Resveratrol, a Polyphenolic Antioxidant, Present in Grape Skin, is Dose Dependent in Providing Health Benefits

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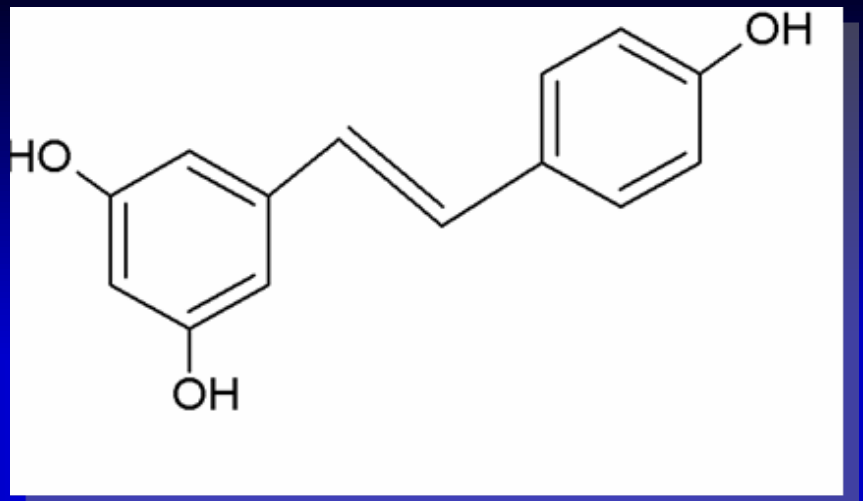
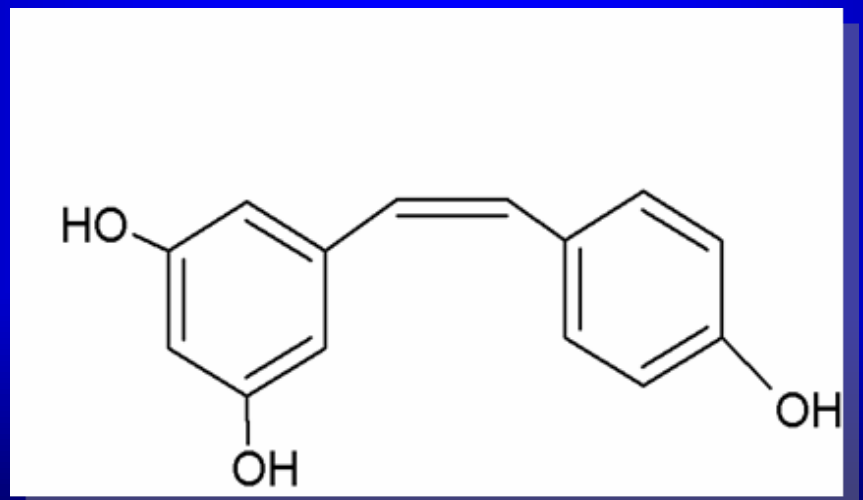


trans - resveratrol



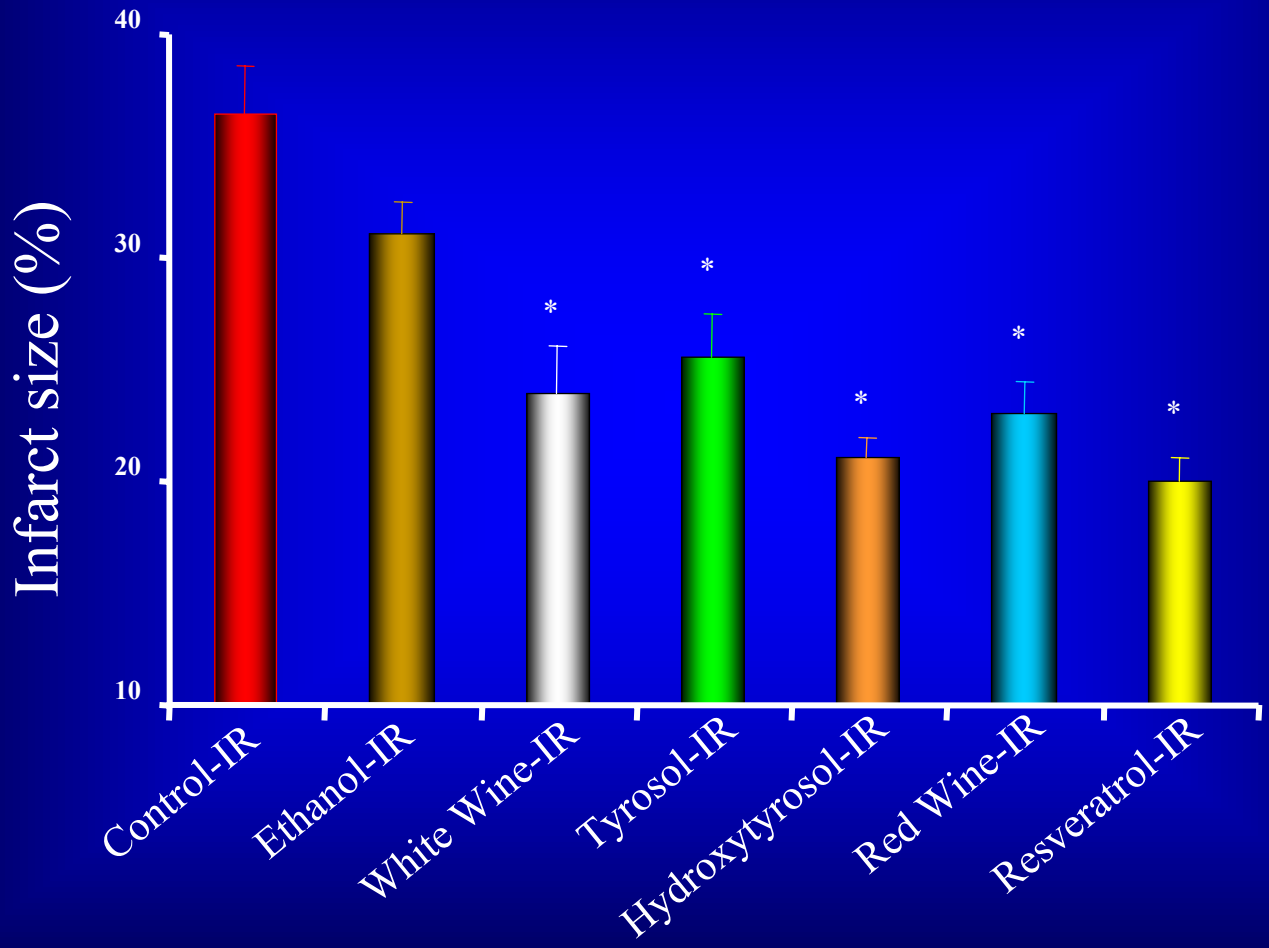
cis - resveratrol

Source	Resveratrol concentration
100% Natural peanut butter	~0.65 µg/g
Bilberries	~16 ng/g
Blueberries	~32 ng/g
Boiled peanuts	~5.1 µg/g
Cranberry raw juice	~0.2 mg/L
Dry grape skin	~24.06 µg/g
Grapes	0.16–3.54 µg/g
Peanut butter	0.3–1.4 µg/g
Peanuts	0.02–1.92 µg/g
Pistachios	0.09–1.67 µg/g
Ports and sherries	<0.1 mg/L
Ref grape juice	~0.50 mg/L
Red wines	0.1–14.3 mg/L
Roasted peanuts	~0.055 µg/g
White grape juice	~0.05 mg/L
White wines	<0.1–2.1 mg/L

The French paradox

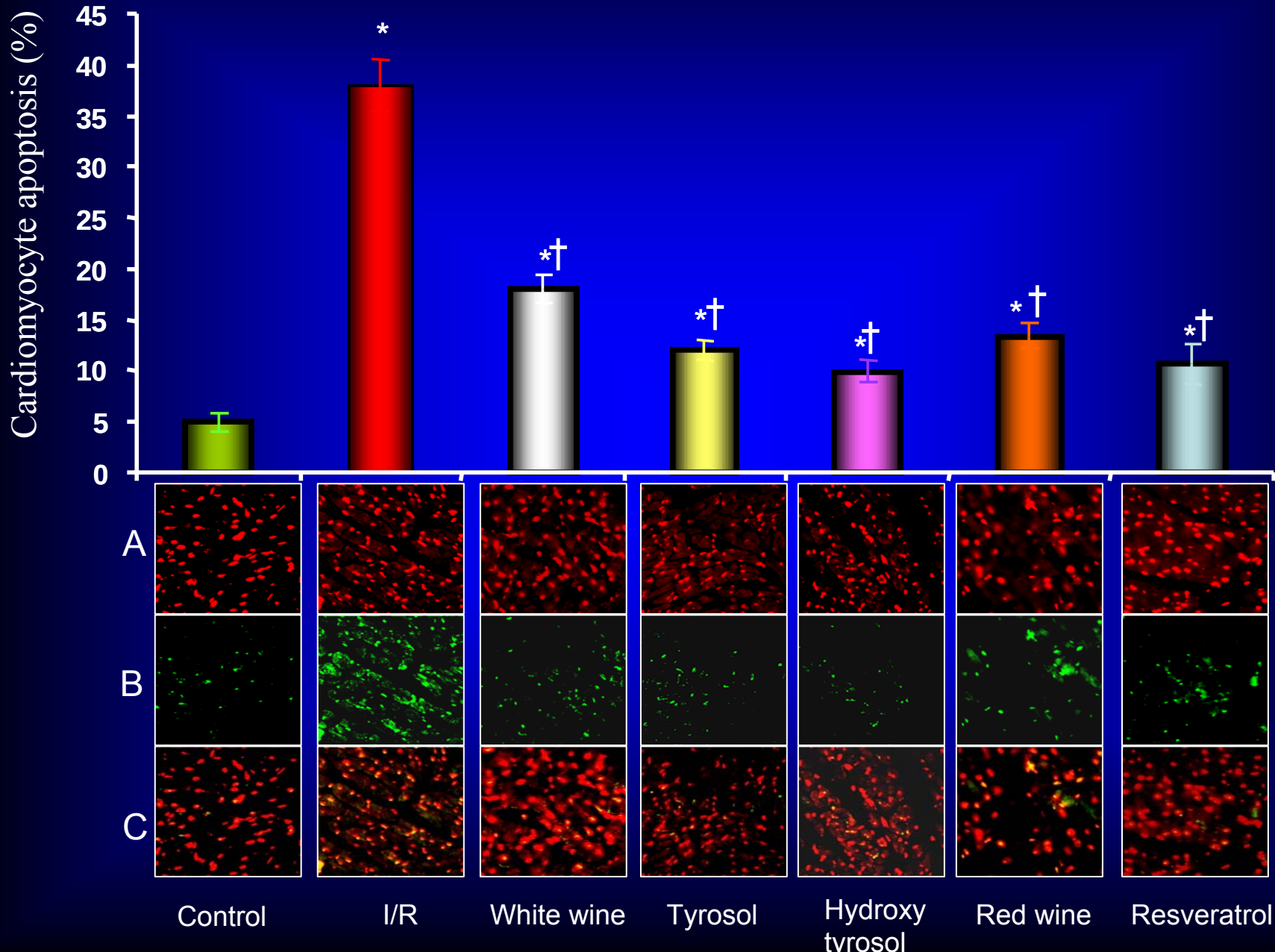
Resveratrol

Effect of white wine, its components tyrosol and hydroxytyrosol, red wine, and resveratrol on the infarct size.

