

Journées Francophones de Nutrition 11-13 Décembre, 2013 Bordeaux

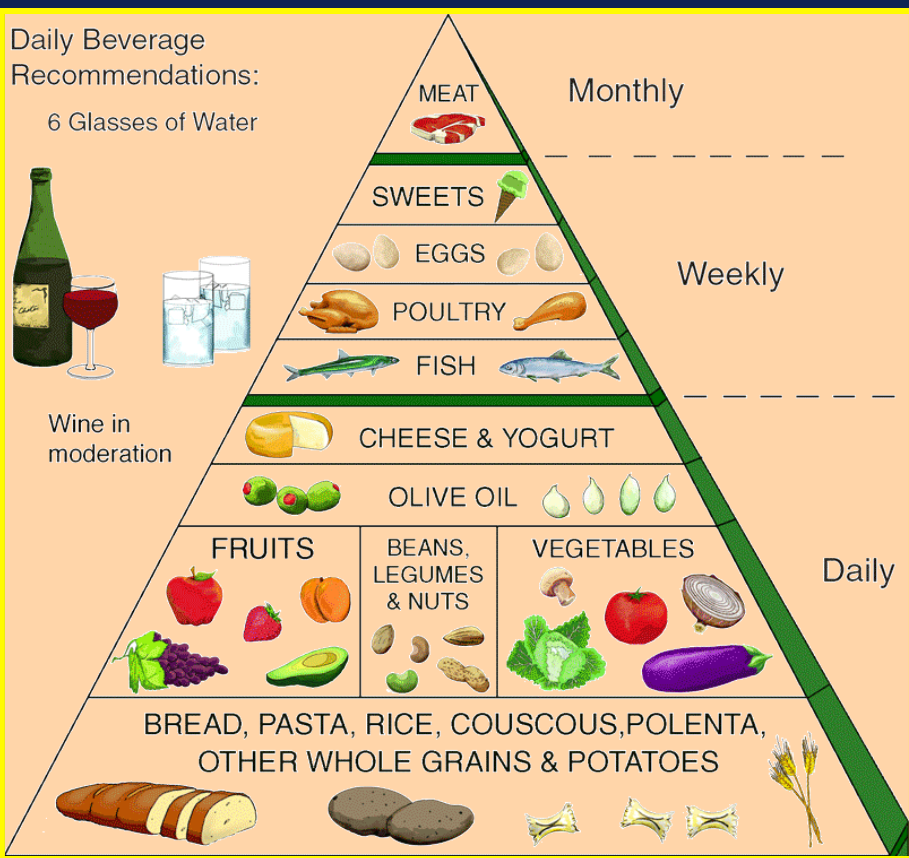


Polyphénols et Effets Vasculoprotecteurs

V.B. Schini-Kerth
(email: valerie.schini-kerth@unistra.fr)

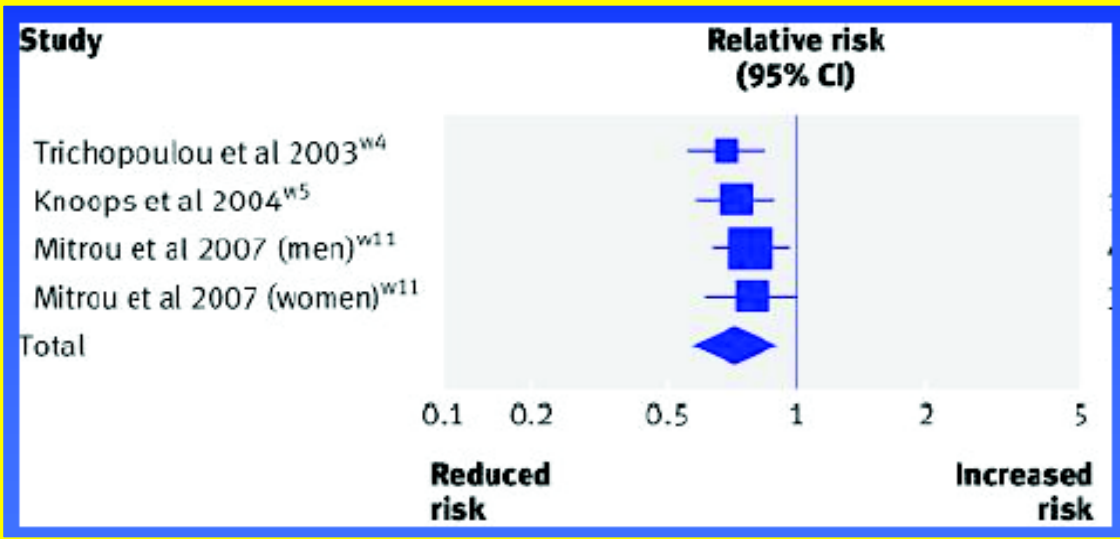
UMR CNRS 7213
Faculty of Pharmacy
Strasbourg University
France

Adherence to the Mediterranean Diet and Human Health



Cardiovascular Diseases

Total of 404 491 subjects

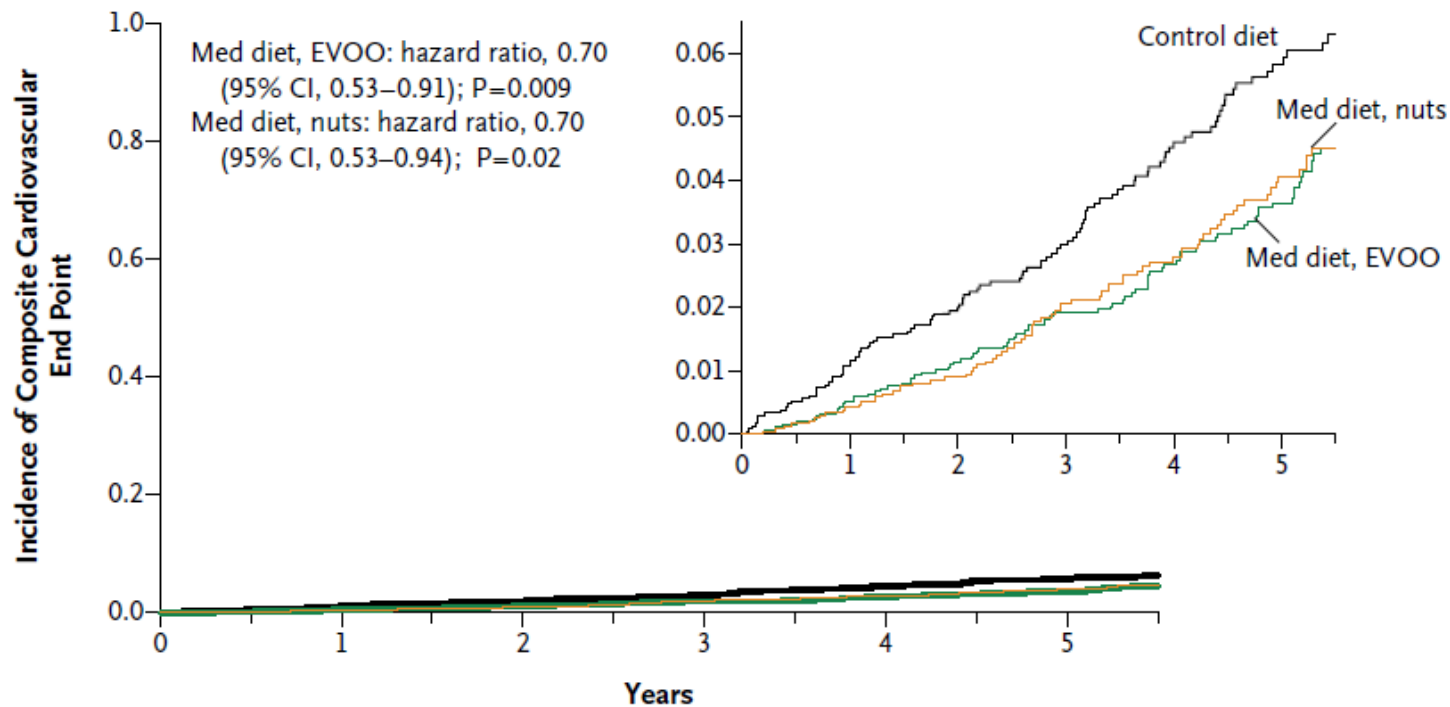


⇒ Significant reduction in mortality from cardiovascular diseases by 9%

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

- 7447 persons at high cardiovascular risk who were initially free of cardiovascular disease

A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)

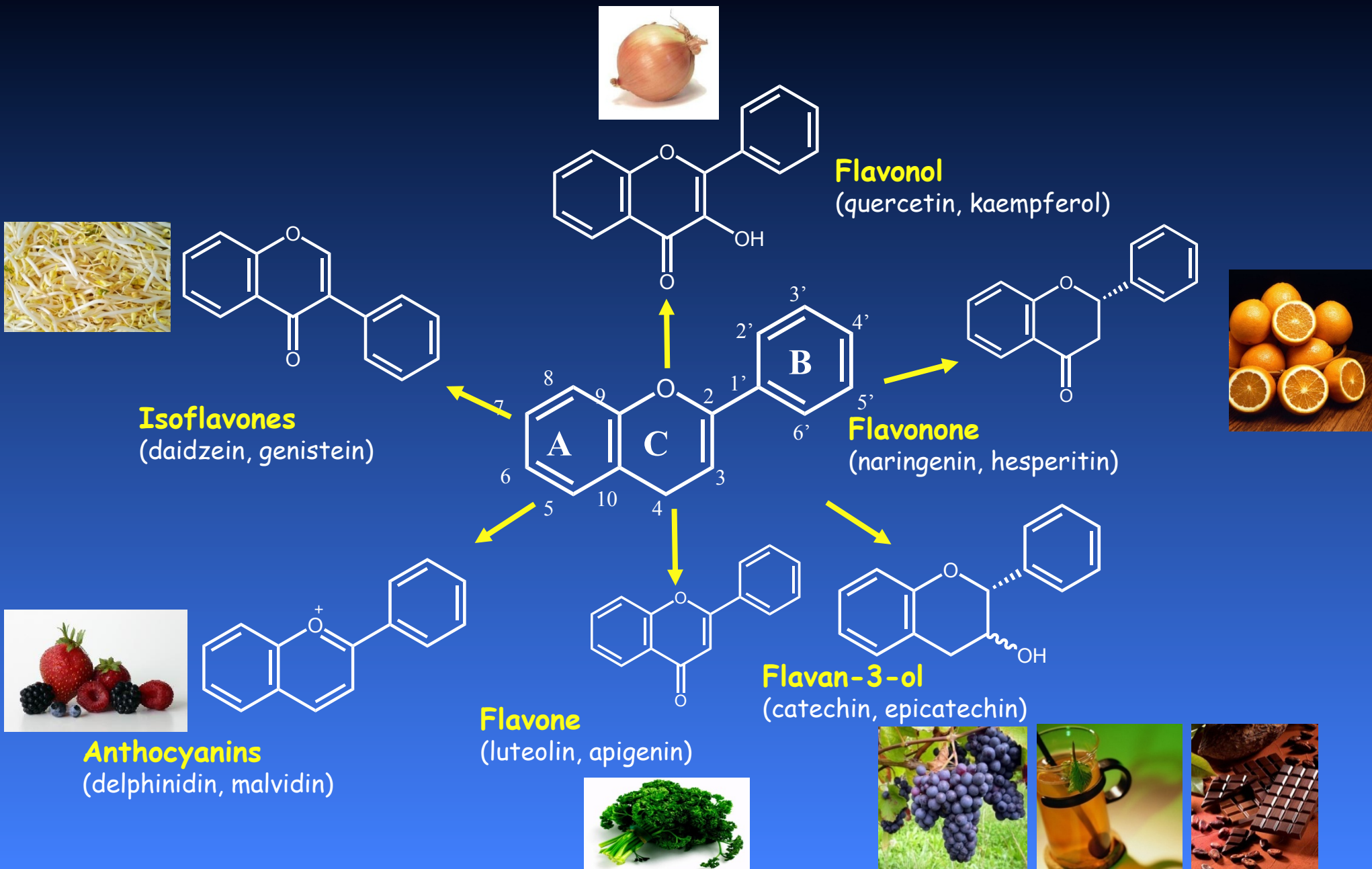


Relative risk reduction of approximately 30 %

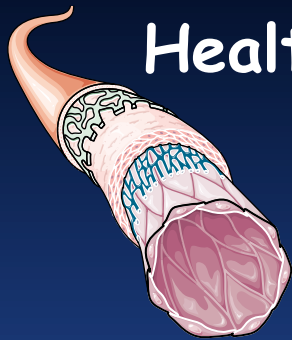
No. at Risk

Control diet	2450	2268	2020	1583	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031

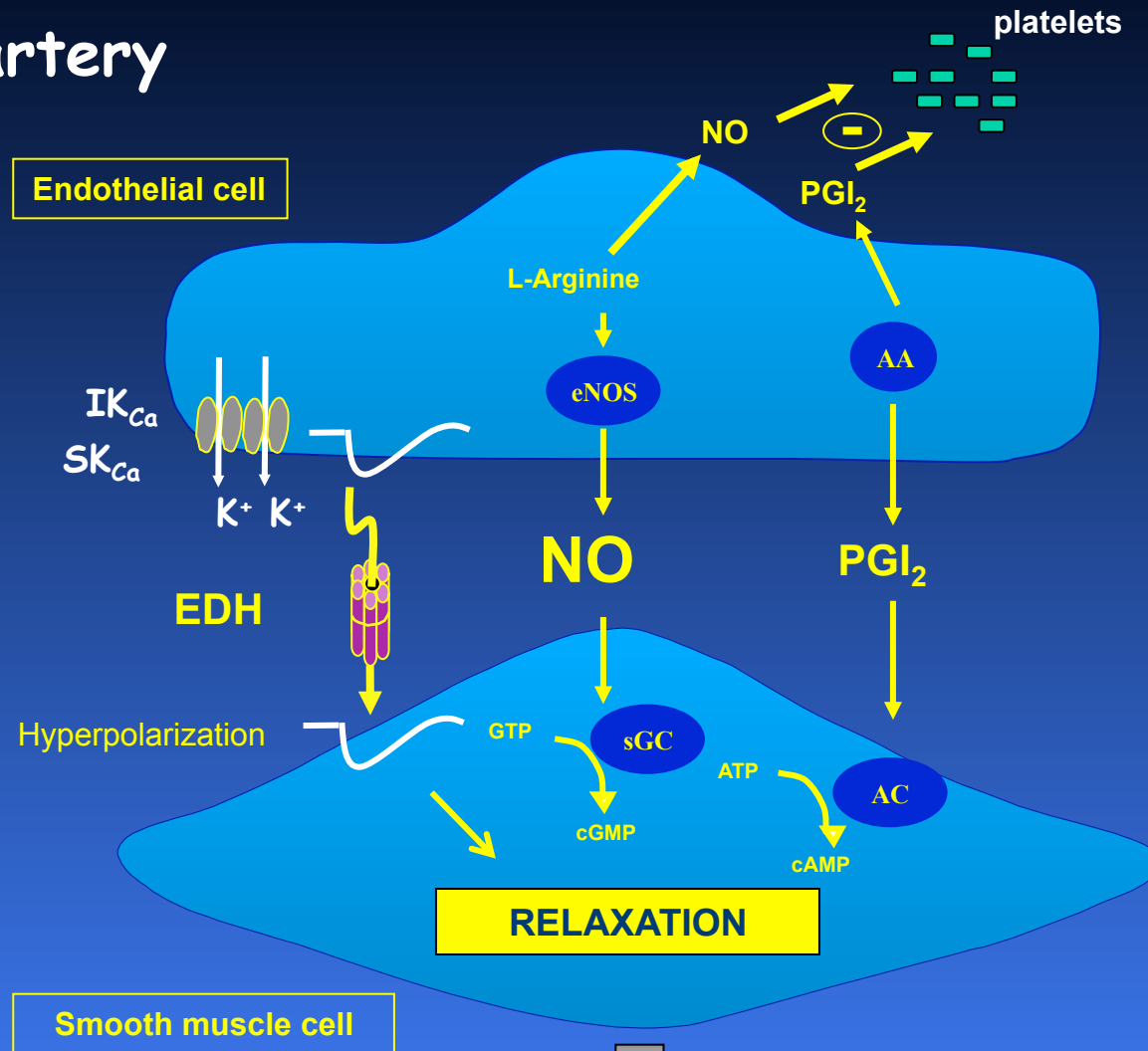
Structure and Sources of Flavonoids



Role of the Endothelium in Vascular Homeostasis

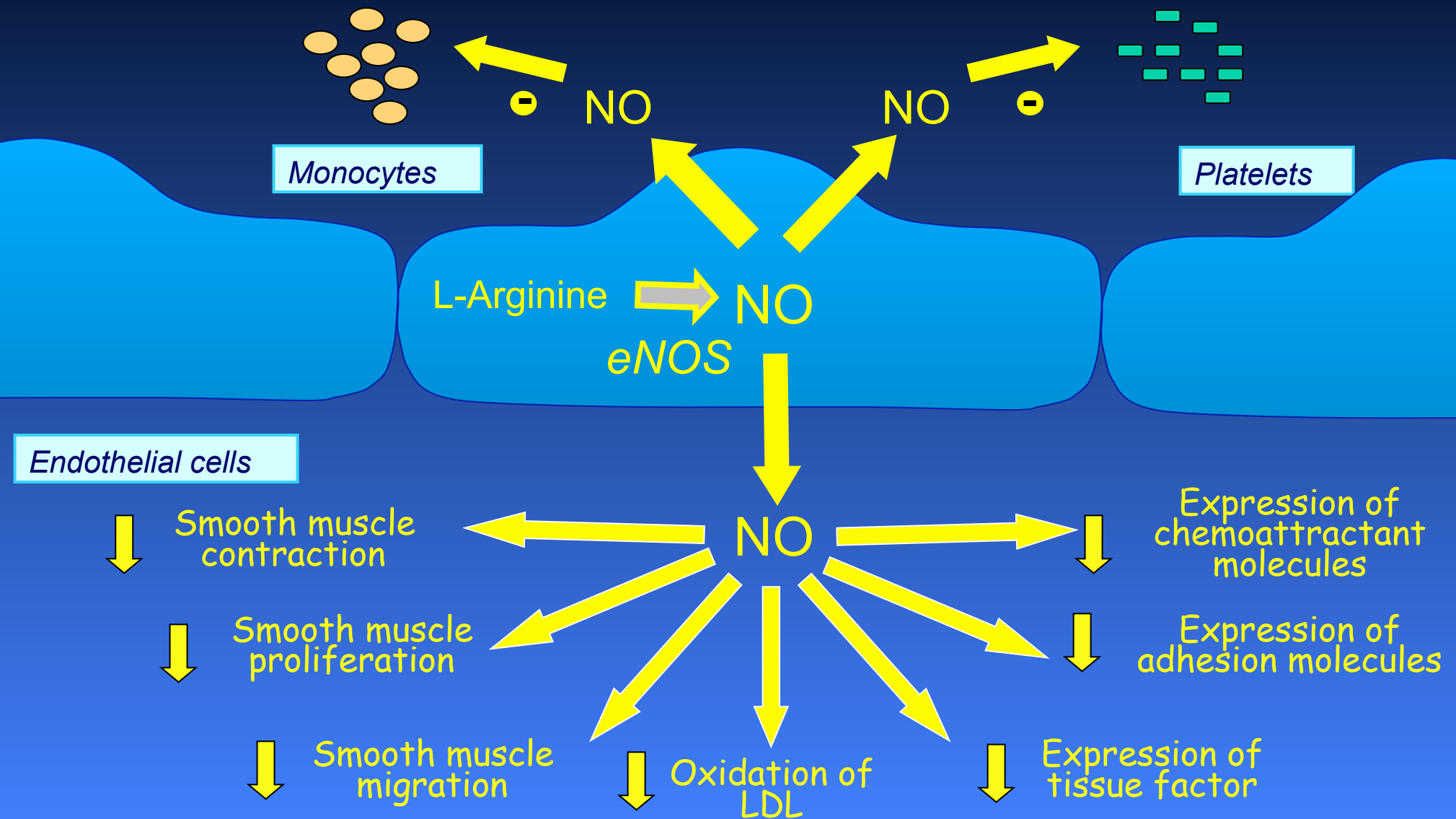


Healthy artery

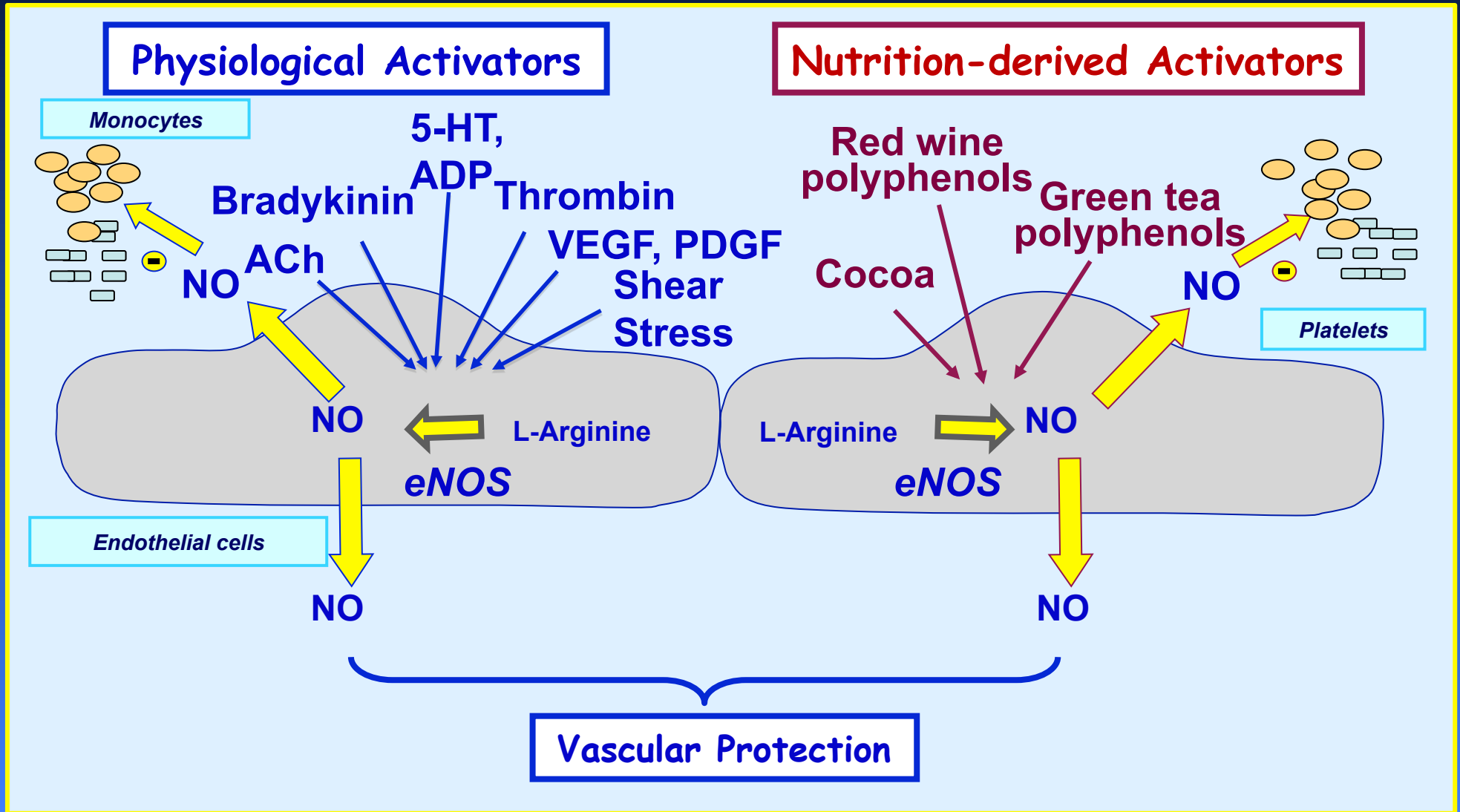


Vascular Protection

Endothelium-derived Nitric Oxide and Vascular Homeostasis



Physiological and Nutrition-derived Activators of the Endothelial Formation of NO



Red Wine Polyphenolic Extract (RWPs)



French Red Wine (Corbières A.O.C.)

