

### ***In vivo* effects of resveratrol.**

Species	Assay	Daily Dose	Route	Result	Refs
<i>Cancer</i>					
Hamster	N-nitrosobis(2-oxopropyl)amine-induced pancreatic cancer	10 ppm	diet	no significant effect on the multiplicities of pancreatic lesions	1
Mouse	s.c. implanted MDA-MB-231 human breast cancer	25 mg/kg	i.p.	decreased tumor size and microvessel density, increased apoptotic index	2
Rat	1,2-dimethylhydrazine-induced colon carcinogenesis	8 mg/kg	per os	reduced tumor incidence and size, and degree of histological lesions, blocked the rise in liver TBARS and fall in colonic mucosa TBARS when given continuously	3
Mouse	UVB-induced skin cancer	25, 50 $\mu$ mol	top.	delayed onset and decreased incidence of tumorigenesis whether resveratrol was applied pre- or post-UVB	4
Rat	potential chemopreventive effects	50, 300 mg/kg	diet	increased plasma antioxidant capacity, non-significant increase in glutathione-S-transferase activity, no change in vitamin E status	5
Mouse	spontaneous development of mammary tumors	~ 0.2 mg/kg	d.w.	delayed tumor development, decreased size and number of tumors, lung metastases, and HER-2/neu expression, increased apoptosis	6
Mouse	intestinal tumor load in familial adenomatous polyposis	~ 60, 240 mg/kg	diet	decreased number of adenomas (240 mg/kg), and PGE <sub>2</sub> in intestinal mucosa	7
Mouse	s.c. implanted human primary gastric carcinoma	500, 1000, 1500 /48 h	inj.	inhibited tumor growth, increased apoptosis	8
Mouse	UVB exposure	10 $\mu$ mol	top.	decreased edema, hyperplasia, leukocyte infiltration, cell cycle proteins, increased p21 and p53	9
Mouse	benzo[a]pyrene (BaP)-induced lung tumorigenesis	6-8 mg/kg	diet	no change in tumor incidence or multiplicity, CYP1A1 or IB1 expression, or BaP protein adducts	10
Mouse	hepatic implanted H22 hepatoma	10, 15 mg/kg	abd.	36.3%, 49.3% reduction in tumor size, further enhanced by 5-FU	11
Mouse	CTX-induced micronucleus formation, DMBA/croton oil-induced skin cancer	25, 50, 100 mg/kg	gav.	decreased micronucleus formation, ODC activity, and incidence and multiplicity of papillomas, increased latency	12
Mouse	s.c. implanted neuro-2a neuroblastoma	40 mg/kg	i.p.	slowed growth, increased survival from 0 to 70%	13
Mouse	markers of proliferation and tumor development in skin following UVB exposure	10 $\mu$ mol	top.	blocked increases in proliferation (Ki-67 immunostaining), COX and ODC activity, and mRNA and phosphorylation levels of survivin	14
Mouse	COX and ODC activity in liver and lungs before and after NDEA treatment	2.5 mg/kg	oral	decreased ODC and COX activity, blocked induction of ODC and COX by NDEA	15
Mouse	intestinal tumor load in familial adenomatous polyposis	4, 20, 90 mg/kg	diet	non-significant decrease in small intestinal tumors, no effect on large intestinal tumors, decrease in PGE <sub>2</sub> in tumor	16
Rat	s.c. and intracerebral implanted RT-2 gliomas	10, 40, 100 mg/kg	i.p.	slowed tumor growth, angiogenesis, increased apoptosis, host survival for subcutaneous and intracerebral (100 mg/kg) tumors	17
Mouse	UVB irradiation	25 $\mu$ mol	top.	decreased edema, leukocyte infiltration, COX and ODC activity, and oxidative damage	18
Rat	prepubertal MNU-induced mammary carcinomas (post-resveratrol)	10, 100 mg/kg	s.c.	10 mg/kg ineffective, 100 mg/kg increased tumor incidence	19
Rat	s.c. implanted AH109A hepatoma	~ 1, 5 mg/kg	diet	decreased levels of LDL, VLDL, and lipid peroxide, non-significant decrease in tumor growth	20
Mouse	hepatic implanted H22 hepatoma	5, 10, 15 mg/kg	abd.	decreased tumor size (10, 15 mg/kg), cyclin B1 and p34cdc2	21
Rat	lymphocytic DNA integrity	1-100 mg/kg	diet	increased lymphocytic DNA damage	22
Mouse	benzo[a]pyrene-induced lung damage	50 /wk	inj.	reduced DNA-adduct formation, CYP1A1 expression, and apoptosis	23
Mouse	implanted (right axilla) H22 hepatoma	500, 1000, 1500 mg/kg	i.p.	31.5%, 45.6%, 48.7% reduction in tumor size	24