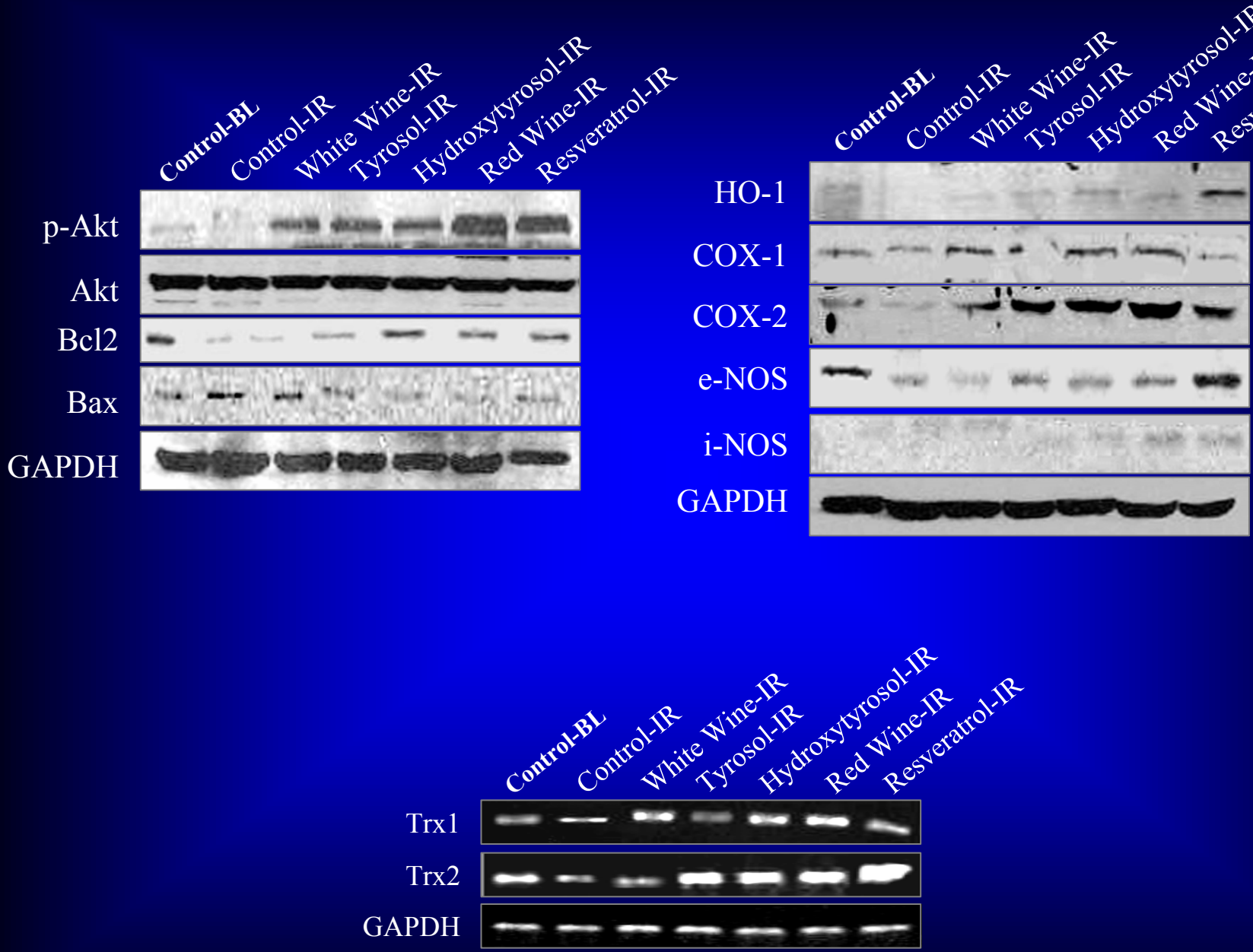


Dudley *et al*., J Agric Food Chem. 2008

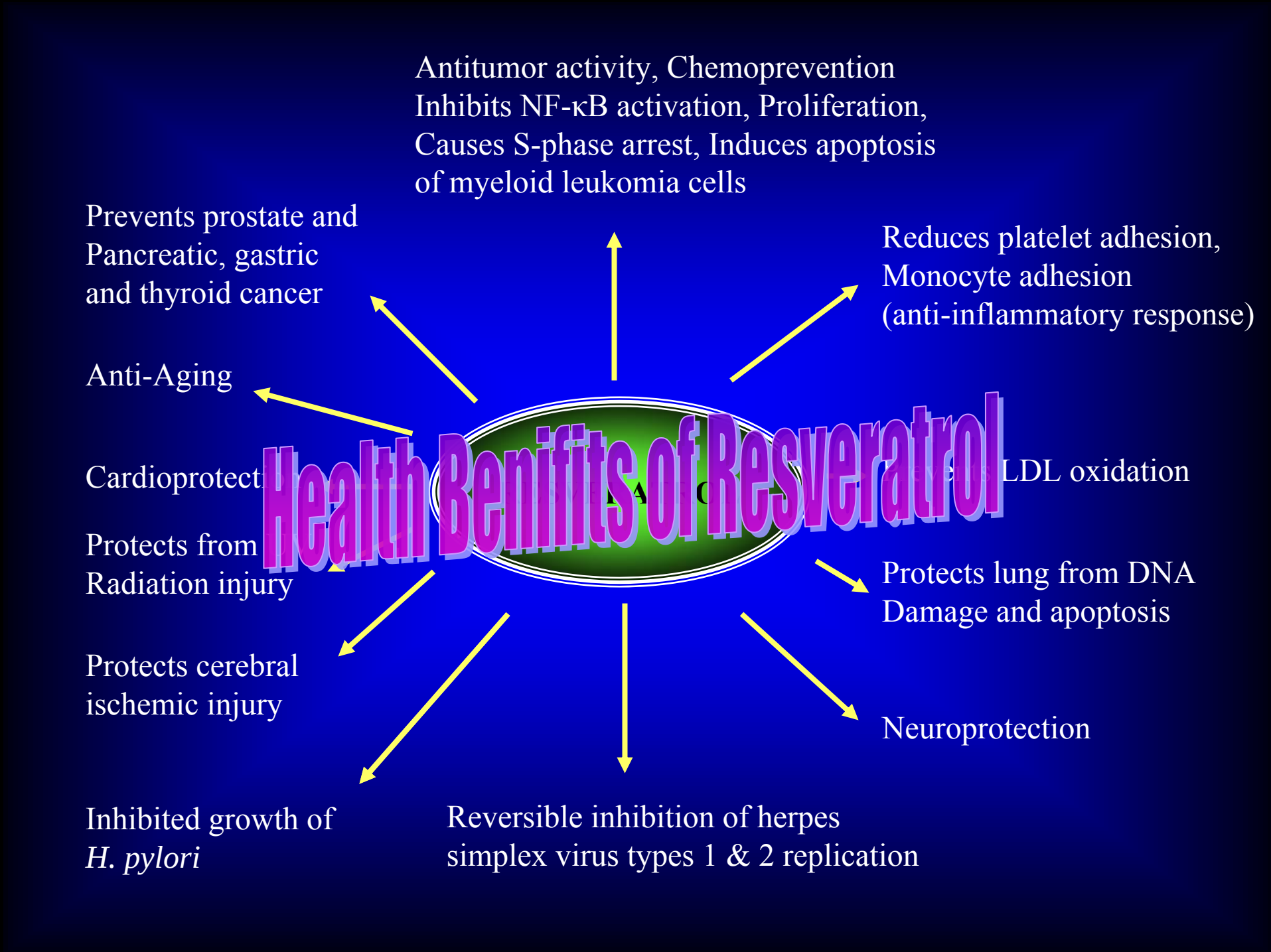
Effect of white wine, its components tyrosol and hydroxytyrosol, red wine, and resveratrol on the infarct size.



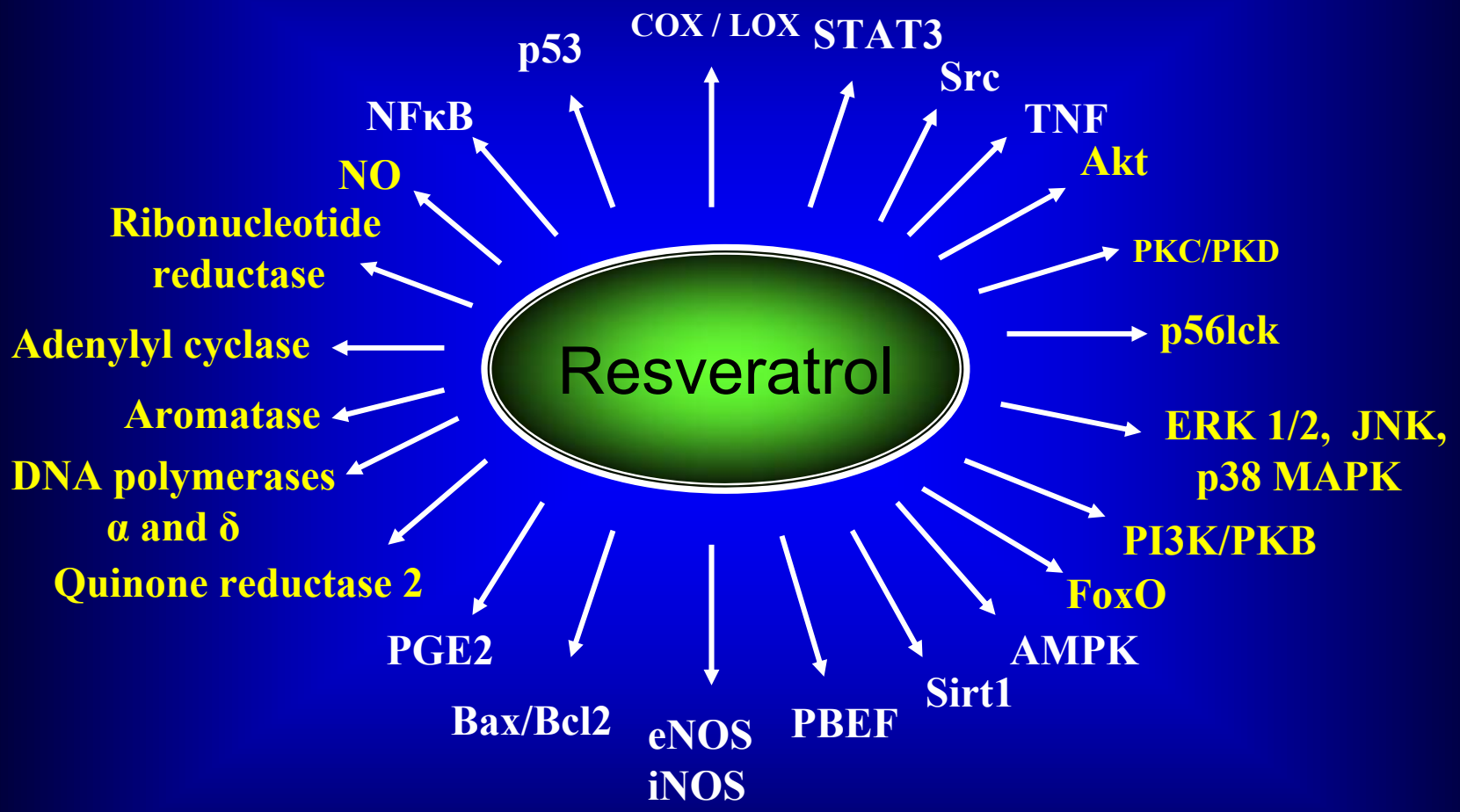
Dudley *et al.*, J Agric Food Chem. 2008



