mg/kg (po) / 28 days	↑TMZ induced-inhibition of the growth of implanted glioma cells in nude mice; ↑AMPK; ↓mTOR, Bcl-2; ↑apoptosis	[39]
Gastric	BALB/C nude mice (female)	10 and 12.5 mg/kg (ip) / 12 days	↑TMZ induced-inhibition of the growth and volume of implanted glioma cells in nude mice; ↓ROS/ERK-mediated autophagy; ↑apoptosis	[40]
		500, 1000, 1500 mg/kg (sc) / 6 times at an interval of 2 days	↓carcinoma growth after subc. injection of human primary gastric cancer cells; ↑apoptosis; ↓Bcl-2; ↑Bax	[41]
	NMRI mice (male)	1 mg/kg (ip) / 3 days	↓tumor growth after implanted MAC16 tumor cells; ↓NF-κB DNA-binding activity	[42]

Esophagus	Sprague–Dawley rats (male)	7 mg/kg (ip) / 5 months	↓esophagitis after esophagoduodenal anastomosis; ↓incidence of intestinal metaplasia; ↓incidence of carcinoma	[43]
	F344 rats (male)	1, 2 mg/kg / 16 weeks (diet), 20 weeks (ip)	↓number of NMBA-induced esophageal tumors; ↓ size of maximum tumors; ↓COX-1, -2, PGE_2 synthesis	[44]
Lung	Immunodeficient mice	20 mg/kg (ip) / 8 weeks	↓tumor growth after subc. injection of A549 cells and A549/FOXC2 cells; ↓metastasis; ↓FOXC2	[45]
	C57BL/6 mice (female)	2.5 and 10 mg/kg (ip) / 22 days	↓tumor growth after subc. injection of Lewis lung carcinoma cells; ↓tumor weight; ↓number of tumor cell colonies compared with the LLC-bearing mice	[46]
Pancreatic	BALB/c nu/nu mice	20, 40 and 60 mg/kg (po) / 6 weeks (5 days a week)	↓PANC-1cells implanted pancreatic tumor growth; ↑apoptosis; ↓cell proliferation in tumor tissues; ↑Bim, p27/KIP1 and p21/CIP1, cleaved caspase-3; ↓PCNA; ↓p-ERK, p-PI3K, p-Akt, p-FOXO and p-FOXO3a	[47]

5-FU, 5-fluorouracil; ACF, aberrant crypt foci; Akt, serine/threonine protein kinase; AMPK, adenosine monophosphate activated protein kinase; AOM, Azoxymethane; APAF-1, apoptotic protease activating factor 1; AR, andogen receptor; BaP, Benzo[a]pyrene; Bcl-2, B-cell lymphoma 2; b.i.d., twice a day; bw, body weight; CAV-1, caveolin-1; COX-2, cyclooxygenase 2; CYP1B1, cytochrome P450 1B1; Cyt-c, cytochrome C; DENA, diethylnitrosamine; DMBA, 7,12-dimethylbenzanthracene; DMH, 1,2-dimethylhydrazine; DOX, doxorubicin; DR4/5, tumour necrosis factor receptor superfamily,member 10a/10b; EGFR, endothelial growth factor receptor; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal regulated kinase; FOXC2, forkhead box protein C2; FOXO3a, Forkhead transcription factor O3; po, per oral; IGF-1, insulin like growth factor-1; IL, interleukin; iNOS, inducible nitric oxide synthase; ig, intragastric; ip, intraperitoneally; LDL, low density lipoprotein; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NFkB, nuclear factor kappa B; NK, natural killer cells; Nrf-2, hepatic nuclear factor E2-related factor 2; p27, cyclin dependant kinase inhibitor 27; p53, tumour protein 53; PGE_2, prostaglandin E2; PI3K, phosphoinositide 3 kinases; ROS, reactive oxygen species; sc, subcutaneously; TMZ, temozolomide; TNFα, tumour necrosis factor alpha; TRAIL, TNF-related apoptosis inducing ligand; VCAM-1,vascular cell adhesion molecule 1; VLDL, very low-density lipoprotein. Effect is indicated by ↓: reduction; ↑: induction; p-: phosphorylate status.

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Supplementary Table 6. Effects of exposure to resveratrol on animal models of cardiovascular disease.

Model	Animal Model	Effect	Treatment	Duration	Reference
Hypertension/Vascular function	Mouse	↓Blood pressure	~10 mg/kg bw/day	2; 4 weeks	[1]
	Rat	↓Blood pressure	1-800 mg/kg bw/day	2h-10 weeks	[2-10]
		→ Blood pressure	2.5 mg/kg bw/day	5; 10 weeks	[11-13]
		↓Cardiac Hypertrophy	2.5-800 mg/kg bw/day	5 days-10 weeks	[5, 8, 13-16]
		↑Survival rate	10-800 mg/kg bw/day	21 days-8 weeks	[5, 16-18]
		↓Right ventricular systolic pressure	3-30 mg/kg bw b.i.d.	14-21 days	[16, 19, 20]
		↓Cardiac contractility	1-3 mg/kg bw/day	14 days; 4 weeks	[6, 20]
		↓Vascular remodeling	2.5; 25 mg/kg bw/day	1-8 weeks	[19, 21]
		↓Cardiac dysfunction	2.5; 18 mg/kg bw/day	2-10 weeks	[12, 13, 15, 17, 18, 22]
		↑Left ventricular function	0.1-20 mg/kg bw/day	1-4 weeks	[23-26]
	Swine	↑Left ventricular function	5 mg/kg bw/day	14 days	[27]
	Mouse	↑SOD activity; ↑GPx-1	10-100 mg/kg bw/day	1; 2 weeks	[28, 29]
		↑GSH	10; 20 mg/kg bw/day	15 days	[28]
		↑HO-1	50 mg/kg bw (3 times/week)	21 days	[30]
		↑eNOS; ↓NOX-2	20 mg/kg bw/day	4 weeks	[31]
	Rat	↑GSH	10; 30 mg/kg bw/day	10 days; 8 weeks	[34, 35]
		↑HO-1; ↓NOX-1; ↓NOX-2, ↓NOX-4; ↓Aortic O_2^-	30 mg/kg (single dose)	-	[32]
		↑SOD activity	5-30 mg/kg bw/day	4-10 weeks	[4, 35, 36]
		↓MPO activity	0.56-30 mg/kg bw/day	2h; 10 days	[34, 37]
		↑Catalase activity	10-100 mg/kg bw/day	7 days-8 weeks	[29, 35, 36]
		↓NO	10 mg/kg bw/day	8 weeks	[30]
		↑NO	5;50 mg/kg bw/day	4; 10 weeks	[4, 33]
		↑Endothelial relaxation	5-10 mg/kg bw/day; 50mg/L in water	3-10 weeks	[2, 4, 8, 38]
		↑eNOS	5 mg/kg bw/day; 50mg/L in water	6-10 weeks	[2, 4, 8]
		↓Superoxide generation	50 mg/kg bw/day; 50mg/L in water	10; 12 weeks	[2, 10]
Myocardial infarction/Ischemia/Heart disease	Rat	↓Mortality	5 mg/kg bw/day	4 weeks	[39]
		↓Myocardial infarct size	1-5mg/kg bw/day	7 days-4 weeks	[25, 39-44]
		→ Myocardial infarct size	17 mg/kg bw/day	3 months	[45]
		↓Acute myocardial ischemia/reperfusion	0.1; 1mg/kg + insulin/day	5 days	[41]
		↓Ventricular dysfunction	5 mg/kg bw/day	2; 4 weeks	[39, 42]
		↑Cardiac microenvironment	2.5 mg/kg bw/day	1-8 weeks	[46]

		↑Capillary density	20 mg/kg bw/day	2 weeks	[26]
	Swine	↑Tissue blood flow during stress; ↑Inferolateral function	100 mg/kg bw/day	7 weeks	[47]
		↓Aortic elastic fibers disruption and alteration; ↓Intima thickness; ↓Aortic accumulation of fatty cells and O_2^-	8 mg/70kg bw/day	12 months	[48]

b.i.d., twice a day; bw, body weight; COX, cyclooxygenase; eNOS, endothelial nitric oxide synthase GPx, glutathione peroxidase; GSH, glutathione; MPO, myeloperoxidase; NO, nitric oxide; SOD, superoxide dismutase; ↓, reduction; ↑, induction; →, no effect.

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Supplementary Table 7. Resveratrol-exposure effects on insulin, glucose and lipid levels of animal models of obesity, diabetes and metabolic dysfunction.