1 liter of wine produced 2.9 g of RWPs

-Flavanol:

- Catechin 8.6 mg/g
- Epicatechin 8.7 mg/g

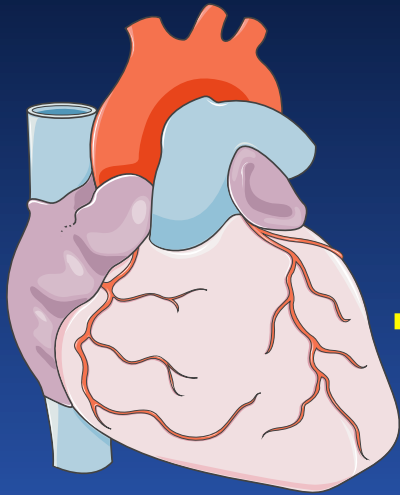
-Anthocyanin:

- malvidin-3-glucoside 11.7 mg/g
- peonidin-3-glucoside 0.66 mg/g
- cyanidin-3-glucoside 0.06 mg/g

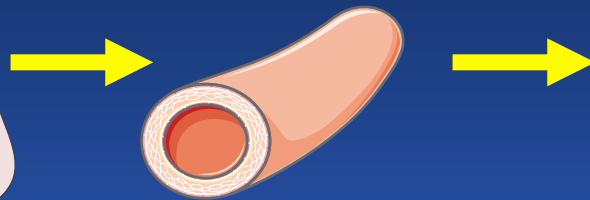
-Phenolic acid:

- gallic acid 5.0 mg/g
- caffeic acid 2.5 mg/g
- caftaric acid 12.5 mg/g

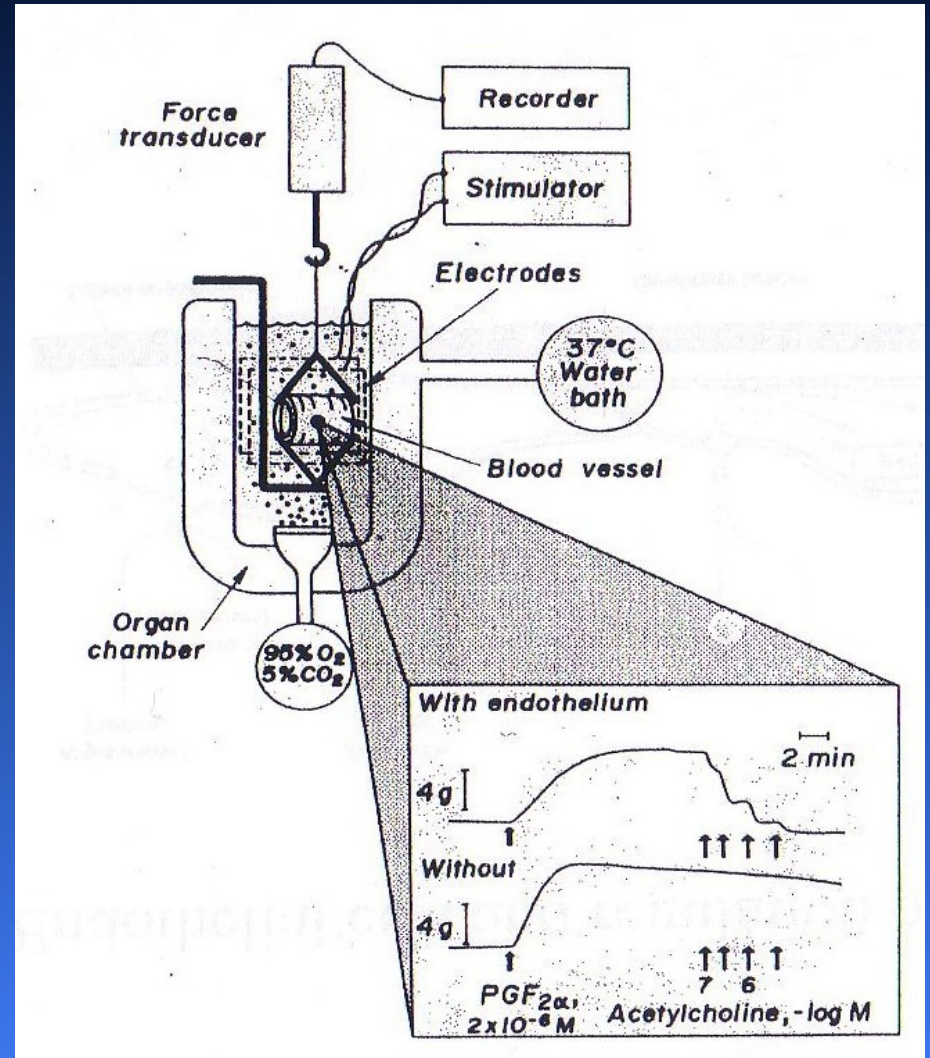
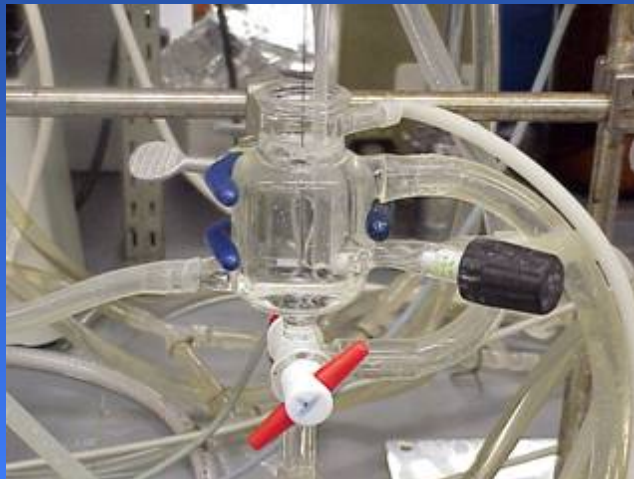
Vascular Reactivity Studies



Left anterior
descending coronary
artery



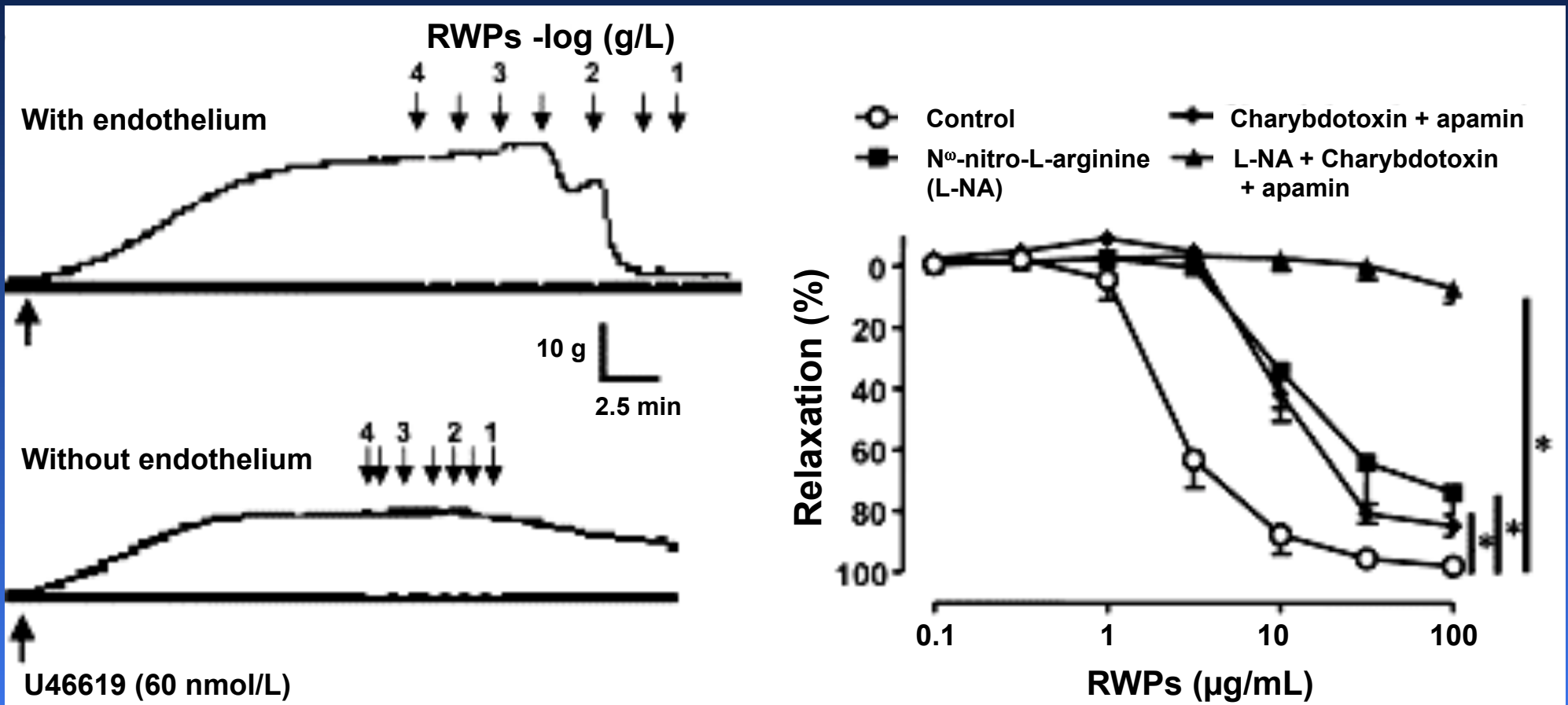
Porcine heart



Lüscher and Vanhoutte, 1990, CRC Press

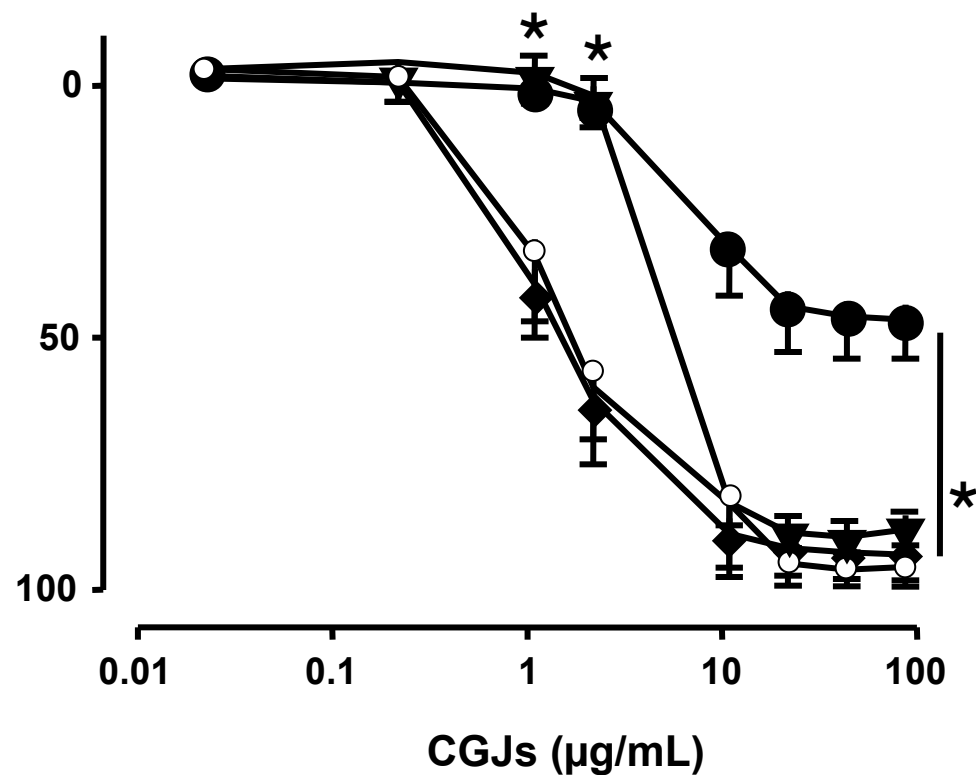
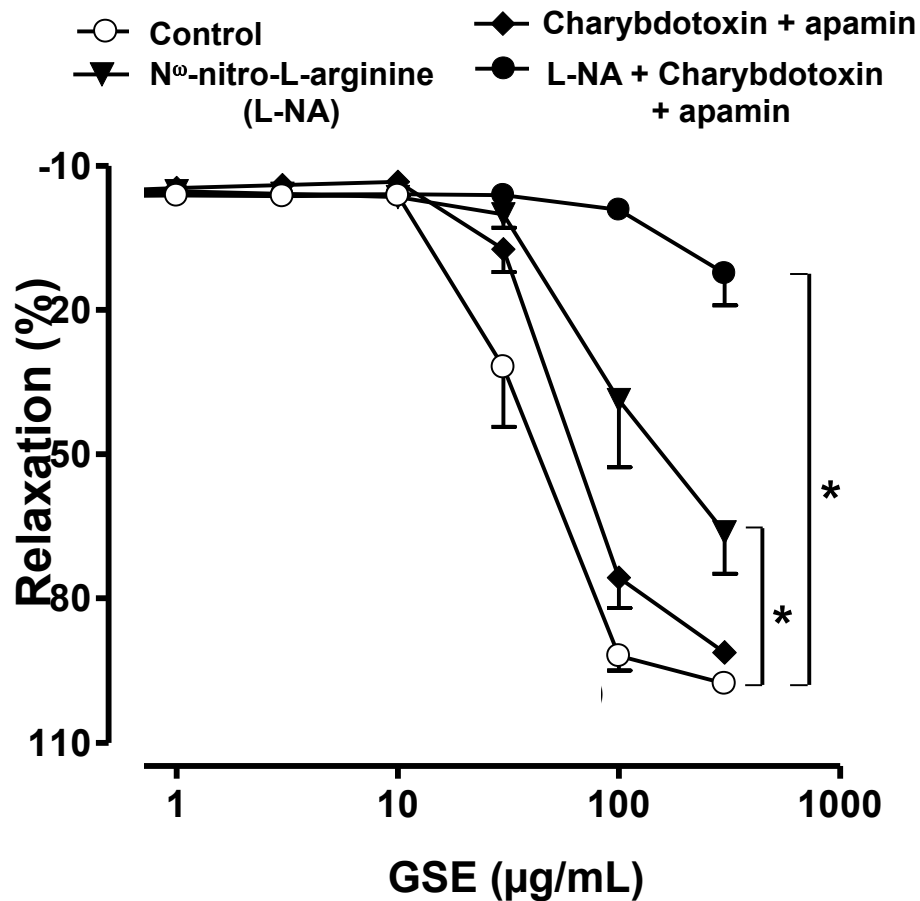
Red Wine Polyphenols cause Endothelium-Dependent Relaxations in the Porcine Coronary Artery

(in the presence of indomethacin)

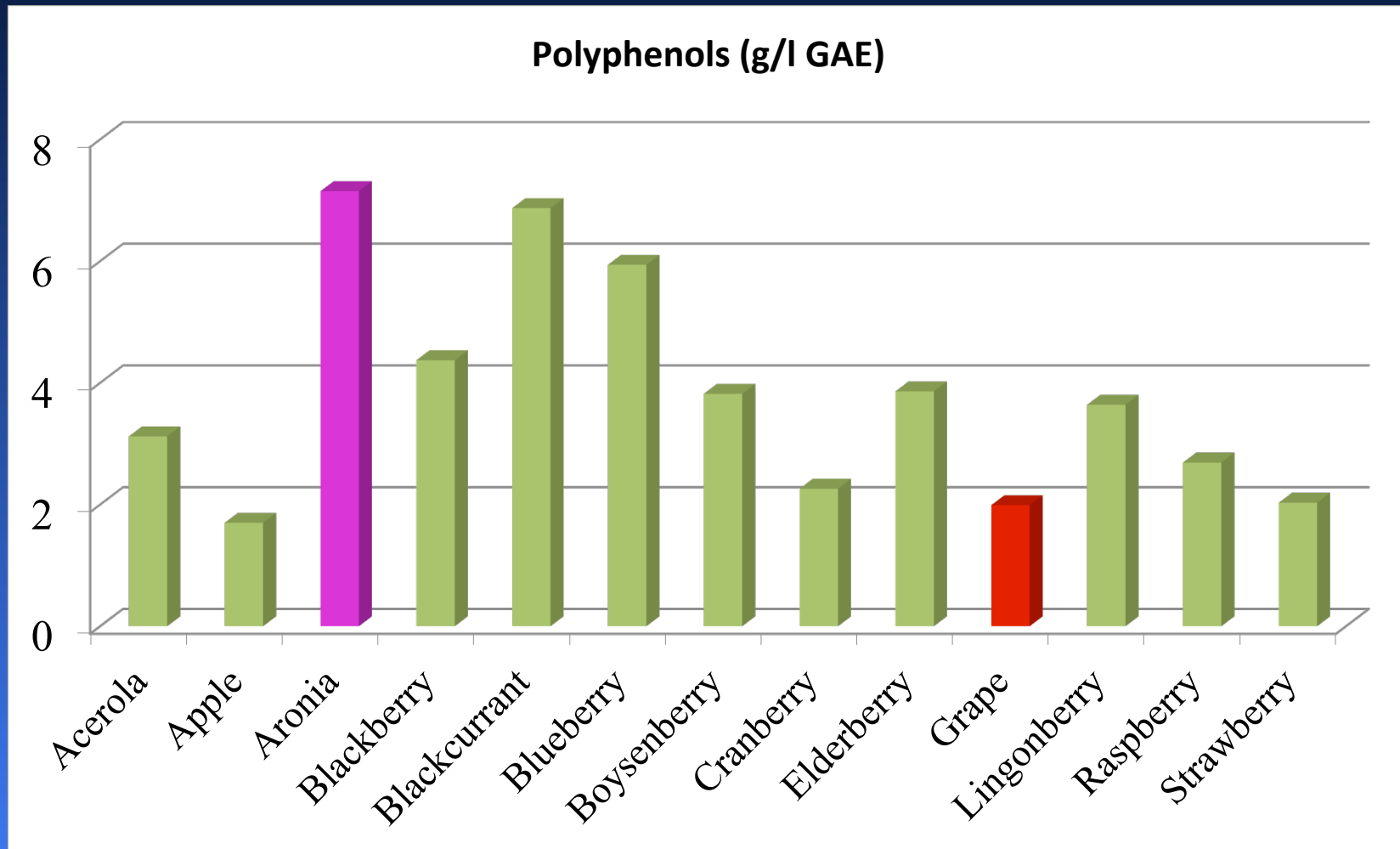


Grape Skin Extract and Concord Grape Juice also cause Endothelium-Dependent Relaxations

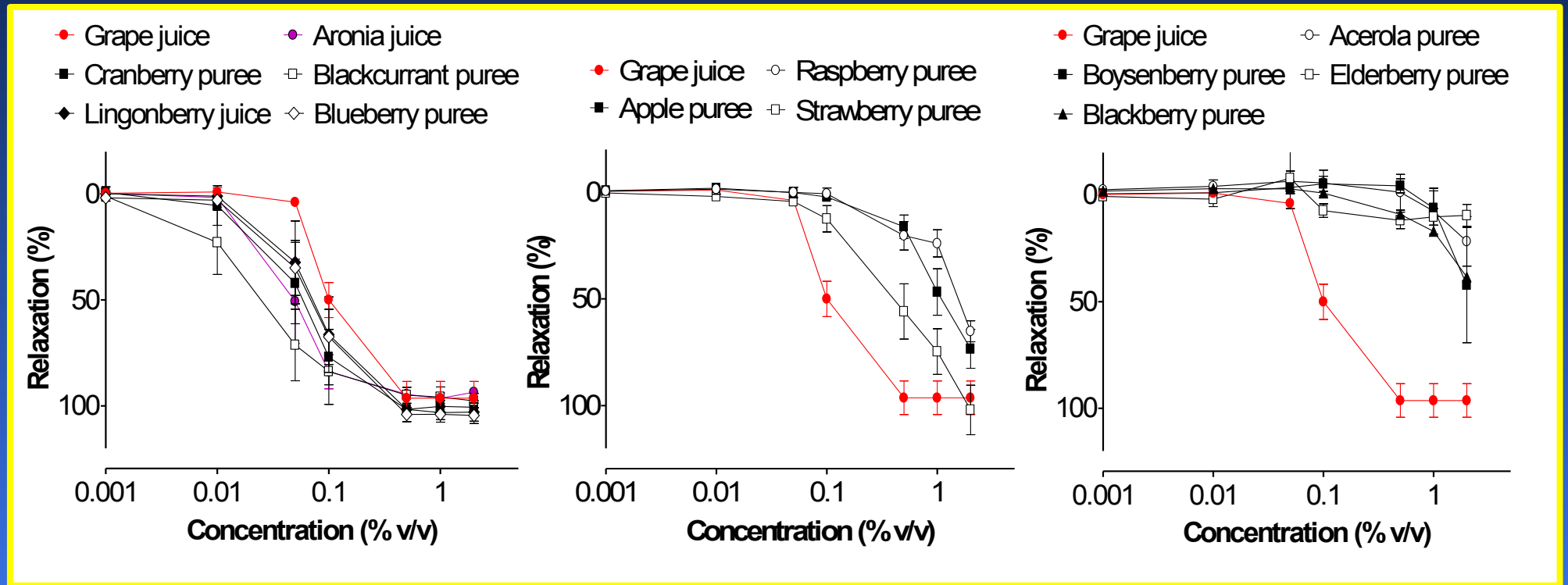
(in the presence of indomethacin)