Dudley *et al.*, J Agric Food Chem. 2008

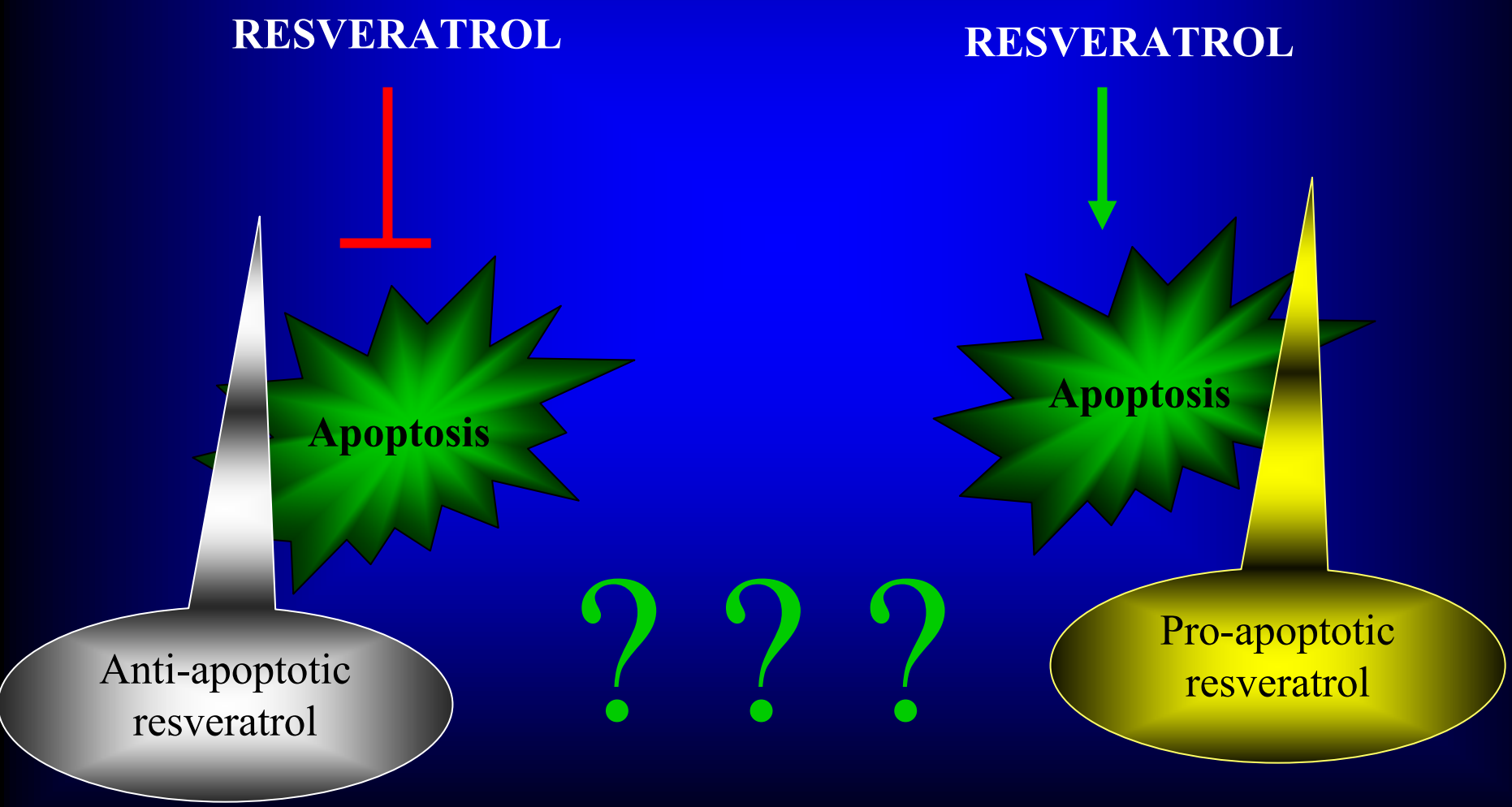

Antitumor activity, Chemoprevention
Inhibits NF-κB activation, Proliferation,
Causes S-phase arrest, Induces apoptosis
of myeloid leukomia cells
Prevents prostate and
Pancreatic, gastric
and thyroid cancer
Reduces platelet adhesion,
Monocyte adhesion
(anti-inflammatory response)
Anti-Aging
Health Benifits of Resveratrol
Cardioprotect
LDL oxidation
Protects from
Radiation injury
Protects lung from DNA
Damage and apoptosis
Protects cerebral
ischemic injury
Neuroprotection
Inhibited growth of
H. pylori
Reversible inhibition of herpes
simplex virus types 1 & 2 replication

Molecular targets of Resveratrol



Myocardial injury and ageing related diseases

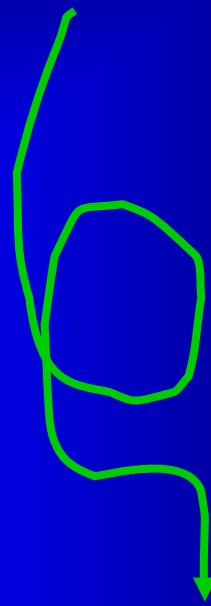
Cancer prevention



Myocardial injury and ageing related diseases

Low dose of resveratrol was used

Cancer prevention



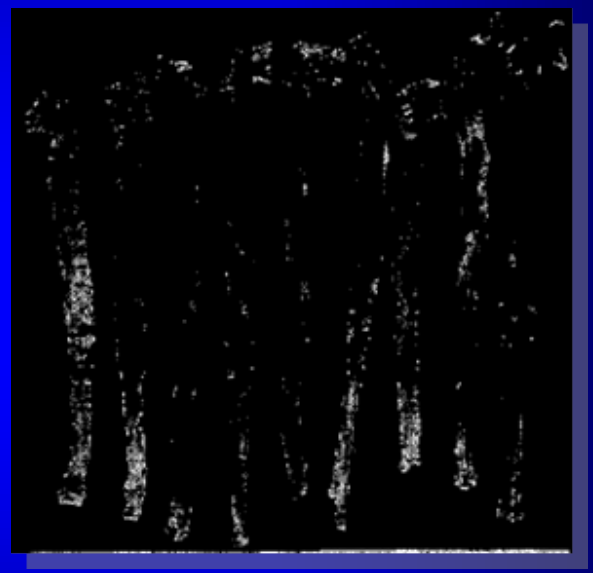
High dose of resveratrol was used

Health beneficiary effects of resveratrol are dose dependent or not?

High dose resveratrol promotes atherosclerosis in case of hypercholesterolemic rabbits

Panel A

Panel B



Sudan-IV stained rabbit aortas with atherosclerotic lesions appearing as darkened areas on a white aortic surface. Panel A) Arteries from control rabbits. Panel B) Arteries from resveratrol-treated rabbits.

Wilson *et al.*, Life Sciences. 1996

Effect of High Dose Resveratrol on Proliferation and Apoptosis in Endothelial and Tumer Cell Culture

	Apoptosis		Mitosis	
	24 h	48 h	24 h	48 h
Control	3	2	5	6
0.1 µg/ml	0	1	6	7
1.0 µg/ml	1	2	6	7
10 µg/ml	4	5	0	0
100 µg/ml	100	100	0	0

Effect of resveratrol on the apoptotic and mitotic index of HUVEC Endothelial cell culture

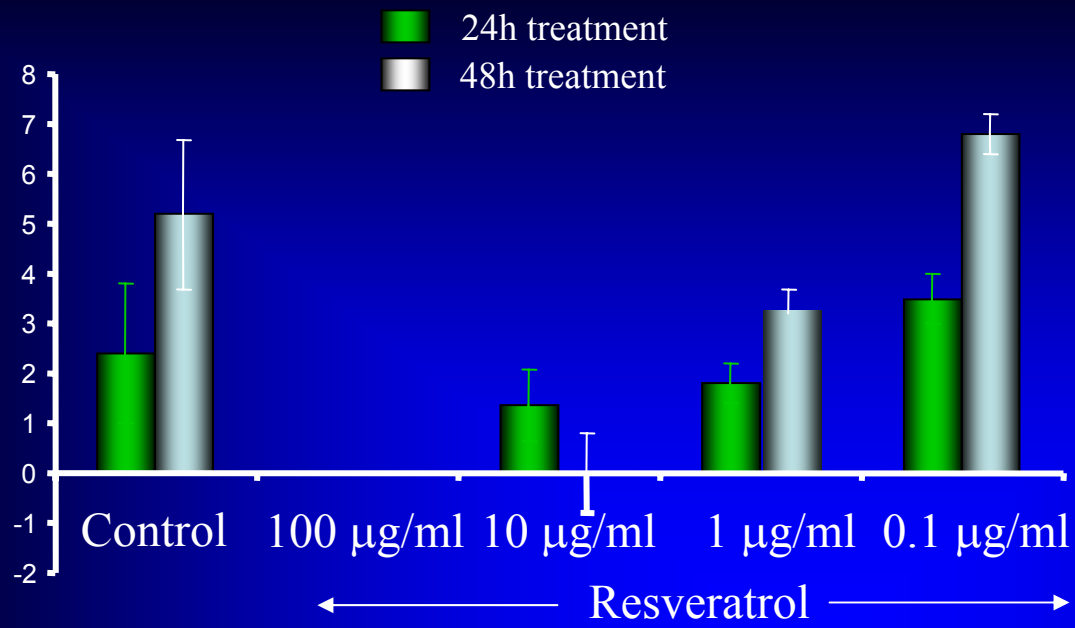
	Apoptosis		Mitosis	
	24 h	48 h	24 h	48 h
Control	3	2	3	3
1 µg/ml	2	2	4	5
10 µg/ml	22	30	2	1
100 µg/ml	75	75	0	0

Effect of resveratrol on the apoptotic and mitotic index of HT-29 cell culture

	Apoptosis		Mitosis	
	24 h	48 h	24 h	48 h
Control	1	1	4	5
1 µg/ml	2	2	2	5
10 µg/ml	2	8	0	1
100 µg/ml	20	80	0	0

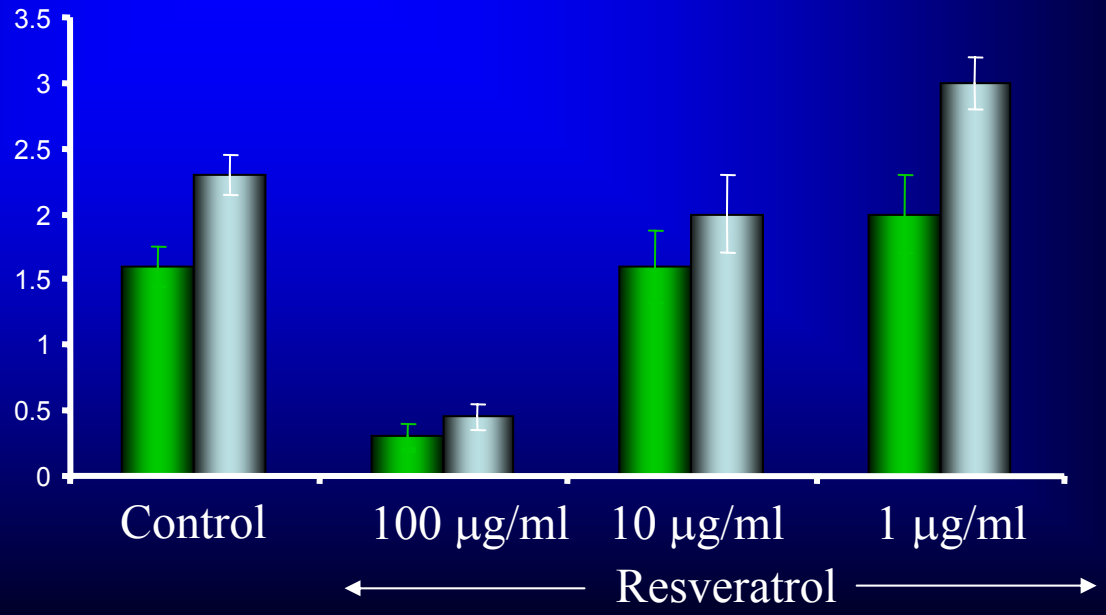
Effect of resveratrol on the apoptotic and mitotic index of HT-1080 human fibrosarcoma cell culture