Mouse	DMBA-induced, TPA-promoted skin cancer	1, 5, 10, 25 $\mu$ mol (twice/wk)	top.	decreased tumor formation (ED <sub>50</sub> ~ 6 $\mu$ mol)	25
Rat	DMBA-induced mammary carcinogenesis	~ 12-15 mg/kg	diet	no effect on body weight, decreased incidence and multiplicity of tumors, COX-2, MMP-9, and NF $\kappa$ B activity	26
Rat	NMBA-induced esophageal tumorigenesis	1, 2 mg/kg	per os or i.p.	reduced number and size of tumors, non-significant decrease in tumor incidence, decreased COX-1, COX-2, and PGE <sub>2</sub>	27
Mouse	foodpad or intrasplenic implanted B16M melanoma	20 (twice/day) or 23 mg/L	oral or d.w.	ineffective for solid tumor, decreased hepatic invasion, no effect on host survival	28
Mouse	implanted 32Dp210 myeloid leukemia	8, 40, 80 mg/kg (5	oral	non-significant increase in survival at 80 mg/kg (2/14 animals vs. 0 in other groups)	29

		days/wk)			
Mouse	s.c. implanted 4T1 breast cancer	1, 3, 5 mg/kg	i.p.	no effect on tumor growth, metastasis, body weight, organ histology, or estrous cycling	30
Mouse	benzo[a]pyrene (BaP)-induced sperm damage	50 /wk	s.c.	decreased DNA adducts and apoptosis	31
Rat	<i>N</i> -methyl- <i>N</i> -nitrosourea-induced mammary tumorigenesis	10, 100 mg/kg (5 days/wk)	i.g.	no effect on body weight, decreased incidence and increased latency of tumors (100 mg/kg)	32
Mouse	intestinal tumor load in familial adenomatous polyposis	0.3-0.4 mg	d.w.	decreased incidence of tumors in large and small intestine, and expression of cell cycle proteins	33
Mouse	s.c. implanted T241 fibrosarcoma	1 mg/kg	d.w.	decreased tumor growth	34
Mouse	s.c. implanted Lewis lung carcinoma	0.6, 2.5, 10 mg/kg	i.p.	decreased tumor volume, weight, metastasis, and neovascularization (2.5, 10 mg/kg)	35
Mouse	intramuscular implanted B16-BL6 melanoma	50 mg/kg	i.p.	decreased tumor volume, no effect on body weight, mortality, or lung colonization	36
Rat	(AOM)-induced colorectal aberrant crypt foci (ACF)	0.2 mg/kg	d.w.	reduced number and multiplicity of ACF, increased bax, decreased p21 in normal mucosa	37
Mouse	lung tumorigenesis induced by a mixture of benzo[a]pyrene and 4-(methyl-nitrosoamino)-1-(3-pyridyl)-1-butanone	500 ppm	diet	no effect on body weight, incidence or multiplicity of tumors	38
Rat	innoculated Yoshida AH-130 ascites hepatoma	1 mg/kg	i.p.	25% decrease in tumor cell number, increase in G <sub>2</sub> /M cells, appearance of an aneuploid peak	39
Mouse	DMBA initiated, TPA-promoted skin cancer	1, 5, 10, 15 μmol (twice weekly)	top.	decrease in multiplicity (98%) and incidence (88%) of skin tumors	40
<i>Heart Disease</i>					
Rat	cardiac hypertrophy induced by partial nephrectomy	10, 50 mg/kg	gav.	decreased systolic blood pressure, heart weight, and serum endothelin and angiotensin II concentrations, increased serum NO	41
Rat, Guinea Pig	aconitine, ouabain, and coronary ligation-induced arrhythmia	5, 15, 45 mg/kg	i.v.	increased the amount of aconitine or ouabain required to cause arrhythmia, decreased arrhythmia, ventricular tachycardia, and mortality following coronary ligation	42
Rabbit	development of atherosclerosis on a 1.5% cholesterol diet	3 mg/kg	d.w.	no effect on plasma cholesterol or triglycerides, decreased atherosclerotic plaques and thickness of the intima layer in thoracic aorta, prevented loss of flow-mediated dilation	43
Rat	permanent left anterior descending coronary artery occlusion	1 mg/kg	d.w.	reduced infarct size, increased capillary density, thioredoxin-1, heme oxygenase-1 (HO-1), and VEGF expression in heart, and improved ventricular function, all effects except thioredoxin-1 and HO-1 expression blocked by an HO-1 inhibitor	44
Rat	fructose-induced biochemical cardiovascular changes	10 mg/kg	gav.	prevented the increase in systolic blood pressure, cardiac hypertrophy, and TBARS, restored mesenteric and cardiac eNOS,	45
Hamster	aortic fatty streak accumulation	0.1428 mg/kg	gav.	decreased aortic fatty streak area and serum cholesterol, no effect on plasma antioxidant capacity or apolipoprotein-B, nonsignificant increase in apolipoprotein-A1	46