Polyphenol Content of Individual Fruit and Berry Juices and Purees



Selected Fruit and Berry Juices and Purees cause Endothelium-dependent Relaxations in the Porcine Coronary Artery



Selected Fruit and Berry Juices and Purees cause Endothelium-dependent Relaxations in the Porcine Coronary Artery

Aronia



Blackcurrant



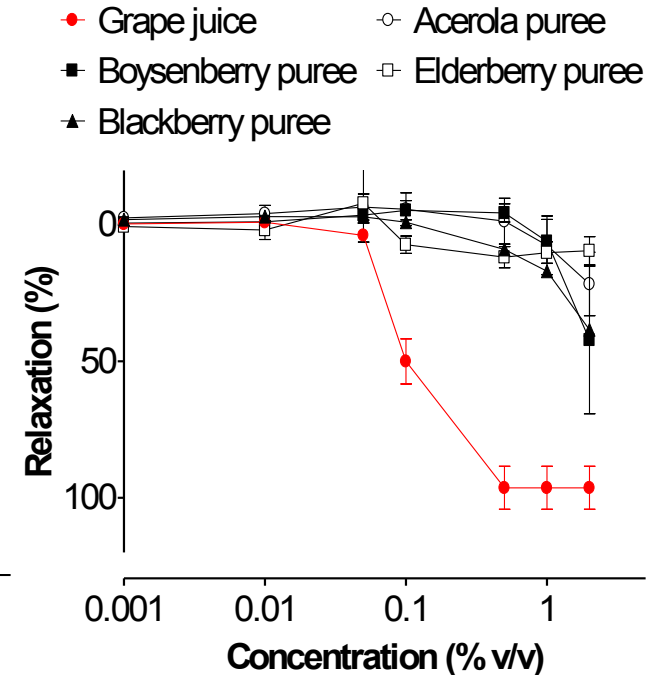
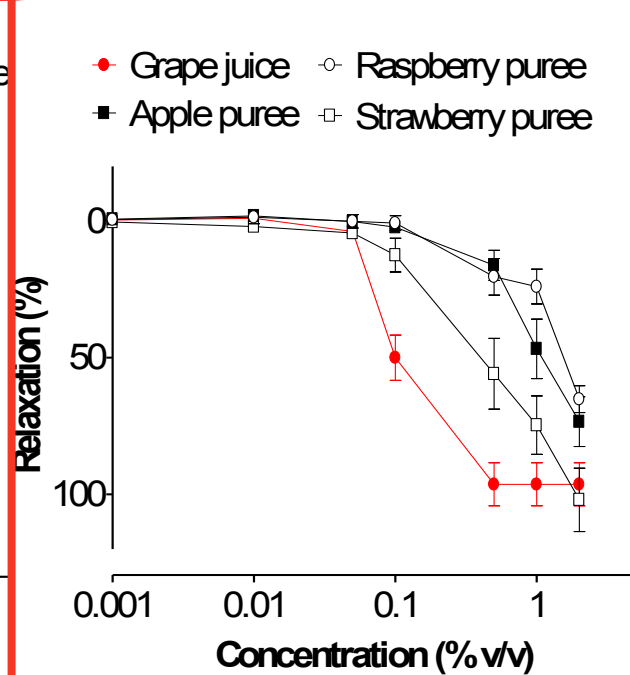
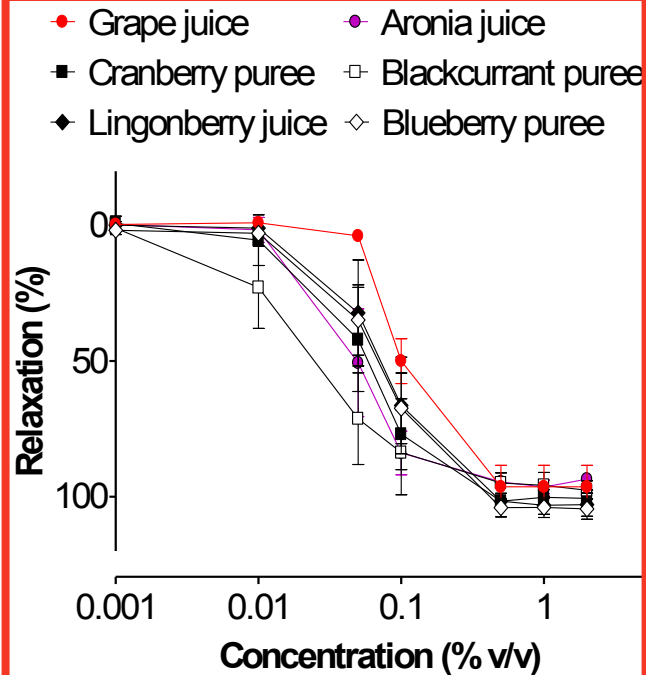
Blueberry



Cranberry

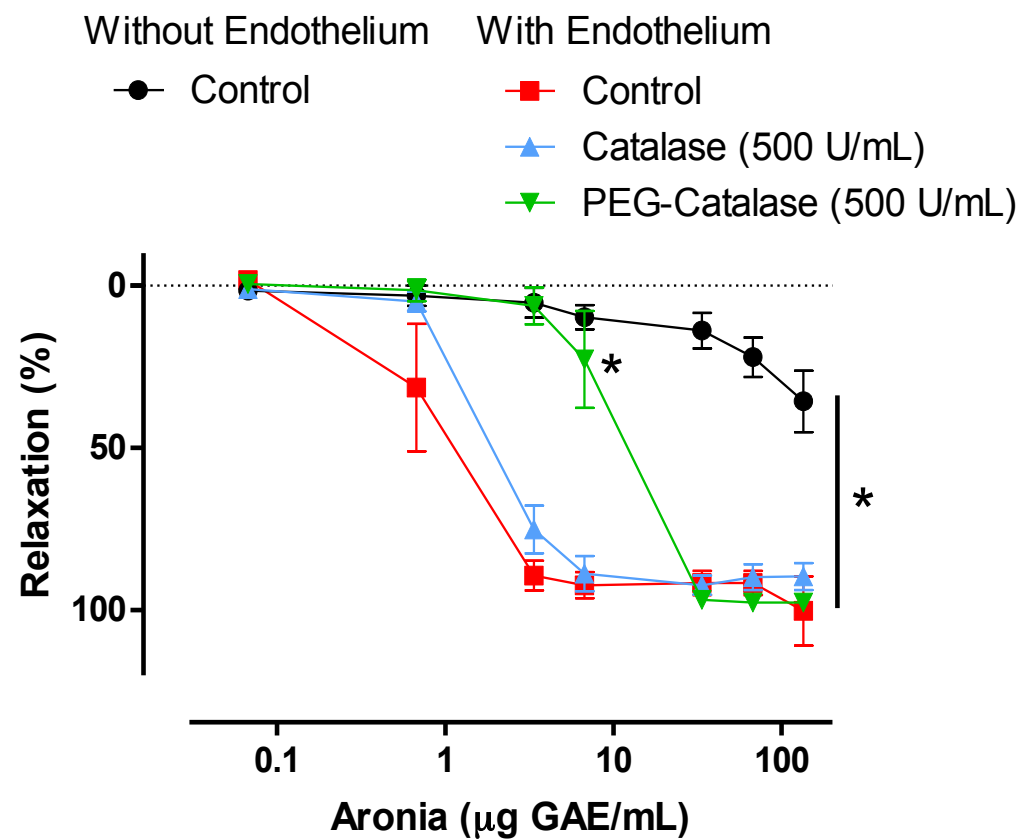
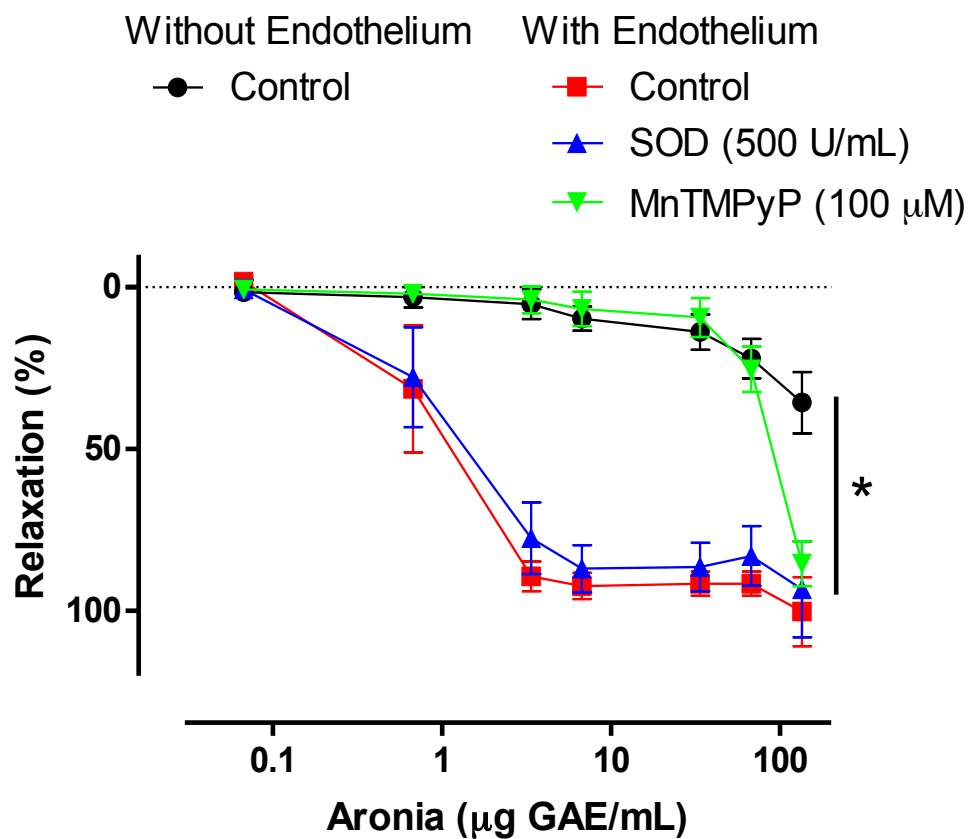


Lingonberry



Aronia Juice induces Redox-sensitive Endothelium-dependent Relaxations in the Porcine Coronary Artery

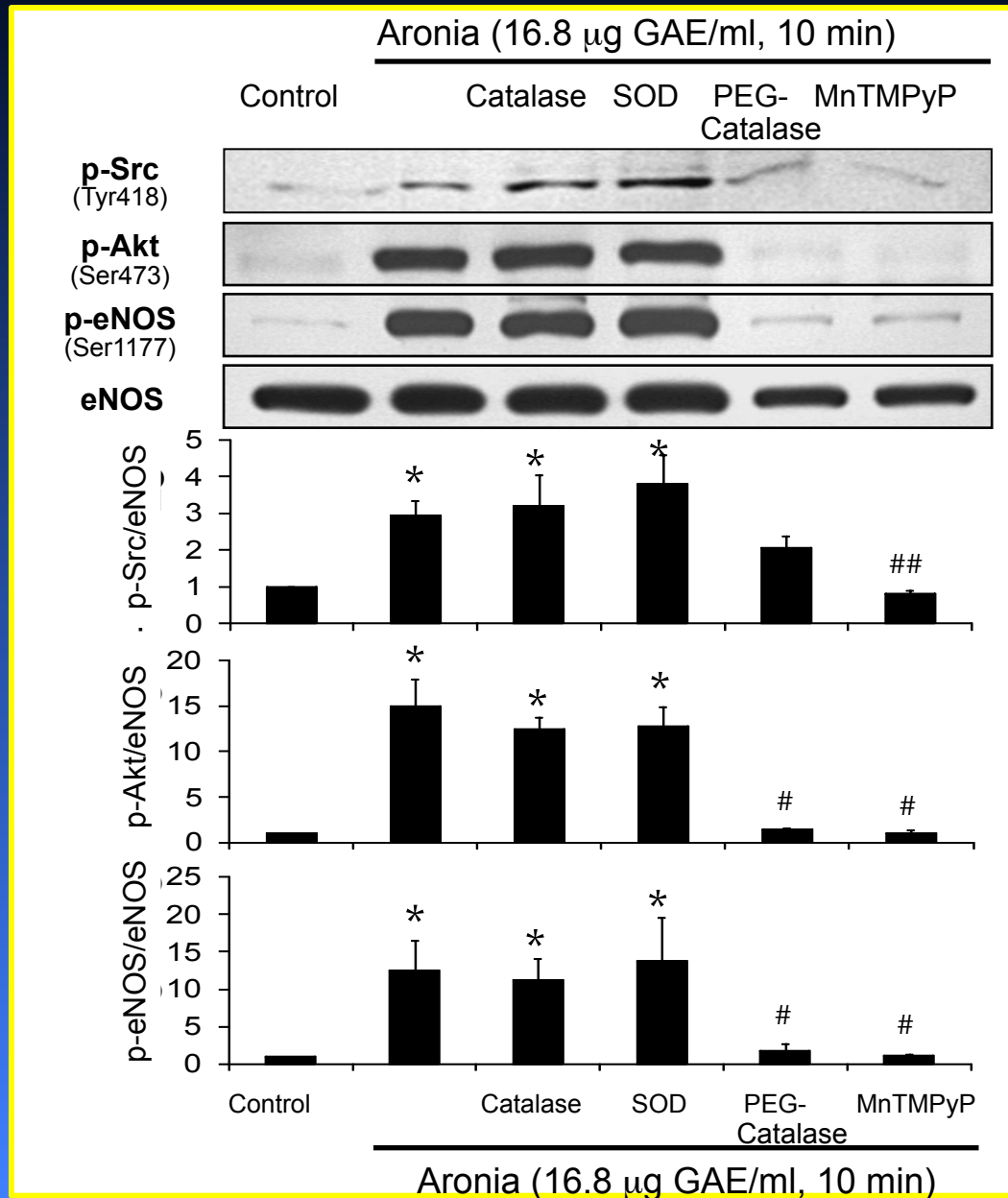
in the presence of indomethacin (10^{-5} M), charybdotoxin (10^{-7} M), and apamin (10^{-7} M)



MnTMPyP:
 cell permeable superoxide dismutase (SOD) mimetic

PEG-catalase (polyethyleneglycol-catalase):
 Kim et al, Nitric Oxide 2013;35C:54-64

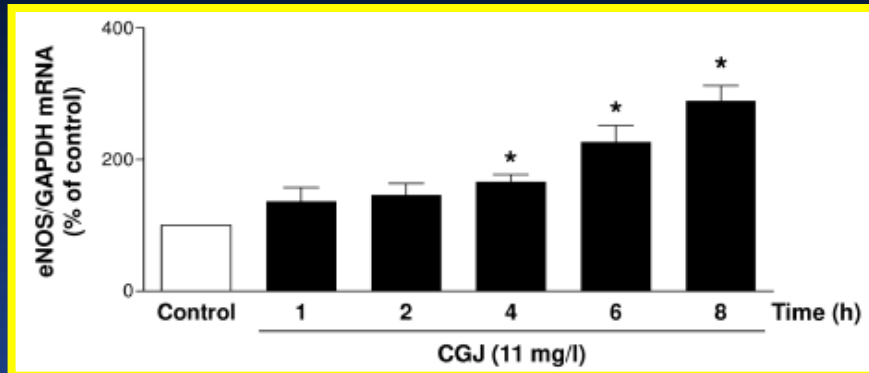
Aronia Juice Induces Phosphorylation of Src, Akt and eNOS through a Redox-sensitive Pathway in Endothelial Cells



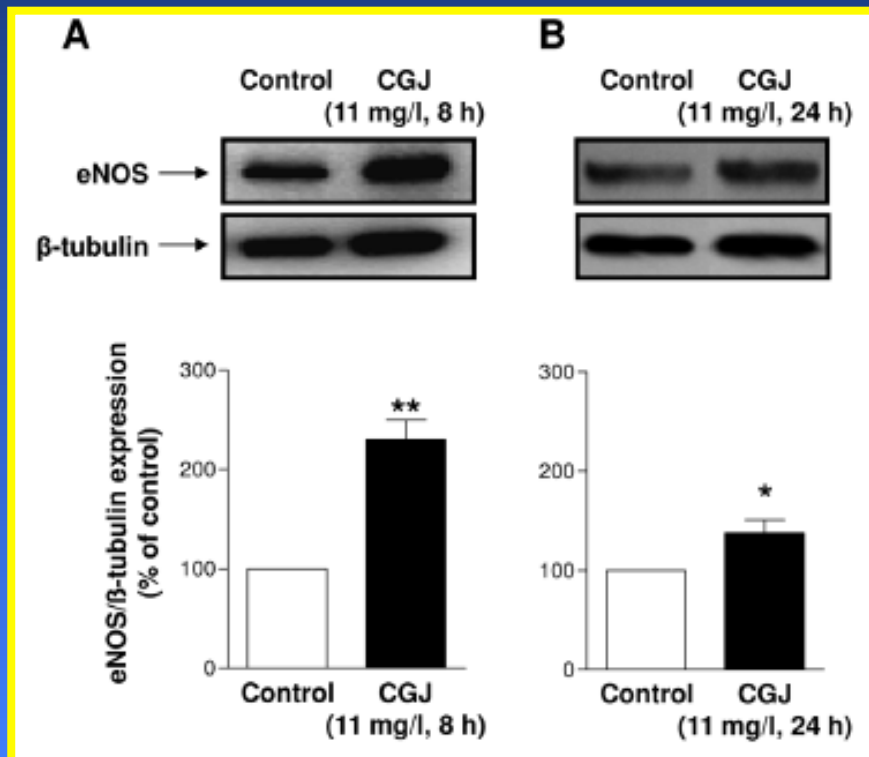
Kim et al., Nitric Oxide
2013;35C:54-64

Purple Grape Juice Upregulates eNOS expression in Endothelial Cells

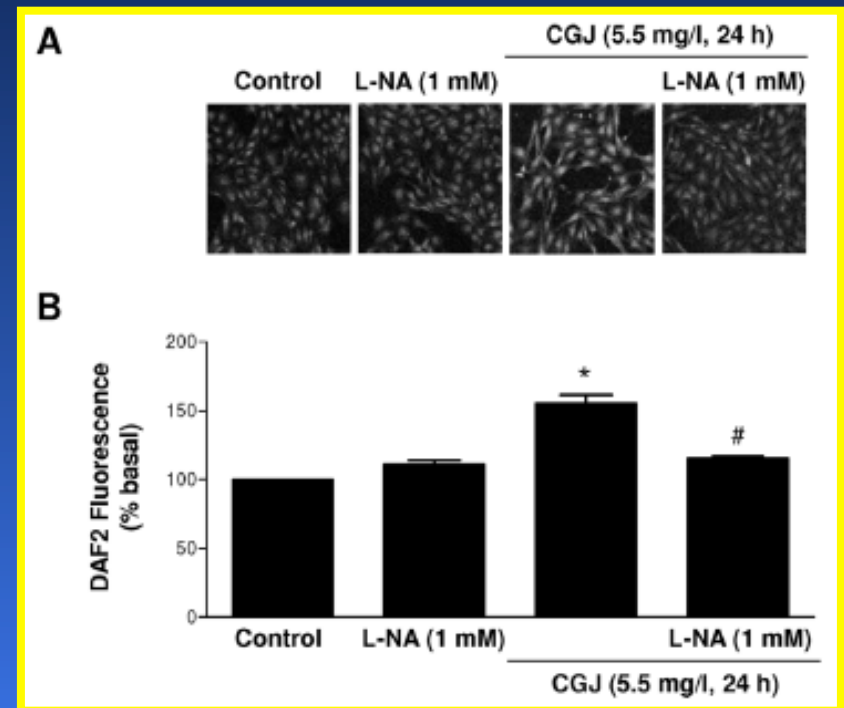
RT-PCR



Western blot



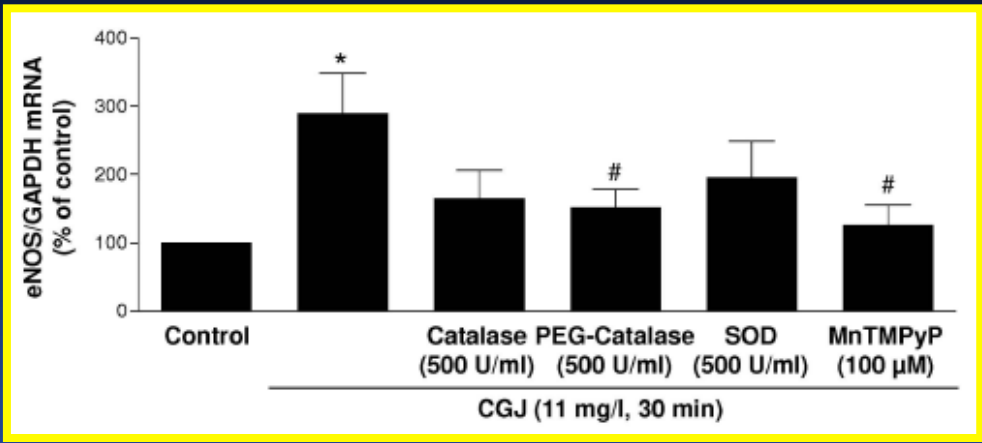
NO formation: DAF2 Fluorescence



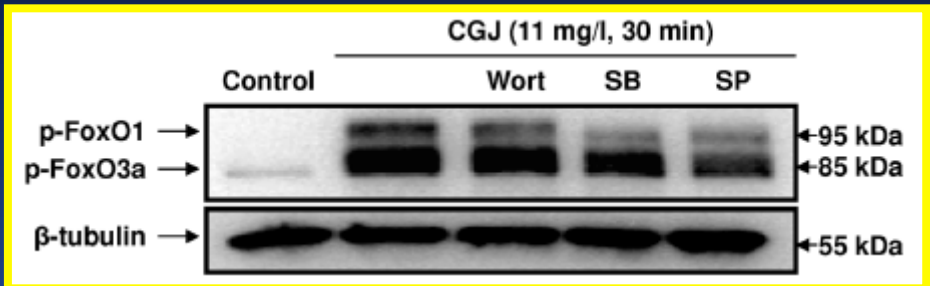
Alhosin et al.,
PLoS ONE
2013;8:e57883

Purple Grape Juice induces a redox-sensitive eNOS expression in Endothelial Cells: Role of PI3K, p38, JNK, FoxOs