Model	Animal Model	Effect	Treatment	Duration	Reference
Obesity/Diabetes/Metabolic dysfunction	Mouse	↓Insulin	~80 ng/day-50 mg/kg bw b.i.d.	2 weeks-6 months	[1-4]
		↑Insulin sensitivity	~2.5-400 mg/kg bw/day	8-20 weeks	[5-7]
		→ Insulin sensitivity (AMPKα1$^{-/-}$)	400 mg/kg bw/day	12 weeks	[8]
	Rat	↓Insulin	5-100 mg/kg bw/day	4-10 weeks	[9-11]
		↑Insulin	2.5 mg/kg bw/day	5 weeks	[12]
		↑Insulin sensitivity	10-300 mg/kg bw/day	8-10 weeks	[11, 13, 14]
	Swine	↑Insulin sensitivity	100 mg/kg bw/day	11 weeks	[15]
	Lemur	↑Insulin sensitivity	200 mg/kg bw/day	33 months	[16]
	Rabbit	↓Insulin; → Glucose	~1.5; 17 mg/kg bw/day	10 weeks	[17]
	Mouse	↓Glucose	~80 ng/day-400 mg/kg bw/day	2 weeks-1 year	[1-4, 18-20]
	Lemur	↓Glucose	200 mg/kg bw/day	33 months	[16]
	Rat	↓Glucose	0.1-10 mg/kg bw/day	1-8 weeks	[9, 10, 12, 14, 21-23]
		→ Glucose	2.5 mg/kg bw/day	1-8 weeks	[24]
	Mouse	↓Total-chol; ↓Triglycerides; ↓FFA	~7-400 mg/kg bw/day	6; 10 weeks	[18, 20]
		↓ApoB/ApoA1; ↑Adiponectin	~7; 30 mg/kg bw/day	6 weeks	[18]
		↓Grade of steatosis	200 mg/kg bw/day	20 weeks	[6]
	Rat	↓Triglycerides	2.5-30 mg/kg bw/day	4-10 weeks	[10, 12, 14, 17, 25, 26]
		↓FFA	10 mg/kg bw/day	8 weeks	[10]
		↑HDL-chol	2.5-15 mg/kg bw/day	4-8 weeks	[12, 26, 27]
		↓LDL-chol	2.5; 10 mg/kg bw/day	4-8 weeks	[12, 26]
		↓Total chol	10-45 mg/kg bw/day	6-8 weeks	[10, 27]
		↓Grade of steatosis	15-44 mg/kg bw/day	4-6 weeks	[25, 27, 28]
		↓Abdominal fat	10; 100 mg/kg bw/day	8-10 weeks	[10, 11]
		↓White adipose tissue size	6, 30, 60 mg/kg bw/day	6 weeks	[29]
	Swine	↓LDL; ↓Total cholesterol	100 mg/kg bw/day	7-11 weeks	[15, 19]
	Mouse	↓Metabolic dysregulation	400 mg/kg bw/day	12 weeks	[8]
	Rat	↓Metabolic dysregulation	1; 50 mg/kg bw/day	5 days-15 weeks	[30, 31]

AMPK, AMP activated protein kinase; Apo, apolipoprotein; b.i.d., twice a day; bw, body weight; chol, cholesterol; FFA, free fatty acids; HDL, high density lipoprotein; LDL, low-density lipoprotein; ↓, reduction; ↑, induction; →, no effect.

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Supplementary Table 8. Anti-inflammatory targets/mechanisms of resveratrol in animal models.

Animal Model	Effects and Mechanisms	Treatment	Duration	Reference
Mouse	↓TNFα	~3-100 mg/kg bw/day	14-62 days	[1-8]
	→ TNFα	500, 1000, 1500 mg/kg bw/day	10 days	[9]
	↓IFNγ	10-100 mg/kg bw/day	14-62 days	[1,6,7]
	↓CRP	20; 40 mg/kg bw/day	20 days	[2]
	↓IL-6	~2-50 mg/kg bw/day	14 days-4 weeks	[6,10-12]
	↑IL-6	10 mg/kg bw/day	30 days	[4]
	↑IL-3; ↓sTNF RI, p55 subunit; ↓IL-6; ↓MIP; ↓MIG; ↓MPO	2.1 mg/kg bw/day	29 days	[11]
	↑IL-10; ↓PGES-1	~3 mg/kg bw/day	26 days	[3]
	↓IL-1β	~3-100 mg/kg bw/day	14-30 days	[3,4,6]
	↓COX-2; ↓iNOS	~3-100 mg/kg bw/day	14-26 days	[3,6]
	↓IL-8	30; 60 mg/kg bw/day	14 days	[7]
	↓Recruitment of leukocytes; ↓IL-4; ↓IL-5	30 mg/kg bw/day	32 days	[13]
	↓MIP1a; ↓MCP-1	100 mg/kg bw/day; P183/1-mixture	32 days; 8 weeks	[14,15]
	↓IL12p40; ↓IL13; ↑IL17; ↑G-CSF; ↓RANTES	100 mg/kg bw/day	32 days	[15]
	↓ODC; ↓COX	25 mol in 200μL acetone/mouse	-	[16]
	↓NF-κB	10, 20 mg/kg bw/day	15 days	[17]
	↓ICAM-1; ↓VCAM-1; ↓hepatic HMG-CoA reductase activity	0.02, 0.06% w/w in chow	20 weeks	[18]
	↑AMPK activation	~7-30 mg/kg bw/day	6 weeks	[19]
	↓Macrophage infiltration	200 mg/kg bw/day	20 weeks	[20]
Rat	↓TNFα	5-~44 mg/kg bw/day	5 days-8 weeks	[21-29]
	↓NF-κBp65	10; 20 mg/kg bw/day	2-10 weeks	[23,24,30]
	↓COX-2	8-40 mg/kg bw/day	2-15/30 weeks	[24,31]
	↑PGE2	10 mg/kg bw/day	2 weeks	[24]
	↓PGE2; ↓PGES-1; ↓NO; ↓COX-2; ↓infiltration of inflammatory cells; 2,655 genes in distal colon mucosa were differentially regulated	1 mg/kg bw/day	25 days	[25]
	↓IL-1β	5-10 mg/kg bw/day	7-30 days	[21,26,27,29]
	↓iNOS	10-25 mg/kg bw/day	~1week	[26,33]
	↓IL-6	5-25 mg/kg bw/day	~1week-4 weeks	[21,23,27,29,33]
	mRNA: ↓IL-6; ↓IL-1; ↓TNFα; ↓PDGFα; ↓PDGFβ; ↓MCP-1	25 mg/kg bw/day	14 or 21 days	[34]
	↓IL-1; ↓ICAM1	25 mg/kg bw/day	~1week	[33]
	↑AMPK activation	2.5 mg/kg bw/day	2 weeks	[35]
	↓PPARα expression	18 mg/kg/day	8 weeks	[36]
	↑Sirt 1	300 mg/kg bw/day; 50 mL/L in water	8; 10 weeks	[37,38]

	↓TGFβ	10 mg/kg bw/day	2 weeks	[29]
Rabbit	↑Platelet aggregation inhibition	4 mg/kg bw/day	12 weeks	[39]

AMPK, AMP activated protein kinase; b.i.d., twice a day; bw, body weight; COX, cyclooxygenase; CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase GCS-F, granulocyte colony-stimulating factor; IL, interleukin; iNOS, inducible nitric oxide synthase; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; MIG, IFNγ-inducible T cell chemoattractant monokine; MPO, myeloperoxidase; NF-κB, nuclear factor-κB-binding; NO, nitric oxide; ODC, colonic mucosal ornithine decarboxylase; PGE2, prostaglandyn E2; PGES-1, prostaglandin E synthase 1; sTNFRI, soluble Tumor Necrosis Factor Receptor I; TNF, tumor necrosis factor; ↓, reduction; ↑, induction; →, no effect.

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Supplementary Table 9. Neuroprotective effects of resveratrol in animal models.

Neurodegenerative Model	Animal Model	Treatment	Effects and Mechanisms	Reference
Parkinson	Male Swiss mice exposed to paraquat/ maneb	10 mg/kg bw/day (ip) / 9 weeks	↑TH/Neu positive cells; ↓Fluoro-Jade B-positive neurons; ↑Dopamine levels;↑VMAT-2 expression; ↓TNFα, IL-1β ↓MT-III;↓p-p53, Bax; ↑ cyp2d22 expression; ↓NF-κB activation; ↓ASK-1, p38MAPK, HO-1	[1]
	Transgenic mice overexpressing PGC-α treated with MPTP	20 mg/kg (ip) / 24h	↓dopaminergic neurons cell death; ↑TH, DAT in SNc; ↑SOD, SOD2, Trx2; PGC-α	[2]
	Male Wistar rats injected of 6-OHDA	20 mg/kg (po) / 2 weeks	↓rotating frecuency behavior; ↑dopaminergic and nigral cell survival; ↓ROS; ↑T-AOC	[3]
	Male Wistar rats injected of 6-OHDA	Pretreatment 20 mg/kg bw/day (ip) / 15 days	↓circling behavior; ↑muscular coordination; ↓TBARS, PC; ↑GSH; ↑Na+/K+-ATPase activity; ↑Dopamine and DOPAC; ↓DA-D2 receptor binding; ↑TH; ↓COX-2; ↓PLA2 activity	[4]
	Sprague–Dawley injected of 6-OHDA	10, 20, 40 mg/kg bw/day (po) / 10 weeks	↓circling behavioral;↓dopaminergic neurons degeneration;↓COX-2, TNFα	[5]
	Male Balb/C mice treated with MPTP	20 mg/kg (iv) / 7 days	↑motor coordination; ↓muscle rigidity; ↓DHBA; ↓neuronal damage	[6]
	C57BL/6 injected MPTP ip	Pretreatment 50 mg/kg bw/day (ig) / 8d; 100 mg/kg bw/day (ig) / 15 days	↑Striatal DA; ↑TH; ↓nigral neuron death	[7]
Ischemia/reperfusion hypoxia/reperfusion	Male Wistar rats	30 mg/kg/day (ip) / 7d before ischemia	↓Fluoro-Jade B-positive neurons; ↓ROS, NO, MDA; ↓SOD, GPx; ↑CAT; ↑Na+,K+-ATPase activity	[8]
	Male Sprague–Dawley rats	Pretreatment 2×10^{-3}, 2×10^{-4}, 1×10^{-4}, 2×10^{-5} mg/kg (iv)	↓Infarct area; ↓efferent renal activity;↑GRP78, GRP94	[9]
	Male Sprague-Dawley rats	15, 30 mg/kg (ip) / 7 days before surgery	↑Neurological score; ↓Infarct volume; ↓MDA; ↑SOD ;↓Apoptosis (Casp3 , TUNEL); ↑Nrf-2; ↑HO-1	[10]
	Male Sprague-Dawley rats	30 mg/kg (ip) / 7 days	↓ neurological deficit score; ↓lactate release; ↑glucose levels; ↑ATP and EC levels; ↑adesonine and inosine; ↓hipoxanthine and xanthine; ↓MDA, XO activity	[11]
	Male and female C57BL/6 mice	1, 2.5, 5 mg/kg (iv) / administered 3 or 6h after arterial oclusion	↓Infarct volume; ↓IL-1β, TNFα; ↓microglial activation (Iba1); ↓ROS	[12]