Hamster	development of atherosclerosis on an atherogenic diet	0.1428 mg/kg	gav.	decreased aortic fatty acid streak area, nonsignificant decrease in apolipoprotein A1, no effect on plasma antioxidant capacity	47
Mouse	atherothrombotic tendency after laser-induced damage to endothelium	9.6, 96 mg/kg	diet	~30% reduction in atheroma, ~25% decrease in thrombus size, no change in plasma lipids	48
Guinea Pig	cardiac DT-diaphorase and catalase activity, menadione-induced ROS	~ 14 mg/kg	d.w.	increased DT-diaphorase and catalase, decrease in menadione-induced ROS	49
Rabbit	endothelial function on a hypercholesterolemic diet	3 mg/kg	i.g.	improved flow-mediated dilation, partially blocked decrease in nitric oxide and increase in endothelin 1	50
Rat	inflammatory responses in mesenteries exposed to ischemia/reperfusion (IR), hypoxanthine/xanthine oxidase (HX/XO), platelet activating factor (PAF), or leukotriene B <sub>4</sub>	0.7 mg/kg	inj.	reduction in adherent and emigrated leukocytes and venular albumin leakage in response to IR, HX/XO, and PAF, but not leukotriene B <sub>4</sub>	51
Rabbit	platelet aggregation on a hypercholesterolemic diet	4 mg/kg	i.g.	reduced platelet aggregation, no effect on LDL, HDL, or total cholesterol	52
Rabbit	serum lipids and platelet aggregation on a hypercholesterolemic diet	4 mg/kg	i.g.	blocked increases in platelet aggregation, no effect on total cholesterol, LDL, HDL, or triglycerides	53
Mouse	TNFα-induced vascular leakage (by liver perfusion with trypan blue)	1 μM	i.p.	complete block of TNFα-induced vascular leakage	54
Rat	urinary and plasma markers of oxidative stress in both genders	1 mg/kg	i.g.	decrease in urinary 8-hydroxyguanosine and plasma glycated albumin, non-significant decrease in hydroperoxide, no change in food intake, b.w., blood pressure, glucose, lipids, albumin	55
Rat	lipid profile, Cu <sup>2+</sup> -dependent formation of thiobarbituric acid reactive substances (TBARS)	20, 40 mg/kg	i.p.	non-significant decrease in triacylglycerides, no change in total, HDL, LDL, or IDL cholesterol, or TBARS in Cu <sup>2+</sup> -treated serum	56
Rabbit	atherosclerotic development on a hypercholesterolemic diet	0.6, then 1 mg/kg	oral	no change in body or liver weight, cholesterol, or LDL oxidation, increase in aortic atherosclerotic lesions	57
Rat	serum lipid levels after feeding an oil mixture	50, 100	oral	reduced total cholesterol and triglycerides in liver, no change in	58

		mg/kg		serum cholesterol, triglycerides, free fatty acids	
Mouse	triglyceride synthesis	25, 50 mg/kg	i.p. or oral	reduced lipogenesis in liver and adipose	58
<i>Ischemic Heart</i>					
Rat	expression of NOS and potential NO targets in heart, ischemia/reperfusion of isolated hearts	2.5 mg/kg	gav.	induction of iNOS and VEGF, followed by KDR and eNOS, improvement in ventricular functional recovery, decrease in infarct size and apoptosis	59
Rat	ischemia/reperfusion of isolated hearts	20, +/- 10 $\mu$ M	i.g., perf.	improved post-ischemic recovery with chronic treatment regardless of acute treatment, partially protected with acute treatment only	60
Rat	low-flow ischemia/reperfusion of isolated hearts	10 $\mu$ M	perf.	increased adenosine release and coronary flow, prevented by perfusion with an adenosine antagonist	61
Rat	low-flow ischemia/reperfusion of isolated heart 24 hours after treatment	~1 mg/kg	d.w.	improved functional recovery, prevented by perfusion with an adenosine antagonist or NOS inhibitor, no effect on ATP or phosphocreatine levels	61
Mouse	ischemia/reperfusion of isolated wild type or iNOS null hearts	10 $\mu$ M	perf.	iNOS-dependent improvement in ventricular functional recovery, decrease in infarct size, apoptosis, and malondialdehyde	62
Rat	ischemia/reperfusion of isolated hearts	10 $\mu$ M	perf.	improved developed pressure and aortic flow, decreased infarct size, apoptosis and malondialdehyde, all effects iNOS-dependent	63