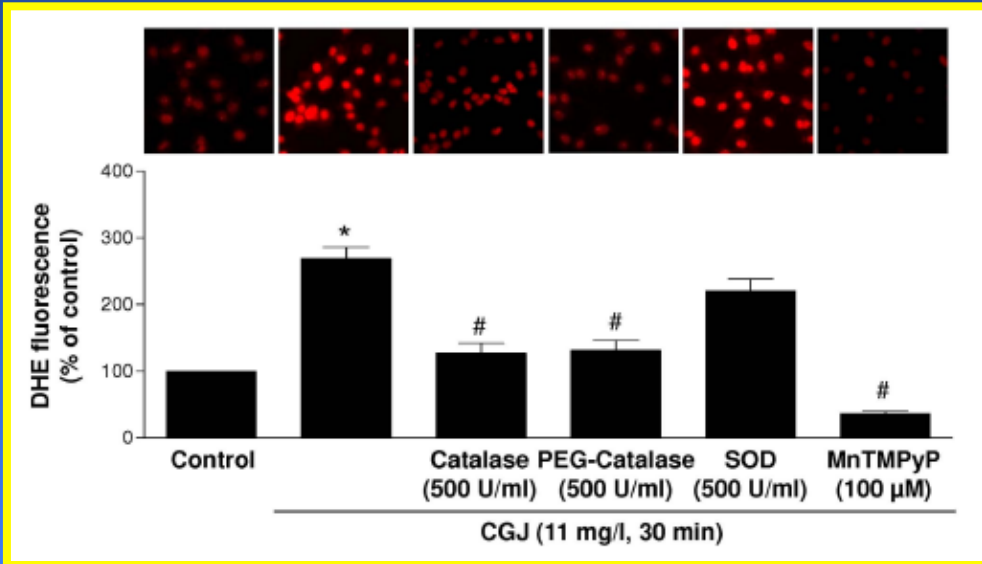
RT-PCR



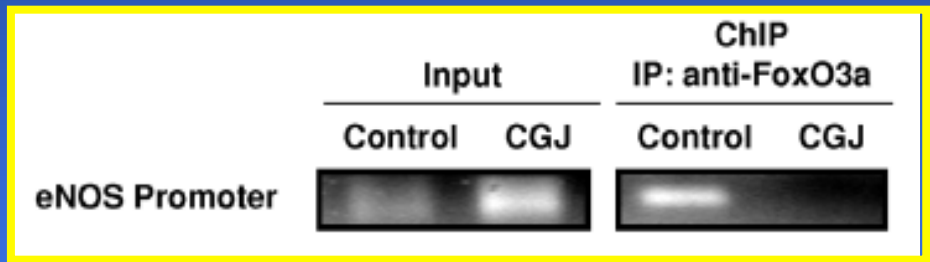
Western blot



ROS formation: DHE Fluorescence



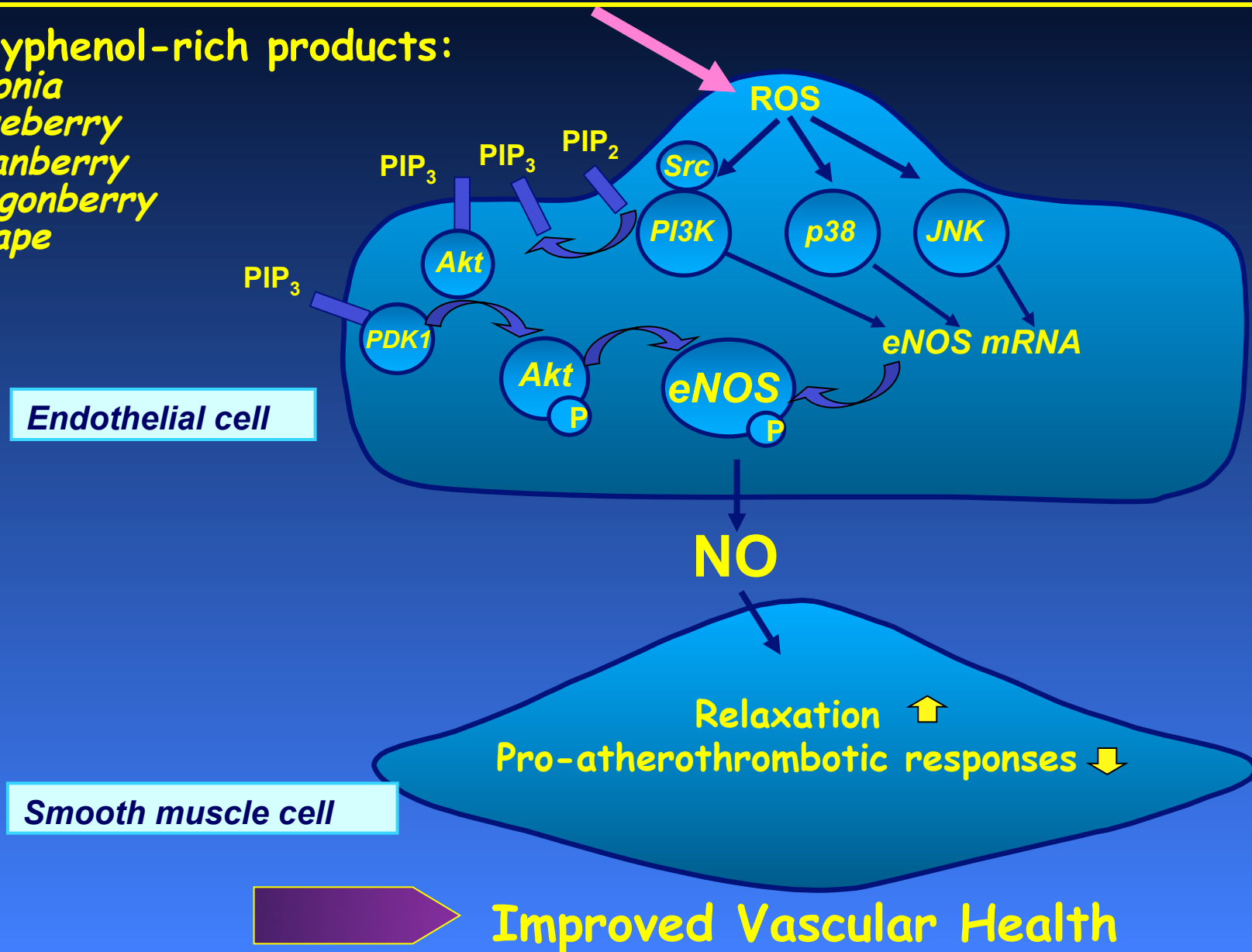
Chromatin immunoprecipitation assay



Natural Product-derived Polyphenols are Potent Inducers of the Endothelial Formation of NO

Polyphenol-rich products:

Aronia
Blueberry
Cranberry
Lingonberry
Grape



Endothelial cell

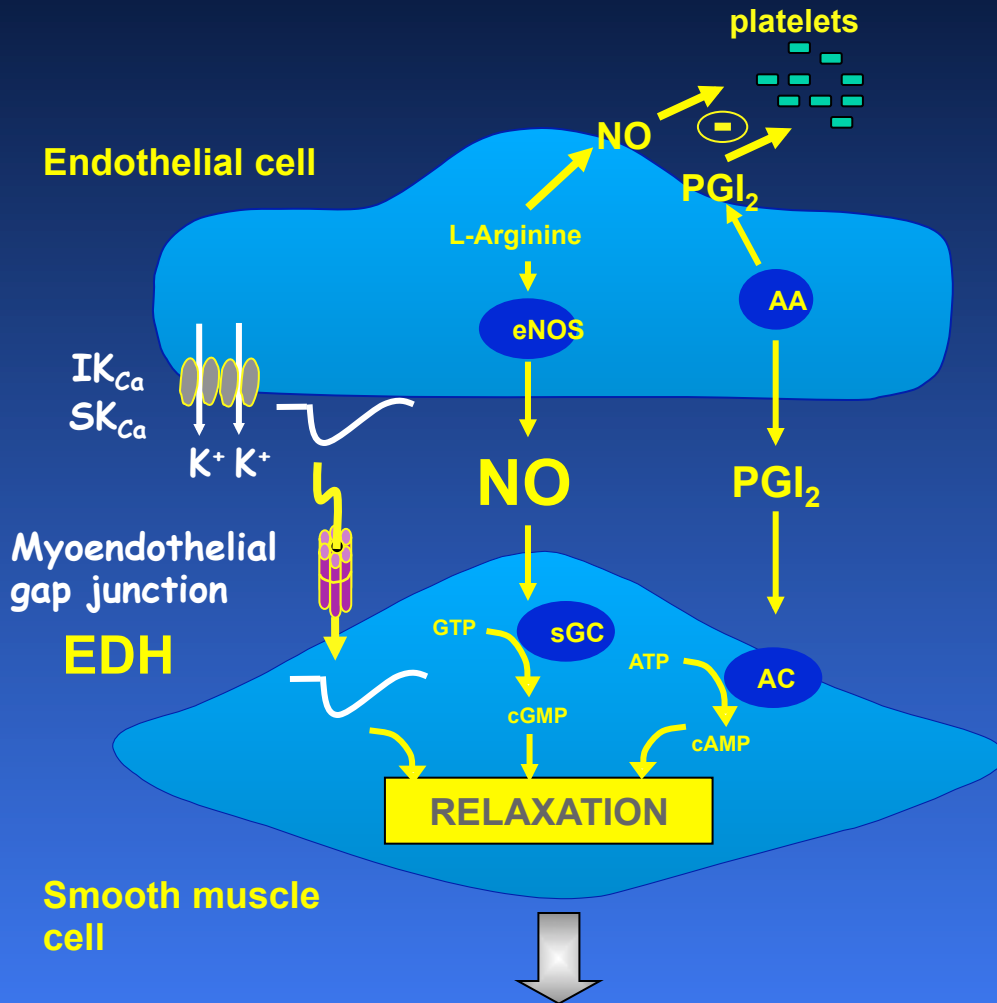
Smooth muscle cell



Improved Vascular Health

Endothelium and the Control of Vascular Responses in Healthy and Diseased Blood Vessels

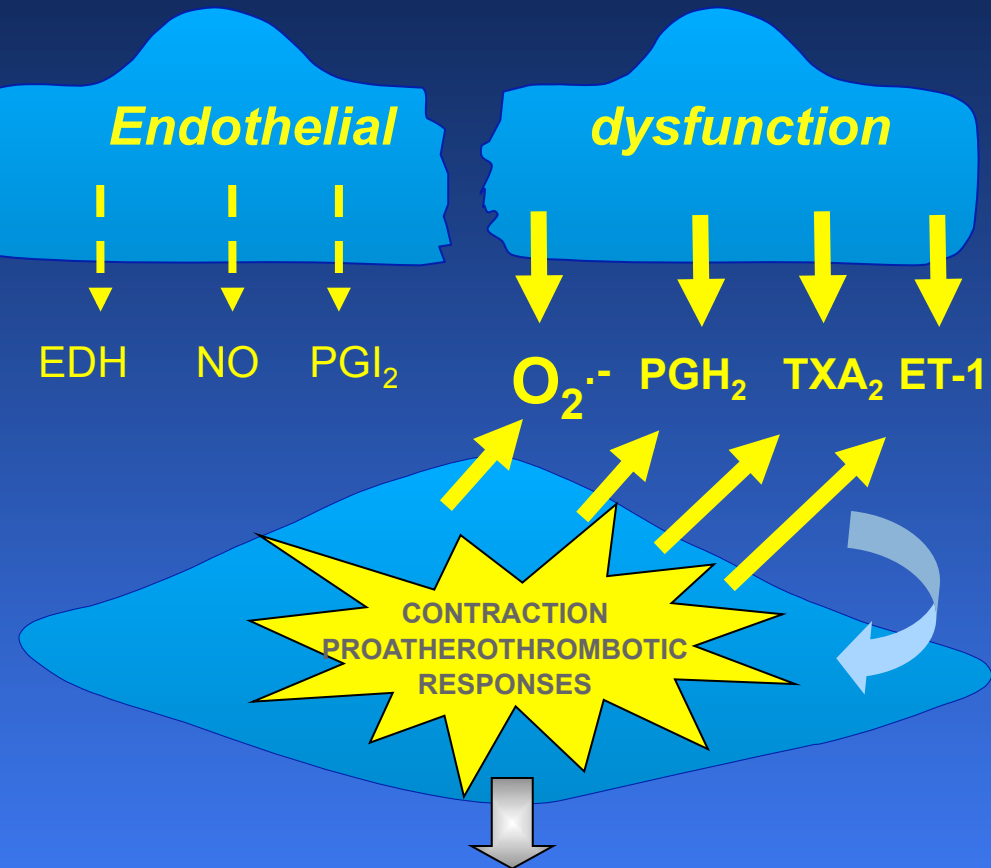
Normal Artery



Vascular Protection

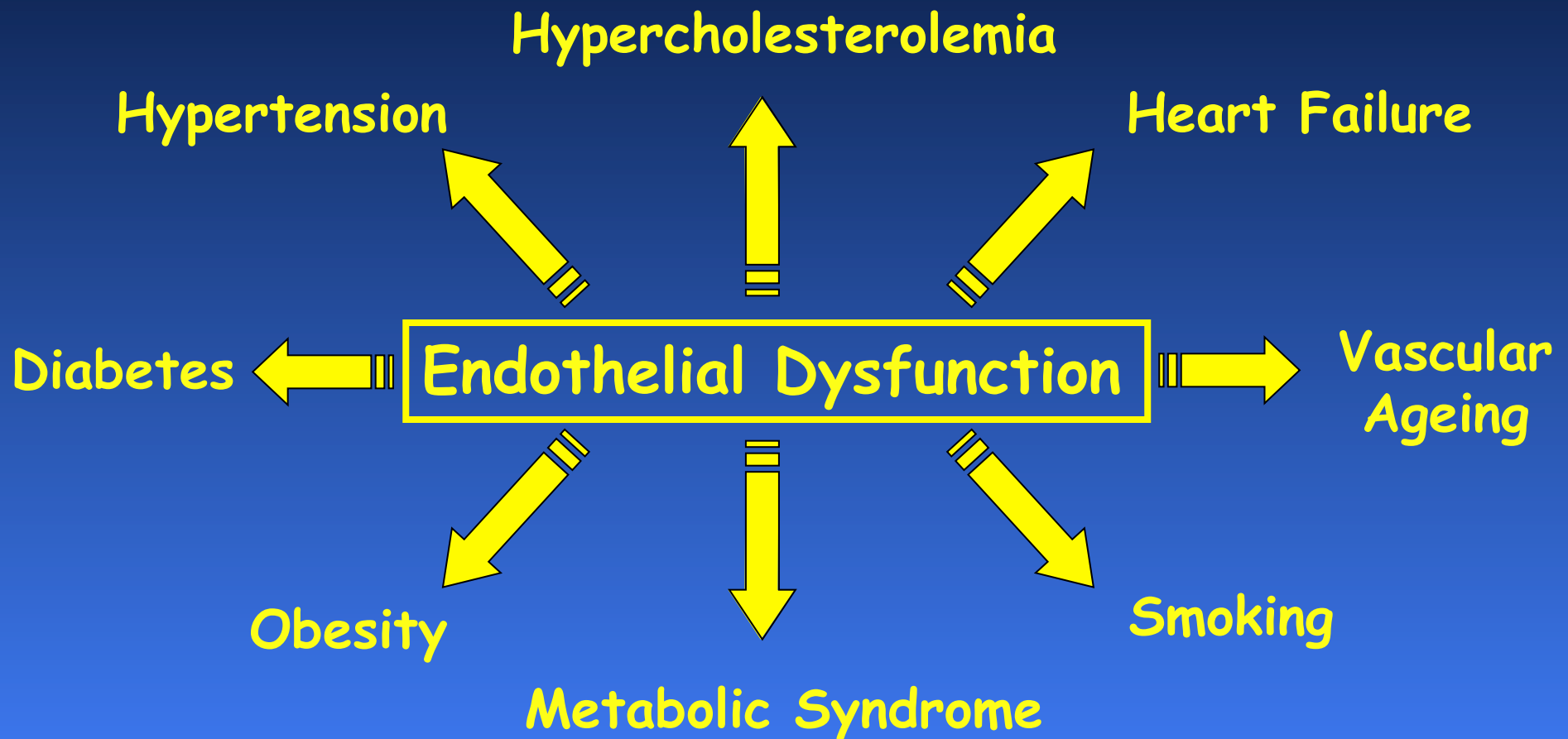
Pathological Artery

Oxidative stress



Development of Cardiovascular Diseases

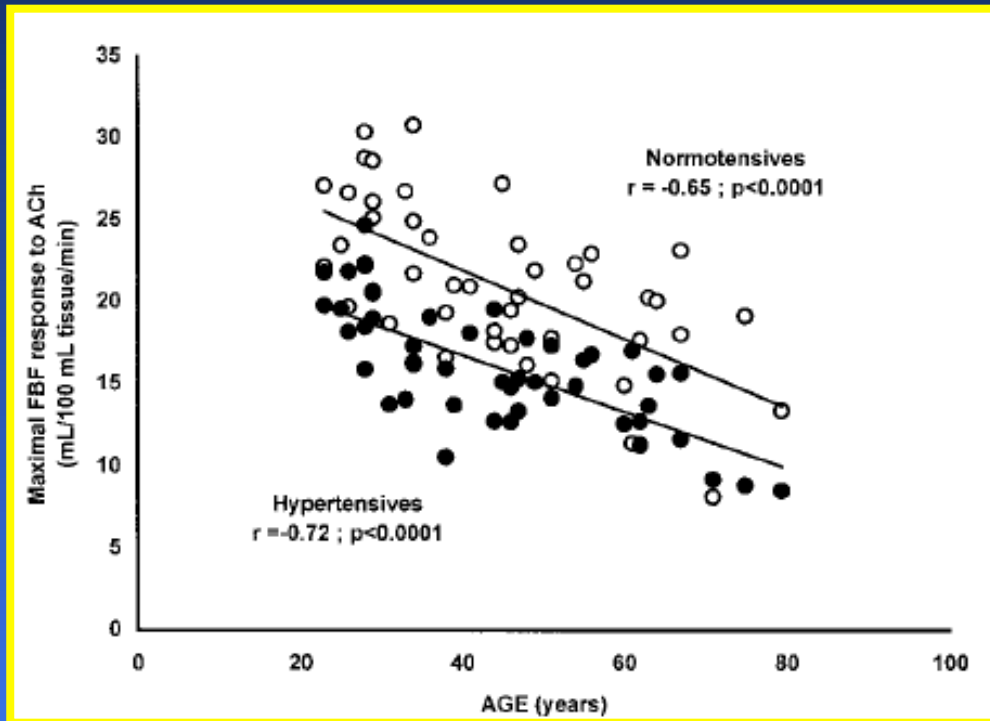
Oxidative Stress-related Endothelial Dysfunction in Cardiovascular Diseases



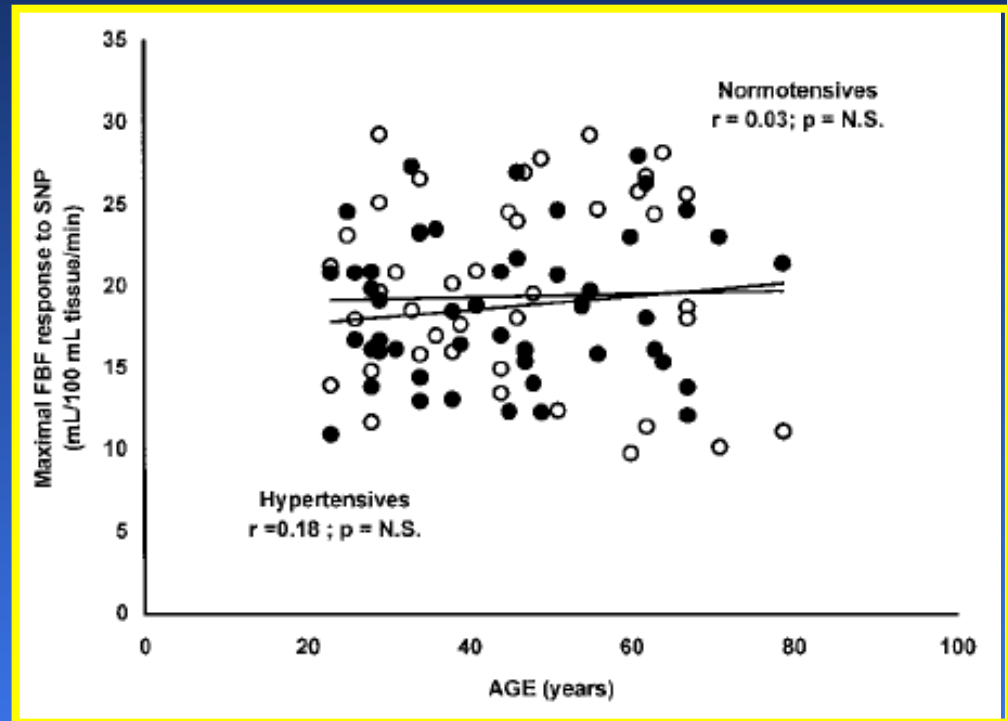
Age-related Endothelial Dysfunction in Normotensive and Hypertensive Humans

Forearm blood flow plethysmography

Endothelium-dependent vasodilator
Acetylcholine



Endothelium-independent vasodilator
Sodium nitroprusside



Ageing-related Endothelial Dysfunction

Male Wistar rats (inbred strain)