	Male Sprague–Dawley rats	30 mg/kg (ip) / 7 days before ischemia	↓Infarct volume; ↓ neurological deficit score; ↓ release Asp, Glu; ↓ GABA, Gly, Tau;↓ PEA, D-ser	[13]
	Sprague–Dawley rats	10-100 mg/kg (ip) / 48 h before the induction of 8 min of asphyxial cardiac arrest	↑normal neuron number; ↑SIRT1 activity; ↓UCP2; ↑ADP/O ratio	[14]
	Male Wistar rats	10^{-7} g/kg (iv) twice / 15 min pre-occlusion and at the time of reperfusion (2h post-occlusion)	↓LPO, H_2O_2, G6-PD, LDH; ↑PC, GSH; ↑ATP, MT, HSP70; ↓Apoptosis (cytochrome c release); ↓DNA damage; ↓Brain edema, infarct volume; ↓Behavioral deficits	[15]
	Male Balb/c mice	50 mg/kg/day (po) / 7 days	↓Infarct volume; ↓ neurological deficit score; ↑microvessels; ↑MMP-2, VEGF	[16]
	Male Long-Evans rats	0.01, 0.1, 1 μg/kg (iv) / after 1h MCA occlusion	↓LDH plasma; ↑NO plasma; ↓iNOS; ↑eNOS; ↓infarct volume; ↓MDA	[17]
	Male Wistar rats	20 mg/kg (iv) / after ischemia	↑hippocampal blood flow; ↑NO; ↓DHBA; ↓SOD activity	[18]
	Male Balb/C	50 mg/kg (po) / 7 days	↓infarct area; ↓MMP-9 expression & activity	[19]
	Male New Zealand rabbits	1, 10 mg/kg / 30 min before SCI	↑Tarlov score; ↓neuronal damage; ↓MDA; ↑NO	[20]
	Long-Evans rats	Pretreatment /treatment groups 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9} g/kg (iv) / 15 min before trauma	↓infarct volume	[21]
	Male and Female Wistar rats	90 mg/kg (ip) / after hypoxia	↑Righting reflex performance; ↑Motor coordination;↑ Reference memory; ↓Brain injury; ↓Demyelinization	[22]
	Male and female C57BL/6-J neonatal	2 μg/kg, 200 μg/kg, 20 mg/kg (ip)	↓Casp 3; ↓Calpain; ↓Tissue loss	[23]
		100 mg/kg (ip) / after trauma	↑Locomotor activity; ↑Memory; ↑neuron survival	[24]
	Male Wistar rats	pretreated with 20 mg/kg (ip) / 21 days and subjected to focal ischemia by MCA occlusion	↓motor impairment; ↓infarct volume; ↓MDA; ↑GSH	[25]
Diabetic neuropathy	STZ-induced diabetes in male Sprague–Dawley rats	10, 20 mg/kg /2 weeks (6 weeks after induction)	Improvement conduction velocity; ↓TNFα, IL-6, COX-2 in sciatic nerve; ↓MDA; ↓NF-κB activation	[26]
	STZ-induced diabetes in Wistar rats	10, 20mg/kg bw day (ip) / 30days (1 week after induction)	↑ATP & ADP hydrolysis; ↓AchE activity	[27]
	Male Wistar rats STZ-induced diabetes	10 mg/kg bw/day (ip) / 6 weeks	↓MDA, XO, NO; ↑GSH	[28]
Alcohol spectrum disorders	Long Evans rat pups exposed to ethanol	2, 20, 40, 100 mg/kg twice (po) / 24 h (1 h before ethanol exposure)	↓Apoptosis (Casp3 , TUNEL) ; ↑Cerebellar granule cell survival; ↓ROS; ↓Thiol levels, MDA, 8-isoPGF2α; ↑SOD; Nfr2	[29]
	Wistar male pups exposed to ethanol	10, 20 mg/kg (po) / 22 days	↑Memory; ↑GSH. SOD, CAT; ↓AChE cortex and hippocampus; ↓LPO; ↓TNFα, IL-1β, TGF-β1;↓Casp3; ↓NF-κB activation	[30]
	middle-aged C57BL/6N female exposed to ethanol	44.2 mg/kg bw/day in combination with etanol / 6 weeks	↑Spatial memory	[31]

Alzheimer's disease	Male Sprague–Dawley treated with Aβ i.c.v	100 μM/5 μl/day (icv) / 7 days	↓hippocampal Aβ accumulation; ↑Spatial memory; ↓iNOS, MDA; ↓neuronal death; ↑HO-1	[32]
	Male Wistar rats injected of colchicine i.c.v.	10, 20 mg/kg (po) / 25d beginning 4 days prior to colchicine	↓MDA, NO_2; ↑GSH, AchE activity	[33]
	Sprague Dawley male rats were treated with kainic acid	30 mg/kg bw/day (ip) / 5 days	↓hippocampal neurons cell death; ↓Glial activation	[34]
	Male Wistar rats	8 mg/kg bw/day in water / 43-45 days	↓GAD activity (neuron cell death)	[35]
Spinal cord injury	Sprague Dawley rats	200 mg/kg 3 times/ day (ip) / 3 days after injury	↑BBB score; ↓Neural damage; ↑SOD; ↓MDA; ↓TNFα, IL-1β, IL-10, MPO; ↓Apoptosis; ↓Bax, Casp3; ↑Bcl-2	[36]
	Male Wistar rats	100 mg/kg (ip) / after injury	↑Motor Function score; ↓Lesion area; ↑GSH; ↓MDA, XO, NO	[37]
	Male Wistar rats	100 mg/kg (ip) / after injury	↓Lesion area; ↑GSH; ↓MDA, XO, NO	[38]
	Sprague-Dawley rats of either sex	50, 100 mg/kg bw (ip) / after injury	↓edema; ↓MDA; ↓LDH activity; ↓cell damage; ↑Na+, K+-ATPase activity	[39]
Huntington disease	Male Sprague–Dawley rats injected of nitropropionic acid	100 mg/kg (ip) / 4 weeks (5 days/week)	↓Motor nerve conduction velocity; ↓axonal degeneration sciatic nerve	[40]
	Wistar rats injected of 3-nitropropionic acid	5, 10 mg/kg bw /day (po) / 8 d beginning 4 days prior to 3-nitropropionic acid administration	↑Motor Function score and memory; ↑GSH, SQR; ↓MDA, NO	[41]
Chronic constriction injury (CCI)	Male Sprague-Dawley rats	100 mg/kg (ip) post-injury	↑motor performance; ↑visuospatial memory; ↓Contusion volume; ↓Hippocampal cell loss	[42]
Multiple sclerosis model	old female SJL/J mice with experimental autoimmune encephalomyelitis	500-1000 mg/kg (po) / 4-6 days	↓Optical neuronal damage; ↓Neuronal disfunction; ↓Loss of axons; ↑SIRT1 activation	[43]
chronic fatigue murine model	Female old BALB/c mice repeated injections of Brucella abortus antigen	40 mg/kg bw/day (po) / 4 weeks	↑Daily running; ↑hippocampal/body weight; ↑Neurogenesis; ↑BDNF; ↓Apoptosis (TUNEL); ↓acetylated-p53	[44]
Not related to pathologies	C57 BL6 mice	200 mg/kg/day (po), 100 mg/kg/day (sc) / 4 weeks	↑MnSOD expression & activity; ↑CAT, GPx activity	[45]
	Male Wistar rats	1.25-25 mg/kg bw/day (ip) / 7 days	↓MDA; ↑Fe-SOD, CAT, POD	[46]