Rat	ischemia/reperfusion of isolated hearts	10 $\mu$ M	perf.	non-significant increase in coronary flow, decrease in infarct size and superoxide	64
Rat	myocardial ischemia by temporary occlusion of the left main coronary artery	0.23, 2.3, 23 $\mu$ g/kg	perf.	no effect on arrhythmias or mortality, reduced incidence and duration of ventricular tachycardia and ventricular fibrillation, increased NO and decreased lactate dehydrogenase in carotid blood	65
Rat	ischemia/reperfusion of isolated heart	10 $\mu$ M	perf.	improved post-ischemic recovery (rate pressure product), decreased phosphorylation potential	66
Rat	ischemia/reperfusion of isolated heart	10 $\mu$ M	perf.	increased developed pressure and aortic flow, decreased infarct size and malondialdehyde	67
Rat	ischemia/reperfusion of isolated heart	10 $\mu$ M	perf.	increased developed pressure and aortic flow, decreased infarct size and malondialdehyde	68
<i>Endocrine Effects</i>					
Rat	streptozotocin (+/- nicotinamide)-induced diabetes	0.1, 0.25, 0.5, 0.75, 0.5 mg/kg (3 times/day)	oral	reduced plasma glucose and triglycerides, weight loss, polyphagia, and polydipsia, enhanced glucose uptake in skeletal muscle, hepatocytes, and adipocytes, and glycogen synthesis in liver, decreased insulin secretion and delayed the onset of insulin resistance in nicotinamide-treated animals	69
Trout	handling-induced, aryl hydrocarbon receptor-dependent stress response (+/- suppression by $\beta$ -naphthoflavone)	20 mg/kg	diet	blocked the ability of $\beta$ -naphthoflavone to stimulate liver and kidney CYP1A expression, to suppress handling-induced increases in plasma cortisol and glucose, and to decrease expression of interrenal, steroidogenic acute regulatory protein, CYP450 cholesterol side chain cleavage, and 11 $\beta$ -hydroxylase in kidney	70
Rat	steroidogenesis in explanted adrenocortical cells	840 mg/kg	diet	increased adrenal weight, decreased CYP450 c21 expression and corticosterone production	71
<i>Neurological Effects</i>					
Mouse	middle cerebral artery occlusion	50 mg/kg	gav.	decreased infarct volume and attenuated the increase in MMP-9 mRNA and protein expression in brain tissue	72
Rabbit	ischemia/reperfusion-induced spinal injury	0.1 mg/kg	i.v.	improved neurologic function (Tarlov score) and survival of motor neurons, decreased myeloperoxidase activity and malondialdehyde in spinal tissue	73
Rat	brain biochemistry following ovariectomy	5 mg/kg	gav.	prevented the decrease in <i>N</i> -acetyl aspartate and increase in choline	74
Rat	kainic acid-induced neurotoxicity	30 mg/kg	i.p.	reduced damage to hippocampal neurons, activation of astrocytes and microglial cells	75
Mouse	permanent middle cerebral artery occlusion	2, 20 mg/kg	oral	3 day treatment with 20 mg/kg reduced infarct volume 36% in wild type but not PPAR $\alpha$ -/- mice	76
Rat	auditory brainstem responses pre- and post 105 dB noise	0.43 mg/kg	gav.	protective effect on hearing loss, significant at 2 of 4 frequencies	77
Rat	permanent middle cerebral artery occlusion	10, 100, 1000 ng/kg	i.v.	ischemic volume and brain water content reduced in 100, 1000 ng/kg, no effect on p65 (NF $\kappa$ B)	78
Rat	experimentally induced spinal cord injury	50, 100 mg/kg	i.p.	decreased spinal edema, lactate dehydrogenase, and malondialdehyde, increased Na <sup>+</sup> , K <sup>+</sup> -ATPase activity	79
Rat	experimentally-induced spinal cord injury	100, 500 mg/kg	i.p.	increased Ca <sup>2+</sup> -ATPase, Mg <sup>2+</sup> -ATPase, and Ca <sup>2+</sup> , Mg <sup>2+</sup> -ATPase activity	80
Rat	intracerebroventricular streptozotocin-induced cognitive impairment and oxidative stress	10, 20 mg/kg	i.p.	prevented decreases in malondialdehyde and glutathione levels in brain, partially restored behavior/cognition	81
Rat	lipopolysaccharide-induced anorexia (COX-2 dependent)	2.5, 10, 40 mg/kg	i.p.	no significant effect on food intake in controls, enhanced anorexia, no effect on PGE <sub>2</sub> levels in cerebrospinal fluid	82