Mesenteric artery

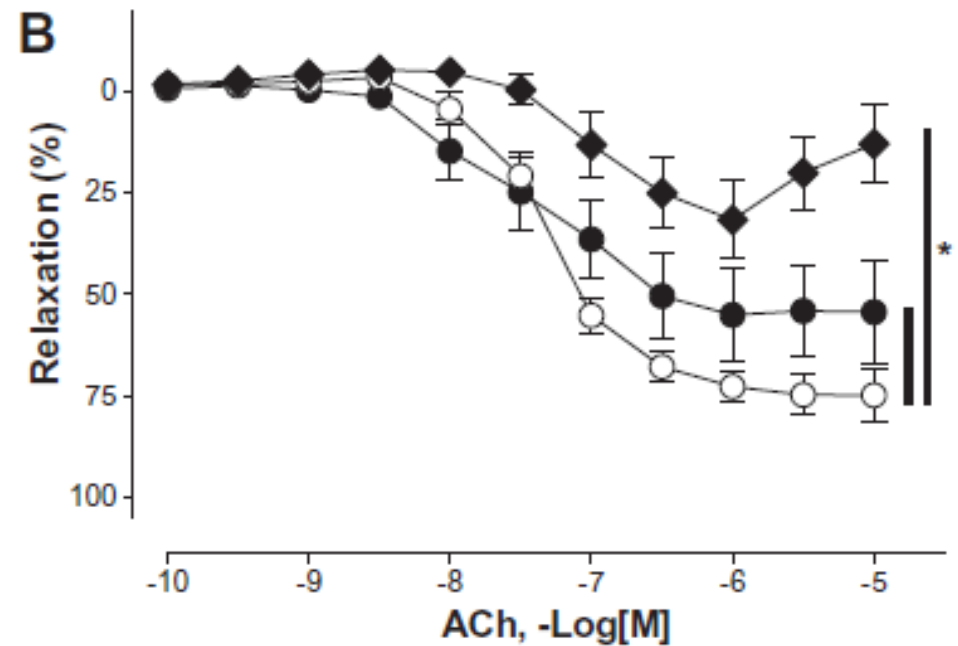
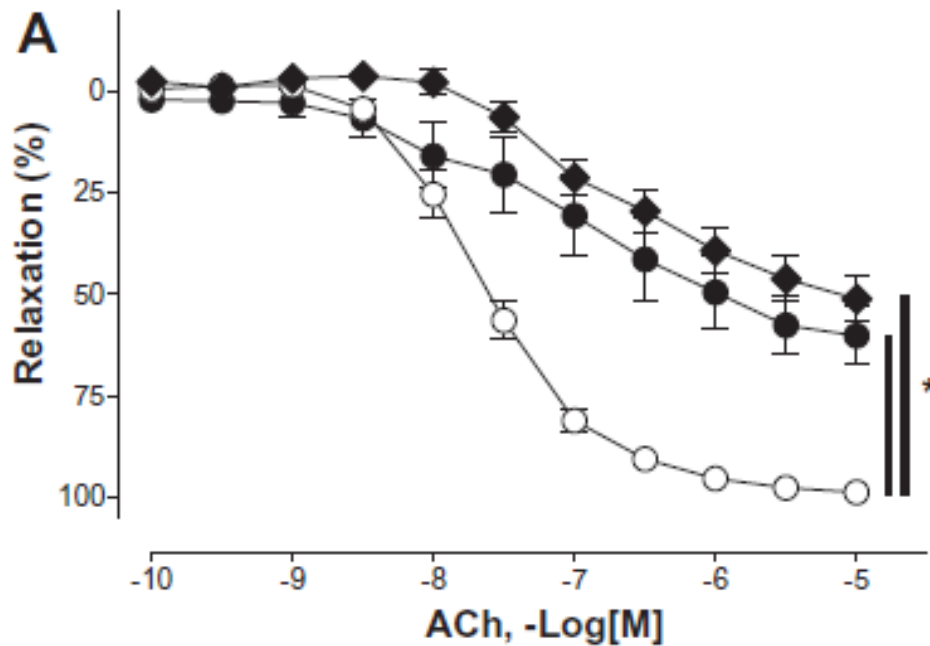
(in the presence of indomethacin,
charybdotoxin and apamin)

(in the presence of indomethacin,
 N^G -nitro-L-arginine)

NO component

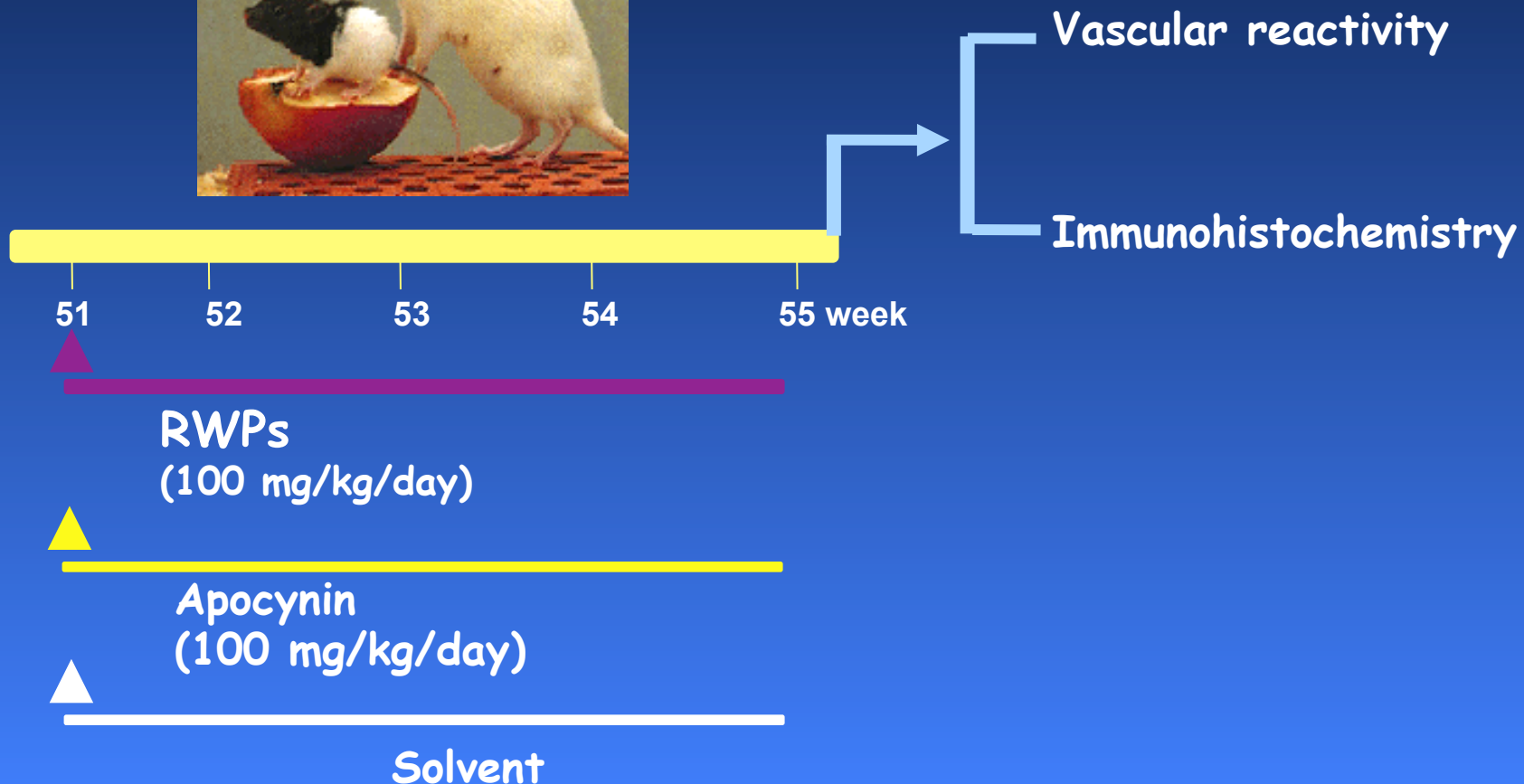
EDH component

○ 12-week-old ● 20-week-old ◆ 40-week-old



RWPs and Endothelial Dysfunction in Ageing

Curative study



RWPs improve an Established Ageing-related Endothelial Dysfunction

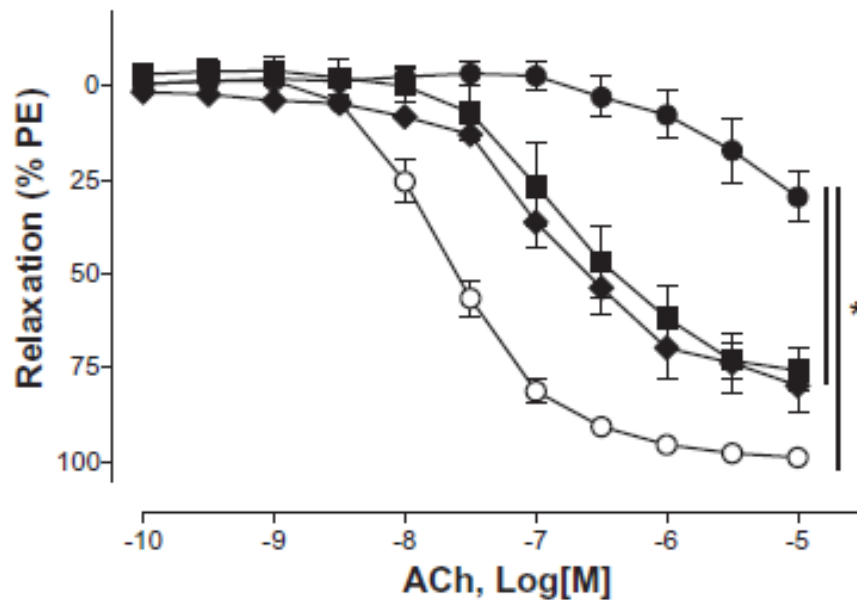
Mesenteric artery

NO component

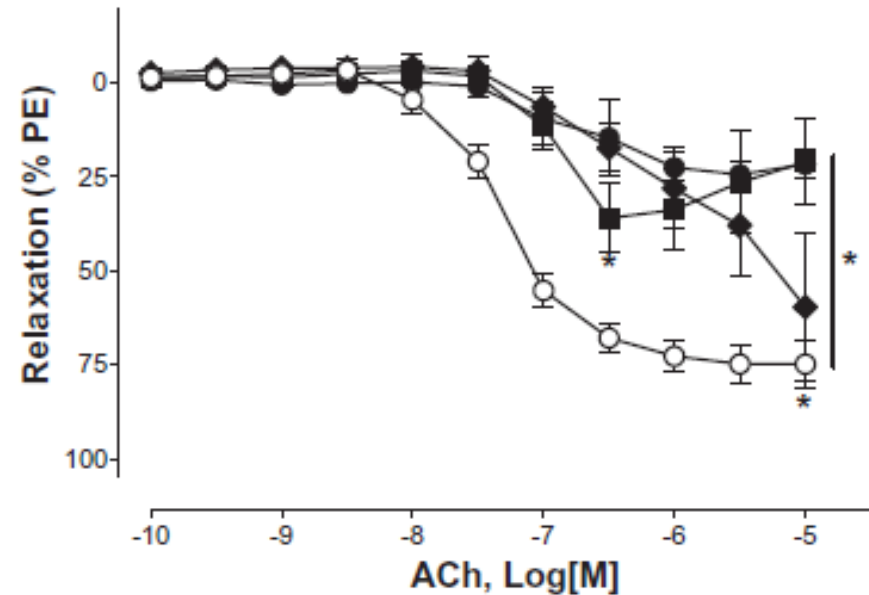
EDH component

○ 12-week old ● 55-week old ■ 55-week old + RWPs (100 mg/kg/day) ◆ 55-week old + Apocynin (100 mg/kg/day)

A

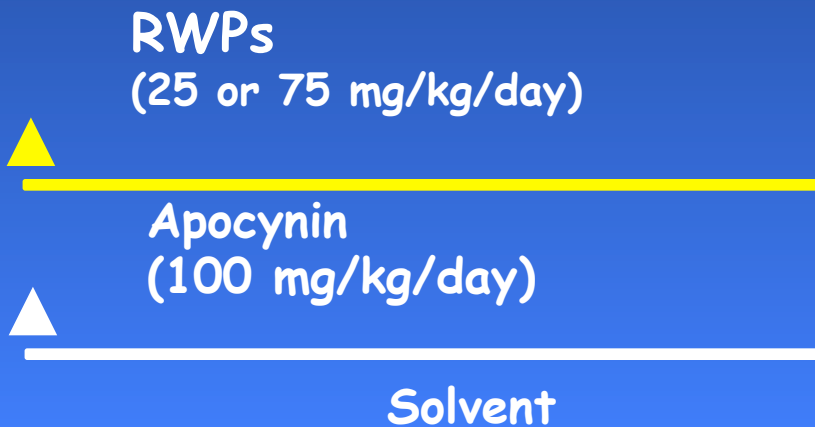


B



RWPs and Endothelial Dysfunction in Ageing

Preventive study

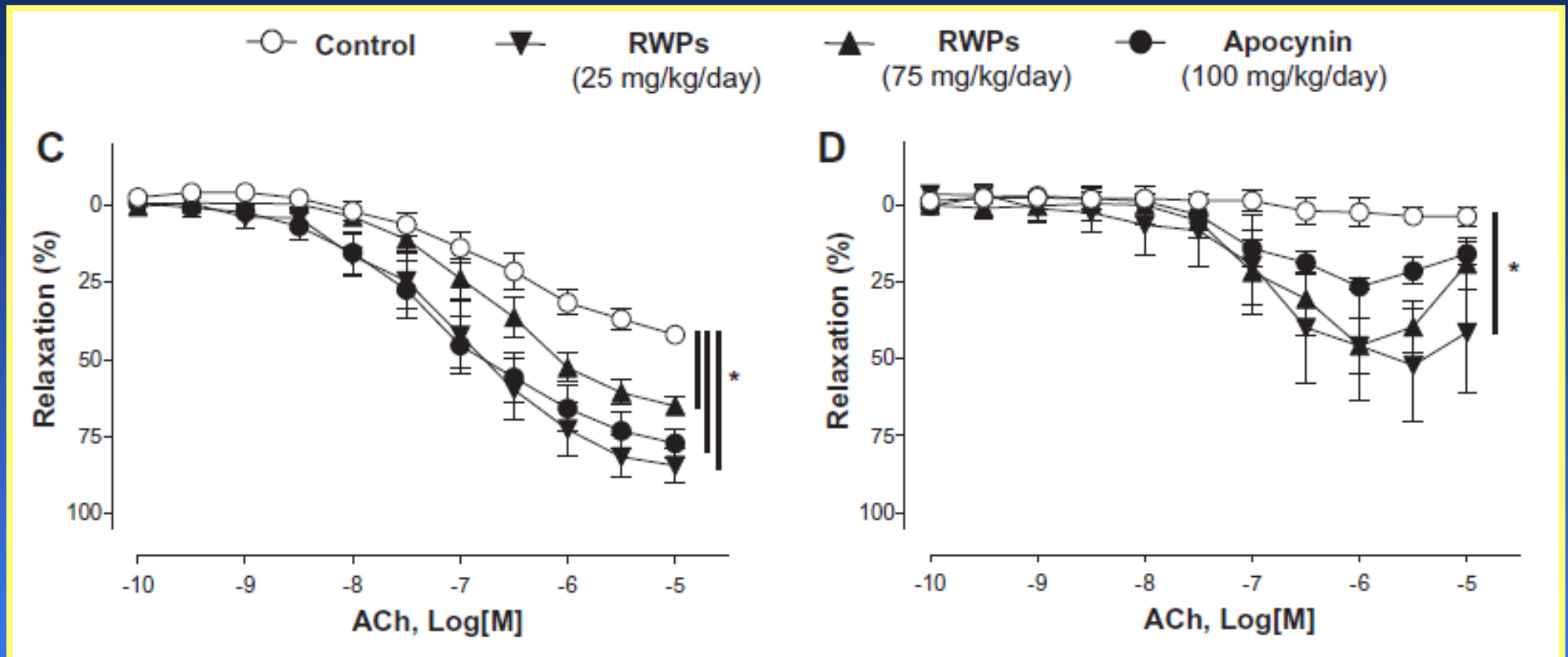


Chronic Intake of RWPs by Young Rats Prevents Ageing-induced Endothelial Dysfunction

Mesenteric artery 40-week old rats

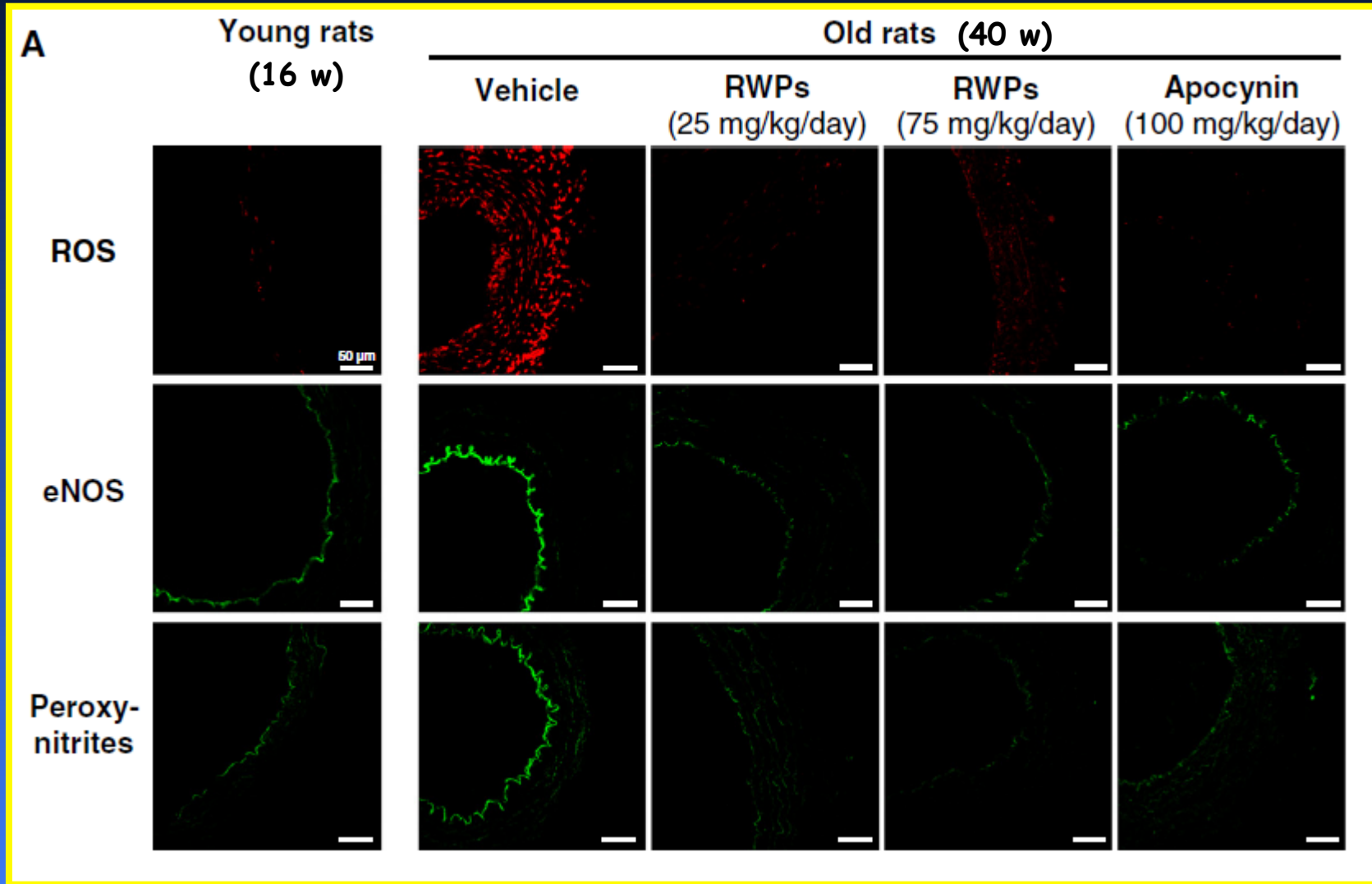
NO component

EDH component

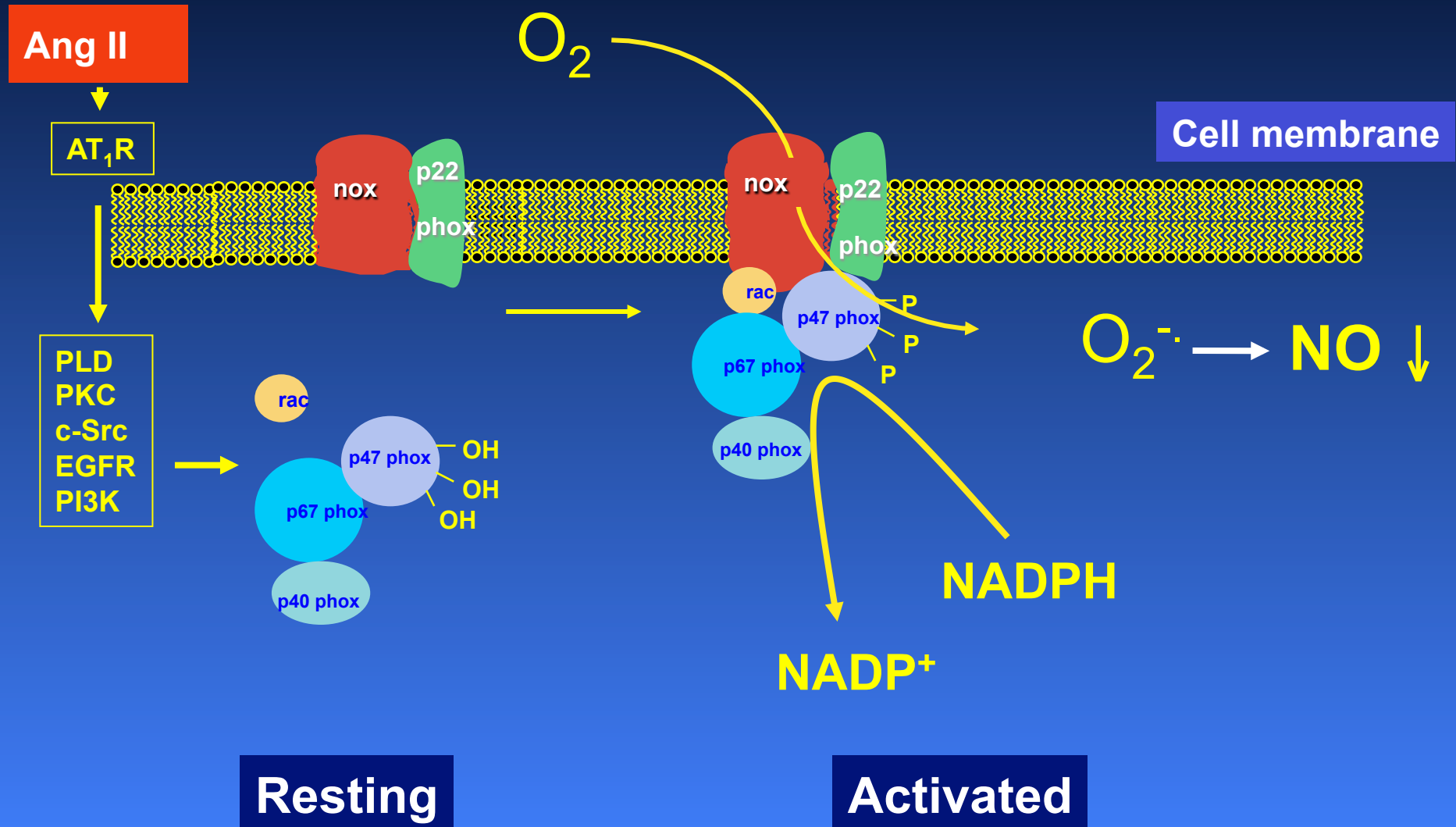


RWPs and Endothelial Dysfunction in Ageing

Mesenteric artery



Vascular NADPH oxidase



Vascular Oxidative Stress in Ageing: Role of NADPH oxidase

Mesenteric artery

12-week old rats

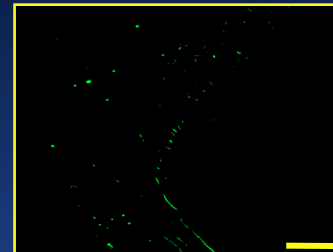
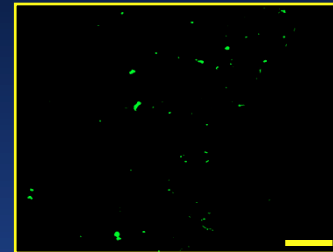
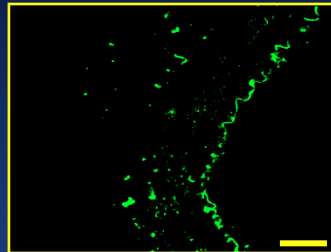
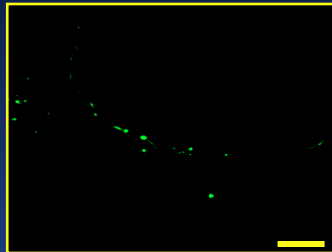
55-week old rats