6-OHDA, 6-hydroxydopamine; 8-iso-PGF2α, 8-iso-prostaglandin-F2α; AchE, acetylcholinesterase; ADP, adenosine diphosphate; ADP/O, adenosine diphosphate-oxygen ratio; AMPK, adenosine monophosphate activated protein kinase; ASK-1, Apoptosis signal-regulating kinase 1; ATP, Adenosine triphosphate; Aβ, amyloid beta peptide; Bax, Bcl2-associated X protein; BBB score, Basso, Beattie and Bresnahan score; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; Casp3, caspase 3; CAT, catalase; COX-2, cyclooxygenase 2; CYP2d22, cytochrome P450, family 2, subfamily d, polypeptide 22; DA-D2, Dopamine D2 receptor; DAT, dopamine transporter; DHBA, dihydroxybenzoic acid; DOPAC, 3,4-Dihydroxyphenylacetic acid; D-ser, D serine; EC energy charge; eNOS, endotelial nitric oxide synthetase; FeSOD, iron superoxide dismutase; G6-PD, glucose-6-phosphate dehydrogenase; GABA, neurotransmitter gamma-aminobutyric acid; GAD, glutamate decarboxylase; Gly, glycine; GPx, glutathione peroxidase; GRP78, endoplasmic reticulum chaperone protein GRP78; GRP94, endoplasmic reticulum chaperone protein GRP94; GSH, glutathione; HO-1, heme oxygenase; HSP70, 70-kDa heat-shock protein; Iba1 ionized calcium binding adaptor molecule 1; icv, intracerebroventricularly; ig, intragastrically; IL, interleukin; iNOS, inducible nitric oxide synthase; ip, intraperitoneally; LDH. lactate dehydrogenase; LPO, lipoperoxidase; MDA, malondialdehyde; MMP, matrix metalloproteinase; MnSOD, manganese superoxide dismutase; MPO, myeloperoxidase; MT, metallothionein; N_2O, nitrous oxide; NFkB, nuclear factor kappa B; Nfr2, nuclear factor (erythroid-derived 2)-like 2; NO, nitric oxide; P38MAPK, p38 mitogen-activated protein kinases; p53, tumour protein 53; PC, protein carbonyl; PEA, phosphoprotein enriched in astrocytes; PGC-α, peroxisome proliferator-activated receptor gamma coactivator 1; PLA2, phospholipase A2; po, per oral; POD, peroxidase; ROS, reactive oxygen species; sc, subcutaneously; SIRT1, sirtuin 1; SNc, substantia nigra cells; SOD, superoxide dismutase; SQR, sulfide quinone reductase; STZ, streptozotocin; T-AOC, total antioxidant capacity; Tau, taurine; TBARS, thiobarbituric acid reactive substances; TGF-β1, transforming growth factor β1; TH, tyrosine hydroxylase; TNFα, tumour necrosis factor alpha; Trx2, thioredoxin 2; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling ; UCP2, mitochondrial uncoupling protein 2; VMAT2, vesicular monoamine transporter 2; XO, xanthine oxidase. Effect is indicated by ↓: reduction; ↑: induction; p-: phosphorylate status.

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Supplementary Table 10. Anti-aging effects of resveratrol in animal models.

Animal Model	Treatment	Effects and Mechanisms	Reference
S. cerevisiae	2-5 μM / 19h	↑yeast replicative lifespan (70%)	[1]
C. elegans *D. melanogaster*	100 μM / thorought life	↑lifespan (14%) ↑lifespan (29%)	[2]
Nothobranchius furzeri	24 μg/g food; 120 μg/g food / from adulthood until death	↑median (33%) and maximum (27%) lifespan; ↓cognitive decline; ↑locomotor activity; ↓neurofibrillary degeneration	[3]
C57BL/6NIA mice	0.04% in high-fat diet / from middle age until death	↓risk of death (31%); ↑motor skills; ↑insulin sensitivity; ↑AMPK in liver; ↓Organ pathology	[4]
C57Bl/6J mice	200 or 400 mg/kg/day with high-fat diet / 15 weeks	↓fat body mass; ↑O_2 consumption; ↑mitochondria structure (size and DNA content); ↑aerobic capacity in muscle; ↑motor function; ↓PGC-α activity	[5]
Nothobranchius guentheri	200 μg/g food / throughout lifespan	↑20% mean lifespan (23% ♂, 13% ♀); ↓Fluoro-Jade B-positive neurons ; ↑Cognitive ability (learning & memory); ↑locomotor activity; ↓Senescence (SA-β-Gal activity); ↓SOD, GPx	[6]
Wistar male rats middle-aged (12 months old) and aged (21 months old)		↓hipersensitivity response; ↑KLH, IG, IG1,IG2α	[7]
Honey bees four-day-old	30, or 130 μM / from adulthood until death	↓Gustatory responsiveness; ↑Lifespan 35%; ↓Food consumption	[8]
Male Wistar rats	low-RES diet (0.0015 mg/kg of chow) and high-RES diet (4 mg/kg of chow) / from 12 days until death	↓p53 expression in vascular tissue; ↑telomere length in aorta cells; ↑telomerase activity in aorta cells	[9]
Mice	50 mg/kg / from 14 months until 30 months of age	↑β-catenin expression in aged heart; ↑Wnt pathway	[10]
SIRT1 knockout mice	25-30 mg/kg (po); 215-235 mg/kg (po) / from 14 months to 30 months of age	↑mitochodrial biogenesis; ↓glucose levels; AMPK/SIRT1	[11]
Mice treated with benzopyrene (lung cancer)	5.7 μg/mL in water	↓premature mitochondrial senescence	[12]
Microcebus murinus	200 mg/kg (po)/ 33 months	↓plasma glucose; ↓insuline; ↓HOMA-IR index	[13]
UM-HET3 mice (heterogeneous mice)	50 mg/kg / from 4 months throughout lifespan	↓body weight in ♀ No effect on survival or locomotor activity	[14]
Microcebus murinus	200 mg/kg (po)	↑active wake-time; ↓parodoxical sleep; ↑mitochodrial biogenesis; ↓slow-wave sleep	[15]
C57BL/6J mice	20 mg/kg (ip), 400 mg/kg (po) / 14 weeks	↑cAMP skeletal muscle and adipose tissue; ↑mitochondrial content muscle	[16]

Wistar male rats High fat/sucrose diet	50, 100 mg/kg / 14 weeks	↓weight; ↓aorta senescence (SA-β-gal); ↓ROS aorta; ↓NADPH oxidase p47phox; ↑SIRT1	[17]
Drosophila melanogaster	100, 200, 400 μM (po) / throughout lifespan	↑mean lifespan ♀ fed high fat diet; ↑mean lifespan ♀ fed high protein diet; ↑mean lifespan sod1RNAi females; ↓dIlp3 & dIlp5; ↓GstD1, HSP68; ↓Prx2540-1 & Prx6005	[18]
Drosophila melanogaster	25-800 μM (po)	↑body weight; ↓body lipid content ♀; ↑preadult viability; ↑longevity ♀; ↑locomotor activity ♂; ↑SOD, CAT ♀& ♂	[19]
C57/BL6 mice middle-aged (18 months)	0.05% diet / 10 months	↑MnSOD activity in muscle; ↓H_2O_2, MDA; ↑fast-twitch fiber contractile function	[20]
C57BWrnΔhel/Δhel	0.04% diet / 9 months	↓liver steatosis; ↓liver sinusoidal endothelial defenestration; ↓HOMA-IR index; ↓DNA damage cardiac tissue; ↓MDA (heart & liver); ↑protein carbonylation; ↓AMPK-α; ↓FASN expression; ↑Glutation metabolism pathway; ↑glycolisis/gluconeogenesis; ↑piruvate metabolism; ↑insulin signaling pathway	[21]
Caenorhabditis elegans	0.5-5 μM	↑mean lifespan; ↑maximum lifespan	[22]
F2 hybrid four-way cross mice (CB6F1 x C3D2F1 (C3H x DBA/2) of three age groups	1.50–2.27 mg/kg bw (po) / 6-12 months	Spleen cells; ↑CD4+, CD8+, CD4+-CD25+ old mice; ↑CD4+,-CD69+ middle age mice; Intracellular CD4+ spleen cells: ↑IL-2, IL-4, IL-10, IFN-γ young mice; ↓IL-4, IL-5, IL-10 middle age & old Extracelular: ↑IL-2, IL-4, IL-10 middle age & old; ↓IFN-γ, TNFα , IL-6 middle age & old; ↓8OHdG	[23]
B6C3F1 mice.	50 mg /kg of diet / from 15 to 30 months of age	↓C4, csprs, Pah, Cxcl14, Scap2 in heart; ↓c1qa in cerebellum	[24]
F2 hybrid four-way cross mice (CB6F1 × C3D2F1 (C3H × DBA/2)) of three age groups	14.09 ± 3.35 mg/L in water / 6-12 months	↓8OHdG liver, kidney young & middle age; ↓8OHdG heart middle age & old; ↓8-iso-PGF2α old mice; ↓PCC liver in old mice; ↓PCC kidney middle age and old mice	[25]
Male C57Bl/6 mice 1 year old	15 mg/kg (po) / 12 months	↑vascular density in brain; ↑cognitive function; ↓microvascular abnormalities	[26]
Senescence-accelerated mice (SAM)	0.2% (w/w) diet (po) / 13 weeks	↑endurance capacity; ↓body weight; ↑adiponectine, Hb; ↓insulin, TG, glucose, Serum and EDL TBARS; ↑oxygen consumption; ↑PGC-1β RNA; ↑CYOX III, IV, MCAD	[27]
Male B6C3F(1) mice	1.25 mg/kg (po) / from 2 to 5 months of age	↑Pdk4, Ucp3	[28]
Male C57BL/6NIA	0.04% resveratrol (po) / beginning at one year of age	↑motor coordination; ↓vascular dysfunction ; ↑aortic elasticity; ↓cataract formation ↑bone mineral density; ↓functional decline; ↓endothelial apoptosis; ↓TNFα, IL-1β, IL-6, ICAM-1, iNOS	[29]
Male C57BL/6×C3H/He F1 hybrid mice	50 mg /kg diet/ starting at 2 & 14 months of age until 30 months	↓cardiac dysfunction; ↓glucose levels; ↓insuline resistence; ↑PGC1-α; ↑F2-isoprostanes in heart &brain	[30]