Rat	focal ischemia induced by middle cerebral artery	20 mg/kg	i.p.	prevented motor impairment, rise in reduced glutathione and	83

	occlusion			malondialdehyde, decreased infarct volume	
Gerbil	transient global cerebral ischemia induced by occlusion of both common carotid arteries for 5 min	30 mg/kg	i.p.	decreased delayed neuronal cell death and glial cell activation in hippocampal CA1 area	84
Rat	pentylentetrazole-induced seizures	20, 40, 80 mg/kg	i.p.	reduced seizures, potentiated the anticonvulsive effects of sodium valproate, diazepam, and adenosine	85
Rat	kainic acid-induced seizures	20, 40 mg/kg	i.p.	single dose ineffective, reduced incidence of seizures and lowered malondialdehyde levels in brain when additional 30 and 90-minute doses were given, no effect on glutathione levels	86
Rat	intracortical FeCl <sub>3</sub> -induced posttraumatic seizures	20, 40 mg/kg	i.p.	delayed the onset and reduced the severity of epileptic EEG discharge, blocked rise in malondialdehyde	87
Rat	focal cerebral ischemia induced by middle cerebral artery occlusion	1, 10, 100, 1000 ng/kg	i.v.	significant reduction in infarct volume at 100, 1000 ng/kg, no effect on heart rate or blood pressure	88
Rat	damage to olfactory cortex and hippocampus caused by systemic injection of kainic acid	8 mg/kg	d.w.	partially blocked the decrease in glutamate decarboxylase in olfactory cortex and hippocampus	89
<i>Longevity</i>					
<i>N. furzeri</i> (fish)	longevity and degenerative phenotypes in a short-lived vertebrate	~1, 2, 6, 30 mg/kg	diet	dose dependent increase in mean survival at 6 and 30 mg/kg, slowed neurofibrillary degeneration, and the decline in locomotor activity and active avoidance behavior	90
<i>Other Protective Effects</i>					
Rat	sodium taurocholate-induced pancreatitis	20 mg/kg	i.v.	decreased lipid peroxidation in cell membranes, serum amylase, pancreatic lesions, and malondialdehyde	91
Rat	sodium taurocholate-induced pancreatitis	10 mg/kg	i.v.	decreased expression of NF- $\kappa$ B and iNOS in peritoneal macrophages, levels of TNF- $\alpha$ , IL-1, and NO in serum and media following culture of macrophages, and pancreatic damage	92
Rat	renal ischemia/reperfusion injury	5 mg/kg	per os	improved renal function and morphology, reduced NO levels and oxidative stress	93
Rat	streptozotocin-induced diabetic nephropathy	5, 10 mg/kg	oral	improved creatinine and urea clearance, decreased proteinuria, and lipid peroxidation, and restored antioxidant enzymes	94
Rat	5/6th nephrectomy	5 mg/kg	per os	blocked the increase in systolic blood pressure, urinary protein excretion, glomerulosclerosis, blood urea nitrogen, and plasma creatinine, restored urinary secretion of NO <sub>2</sub> + NO <sub>3</sub> , all effects attenuated by coadministration of a NOS inhibitor	95
Rat	renal ischemia	5 mg/kg	oral	decreased kidney damage, plasma creatinine, blood urea nitrogen, and TBARS, increased renal and urine NO, creatinine clearance, reduced glutathione, catalase, and SOD, similar to the effects of ischemic preconditioning, all effects abolished by NO synthase inhibitor	96
Rat	apoptosis in germ cells following testicular torsion	30 mg/kg	i.p.	decreased TUNEL staining and caspase 3 activation	97
Rat	half mustard gas-induced acute lung injury	100 $\mu$ L	liposomes	48% decrease in lung injury (leakage of <sup>125</sup> I-albumin from blood)	98
Rat	liver injury induced by chronic biliary obstruction	10 mg/kg	i.p.	decreased ductular proliferation and lymphocytic infiltration, plasma bilirubin, alanine and aspartate aminotransferases, liver malondialdehyde, NO, IL-1 $\alpha$ , IL-6, and TNF- $\alpha$ , increased liver reduced glutathione	99,100
Rat	tert-butyl hydroperoxide-induced pancreatitis	~6.6 mg/kg	i.p.	decreased serum amylase and pancreatic mass, decreased edema, vacuolization, bleeding, necrosis, carbonyl groups, and damage to ER and mitochondria, and increased reduced glutathione in pancreatic tissue	101