Szende *et al.*, Experimental And Molecular Medicine 2000



Effect of resveratrol on the proliferation of HUVEC human endothelial cells

Effect of Reserveratol on the proliferation of HT-29 human colon carcinoma cells



Szende *et al.*, Experimental And Molecular Medicine 2000

Resveratrol Associated Renal Toxicity is Dose Dependent

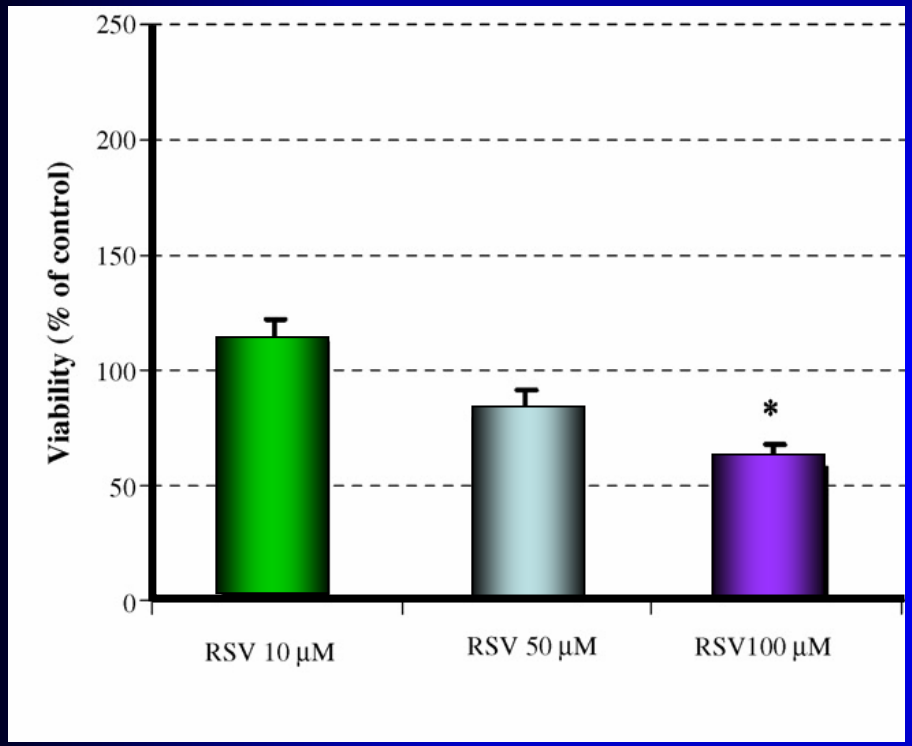
Histologic Changes in the Kidneys of Rats Administered Resveratrol Orally for 4 Weeks

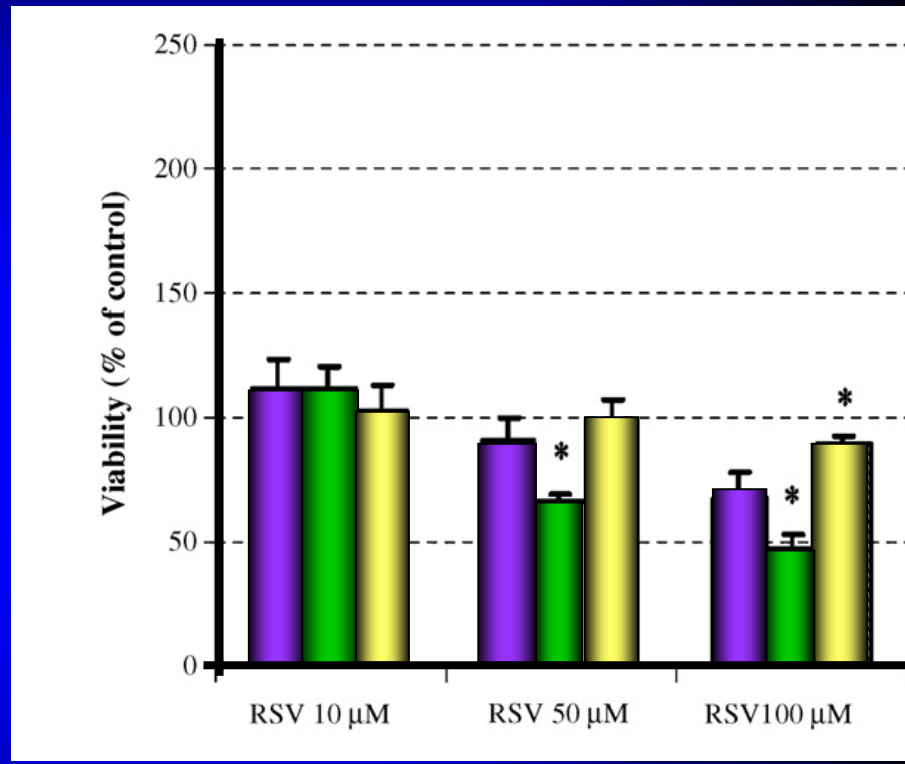
	0		300		1000		3000	
Dose mg/kg bwt/day	M	F	M	F	M	F	M	F
Kidney lesion								
Tubule dilatation	0/20	0/20	0/20	0/19	0/20	0/20	8/17 (1.24)[a]	9/20 (1.25)
Papillary necrosis	0/20	0/20	0/20	0/19	0/20	0/20	2/17 (0.12)	5/20 (0.45)
Ulceration, pelvic epithelium	0/20	0/20	0/20	0/19	0/20	0/20	1/17 (0.18)	1/20 (0.15)
Inflammation, acute pelvic	0/20	0/20	0/20	0/19	0/20	0/20	1/17 (0.06)	3/20 (0.30)
Inflammation, acute pelvic adventitia	0/20	0/20	0/20	0/19	0/20	0/20	2/17 (0.29)	2/20 (0.15)
Glomerular necrosis	0/20	0/20	0/20	0/19	0/20	0/20	2/17 (0.18)	3/20 (0.25)
Papillary fibrosis	0/20	0/20	0/20	0/19	0/20	0/20	2/17 (0.18)	3/20 (0.20)
Hyperplasia, pelvic epithelium	0/20	0/20	2/20 (0.20)	0/19	1/20 (0.10)	0/20	12/17 (2.00)	10/20(1.05)
Nephropathy	11/20 (0.65)	8/20 (0.50)	12/20 (0.60)	6/19 (0.32)	12/20 (0.65)	7/20 (0.35)	16/17 (1.82)	15/20(1.70)

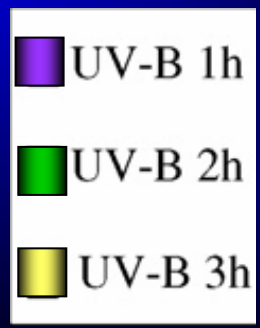
[a]Values represent incidence (mean group severity score).

Crowell *et al.*, Toxicological Sciences. 2004

Influence of resveratrol (RSV) concentration on the viability of HEK 293 cells before and after UV irradiation







Caddeo *et al.*, International Journal of Pharmaceutics. 2008

Dumazet *et al.* (2002) showed that at higher dose resveratrol inhibits the growth and induces apoptosis in case of both normal and leukemic hematopoietic cells

Zhou *et al*., (2003) showed that in human esophageal carcinoma cells, resveratrol induces apoptosis when used in high concentration (100 mM) and this high dose of resveratrol also downregulated Bcl2 protein expression and upregulated Bax protein expression

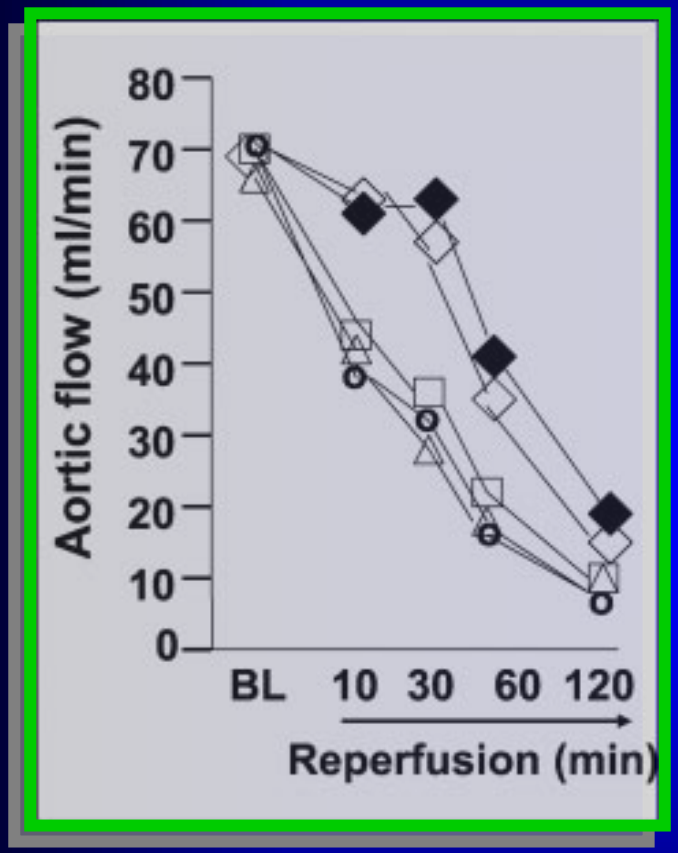
Signorelli *et al*., (2005) showed that in androgen – sensitive prostate cancer cells, resveratrol had a proliferative activity at a low dose (5 μM), whereas it had a pro-apoptotic activity at a high dose (15 μM or higher)

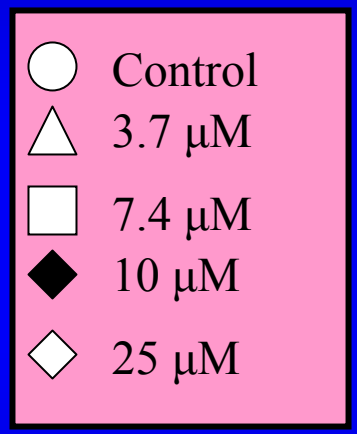
Jang *et al.*, (2006) showed that low concentration (5μM), resveratrol appears to increase cell proliferation, whereas apoptosis is induced in various cancer cells at 15 μM or higher concentration.

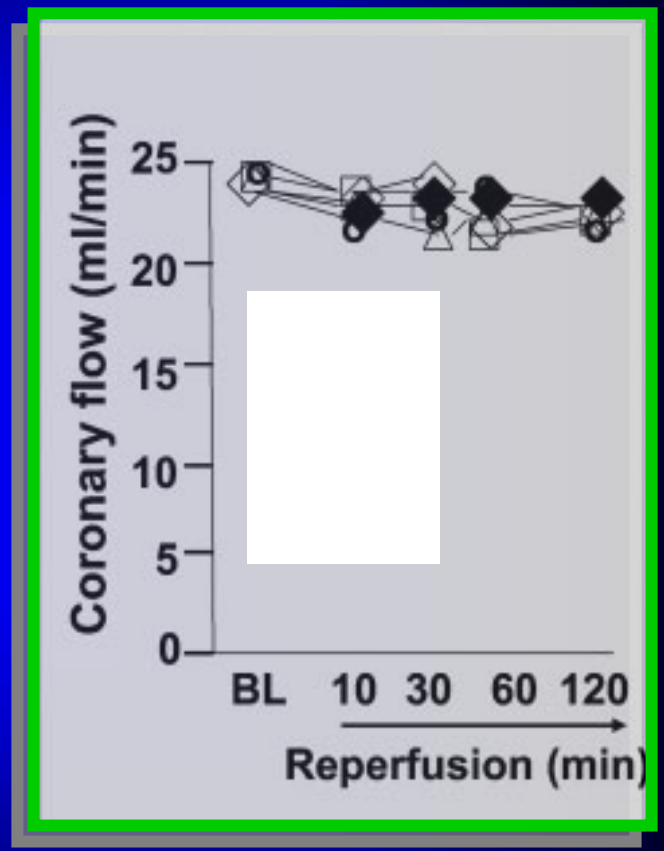
Kyungmin *et al*. (2006) showed that 100 μM resveratrol induced apoptosis by cleavage of caspase 3 and resveratrol has an inhibitory effect on cell migration.