8-iso-PGF2α, 8-iso-prostaglandin-F2α; 8OHdG, 8-Oxo-2'-deoxyguanosine; AMPK, adenosine monophosphate activated protein kinase; C1qa, complement component 1q; C4, complement component 4; cAMP, cyclic adenosine monophosphate; CAT, catalase; CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; CD25, cluster of differentiation 25; CD69, cluster of differentiation 69; Csprs component of Sp100-rs; Cxcl14, chemokine (C-X-C motif) ligand 14; CYOX, cytochrome c oxidase; dILp, insulin related peptide; EDL, extensor digitorium longus; FASN, fatty acid synthase; GPx, glutathione peroxidase; GstD1, glutathione S transferase D1; HSP68, heat shock protein 68; HOMA-IR, homeostatic model assessment-insulin resistance; ICAM-1, intercellular adhesion molecule 1; IFN-γ, interferon-gamma; IG, immunoglobulin; IL-2, interleukin 2; IL-4, interleukin 4; IL-5, interleukin 5; IL-6, interleukin 6; IL-10, interleukin 10; IL-1β, interleukin 1-beta; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; KLH, keyhole limpet hemocyanin; MCAD, medium-chain acyl-CoA dehydrogenase; MDA, malondialdehyde; MnSOD, manganese superoxide dismutase; NADPH, nicotinamide adenine dinucleotide phosphate; p53, tumour protein 53; Pah, phenylalanine hydroxylase; Pdk4, pyruvate dehydrogenase kinase isoform 4; PCC, acetyl-CoA carboxylase; PGC-β, peroxisome proliferator-activated receptor gamma coactivator 1 beta; Prx2540-1, peroxiredoxin 2540-1; Prx6005, Peroxiredoxin 6005; ROS, reactive oxygen species; SA-β-Gal, senescence-associated beta-galactosidase; SIRT1, sirtuin 1; SKAP2, src kinase associated phosphoprotein 2; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; TG, tryglyceride; TNFα, tumour necrosis factor alpha; Ucp3, mitochondrial uncoupling protein 3. Effect is indicated by ↓: reduction; ↑: induction; p-: phosphorylate status

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Supplementary Table 11. Human trials dealing with resveratrol and registered at clinicaltrials.gov.

Status*	Trial Title and Features	
Active, not recruiting	Resveratrol With or Without Piperine to Enhance Plasma Levels of Resveratrol	
	Condition:	Pharmacokinetics
	Interventions:	Dietary Supplement: Resveratrol; Dietary Supplement: Resveratrol 2.5 g with 5 mg piperine; Dietary Supplement: Resveratrol 2.5 g with 25 mg piperine
	Gender:	Both
	Number Enrolled:	24
	Study Design:	Allocation: Randomized; Endpoint Classification: Pharmacokinetics Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Prevention
	Start Date:	March 2011
	Outcome Measures:	Blood levels of study drugs; Side effects of study drugs
Active, not recruiting	A Study of Resveratrol as Treatment for Friedreich Ataxia	
	Condition:	Friedreich Ataxia
	Intervention:	Drug: Resveratrol
	Gender:	Both
	Number Enrolled:	30
	Study Design:	Allocation: Non-Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Open Label; Primary Purpose: Treatment
	Start Date:	April 2011
	Outcome Measures:	Lymphocyte frataxin level; Oxidative stress markers; Clinical rating scales of ataxia; Echocardiogram measures; Pharmacokinetic studies of resveratrol
Active, not recruiting	Resveratrol for Improved Performance in the Elderly	
	Condition:	Memory
	Interventions:	Dietary Supplement: Placebo; Drug: Low dose Resveratrol; Drug: High dose Resveratrol
	Gender:	Both
	Number Enrolled:	30
	Study Design:	Allocation: Randomized; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
	Start Date:	November 2009
	Outcome Measures:	Safety Outcomes; Cognitive Outcomes; Physical Outcomes
Active, not recruiting	The Effects of Resveratrol Supplementation on Measurements of Health and Human Performance	
	Condition:	Inflammation
	Interventions:	Dietary Supplement: resveratrol; Other: Placebo Comparator: Sugar Pill
	Gender:	Both

	Number Enrolled:	44
	Study Design:	Allocation: Randomized; Endpoint Classification: Safety Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver); Primary Purpose: Treatment
	Start Date:	November 2010
	Outcome Measures:	Vascular function; Body fat percentage; inflammation biomarkers; cognitive function
Active, not recruiting		Regulation of Intestinal and Hepatic Lipoprotein Secretion by Resveratrol
	Conditions:	Dyslipidaemia; Insulin Resistance
	Intervention:	Drug: Resveratrol
	Gender:	Both
	Number Enrolled:	15
	Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Crossover Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Basic Science
	Start Date:	October 2011
	Outcome Measures:	Examine the effect of resveratrol on ApoB 100 and ApoB 48 production in humans; Assess the change in insulin sensitivity with resveratrol treatment
Active, not recruiting		Randomized Trial of a Nutritional Supplement in Alzheimer's Disease
	Condition:	Alzheimer's Disease
	Interventions:	Dietary Supplement: Resveratrol with Glucose, and Malate; Dietary Supplement: Placebo
	Gender:	Both
	Number Enrolled:	60
	Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Treatment
	Start Date:	January 2008
	Outcome Measures:	Alzheimer Disease Assessment Scale (ADAScog); CGIC
Active, not recruiting		Resveratrol in Postmenopausal Women With High Body Mass Index
	Condition:	Healthy, no Evidence of Disease

	Outcome Measures:	Change in serum estradiol levels from baseline (BL) to post-intervention (PI) in postmenopausal women with high BMI; Change in other circulating sex-steroid hormones, including serum estrone, testosterone, and sex hormone-binding globulin (SHBG), from BL to PI; Change in serum levels of insulin and C-peptide from BL to PI; Change in adipocytokine expression and secretion, measured by serum leptin and adiponectin, from BL to PI; Change in inflammatory markers, measured by serum C-reactive protein, from BL to PI; Change in oxidative stress as measured by urinary 8-iso-PGF2α and 8OHdG, from BL to PI; Safety of resveratrol intervention as measured by reported adverse events and changes in CBC/diff, blood chemistry, and lipids; Correlation between biomarker changes and systemic resveratrol levels
Active, not recruiting		Effects of Resveratrol Supplements on Vascular Health in Postmenopausal Women
	Condition:	Cardiovascular Disease
	Interventions:	Dietary Supplement: ResA; Dietary Supplement: Resveratrol; Dietary Supplement: Placebo
	Gender:	Female
	Number Enrolled:	30
	Study Design:	Allocation: Randomized; Endpoint Classification: Bio-availability Study; Intervention Model: Crossover Assignment; Masking: Double Blind (Subject, Investigator); Primary Purpose: Prevention
	Start Date:	March 2012
	Outcome Measures:	Bioavailability of a novel formulation of resveratrol (ResA) compared to a standard resveratrol supplement; Change in vascular function in response to ResA compared to native resveratrol; Change in platelet reactivity in response to ResA intake
Recruiting		Dietary Polyphenols and Lipid Oxidation
	Condition:	Obesity, Insulin Sensitivity, Type 2 Diabetes Mellitus
	Intervention:	Dietary Supplement: Comparison of different combinations of polyphenols with respect to effects on fat oxidation
	Gender:	Both
	Number Enrolled:	18
	Study Design:	Allocation: Randomized; Intervention Model: Crossover Assignment; Masking: Double Blind (Subject, Investigator); Primary Purpose: Basic Science
	Start Date:	February 2011
	Outcome Measure:	postprandial fat oxidation
Recruiting		Influence of Caloric Restriction and Resveratrol in the Sirtuin System in Women and Men Aged 55 to 65 Years
	Conditions:	Vascular System Injuries; Lipid Metabolism Disorders; Endothelial Disfunction
	Interventions:	Drug: Resveratrol; Behavioral: Caloric restriction
	Gender:	Both
	Number Enrolled:	48
	Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Parallel Assignment; Masking: Open Label; Primary Purpose: Prevention
	Start Date:	August 2012
	Outcome Measures:	Direct evaluation of the Sirtuin 1 levels; Influence of the Sirtuin 1 system on biomarkers and endothelial function.
Recruiting		Resveratrol for Alzheimer's Disease
	Condition:	Alzheimer's Disease