Solvent

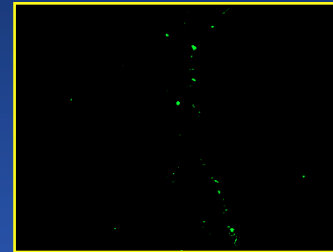
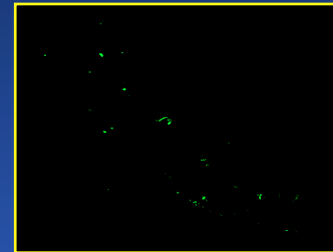
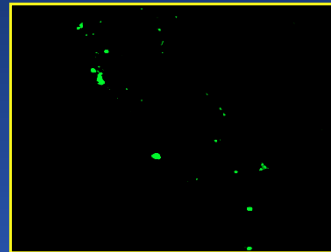
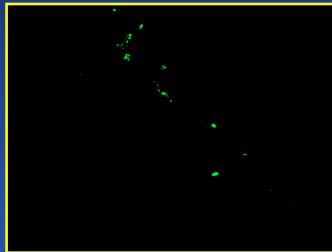
RWPs

Apocynin

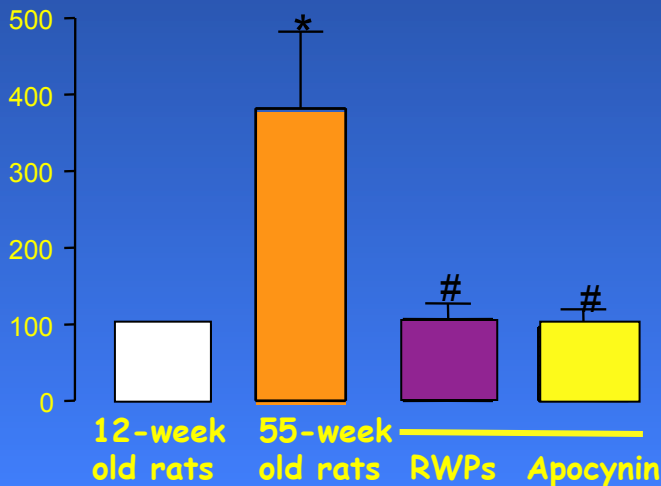
p22phox



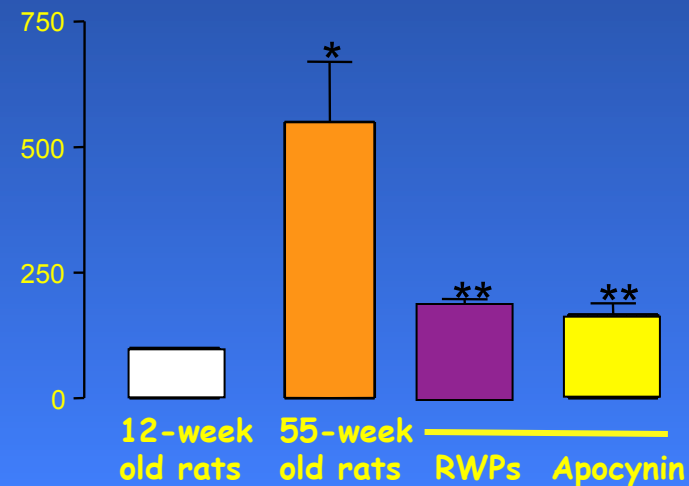
nox1



p22phox fluorescence

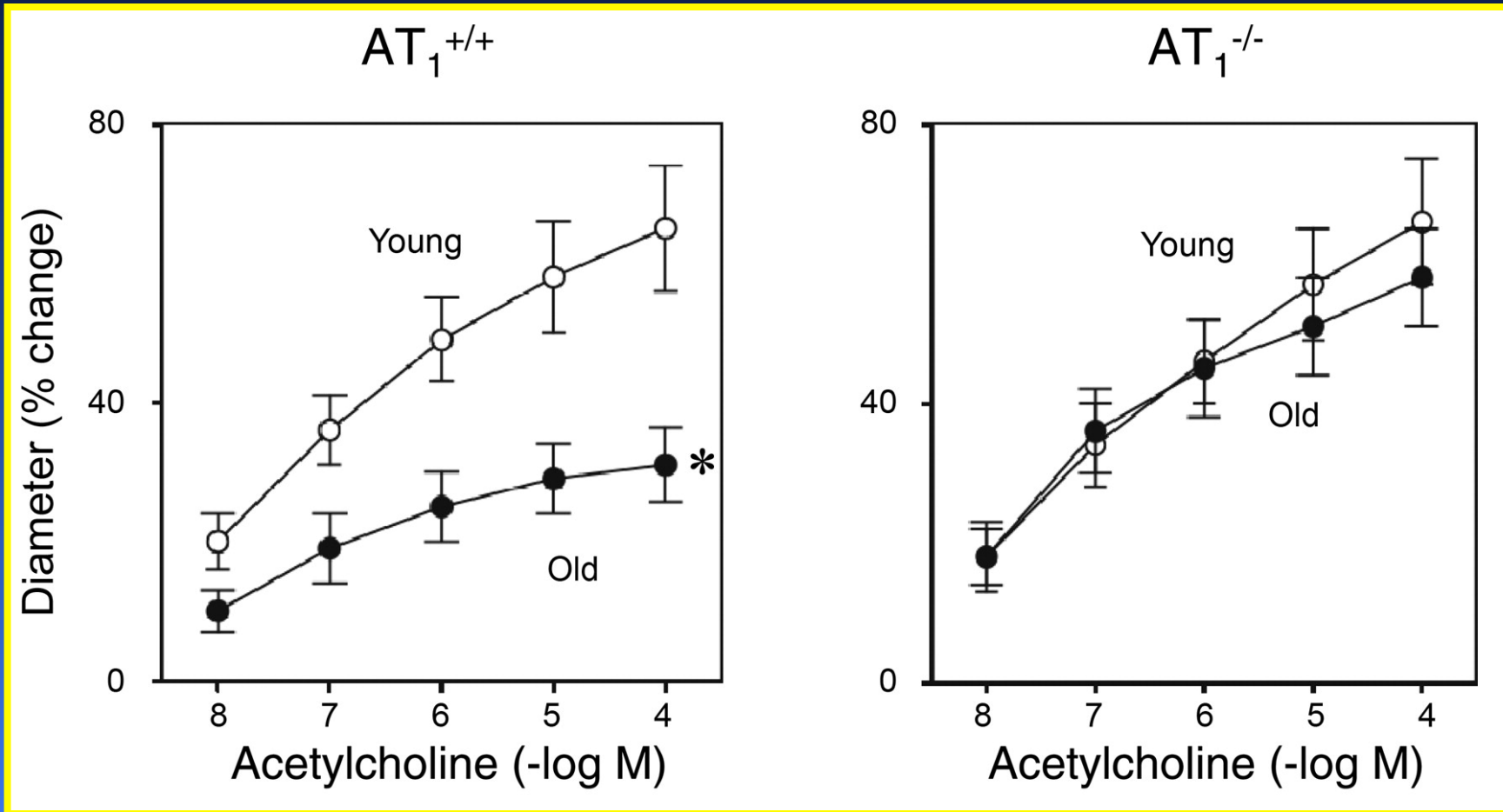


nox1 fluorescence



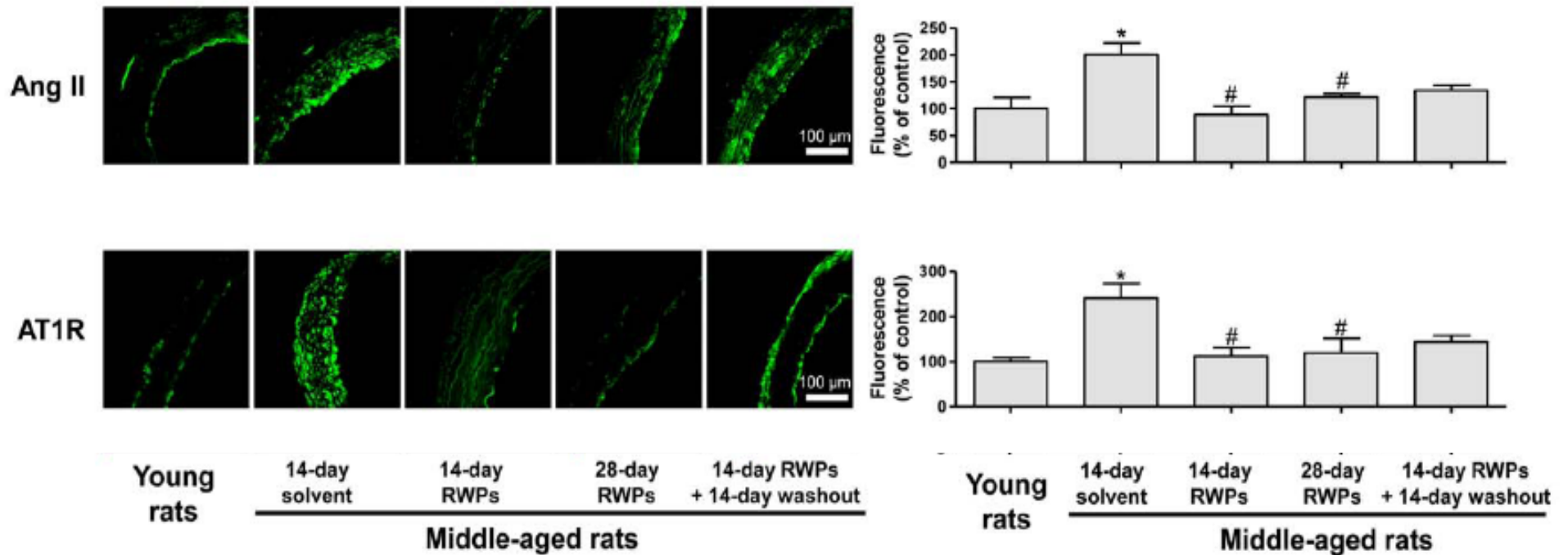
Ageing-related Endothelial Dysfunction: Role of the Angiotensin System

Mice basilar artery rings



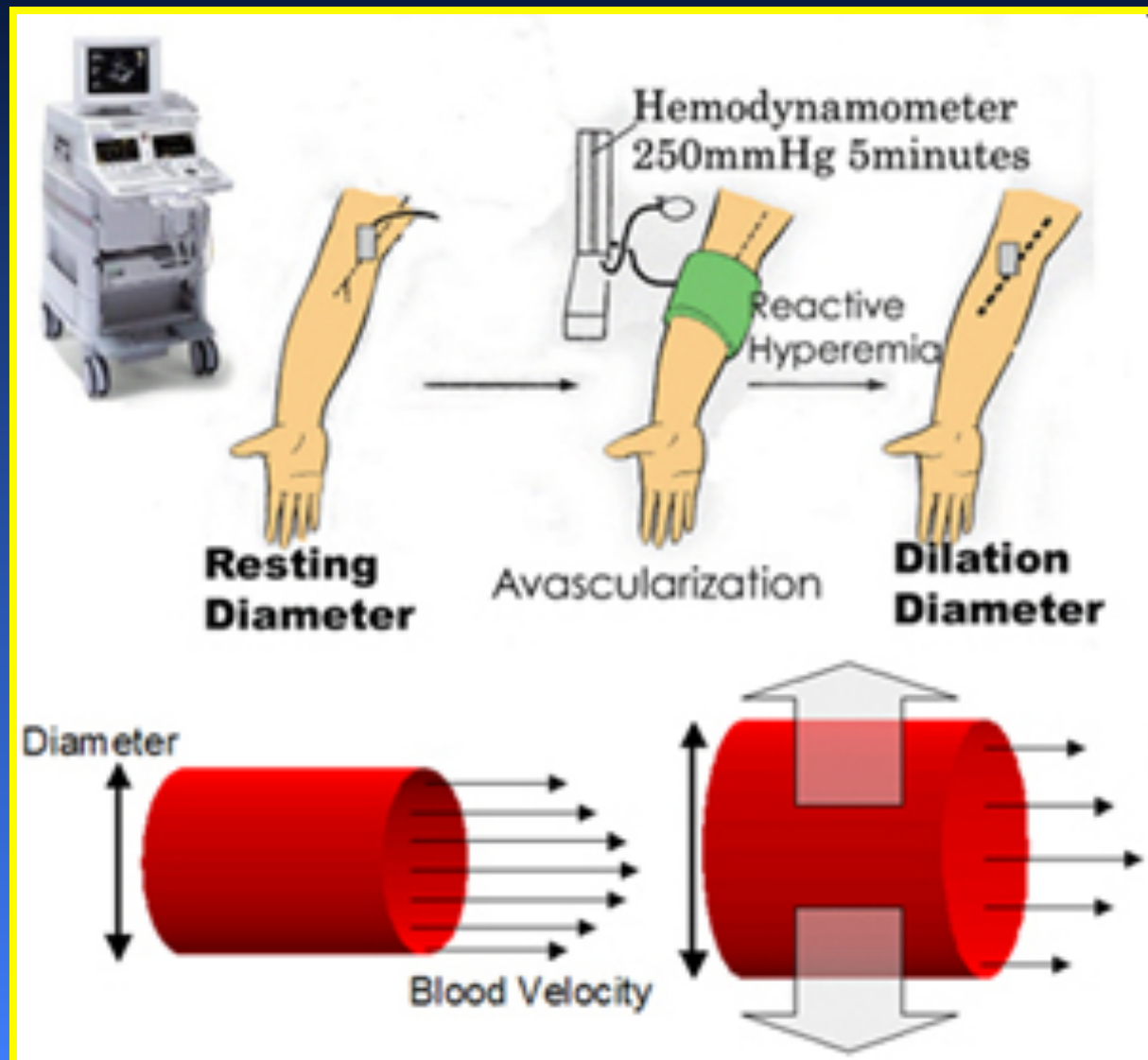
Ageing-related Endothelial Dysfunction and the Angiotensin System

Mesenteric artery

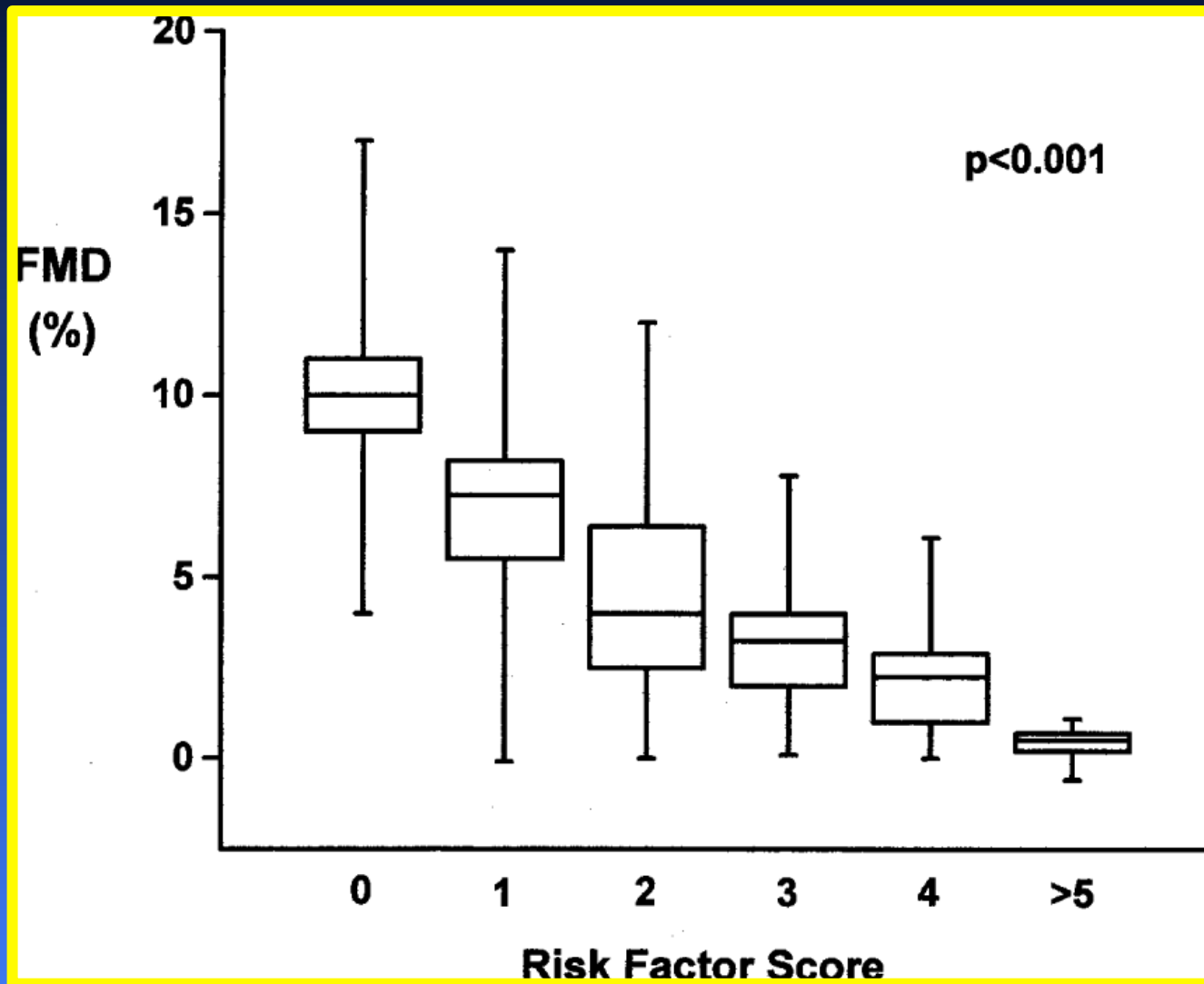


Endothelial Function in Humans

Flow-mediated vasodilatation



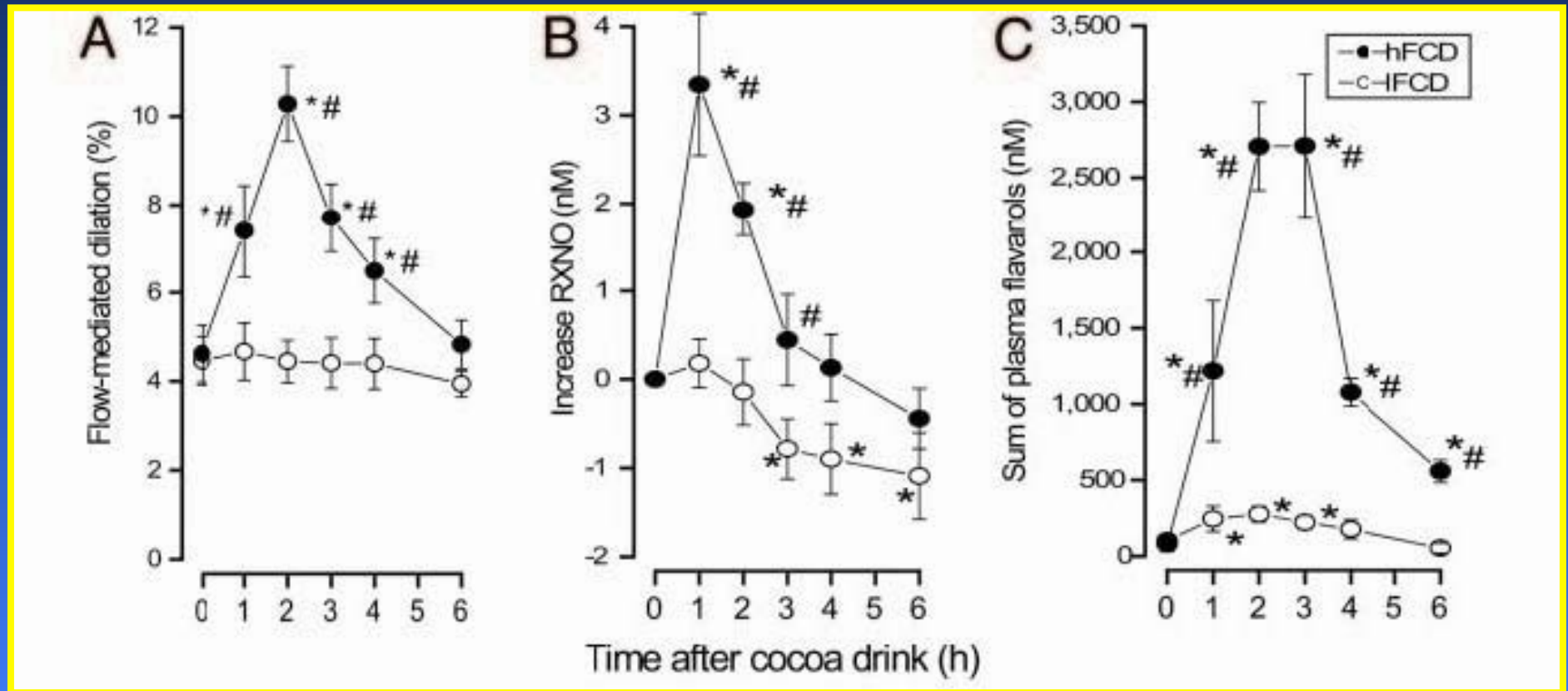
Relationship between Vascular Risk Factors and Flow-mediated Dilatation (FMD)