Howitz *et al*. (2003) showed that the photoprotective effect of resveratrol from radiation induced apoptosis in HEK 293 cells was reversed at concentrations greater than 50 μM.

Dose-response curve of the effects of resveratrol on myocardial performance

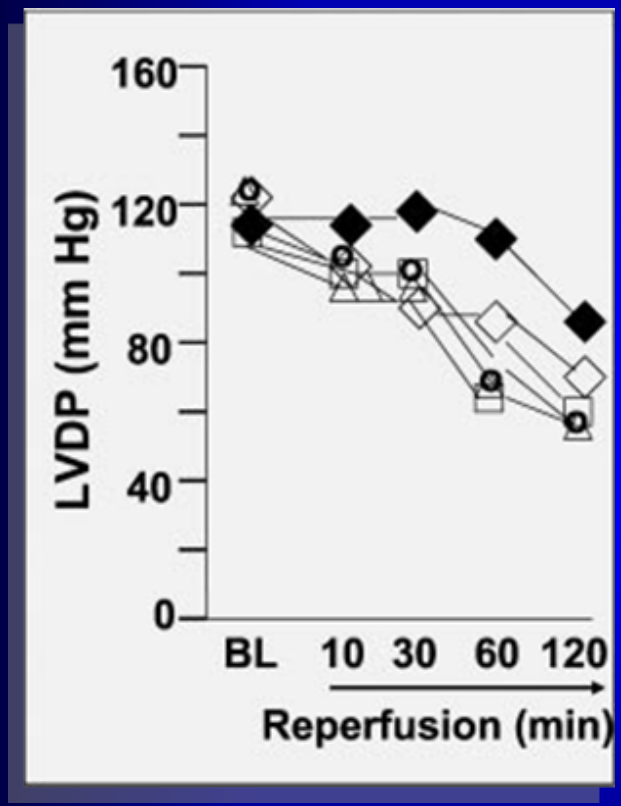


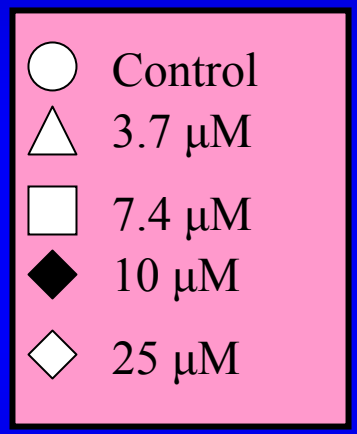


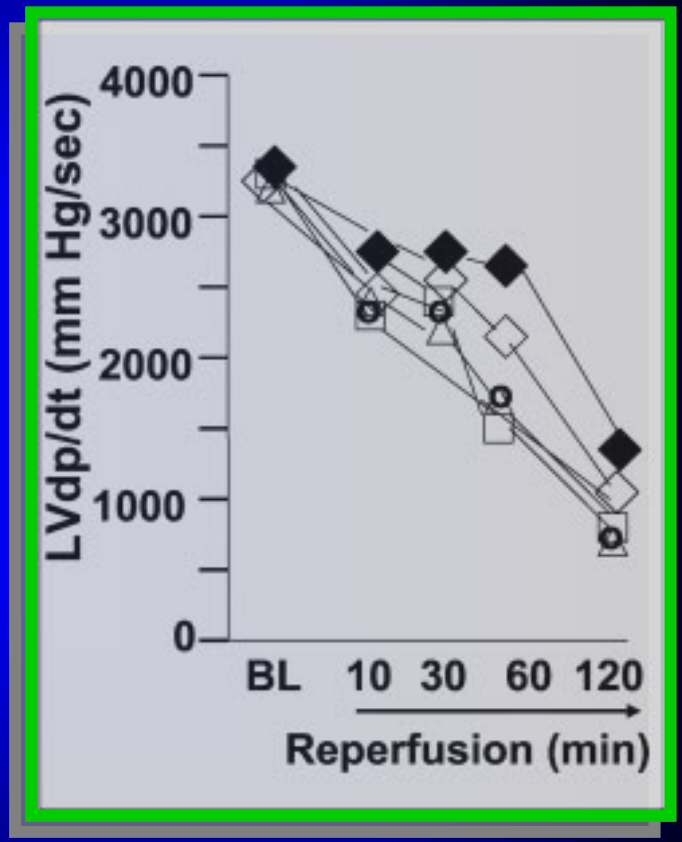


Das *et al.*, J Pharmacol Exp Ther. 2006

Dose-response curve of the effects of resveratrol on myocardial performance

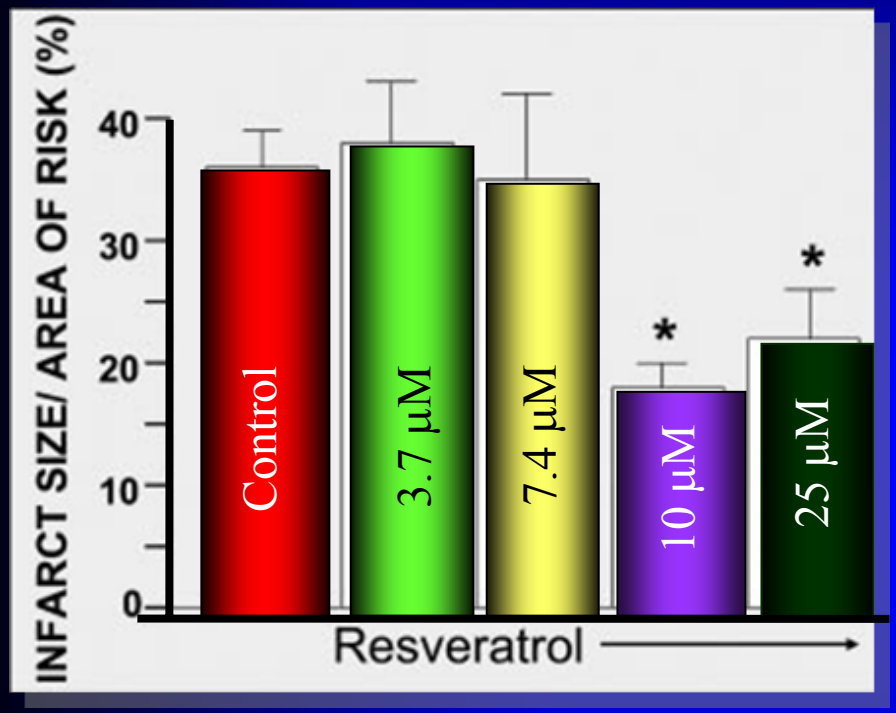


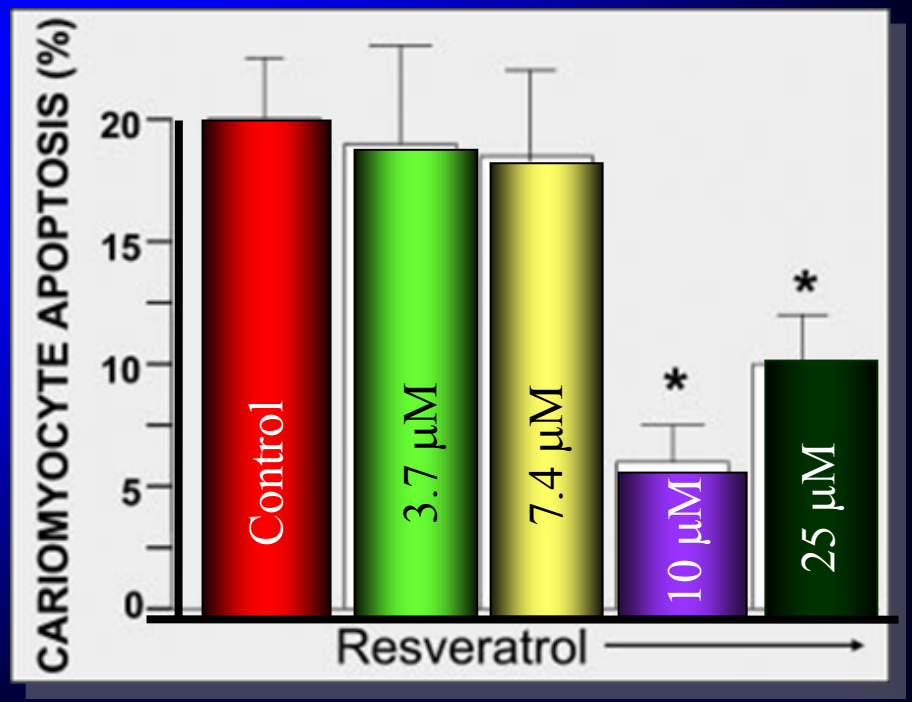




Das *et al.*, J Pharmacol Exp Ther. 2006

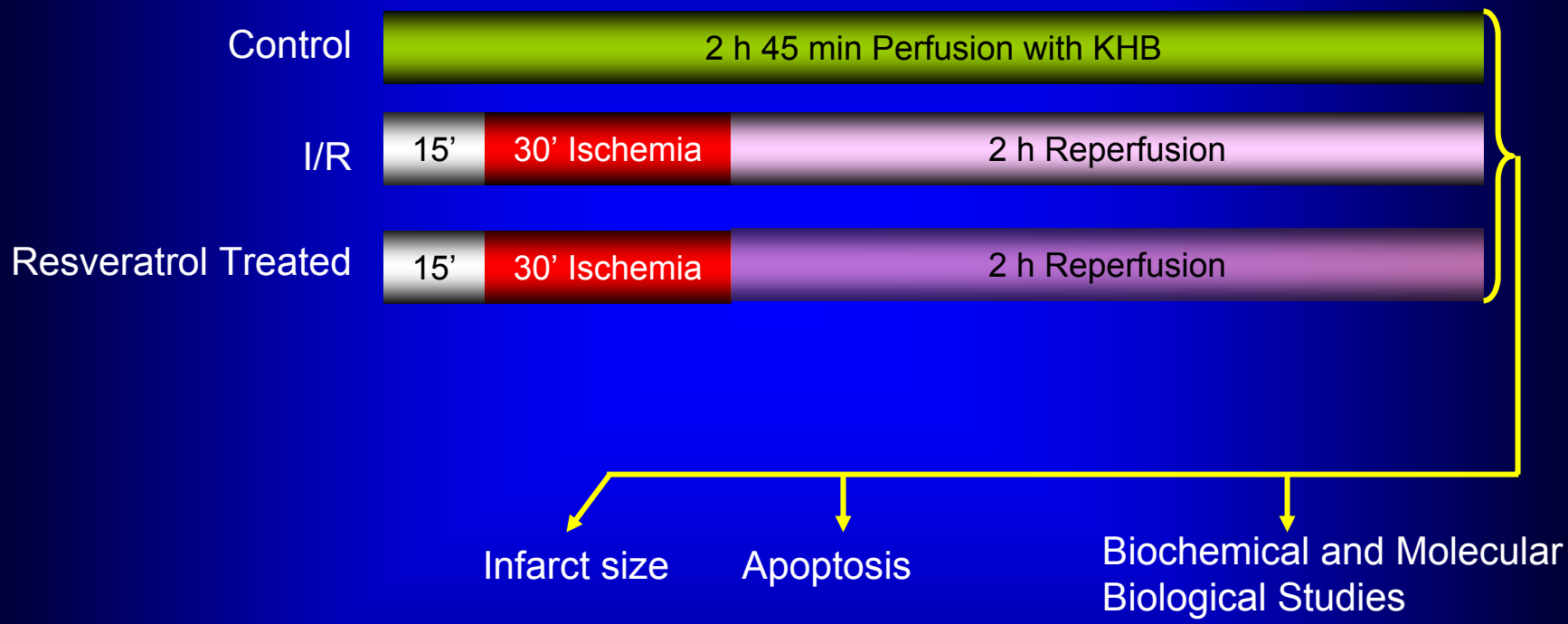
Dose-response curve of the effects of resveratrol on myocardial infarction and cardiomyocyte apoptosis.