	Interventions:	Drug: Resveratrol; Drug: Placebo
	Gender:	Both
	Number Enrolled:	120
	Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Treatment
	Start Date:	May 2012
	Outcome Measures:	Rate of change over time on putative biomarkers of AD, particularly CSF total tau, CSF Abeta42, CSF Abeta40, and CSF phospho-tau181; Inter-arm differences in the assessment of the safety and tolerability of treatment with resveratrol; Change from baseline in volumetric magnetic resonance imaging (MRI); Change in Mini-Mental State Examination (MMSE); Change in Alzheimer's Disease Assessment Scale-Cognitive (ADAScog); Change in Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL); Change in Clinical Dementia Rating Scale (CDR-SOB); Change in Neuropsychiatric Inventory (NPI); Comparison of the response to treatment of resveratrol based on ApoE genotype; Changes in cognition, mood, and AD CSF and imaging biomarkers associated with changes in insulin and glucose metabolism
Recruiting		Pilot Study of Resveratrol in Older Adults With Impaired Glucose Tolerance
	Condition:	Impaired Glucose Tolerance
	Interventions:	Dietary Supplement: resveratrol; Drug: Placebo
	Gender:	Both
	Number Enrolled:	30
	Study Design:	Allocation: Randomized; Intervention Model: Crossover Assignment; Masking: Double Blind (Subject, Investigator); Primary Purpose: Treatment
	Start Date:	April 2011
	Outcome Measures:	post meal glucose area under the curve; insulin sensitivity
Recruiting		Long-term Investigation of Resveratrol in Obesity
	Conditions:	Obesity; Inflammation; Insulin Sensitivity; Osteoporosis
	Intervention:	Dietary Supplement: Resveratrol
	Gender:	Male
	Number Enrolled:	72
	Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Basic Science
	Start Date:	August 2011
	Outcome Measure:	Changes from Baseline in markers of inflammation (hs-CRP) in blood after 4 months of treatment with either resveratrol or placebo
Recruiting		Long-term Investigation of Resveratrol on Fat Metabolism in Obese Men
	Conditions:	Obesity; Non-alcoholic Fatty Liver Disease

	Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Basic Science
	Start Date:	November 2011
	Outcome Measures:	Hepatic VLDL-TG secretion and peripheral VLDL-TG clearance; Basal and insulin stimulated FFA and glucose turnover; VLDL-TG oxidation; Body composition (fat mass, fat-free mass, percent fat, visceral fat mass); LPL-activity and fat cell size in abdominal and femoral adipose tissue biopsy; Baseline data
Recruiting		Resveratrol and Serum Apo A-I
	Condition:	Dyslipidemia
	Intervention:	Dietary Supplement: Resveratrol capsules
	Gender:	Both
	Number Enrolled:	50
	Study Design:	Allocation: Randomized; Intervention Model: Crossover Assignment; Masking: Double Blind (Subject, Investigator, Outcomes Assessor); Primary Purpose: Basic Science
	Start Date:	January 2011
	Outcome Measures:	ApoA-I level; Endothelial function and arterial stiffness; Endothelial function of the retinal microvasculature; Lipid and glucose metabolism during the fasting and postprandial phase; biomarkers for low-grade systemic inflammation and endothelial function
Recruiting		Resveratrol and Type 2 Diabetes
	Condition:	Type 2 Diabetes
	Interventions:	Dietary Supplement: placebo; Dietary Supplement: resveratrol
	Gender:	Male
	Number Enrolled:	24
	Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Crossover Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Treatment
	Start Date:	May 2012
	Outcome Measures:	insulin sensitivity (overall, muscle- and liver specific); muscle mitochondrial oxidative capacity; intramyocellular lipid content; intrahepatic lipid content; intracardiac lipid content; heart function
Recruiting		Resveratrol-Leucine Metabolite Synergy in Pre-diabetes
	Condition:	Impaired Glucose Tolerance
	Interventions:	Dietary Supplement: Resveratrol; Dietary Supplement: resveratrol /HMB; Other: Placebo treatment
	Gender:	Both
	Number Enrolled:	36
	Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Investigator); Primary Purpose: Treatment
	Start Date:	February 2012
	Outcome Measures:	Glucose Control; Metabolic Markers
Recruiting		Resveratrol in Patients With Non-alcoholic Fatty Liver Disease

	Condition:	Fatty Liver
	Interventions:	Dietary Supplement: Resveratrol; Dietary Supplement: Placebo
	Gender:	Both
	Number Enrolled:	48
	Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Treatment
	Start Date:	September 2011
	Outcome Measures:	Change in hepatic steatosis and inflammation; Assessment of tolerability and side-effects
Recruiting		Effect of resVida on Liver Fat Content
	Condition:	Elevated Liver Fat Content and Insulin Resistance
	Interventions:	Dietary Supplement: resveratrol; Dietary Supplement: Placebo
	Gender:	Both
	Number Enrolled:	100
	Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Prevention
	Start Date:	June 2012
	Outcome Measures:	Liver fat content; Body composition; Insulin sensitivity; Intima-media thickness; Blood analytes; Cardiorespiratory fitness
Recruiting		The Effects of Red Wine Polyphenols on Microvascular Dysfunction
	Condition:	Obesity
	Interventions:	Dietary Supplement: Red Wine Polyphenols 600 mg/day; Dietary Supplement: placebo
	Gender:	Both
	Number Enrolled:	60
	Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Treatment
	Start Date:	
	Outcome Measures:	Insulin sensitivity as determined by euglycemic clamp tests; Molecular mechanisms in muscle tissue; Biomarkers such as lipoproteins, adipocytokines, and markers of systemic inflammation; Glucose tolerance as assessed by the area under the curve for glucose (AUCgluc) during a standardized meal test; microvascular function (baseline and during hyperglycemia); Blood pressure 24 hr measurement
Recruiting		Effects of Dietary Interventions on the Brain in Mild Cognitive Impairment (MCI)
	Condition:	Mild Cognitive Impairment

	Start Date:	August 2010
	Outcome Measures:	Alzheimer's Disease Assessment Scale - cognitive subscale; Functional/Structural brain changes; Plasma biomarkers
Recruiting	Evaluation of Oral Lipid Ingestion in Relation to Ovarian Androgen Secretion in Polycystic Ovary Syndrome (PCOS)	
	Condition:	Polycystic Ovary Syndrome
	Intervention:	Drug: Salsalate and resveratrol
	Gender:	Female
	Number Enrolled:	60
	Study Design:	Allocation: Non-Randomized; Intervention Model: Parallel Assignment; Masking: Open Label; Primary Purpose: Basic Science
	Start Date:	February 2012
	Outcome Measures:	White blood cell nuclear factor kappa B (NFkappaB) activation in response to oral lipid ingestion and ovarian androgen secretion in response to human chorionic gonadotropin (HCG) stimulation.; White blood cell NFkappaB activation following oral lipid ingestion in response to 12 weeks of salsalate or PCE administration.; Ovarian androgen secretion following HCG administration in response to 12 weeks of salsalate or PCE administration.; Body composition status measured by DEXA in response to 12 weeks of salsalate or PCE administration.; Insulin sensitivity derived from an OGTT in response to 12 weeks of salsalate or PCE administration.; Ovulation rates documented by serum progesterone in response to 12 weeks of salsalate or PCE administration
Recruiting	Effects of Dietary Interventions on the Aging Brain	
	Condition:	Healthy
	Interventions:	Behavioral: Caloric restriction; Dietary Supplement: Omega-3 (fish oil capsules); Dietary Supplement: Placebo; Dietary Supplement: Resveratrol
	Gender:	Both
	Number Enrolled:	300
	Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Parallel Assignment; Masking: Single Blind (Investigator); Primary Purpose: Prevention
	Start Date:	November 2009
	Outcome Measures:	Auditory verbal Learning Task; Functional/Structural brain changes; Plasma biomarkers
Recruiting	Resveratrol in Type2 Diabetes and Obesity	
	Conditions:	Type 2 Diabetes; Obesity; Insulin Resistance
	Interventions:	Drug: Placebo; Drug: Resveratrol 40 mg oral three times a day; Drug: Resveratrol 500 mg oral once daily.
	Gender:	Both
	Number Enrolled:	102
	Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Parallel Assignment; Masking: Single Blind (Subject); Primary Purpose: Treatment
	Start Date:	December 2008
	Outcome Measures:	NF-Kb; GLP-1
Recruiting	Effect of Resveratrol on Age-related Insulin Resistance and Inflammation in Humans	