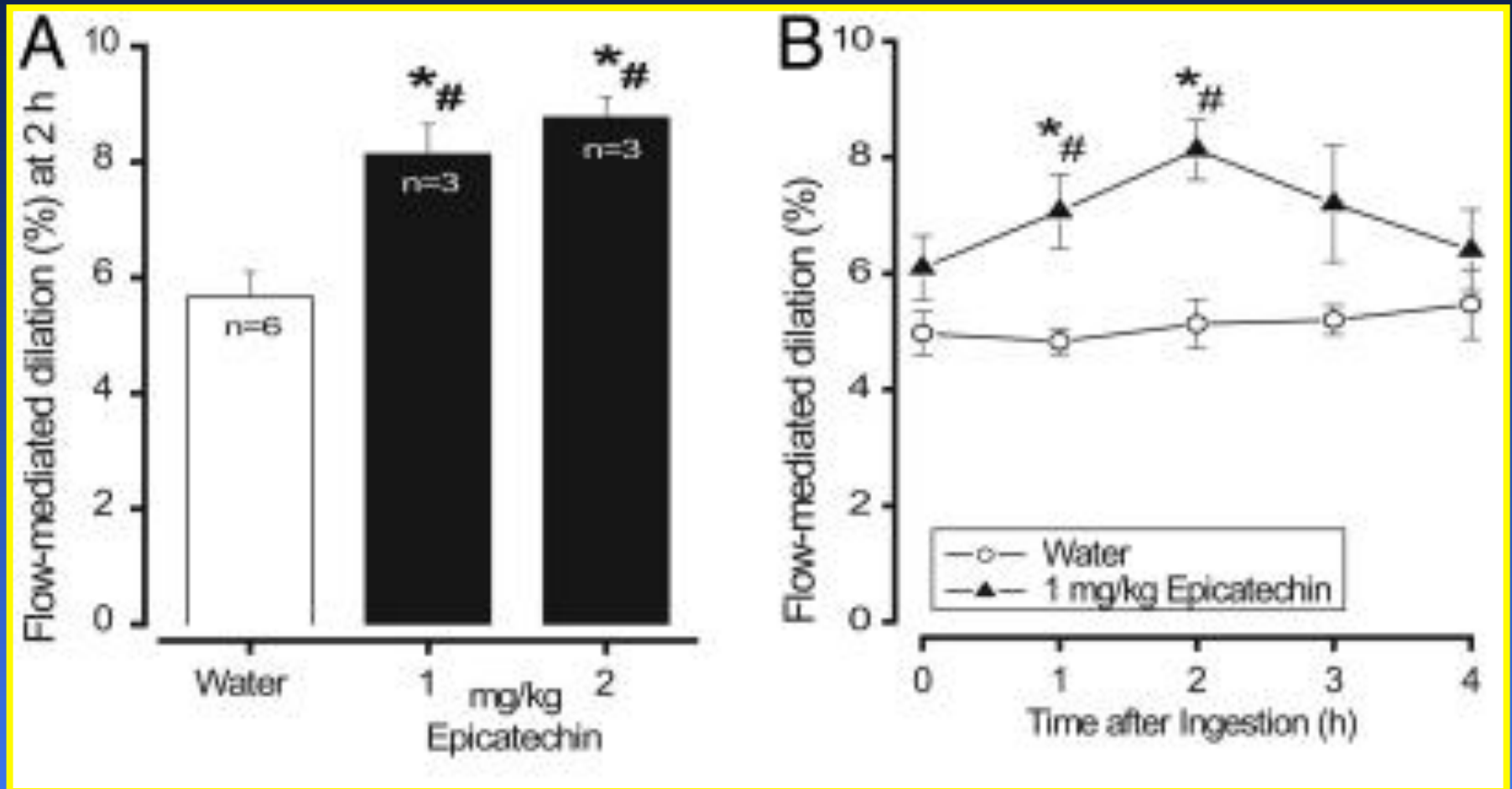
Risk factors:
Smoking history
Cholesterol level
Diabetes
Hypertension
Age
Male gender
Family history

Ingestion of Flavanol-rich Cocoa Enhanced Flow-mediated Vasodilatation in Healthy Adults

- High-flavanol cocoa drink (hFCD) 917 mg
- Low-flavanol cocoa drink (lFCD) 37 mg of total flavanols

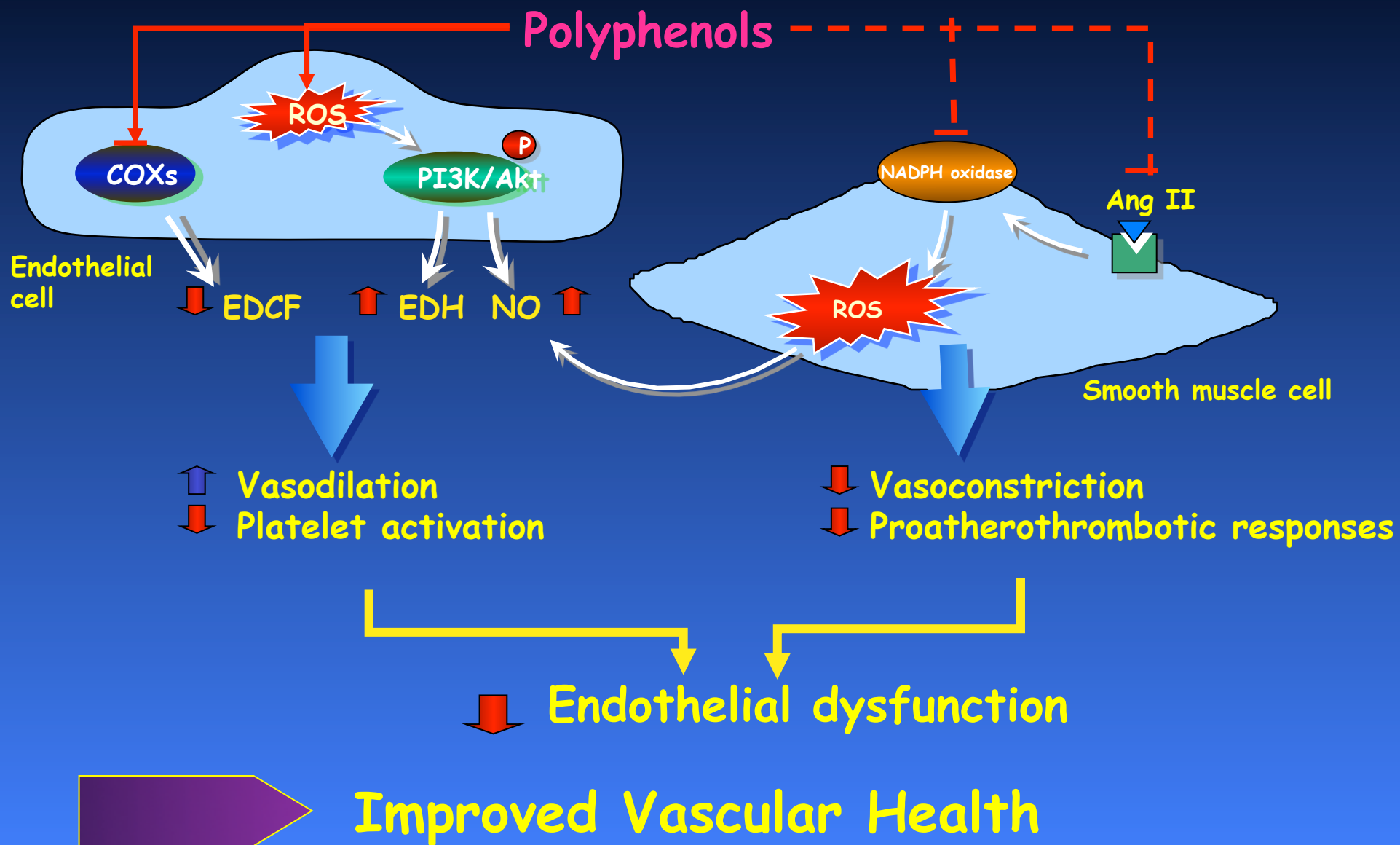


Ingestion of (-)-Epicatechin Enhanced Flow-mediated Vasodilatation in Healthy Adults



Schroeter *et al.*
PNAS 2006; 103: 1024-1029

Vascular Protective Effects of Polyphenols





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J.-M. Tokoudagba, Cotonou, Benin

P.M. Vanhoutte, Hong Kong





Red Wine Polyphenolic Extract (RWPs)



French Red Wine (Corbières A.O.C.)

1 liter of wine produced 2.9 g of RWPs

-Flavanol:

- Catechin 8.6 mg/g
- Epicatechin 8.7 mg/g

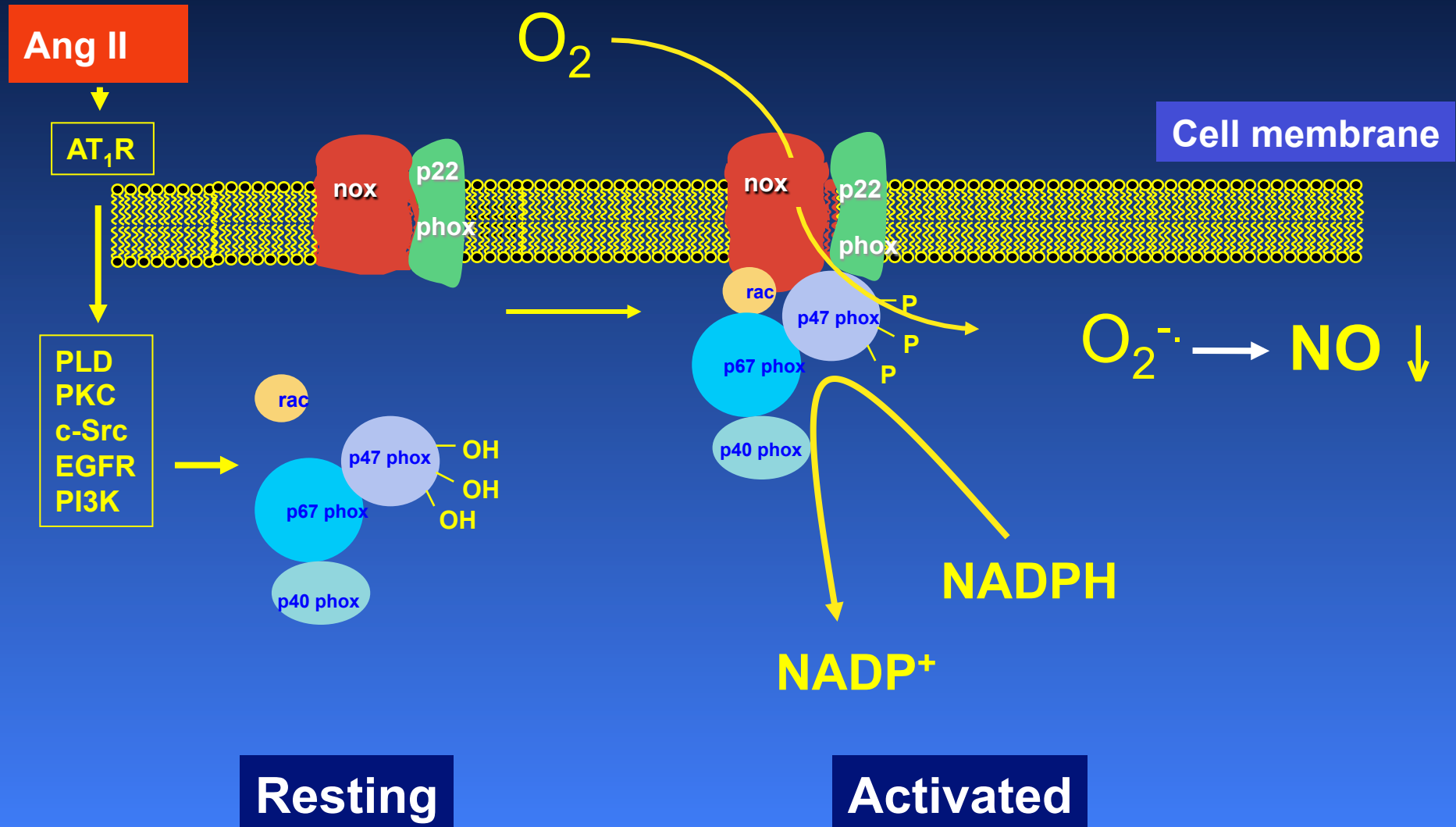
-Anthocyanin:

- Malvidin-3-glucoside 11.7 mg/g
- Peonidin-3-glucoside 0.66 mg/g
- Cyanidin-3-glucoside 0.06 mg/g

-Phenolic acid:

- Gallic acid 5.0 mg/g
- Caffeic acid 2.5 mg/g
- Caftaric acid 12.5 mg/g

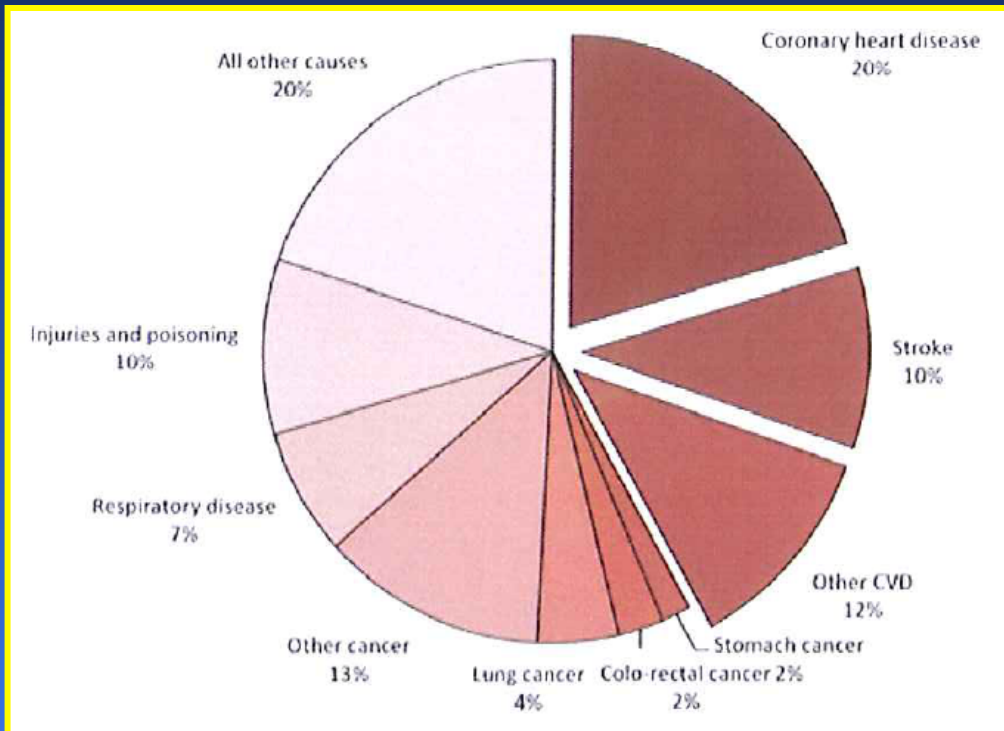
Vascular NADPH oxidase



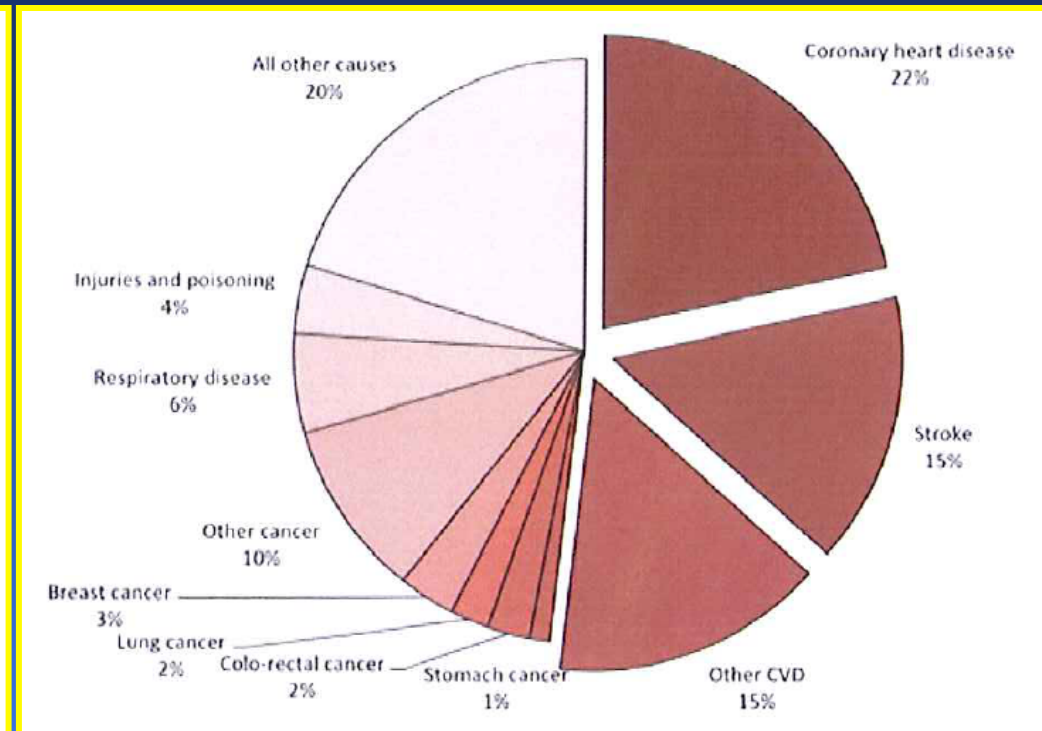
Cardiovascular Diseases: Leading Cause of Death Worldwide

European Cardiovascular Disease Statistics, 2012

Men



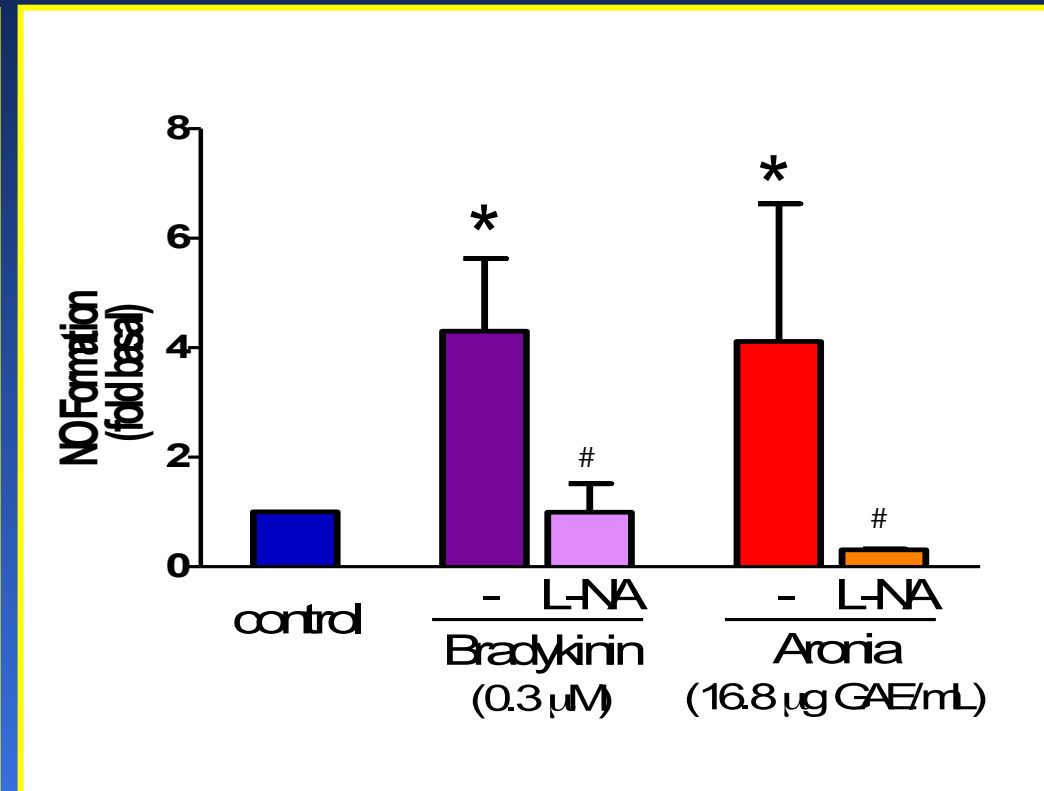
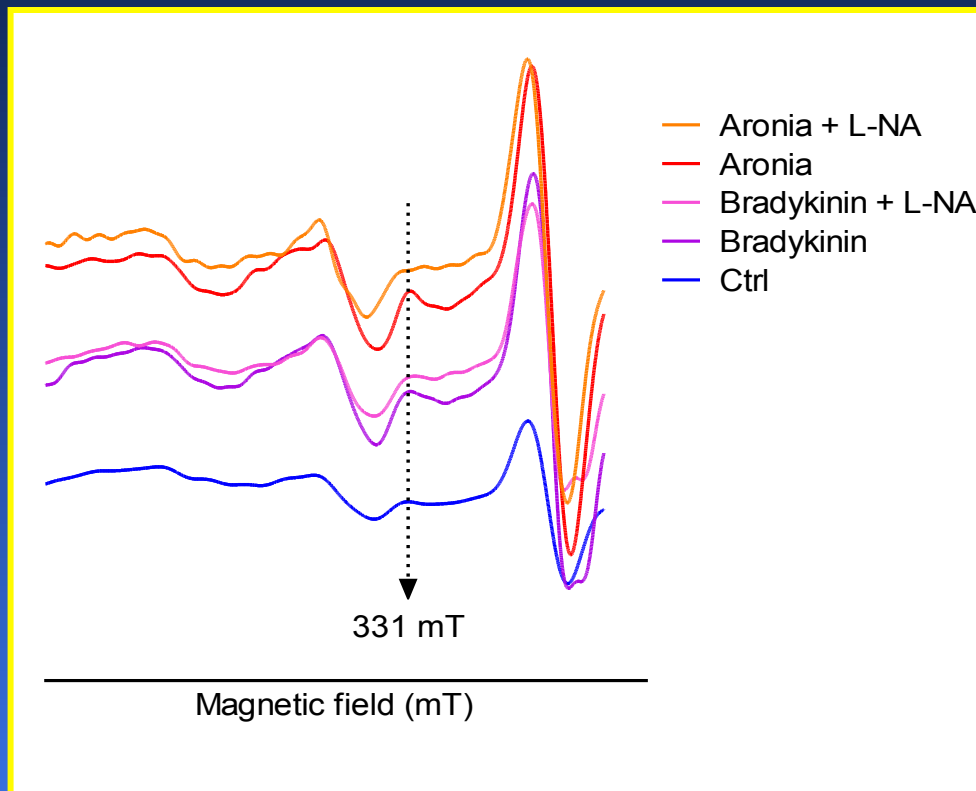
Women