Rat	ischemia-reperfusion injury induced by testicular torsion	30 mg/kg	i.p.	decreased testicular injury and malondialdehyde, increased glutathione	102
Rat	cyclosporine-induced nephrotoxicity	2, 5, 10 mg/kg	oral	NOS-dependent improvement in renal function, NO levels, oxidative stress, and renal morphology	103
Rat	bone loss following ovariectomy	0.7 mg/kg	gav.	partially restored femoral epiphysis bone mineral density and bone calcium content, no effect on femoral midpoint bone mineral density	104
Rat	ischemia/reperfusion injury in kidney	4 mg/kg	i.p.	prevented the increase in serum creatine levels and CD86 expression in kidney	105
Rat	sperm production	20 mg/kg	gav.	increased sperm counts, gonadotrophins and testosterone, no effect on testes weight or sperm quality, decreased diameter and increased density of seminiferous tubules	106
Rat	toxicogenomics in liver	300, 1000, 3000 mg/kg	gav.	some liver and kidney toxicity at the highest dose, general decrease in the expression of phase I drug metabolizing enzymes and increase in the expression of phase II enzymes	107
Rat	microcirculatory disorders following severe acute pancreatitis	0.1 mg/kg	i.p.	improved blood flow and decreased microcirculatory disorder in lung	108
Rat	electron paramagnetic resonance of liver mitochondrial phospholipid bilayer structure after gavage with CCl <sub>4</sub>	~ 75 mg/kg	gav.	prevented disordering of the bilayer by 50%	109
Rat	intestinal transit (Evans blue migration) after skin incision, laparotomy, or laparotomy plus gut	10 mg/kg	s.c.	in combination with tin protoporphyrin-IX, reversed the inhibitory effects of laparotomy and gut handling on intestinal transit	110

	evisceration and handling				
Rat	TNBS (10 mg/animal)-induced colitis	5, 10 mg/kg	gav.	reduced colonic injury, neutrophil count, IL-1 $\beta$ , PGD <sub>2</sub> , and COX-2 expression, no effect on PGE <sub>2</sub> or COX-1 expression, enhanced apoptosis	111
Rat	intestinal transit following laparotomy and gut manipulation	1, 3, 10 mg/kg	i.v.	significant improvement in 3, 10 mg/kg, but not 1 mg/kg	112
Rat	gentamicin-induced nephrotoxicity	120 mg/kg	gav.	improved glomerular filtration rate and renal blood flow, prevented increases in N-acetyl-beta-D-glucosaminidase and lipid peroxidation	113
Rat	enzymatic activities in duodenum, jejunum, and ileum	20 mg/kg	oral	no significant change in maltase, sucrase, trehalase, lactase, or alkaline phosphatase	114
Rat	half-mustard-gas-induced acute lung injury	50 mg/kg	i.p.	61% decrease in lung injury (extravasation)	115
Rat	computer morphometric analysis of kidney morphology following ischemia/reperfusion injury	1 nmol	inf.	decreased mortality from 50% to 10%, prevented decrease in glomerular volume, improved shape, decreased endocapillary clots and serum creatine	116
Rat	b.w., food and water consumption, histopathology	20 mg/kg	oral	no effect on b.w., food or water consumption, hematological or clinical biochemistry variables, or histopathology	117
Rat	i.v. injection of anti-rat kidney glomerular basement membrane rabbit antiserum	0.5 mg/kg	oral	reduced enlargement of kidney and liver, reduced weight loss, reduced urinary protein secretion, increased serum albumin, reduced hyperlipidemia	118
Rat	ischemia/reperfusion injury in kidney	0.23 $\mu$ g/kg	inf.	reduced mortality from 50% to 10%, partially blocked increase in creatine and decrease in NO, blocked rise in thiobarbituric acid-reactive substances	119
Rat	potassium bromate-induced oxidative damage to kidney DNA	16 mg/kg	i.p.	blocked increase of 8-oxo-7,8-dihydro-2'-deoxyguanosine and increase in kidney weight	120
Mouse	12-O-tetradecanoylphorbol-13-acetate-induced oxidative events and gene expression in skin	1, 5, 10, 25 $\mu$ mol	top.	restored H <sub>2</sub> O <sub>2</sub> , glutathione, myeloperoxidase, oxidized glutathione reductase, and super oxide dismutase to control levels, prevented upregulation of <i>c-fos</i> and <i>TGF-<math>\beta</math>1</i>	121