	Conditions: Type 2 Diabetes Mellitus; Insulin Resistance Intervention: Drug: Resveratrol Gender: Both Number Enrolled: 80 Study Design: Endpoint Classification: Efficacy Study; Intervention Model: Single Group Assignment; Masking: Open Label; Primary Purpose: Treatment Start Date: March 2008 Outcome Measures: Peripheral Insulin Sensitivity; Hepatic insulin sensitivity; Muscle mitochondrial function; Inflammatory and Anti-inflammatory Markers in adipose tissue; Neuropsychological assessment
Recruiting	A Biological Study of Resveratrol's Effects on Notch-1 Signaling in Subjects With Low Grade Gastrointestinal Tumors Condition: Neuroendocrine Tumor Intervention: Dietary Supplement: Resveratrol Gender: Both Number Enrolled: 7 Study Design: Endpoint Classification: Safety/Efficacy Study; Intervention Model: Single Group Assignment; Masking: Open Label; Primary Purpose: Treatment Start Date: December 2011 Outcome Measures: Notch1 activation in post-treatment tumor biopsy specimens when compared to pretreatment levels; Demonstrate that resveratrol at 5 gm per day will be well tolerated with minimal dose limiting toxicities in this patient population.; Describe the effect of resveratrol on tumor growth as demonstrated by standard cross sectional imaging and tumor markers.
Completed	Resveratrol-enriched Grape Extract (Stilvid) in Primary and Secondary Prevention of Cardiovascular Disease Condition: Cardiovascular Diseases Interventions: Dietary Supplement: Placebo in primary cardiovascular prevention (PP); Dietary Supplement: Placebo in secondary prevention; Dietary Supplement: Grape extract in primary prevention (PP); Dietary Supplement: Grape extract in SP; Dietary Supplement: Resveratrol-enriched grape extract in PP; Dietary Supplement: Resveratrol-enriched grape extract in SP Gender: Both Number Enrolled: 150 Study Design: Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Prevention Start Date: April 2009 Outcome Measures: Apolipoprotein-B; oxidized LDL particles; Plasminogen activator inhibitor type 1 (PAI-1); Adiponectin; C Reactive Protein; Interleukin-6; Interleukin-10; Interleukin-18; sICAM-1; sVCAM-1; D-dimer; Fibrinogen; Glycated hemoglobin; Glucose; GGT; AST; Urate; ALT; LDH; TSH; Thyroxine; ALP; CPK; Bilirubin; Creatinin; Albumin; Total cholesterol; LDL-cholesterol; HDL-cholesterol; Triglycerides; Hematocrit; Hemoglobin; Mean corpuscular volume; Leucocytes; Neutrophils; Lymphocytes; Eosinophils; Platelets; Mean platelet volume; Sedimentation rate volume; Gene expression profile in peripheral blood mononuclear cells (PBMNCs); Total homocystein levels; Measurement of atheroma plaque and carotid intim thickness
Completed	Effects of Resveratrol in Patients With Type 2 Diabetes Condition: Type 2 Diabetes

	Gender:	Male
	Number Enrolled:	10
	Study Design:	Allocation: Randomized; Endpoint Classification: Pharmacokinetics/Dynamics Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Basic Science
	Start Date:	December 2008
	Outcome Measures:	Skeletal muscle sirtuin 1 (SIRT1) expression; Skeletal muscle 5'-AMP-activated protein kinase (AMPK) expression; Skeletal muscle phosphorylated-AMPK-Thr172 (p-AMPK) expression; Skeletal muscle glucose transporter type 4 (GLUT 4) expression; Glycated hemoglobin (HbA1c); Body weight; Insulin sensitivity; Lipid profile; Energy expenditure; Physical activity level; Abdominal adipose tissue distribution; Skeletal muscle fibre type composition; Renal function; Liver function
Completed		Resveratrol and Midazolam Metabolism
	Condition:	Healthy
	Interventions:	Drug: Midazolam; Dietary Supplement: resveratrol (single dose); Dietary Supplement: resveratrol (multiple dose)
	Gender:	Both
	Number Enrolled:	6
	Study Design:	Allocation: Non-Randomized; Endpoint Classification: Pharmacokinetics Study; Intervention Model: Parallel Assignment; Masking: Open Label; Primary Purpose: Basic Science
	Start Date:	July 2010
	Outcome Measures:	Inhibition of midazolam clearance; Resveratrol accumulation
Completed		The Cognitive and Cerebral Blood Flow Effects of Resveratrol
	Condition:	Cognitive and Cerebral Blood Flow Effects of Resveratrol
	Interventions:	Dietary Supplement: Trans- resveratrol; Other: Placebo (silica)
	Gender:	Both
	Number Enrolled:	24
	Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Crossover Assignment; Masking: Double Blind (Investigator, Outcomes Assessor); Primary Purpose: Basic Science
	Start Date:	June 2008
	Outcome Measures:	Modulation of Levels of Total Haemoglobin; Modulation of Deoxygenated Levels of Haemoglobin; Number of Participants With Significant Modulation of Cognitive Performance
Completed		Resveratrol for Patients With Colon Cancer
	Conditions:	Colon Cancer; Cancer

	Outcome Measure:	Test the hypothesis that resveratrol modulates Wnt signaling *in vivo* in colon cancer and normal colonic mucosa
Completed	Anti-inflammatory and Antioxidant Effects of Resveratrol on Healthy Adults.	
	Conditions:	Chronic Subclinic Inflammation; Redox Status
	Interventions:	Dietary Supplement: Resveratrol; Dietary Supplement: resveratrol
	Gender:	Both
	Number Enrolled:	40
	Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Crossover Assignment; Masking: Double Blind (Subject, Caregiver); Primary Purpose: Prevention
	Start Date:	July 2011
	Outcome Measures:	C-reactive protein; TAS (total antioxidant status); 4-hydroxynonenal; nitrotyrosine; endothelial nitric oxide synthase (eNOS)-polymorphism; superoxide dismutase (SOD2)-polymorphism; catalase-polymorphism; interleukin-6; pentraxin 3; tumor necrosis factor-α
Completed	Pilot Study Of The Effects Of Resveratrol On Endothelial Function In Subjects With Type 2 Diabetes Mellitus	
	Condition:	Type 2 Diabetes Mellitus
	Intervention:	Dietary Supplement: Resveratrol
	Gender:	Both
	Number Enrolled:	20
	Study Design:	Allocation: Non-Randomized; Intervention Model: Single Group Assignment; Masking: Open Label; Primary Purpose: Basic Science
	Start Date:	January 2010
	Outcome Measures:	Brachial artery flow-mediated dilation; Blood markers of inflammation, oxidative stress, insulin resistance
Completed	Cerebral Blood Flow Effects of Resveratrol and Piperine in Humans	
	Condition:	Healthy
	Interventions:	Dietary Supplement: Trans- resveratrol; Other: Placebo (silica)
	Gender:	Both
	Number Enrolled:	23
	Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Factorial Assignment; Masking: Double Blind (Subject, Investigator)
	Start Date:	April 2010
	Outcome Measures:	Modulation of levels of total haemoglobin; Modulation of levels of deoxygenated haemoglobin; Modulation of levels of oxygenated haemoglobin; Number of participants displaying significant modulation of cognitive performance
Completed	Use of Resveratrol to Decrease Acute Secondary Brain Injury Following Sports-Related Concussions in Boxers	
	Condition:	Sports Concussion

	Number Enrolled: 12 Study Design: Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Investigator, Outcomes Assessor); Primary Purpose: Treatment Start Date: March 2011 Outcome Measures: To determine the number of adverse events that may be associated with the use of resveratrol in this population.; Cognitive Outcomes; Axonal Injury
Completed	A Clinical Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of SRT501 in Subjects With Colorectal Cancer and Hepatic Metastases Conditions: Neoplasms, Colorectal; Colorectal Cancer Interventions: Drug: Placebo; Drug: SRT501 Gender: Both Number Enrolled: 9 Study Design: Allocation: Randomized; Endpoint Classification: Pharmacokinetics/Dynamics Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator); Primary Purpose: Basic Science Start Date: August 2008 Outcome Measures: To determine the safety and tolerability of SRT501 when administered once daily for 14 days.; To characterize the pharmacokinetic profile of SRT501 in blood and normal and malignant metastatic tissues when administered once daily for 14 days.; To examine the pharmacodynamics of SRT501 activity in both normal and malignant tissue samples and blood.
Completed	Resveratrol Supplementation on Exercise in Healthy Sedentary Adults Condition: Sedentary Lifestyle Interventions: Drug: Resveratrol; Drug: placebo Gender: Both Number Enrolled: 13 Study Design: Allocation: Randomized; Intervention Model: Crossover Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Basic Science Start Date: February 2009 Outcome Measures: Change from baseline in duration of constant load exercise; Change from baseline in aerobic capacity(peak VO2); Number of participants with Adverse Events
Completed	Resveratrol in Healthy Adult Participants Condition: Melanoma (Skin)

		pi levels in blood lymphocytes and serum bilirubin level from baseline to end of resveratrol intervention; Safety as measured by assessing the frequency and severity of adverse events, blood chemistry, and hematology
Completed		Potential Beneficial Effects of Resveratrol
	Conditions:	Metabolic Syndrome; Obesity
	Interventions:	Dietary Supplement: Resveratrol; Other: Placebo
	Gender:	Male
	Number Enrolled:	24
	Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator); Primary Purpose: Basic Science
	Start Date:	October 2010
	Outcome Measures:	Metabolic parameters; Pathways of substrate metabolism.
Completed		Chronic Resveratrol Supplementation in Healthy Humans
	Condition:	Healthy
	Interventions:	Dietary Supplement: Resveratrol; Other: Placebo
	Gender:	Both
	Number Enrolled:	60
	Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Investigator); Primary Purpose: Basic Science
	Start Date:	February 2011
	Outcome Measures:	Chronic modulation of cerebral blood flow; Number of participants with modulated mood; Number of participants with modulated cognitive performance; Number of participants with significant modulation of sleep; Number of participants with significant modulation of health; Number of participants with significant modulation of blood pressure; Number of participants with significant modulation of CBF in MCA
Completed		Resveratrol in Treating Patients With Colorectal Cancer That Can Be Removed By Surgery
	Condition:	Colorectal Cancer
	Interventions:	Drug: resveratrol; Other: immunohistochemistry staining method; Other: immunologic technique; Other: laboratory biomarker analysis; Other: pharmacological study; Procedure: biopsy; Procedure: endoscopic biopsy; Procedure: neoadjuvant therapy
	Gender:	Both
	Number Enrolled:	20
	Study Design:	Allocation: Non-Randomized; Masking: Open Label; Primary Purpose: Treatment
	Start Date:	December 2006
	Outcome Measure:	Concentration of M1G
Completed		UMCC 2003-064 Resveratrol in Preventing Cancer in Healthy Participants
	Condition:	Unspecified Adult Solid Tumor, Protocol Specific