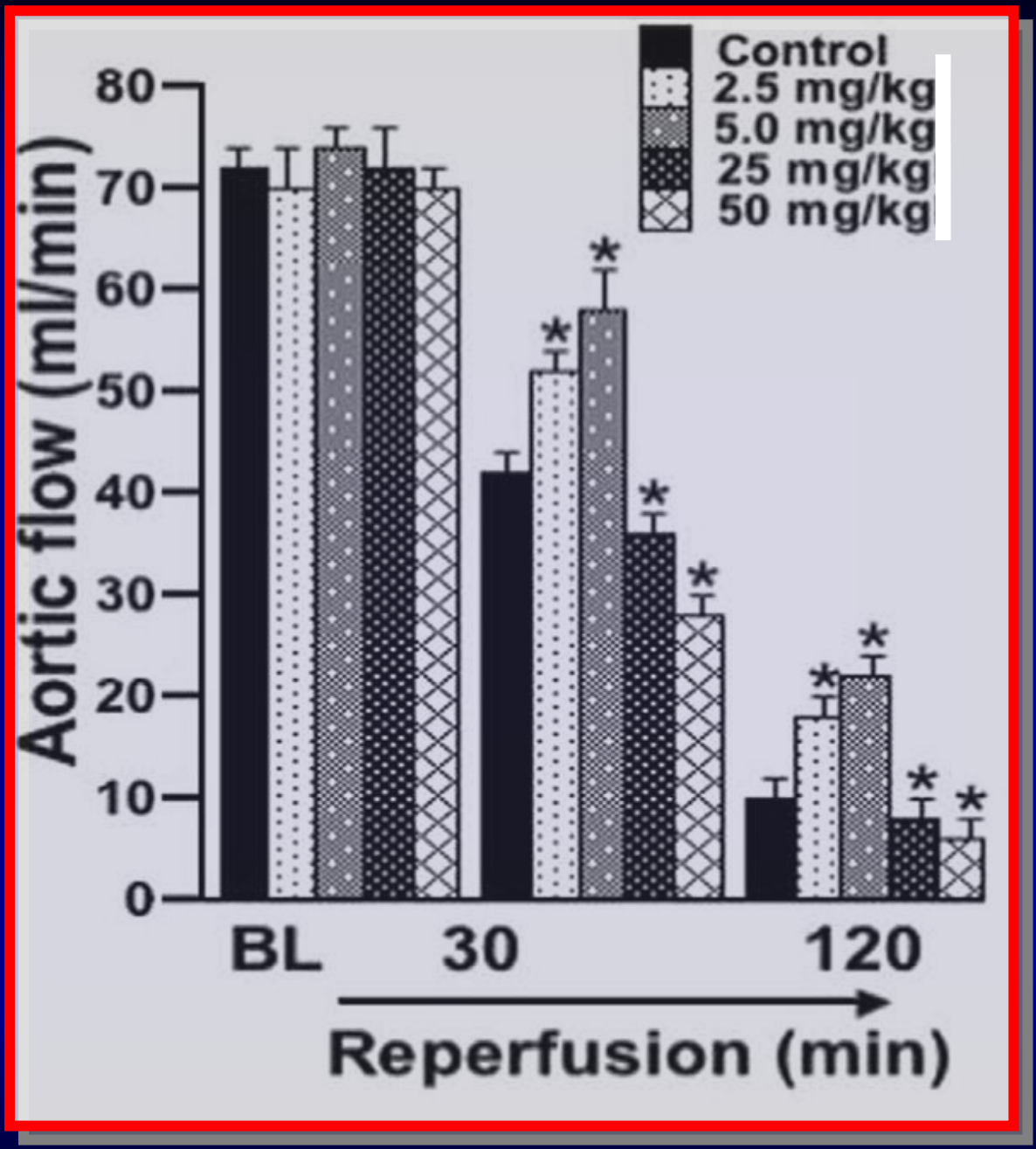




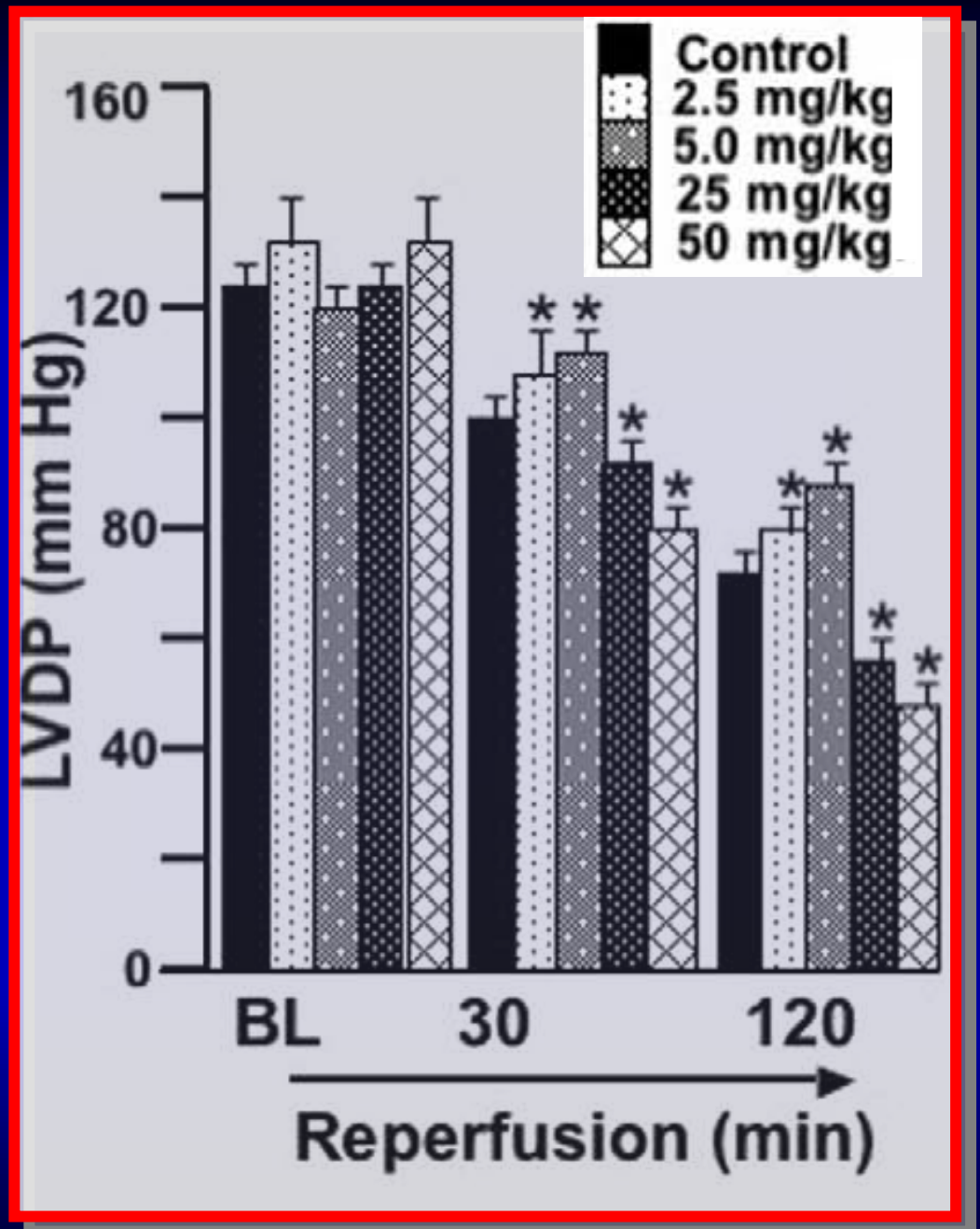
Das *et al.*, J Pharmacol Exp Ther. 2006