<i>Prevention of Mild (Protective) Stresses</i>					
Rat	protection of pancreas from cerulein-induced injury by ischemic preconditioning	10 mg/kg	i.g.	blocked the protective effect of preconditioning, to a lesser extent than rofecoxib	122
Rat	protection of gastric mucosa from ischemic injury by preconditioning with brief exposures to ischemia	10 mg/kg	i.g.	blocked the protective effect of preconditioning, unless PGE <sub>2</sub> was also given	123
Rat	protection of gastric mucosa from ischemic injury by preconditioning with brief exposures to ischemia	10 mg/kg	i.g.	blocked the protective effect of preconditioning, unless PGE <sub>2</sub> was also administered	124
Rat	protection from caerulein-induced pancreatitis by pre-treatment with low dose LPS	2, 10 mg/kg	i.p.	prevented LPS-induced decrease in edema, leukocyte infiltration, and pancreatic weight, prevented increase in pancreatic blood flow	125
Rat	protection from gastric mucosal damage due to water immersion and restraint stress (WRS) by pre-exposure to mild WRS	10 mg/kg	i.g.	no effect on WRS, but decreased the protective effect of pre-exposure on gastric lesions and blood flow unless PGE <sub>2</sub> was also administered	126
<i>Immunological/Inflammatory Effects</i>					
Mouse	xylene-induced ear edema	200 mg/kg	oral	reduced ear weight by 38.9% (similar to ibuprofen)	127
Mouse	vaginal HSV-1 and HSV-2 infection	6.25, 12.5, 19% cream	top.	decreased viral titers and extravaginal lesions, HSV-2 mortality was reduced from 37% (control) to 40%, 24%, and 3% respectively	128
Rat	allograft rejection following orthotopic liver transplantation	25, 50, 100 mg/kg	i.p.	increased NF $\kappa$ B activity in peripheral blood lymphocytes (all groups), increased survival and serum albumin, decreased serum bile acid, alanine aminotransferase, IL-2, and interferon $\gamma$ (significant only at 100 mg/kg)	129
Rat	allograft rejection following orthotopic liver transplantation	100 mg/kg	i.p.	in combination with cyclosporine, increased survival and serum albumin, decreased serum bile acid, alanine aminotransferase, IL-2, and interferon $\gamma$ , NF $\kappa$ B activation in peripheral blood T lymphocytes, and histological damage as compared to cyclosporine alone or control	130
Rabbit	osteoarthritis induced by ligament transection	~ 2.3 mg/kg	inj.	reduced loss of cartilage tissue and matrix proteoglycan, non-significant decrease in synovial inflammation	131
Rat	lipopolysaccharide-induced airway inflammation	1, 3, 10, 30 mg/kg	trach.	reduced neutrophilia, pro-inflammatory cytokines, PGE <sub>2</sub> levels (30 mg/kg)	132
Rat	inflammatory effects following severe acute pancreatitis	30 mg/kg	i.p.	decreased expression of NF $\kappa$ B and inflammatory markers	133
Mouse	skin lesions formed in response to HSV-1 infection	12.5, 25% cream	top.	decreased skin lesions in wild type or acyclovir-resistant HSV-1	134
Mouse	b.w., cell counts in blood, marrow, and spleen, cytokine levels, T cell proliferation	~ 10-12 mg/kg	oral	no significant change in weight, cell counts, or IL-12, reduced TNF- $\alpha$ and marginally reduced allo-antigen induced T cell proliferation	135
Mouse	DNFB-induced delayed type hypersensitivity (DTH) response	4, 16 mg/kg	oral	increased DTH, MHC class I and II expression on spleenocytes, antagonized EtOH-induced decrease in macrophage number	136
Rat	conavalin A-induced rise in the cytosolic Ca <sup>2+</sup> content of splenic T cells during sepsis	10 mg/kg	i.p.	no effect on Ca <sup>2+</sup> response in controls, non-significant further decrease in septic animals	137
Rat	carrageenan-induced inflammation	3, 8 mg/kg	oral	decreased acute and chronic edema (paw volume)	40
<i>Angiogenesis/Wound Healing</i>					

Mouse	corneal micropocket assay for vascularization	~ 48 µg/kg	d.w.	decreased corneal vascularization (number of microvessels)	34