	Number Enrolled:	40
	Study Design:	Masking: Open Label; Primary Purpose: Prevention
	Start Date:	September 2004
	Outcome Measure:	
Completed	Effect of resVida, a Comparison With Calorie Restriction Regimen	
	Conditions:	Obesity; Metabolic Syndrome; Diabetes; Aging
	Interventions:	Dietary Supplement: resveratrol; Other: placebo; Behavioral: Calorie Restriction
	Gender:	Female
	Number Enrolled:	49
	Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator); Primary Purpose: Prevention
	Start Date:	January 2009
	Outcome Measures:	global skeletal muscle gene expression profile; insulin sensitivity; intrahepatic triglyceride content, body composition; blood lipid levels, markers of inflammation and plasma hormones; safety and tolerability
Completed	resVida and Fat Oxidation	
	Condition:	Obesity
	Interventions:	Dietary Supplement: resVida; Dietary Supplement: placebo
	Gender:	Male
	Number Enrolled:	18
	Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Crossover Assignment; Masking: Double Blind (Subject, Investigator); Primary Purpose: Treatment
	Start Date:	October 2009
	Outcome Measures:	difference in fat oxidation between resVida and placebo treated group; difference in mitochondrial biogenesis, function, and lipolysis in adipose and skeletal muscle tissue between resVida and placebo treated group
Completed	Bioavailability Study of Different Dietary Antioxidants in Volunteers	
	Condition:	Cardiovascular Disease
	Intervention:	
	Gender:	Both
	Number Enrolled:	90
	Study Design:	
	Start Date:	September 2009
	Outcome Measures:	AUCt - Area under the serum concentration-time curve from the first time point [t=0] to the time point of the last measured concentration [t(last)]; AUC∞ - Area under the serum concentration-time curve from the time point [t=0] to infinity [∞]; Cmax - Maximum serum concentration; tmax - Time of maximum serum concentration; t½ - Elimination half life; AUC(last)-∞ - Difference between AUC∞and AUCt expressed as percentage value; AUCt/AUC∞ - calculated as quotient of AUCt and AUC∞; f = Cmax/ AUCt (indication of rate of absorption)
Completed	Effects of Peanut and Peanut Butter Consumption on Blood Lipids and Glycemic Control in Adults With Type 2 Diabetes	

	Condition:	Type 2 Diabetes
	Intervention:	Dietary Supplement: Peanuts and peanut butter
	Gender:	Both
	Number Enrolled:	60
	Study Design:	Allocation: Randomized; Intervention Model: Parallel Assignment; Masking: Single Blind (Outcomes Assessor); Primary Purpose: Treatment
	Start Date:	June 2009
	Outcome Measures:	The primary outcome measure is HDL-C; Serum lipids, glucose, HbA1c, anthropometrics and blood pressure
Unknown †		Pilot Study of the Effects of Resveratrol Supplement in Mild-to-Moderate Alzheimer's Disease
	Condition:	Alzheimer Disease
	Interventions:	Dietary Supplement: Longevinex brand resveratrol supplement; Dietary Supplement: placebo
	Gender:	Both
	Number Enrolled:	50
	Study Design:	Allocation: Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Treatment
	Start Date:	September 2008
	Outcome Measures:	cognition; function; behavior
Unknown †		Phase I Biomarker Study of Dietary Grape-Derived Low Dose Resveratrol for Colon Cancer Prevention
	Condition:	Colon Cancer
	Intervention:	Dietary Supplement: grapes
	Gender:	Both
	Number Enrolled:	30
	Study Design:	Allocation: Randomized; Intervention Model: Parallel Assignment; Masking: Open Label; Primary Purpose: Prevention
	Start Date:	January 2008
	Outcome Measures:	Expression and cellular localization of beta-catenin in intestinal mucosa: localization of β-catenin. Expression of Wnt pathway target genes in intestinal mucosa: Wnt target gene expression; Define whether grape supplemented diet affects colonic mucosa cell proliferation. Ki67 staining method will be utilized on the pre- and post-resveratrol biopsy specimens.; Define any side-effects associated with the resveratrol-rich dietary program. Laboratory testing is performed at specified timepoints in this protocol, along with history & physical, for the purposes of toxicity monitoring; Monitor resveratrol content of grapes throughout the course of the study. Grapes will be obtained from the same source as participants monthly throughout the study and the content of resveratrol will be measured.
Unknown †		Dietary Intervention in Follicular Lymphoma
	Condition:	Follicular Lymphoma

	Study Design:	Allocation: Non-Randomized; Endpoint Classification: Efficacy Study; Intervention Model: Single Group Assignment; Masking: Open Label; Primary Purpose: Treatment
	Start Date:	April 2007
	Outcome Measures:	Apoptosis an proliferation rate in tumor cells,; Levels of: proinflammatory cytokines,tumor immune cell infiltrate
Unknown †		Physiological Effects of Grape Seed Extract in Diastolic Heart Failure
	Conditions:	Diastolic Heart Failure; Hypertensive Heart Disease; Heart Failure With Preserved Ejection Fraction; Hypertension; Oxidative Stress
	Intervention:	Drug: grape seed extract (MegaNatural BP, Polyphenolics, Inc.)
	Gender:	Both
	Number Enrolled:	25
	Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Crossover Assignment; Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor); Primary Purpose: Treatment
	Start Date:	August 2010
	Outcome Measures:	Brachial artery flow-mediated dilation (FMD); 24-hour blood pressure; EndoPAT arterial endothelial function; Carotid-femoral pulse wave velocity; Maximal exercise capacity and oxygen consumption; Resting and post-exercise ventricular systolic and diastolic function; Urinary 8-isoprostanes; Heart failure related quality of life
Withdrawn		Safety and Efficacy of a Dietary Supplement in Females With Cellulite
	Condition:	Cellulite (Orange Peel Skin)
	Interventions:	Dietary Supplement: dietary supplement for cellulite (PUFA, resveratrol, lycopene, beta carotene, lutein); Dietary Supplement: Viatmin E
	Gender:	Female
	Number Enrolled:	8
	Study Design:	Allocation: Randomized; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Investigator, Outcomes Assessor); Primary Purpose: Treatment
	Start Date:	May 2011
	Outcome Measures:	Clinical biochemistry (hematology, blood chemistry, blood coagulation); vital signs; adverse events and tolerability; cellulite severity; Thigh circumference; Digital photography; Ultrasound sonography; Magnetic resonance; satisfaction questionnaire; dermatology life quality index; celluquol questionnaire; cutometry; corneometry; skin profilometry; liquichip analysis
Withdrawn		Mechanisms of Metabolic Regulation of Resveratrol on Humans With Metabolic Syndrome
	Condition:	Insulin Resistance

		tabolism (lower LDL, raise HDL and lower triglyceride (TG) levels); and 3) physical activity levels measured by pedometer and 7 day physical activity recall (PAR)
Withdrawn	A Clinical Study to Assess the Safety and Activity of SRT501 Alone or in Combination With Bortezomib in Patients With Multiple Myeloma	
	Condition:	Multiple Myeloma
	Interventions:	Drug: 5.0 g SRT501; Drug: Bortezomib
	Gender:	Both
	Number Enrolled:	24
	Study Design:	Endpoint Classification: Safety/Efficacy Study; Intervention Model: Single Group Assignment; Masking: Open Label; Primary Purpose: Treatment
	Start Date:	March 2009
	Outcome Measures:	Safety and tolerability of SRT501 with or without bortezomib administration.; Efficacy and response. Overall response rates will be calculated. Response will be defined as either a CR, PR, MR or SD after every two cycles of therapy.; Pharmacokinetics. Plasma samples will be collected from 15 subjects enrolled for SRT501 concentration during Cycle 1.

*It should be noted that trial status is referred at the time of submission of the present review (October-2012). In addition, some sponsors do not update often the status of the trial.