Isolated Working Heart Model of Ischemia-Reperfusion





Dudley *et al*., Journal of Nutritional Biochemistry. 2008



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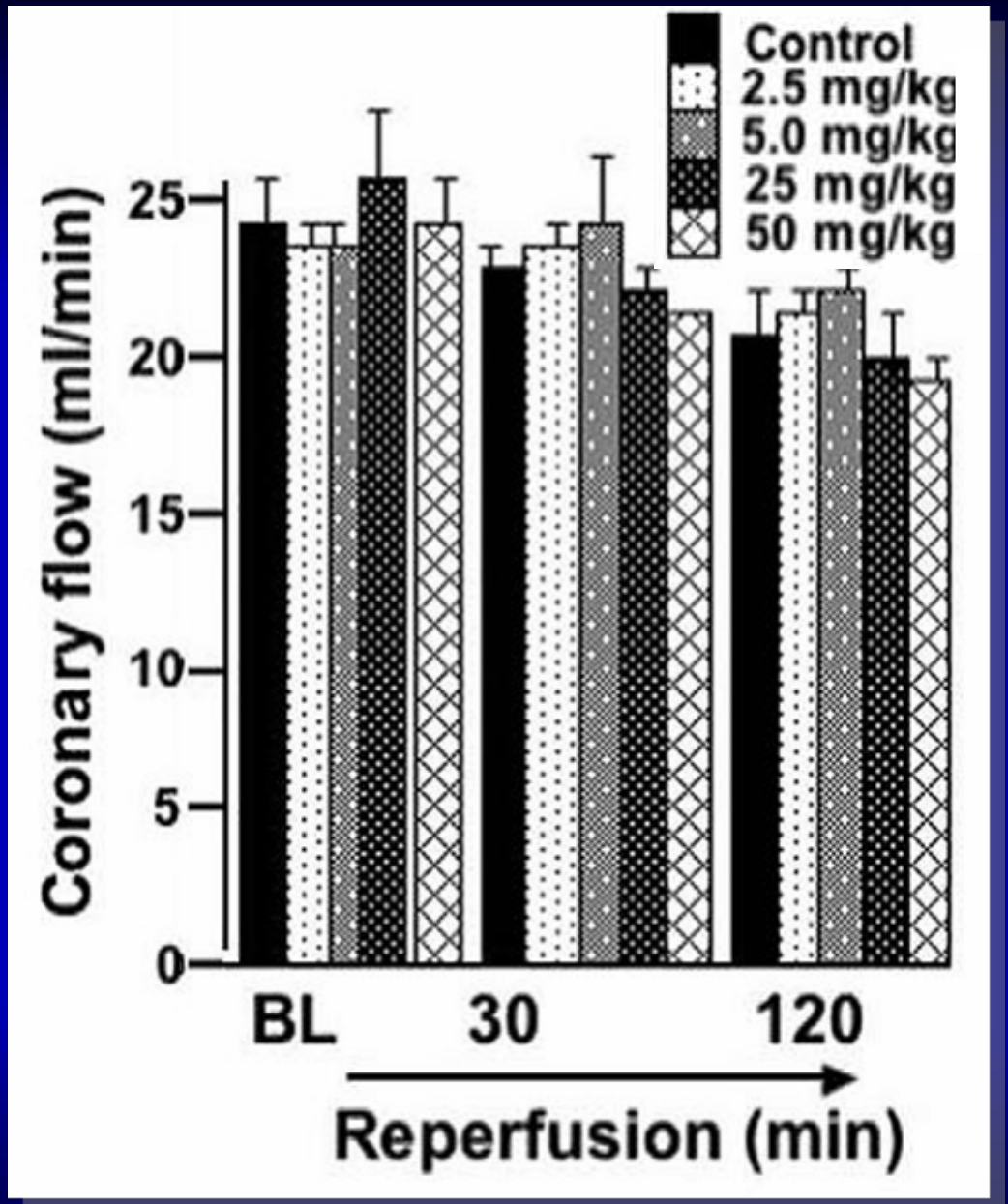
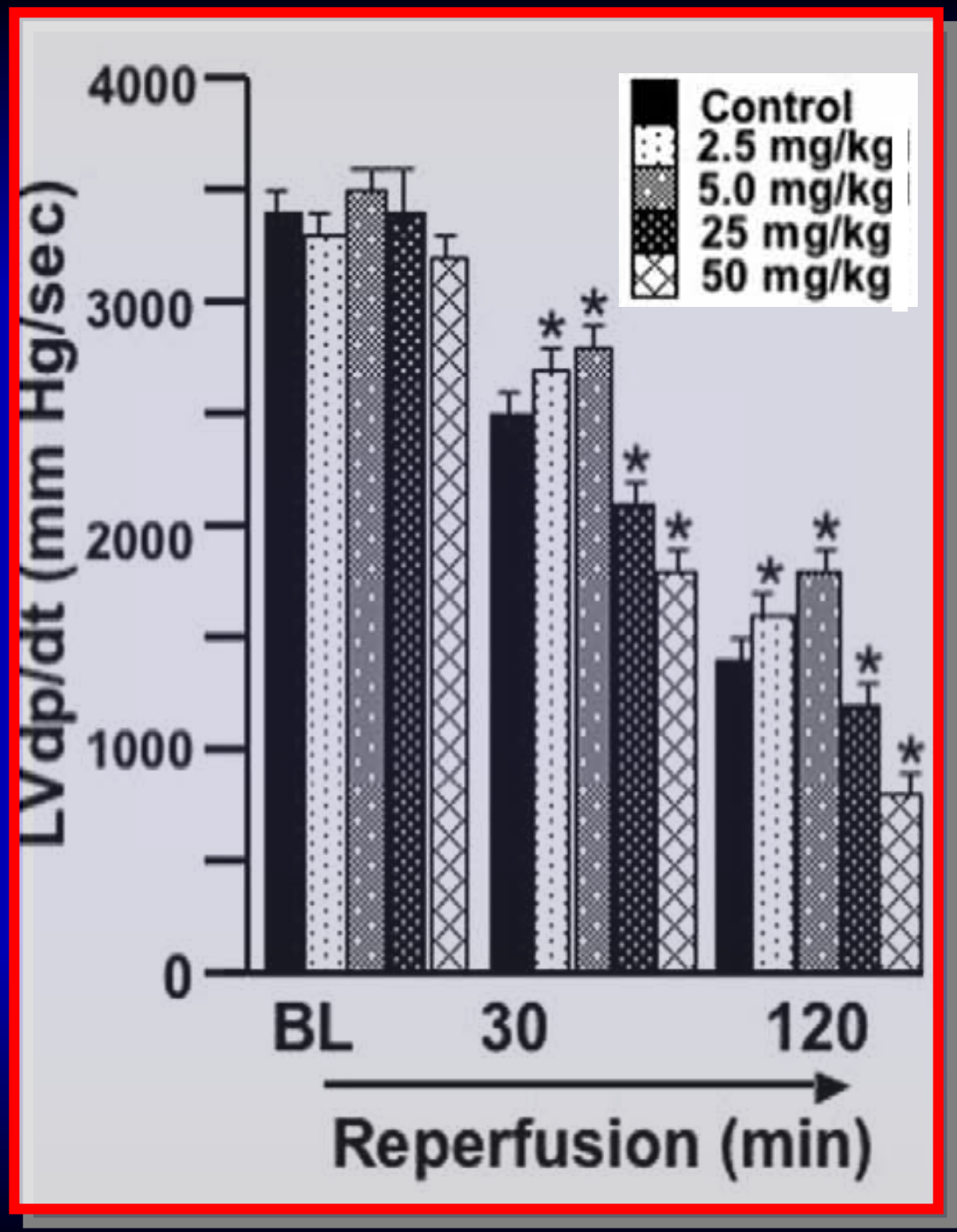
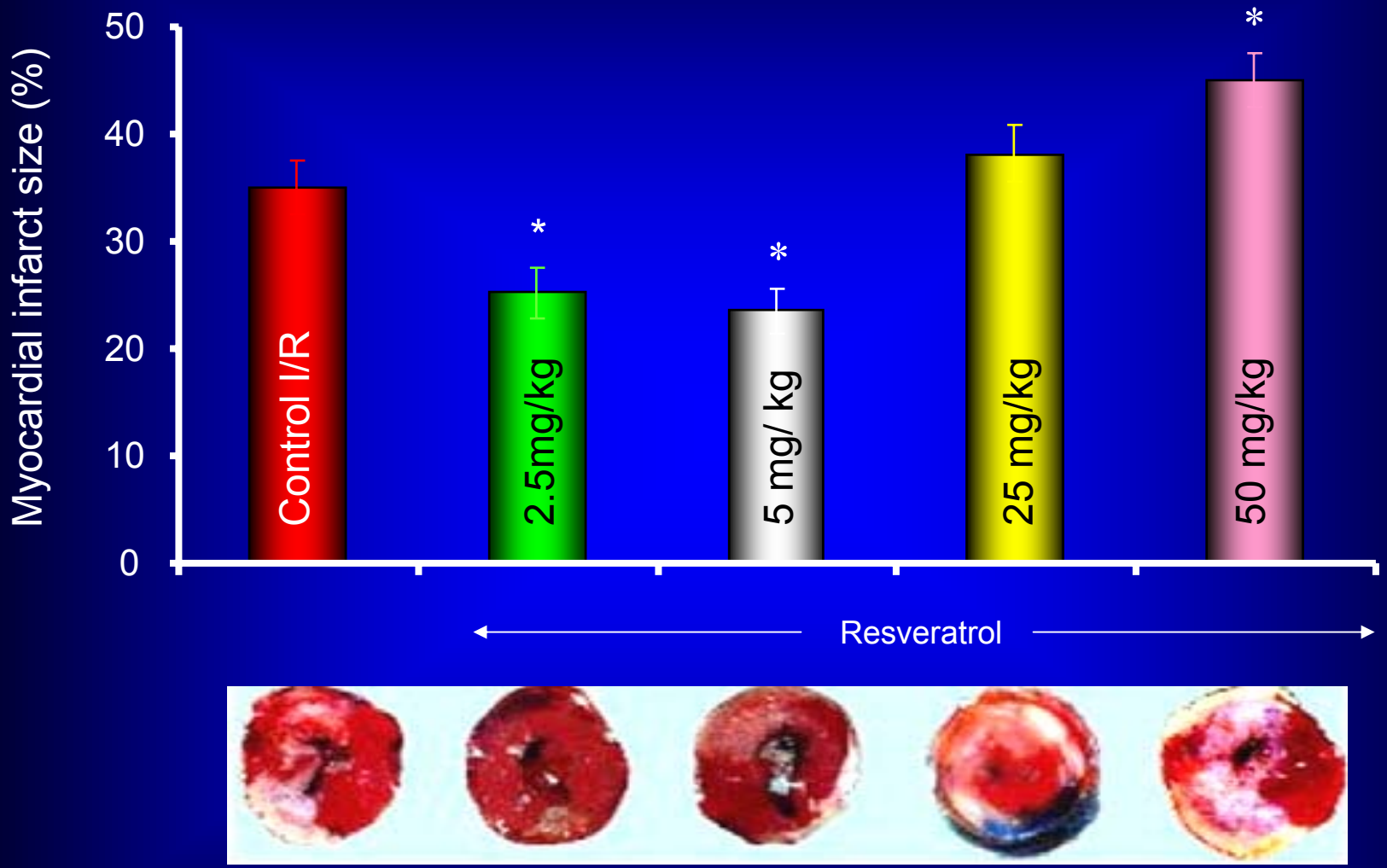


Dudley *et al*., Journal of Nutritional Biochemistry. 2008


Control
2.5 mg/kg
5.0 mg/kg
25 mg/kg
50 mg/kg
LV dp/dt (mm Hg/sec)
4000
3000
2000
1000
0
BL
30
120
Reperfusion (min)