Mouse	wound healing in skin	5.7 µg/mL	d.w.	prolonged wound healing (increased wound size and percentage of open wounds)	34
Rat	gastric ulcers produced by serosal application of acetic acid	10 mg/kg	i.g.	prolonged ulcer healing, decreased PGE <sub>2</sub> production, increased plasma TNF $\alpha$ and IL-1 $\beta$	138
Rat	gastric lesions resulting from ischemia/reperfusion by clamping the celiac artery	10 mg/kg	i.g.	augmented gastric lesions and delayed healing, decreased PGE <sub>2</sub> generation	139
<i>Analgesic Effects</i>					
Rat	antinociception by the formalin test (flinching behavior after local injection of formalin)	25, 50, 100, 200 µg	inj.	decrease in flinching behavior that was blocked by inhibitors of Ca <sup>2+</sup> and voltage-dependent K <sup>+</sup> channels, but not inhibitors of ATP-sensitive K <sup>+</sup> channels	140
Rat	antinociception by the formalin test (flinching behavior following injection of 1 or 5% formalin into paw)	50, 100, 200 µg	inj.	reduction in phase II (15-60 min) flinching, no effect when injected into the contralateral paw	141
Rat	hyperalgesia, edema, and swelling induced by injection of carrageenan into the paw	0.4, 2, 10, 50 mg/kg	i.p.	analgesic effects at 2, 10 mg/kg by vocalization threshold (50 mg/kg caused agitation), no effect on paw circumference	142
<i>Estrogenic/Developmental Effects</i>					
Rat	vaginal epithelial maturation following ovariectomy	5 mg/kg	per os	restored the proportions parabasal and superficial, but not intermediate and anuclear cells in vaginal smears	143
Mouse	development of the reproductive tract and mammary glands after prepubertal exposure	10 mg/kg	s.c.	no effect on vaginal opening, estrous cyclicity, vaginal morphology, or mammary gland growth	144
Mouse	estrous cycling and onset of puberty after treatment from gestational day 15	0.5, 10 mg/kg (4 times/day)	s.c.	increased body weight, no effect on vaginal opening, elongated estrous cycle, transient effects on reproductive tract and mammary gland development at 10 mg/kg	145
Mouse	b.w., organ weight, reproductive fitness over two generations	3 mg/L	d.w.	no effect on b.w., decreased liver and spleen weight in P, kidney weight in F1, no effect on acrosomal integrity, sperm quality, or litters	146
Rat	sexual differentiation, open field behavior, brain development during fetal and suckling periods	5 mg/L	d.w.	abolished sex difference in locus coeruleus size, inhibited female sexual behavior, delayed vaginal opening, no effect on open field behavior	147
Mouse	female sexual development	2 mg/kg	oral or s.c.	shortened latency to vaginal opening	148
Rat	b.w. and estrous cycling, estrogen sensitivity and sociosexual behavior following ovariectomy	100 µM, or 10, 100, 1000 µg	d.w. or s.c.	decreased b.w., ovarian hypertrophy, disrupted estrous cycling, failure to mimic the action of 17 $\beta$ -estradiol benzoate in ovariectomized animals	149
Rat	uterine weight, histopathological changes, ER $\alpha$ and progesterone receptor (PR) expression, peroxidase induction	18, 58, 575 mg/kg	s.c.	mild decrease in uterine weight, no change in histology, decrease in ER $\alpha$ protein levels, no change in PR protein or mRNA, no peroxidase induction	150
Rat	ovariectomy-induced hypertension and bone loss	5 mg/kg	diet	no significant effect on body weight, lowered systolic blood pressure, improved acetylcholine-induced vascular relaxation and bone strength	151
Rat	comparison to estradiol (100 µg) for effects on growth, development, and gene expression	1, 4, 10, 40, 100, 1000 µg	gav.	no significant effect on body weight, serum cholesterol, radial bone growth, epithelial cell height, or IGF-1 expression, antagonized the cholesterol-lowering effect of estradiol	152

i.p. – intraperitoneal, top. – topical, d.w. – drinking water, inj. – injection, adb. – abdominal injection, gav. – gavage, s.c. – subcutaneous injection, i.g. – intragastric, i.v. – intravenous injection, perf. – perfusion.

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