Effects of high and low doses of resveratrol on the myocardial infarct size



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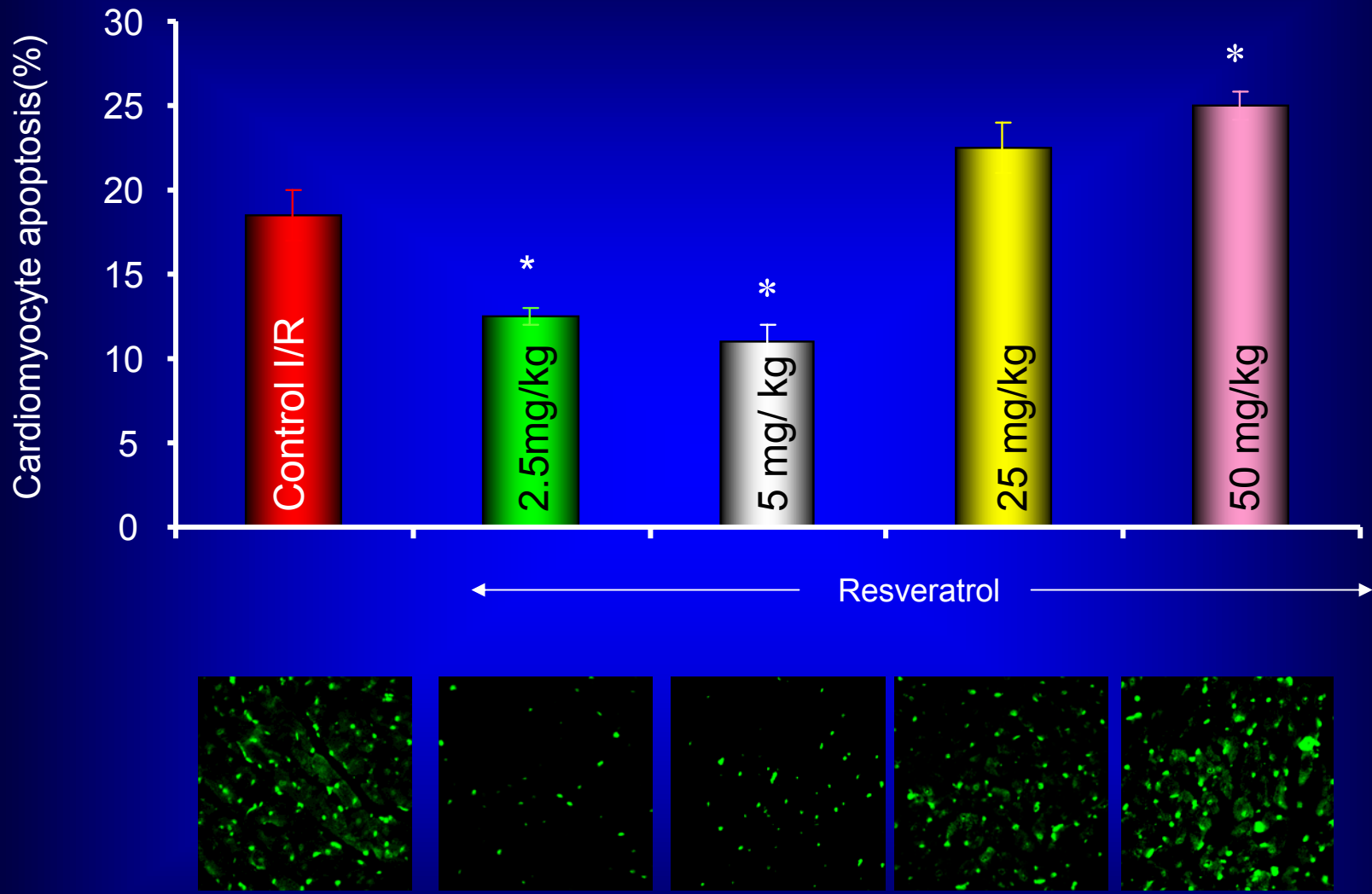
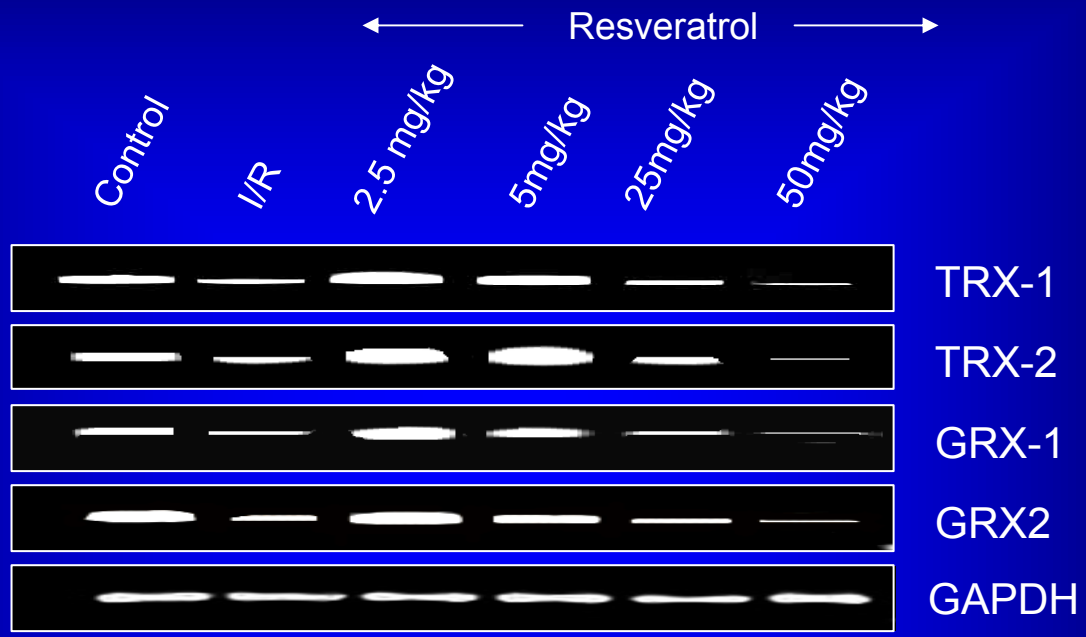


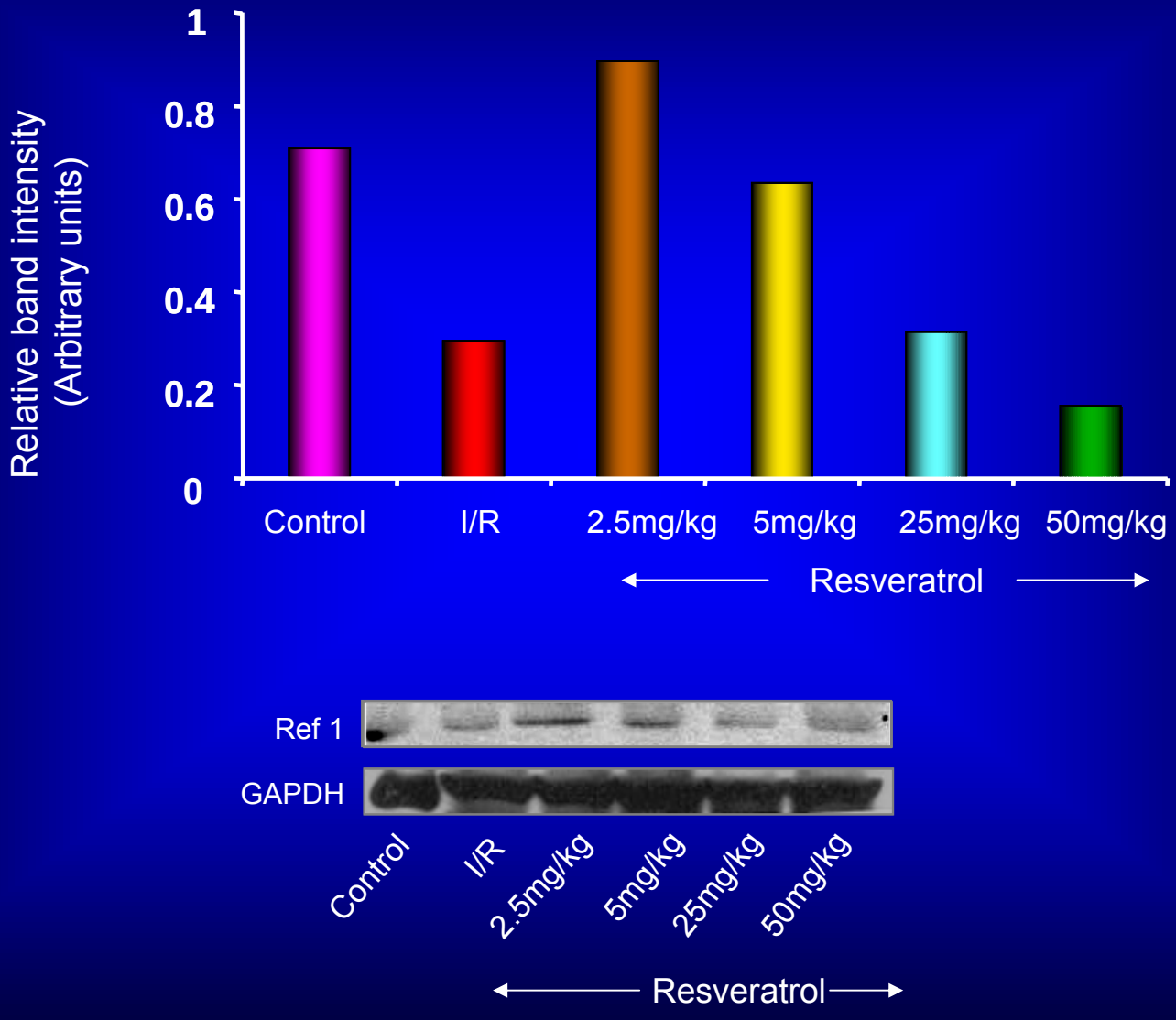
Dudley *et al*., Journal of Nutritional Biochemistry. 2008

Effects of high and low doses of resveratrol on mRNA transcript of some redox genes



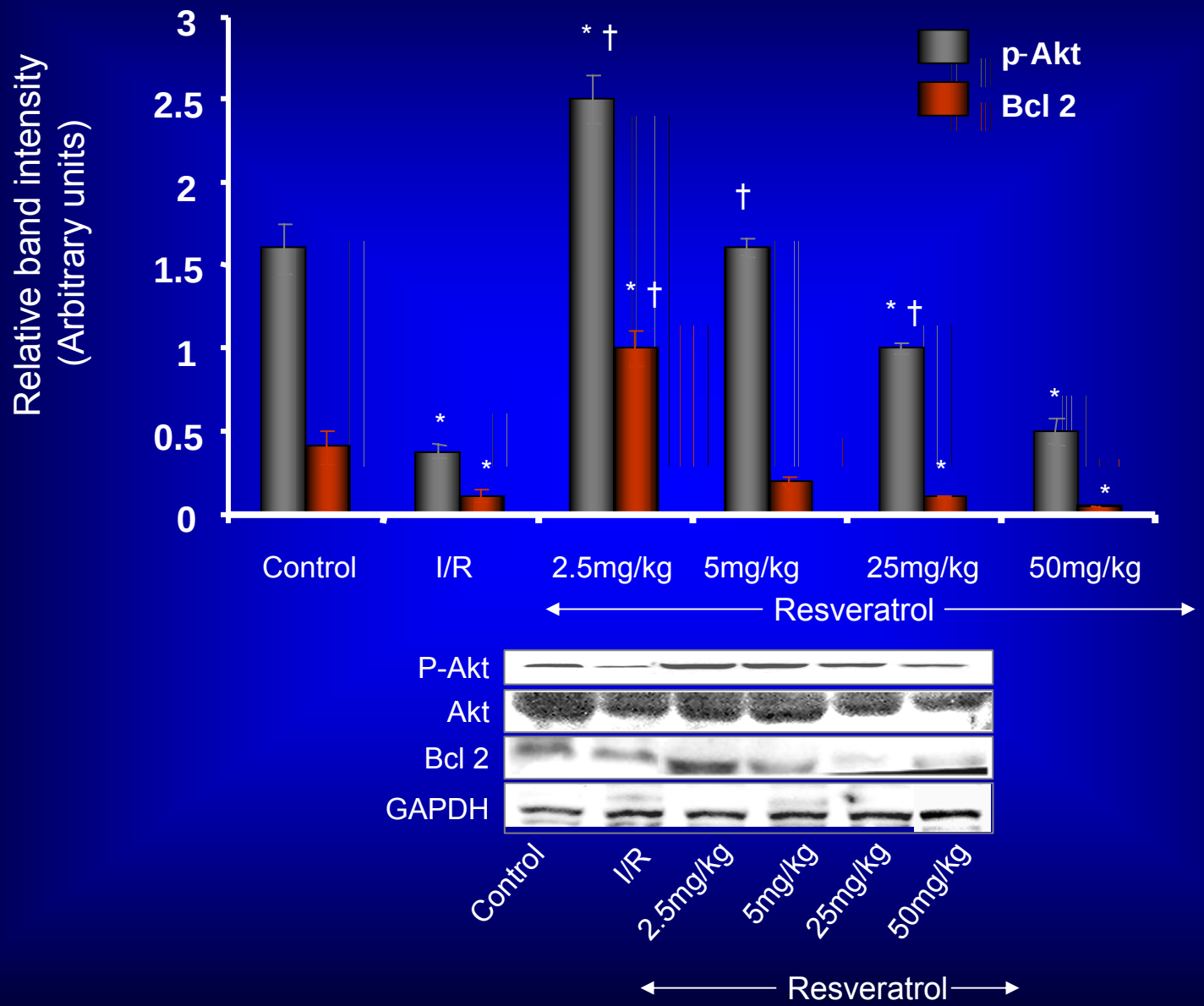
Dudley *et al*., Journal of Nutritional Biochemistry. 2008

Effects of high and low doses of resveratrol on Ref1 protein induction



Dudley *et al*., Journal of Nutritional Biochemistry. 2008

Effects of high and low doses of resveratrol on survival signal



Dudley *et al.*, Journal of Nutritional Biochemistry. 2008

CONCLUSION

•Resveratrol is good for health but the health benefit of resveratrol is dose dependent.

•Low doses resveratrol protects from different types of diseases such as cardiovascular, ageing etc.

• High doses resveratrol can be detrimental for normal tissue but it can be used in cancer prevention.