Nichols et al., European Cardiovascular Disease Statistics, 2012
European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis

Aronia Juice Stimulates the Formation of NO in Coronary Artery Endothelial Cells

Electron Paramagnetic Resonance (EPR)



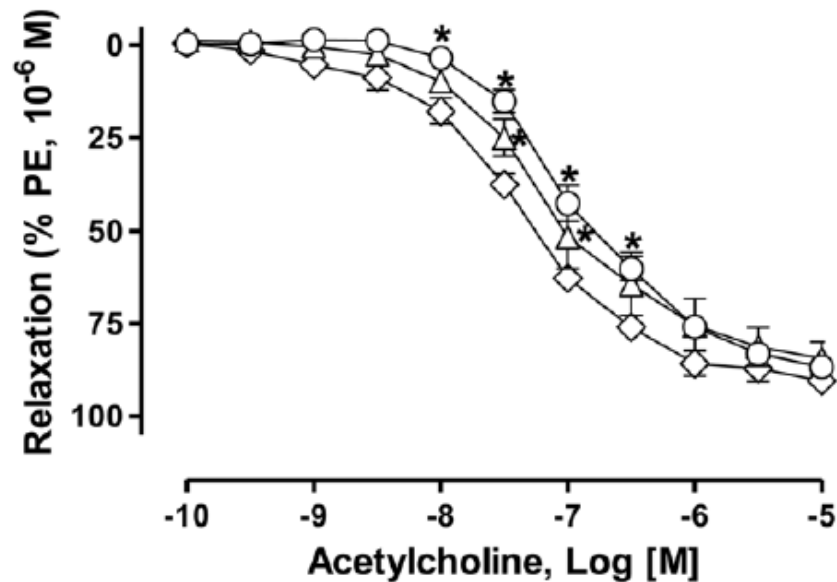
Ageing-related Endothelial Dysfunction

Male Wistar rats (commercial supplier)

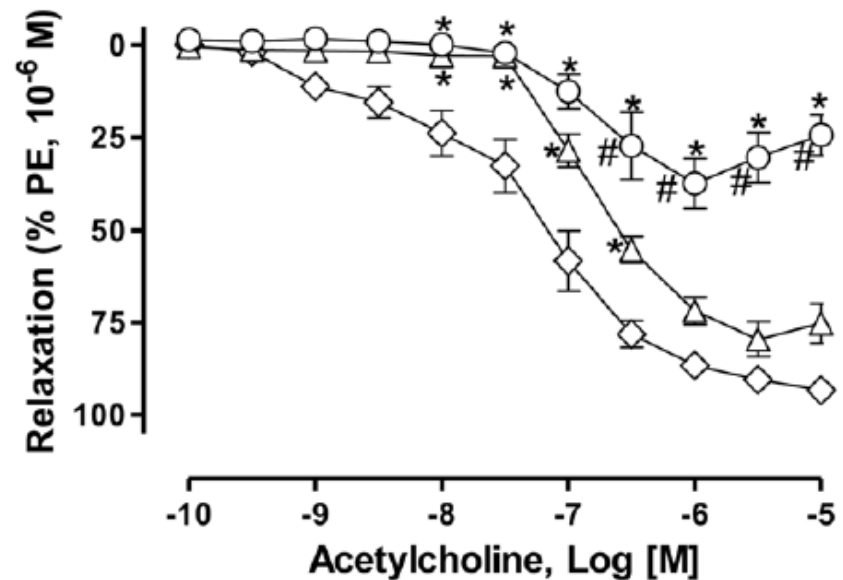
Mesenteric artery

◇ Young rats (16 w) △ Mature-adult rats (25 w) ○ Middle-aged rats (46 w)

A NO-mediated relaxation

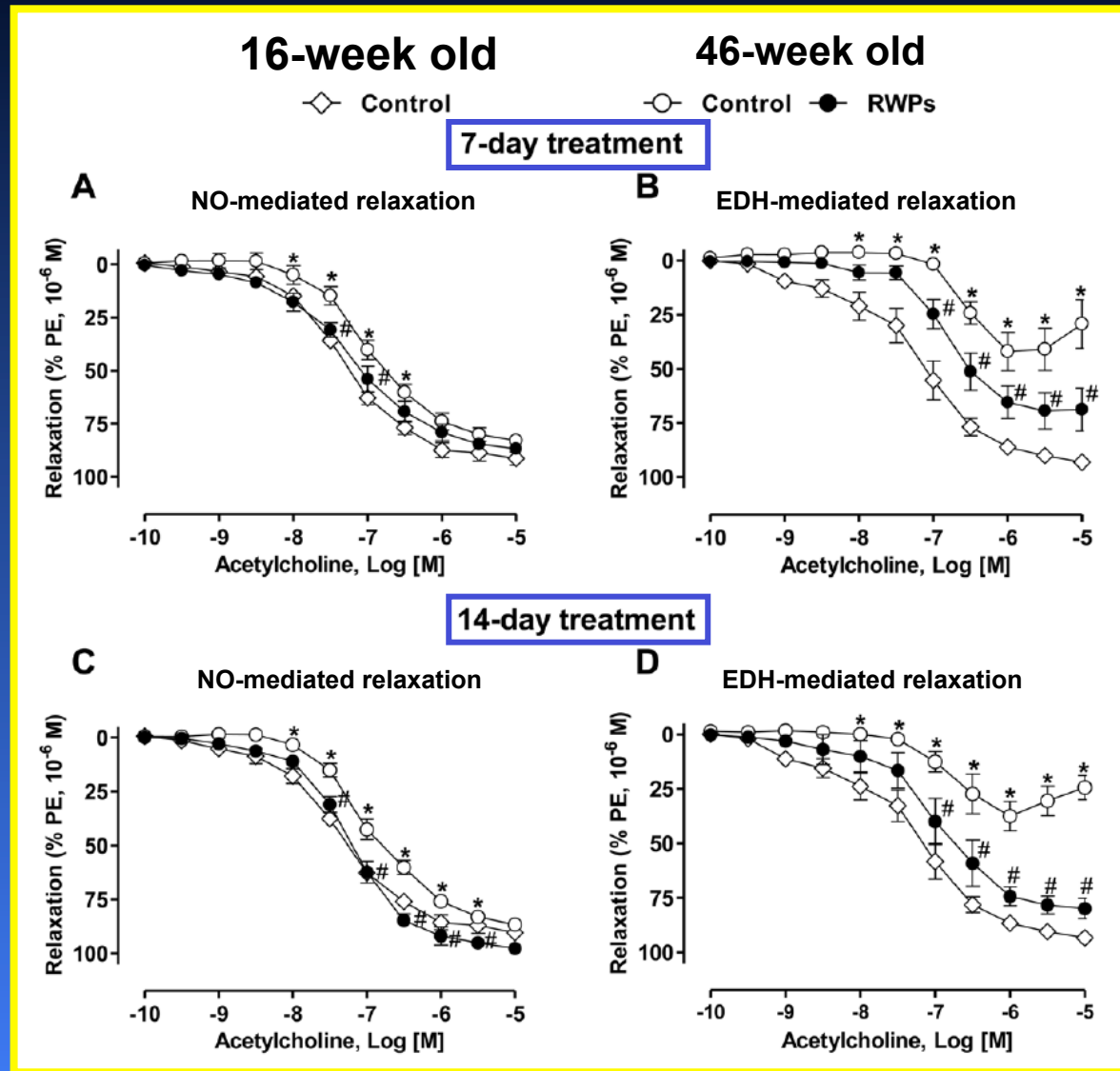


B EDH-mediated relaxation



RWPs improve Ageing-related Endothelial Dysfunction

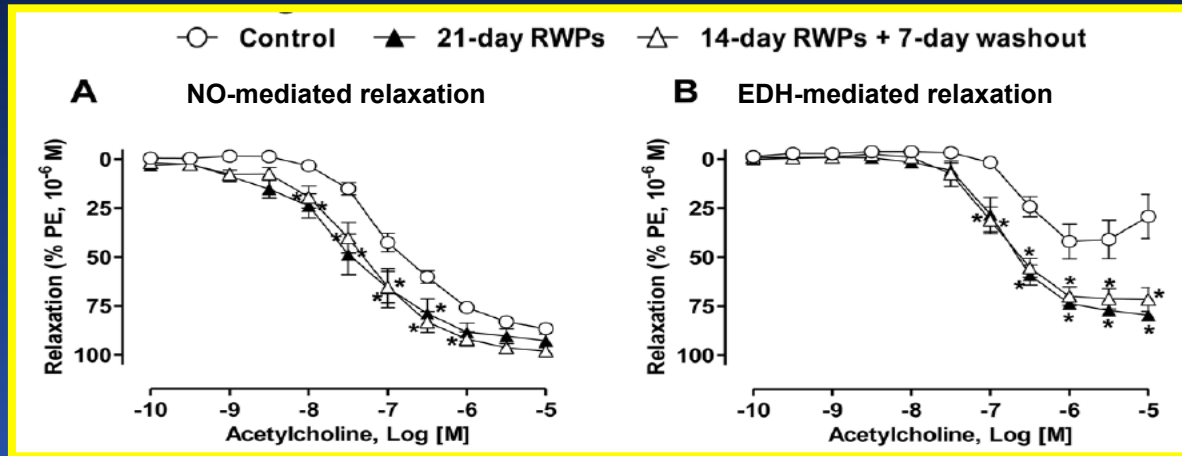
Mesenteric artery



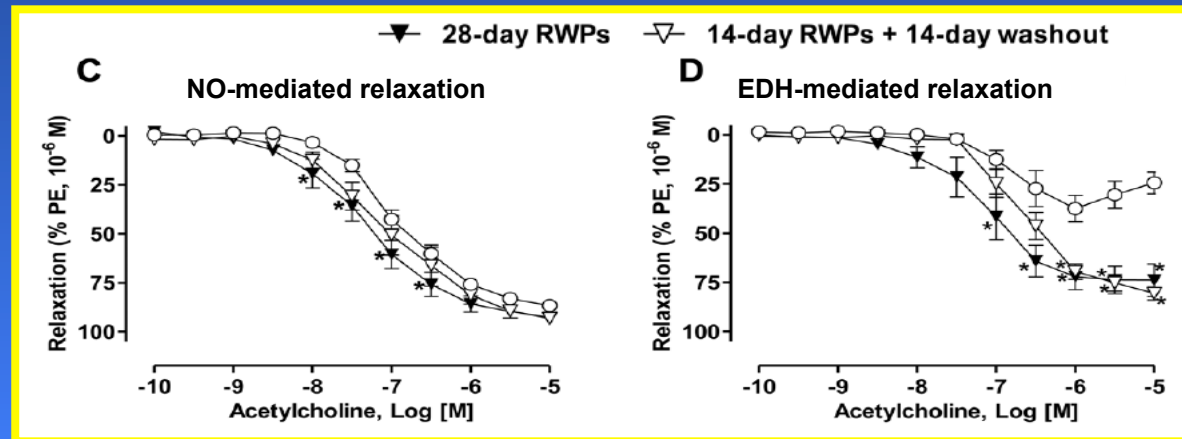
Ageing-related Endothelial Dysfunction

Mesenteric artery (46 w)

14-day RWP treatment + 7-day washout

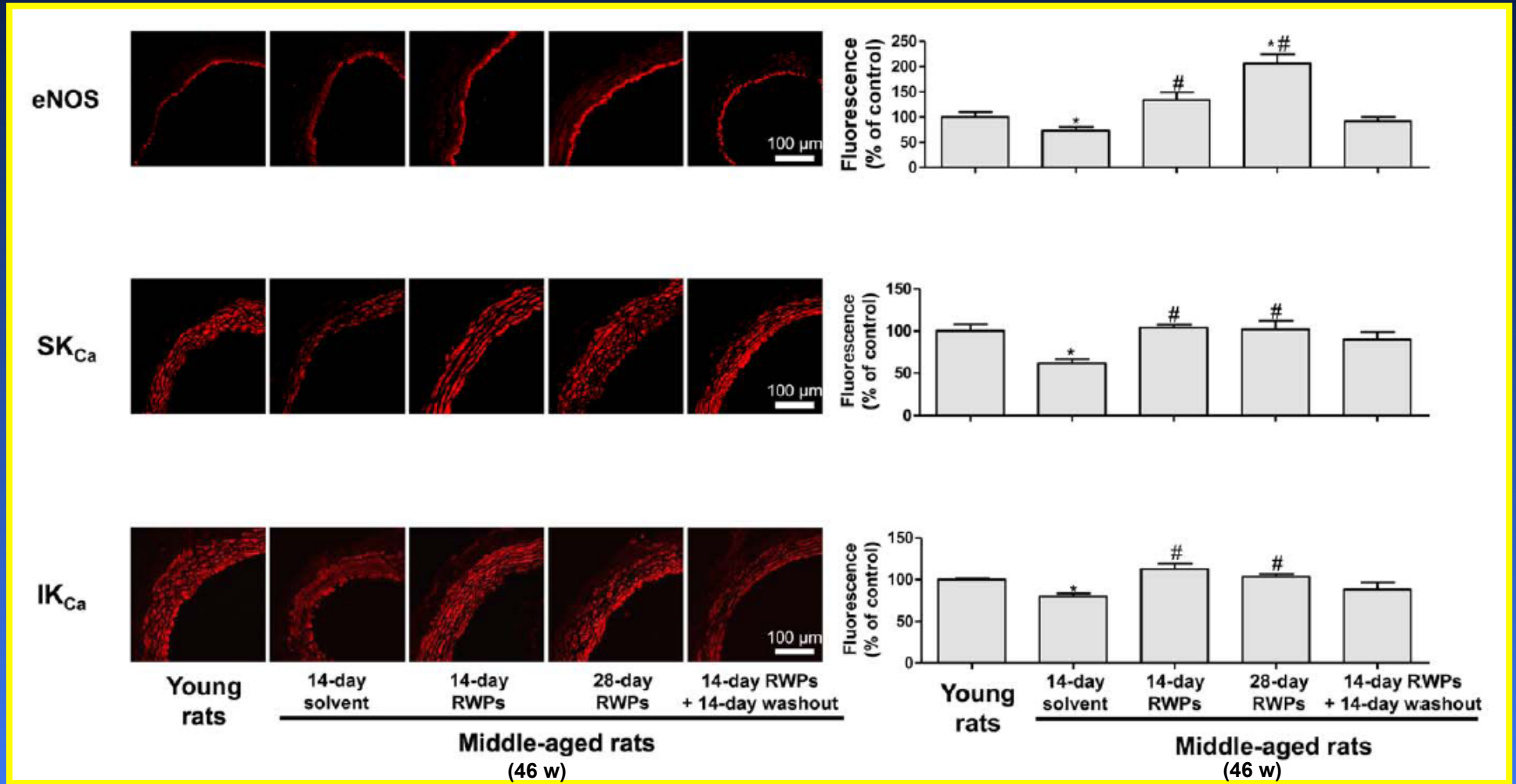


14-day RWP treatment + 14-day washout



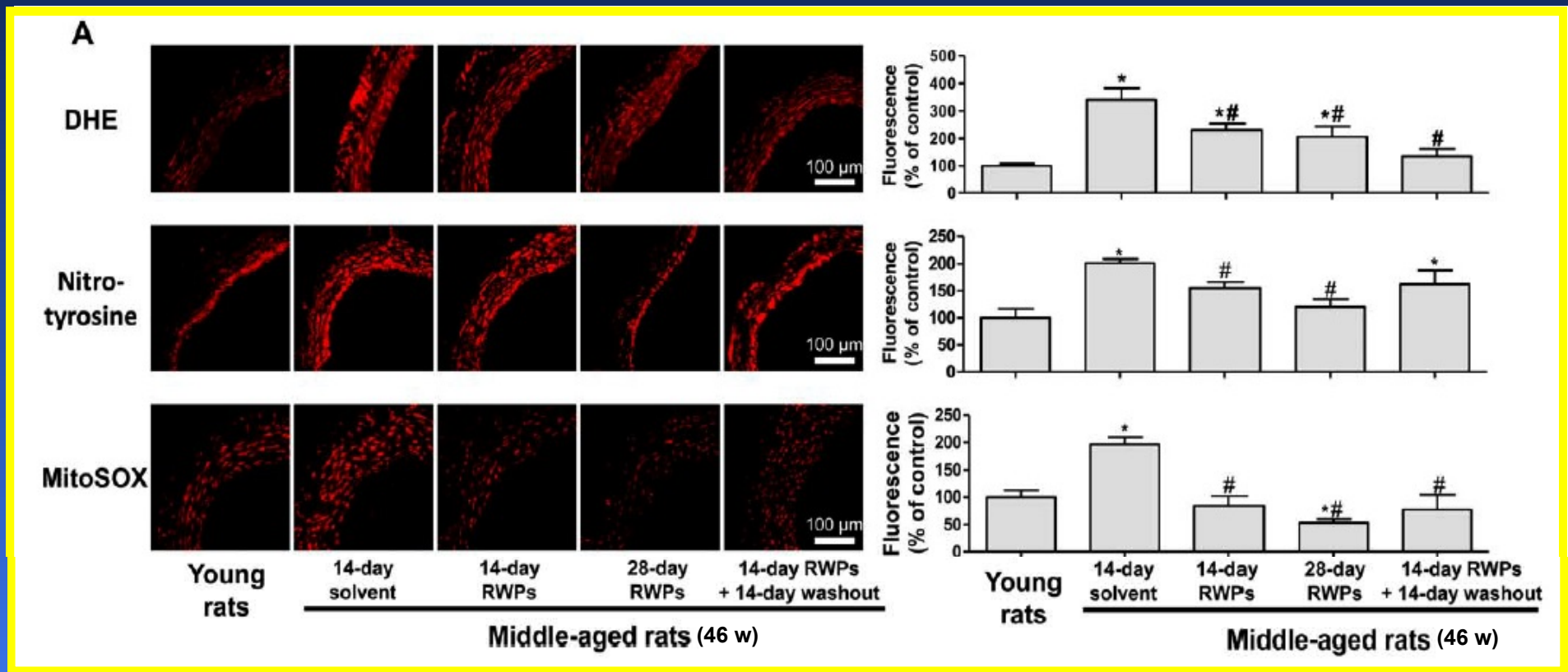
Ageing-related Endothelial Dysfunction

Mesenteric artery



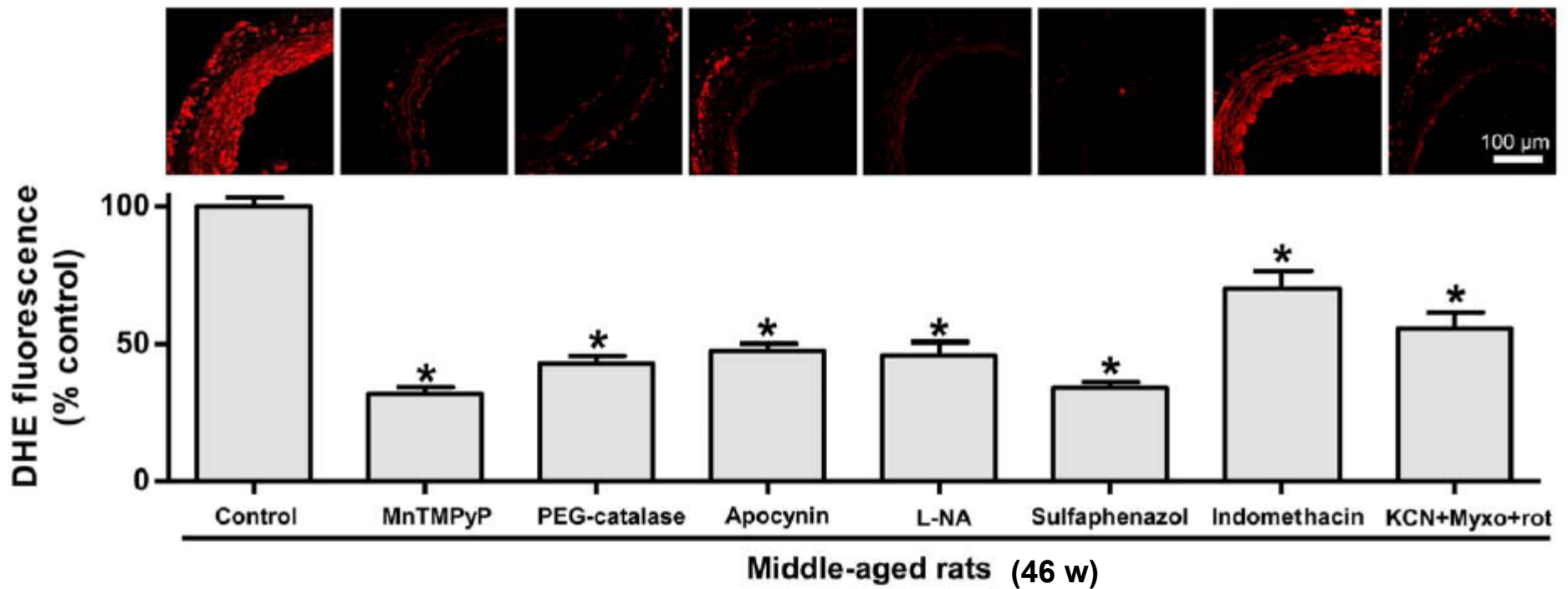
Vascular oxidative stress in Ageing

Mesenteric artery



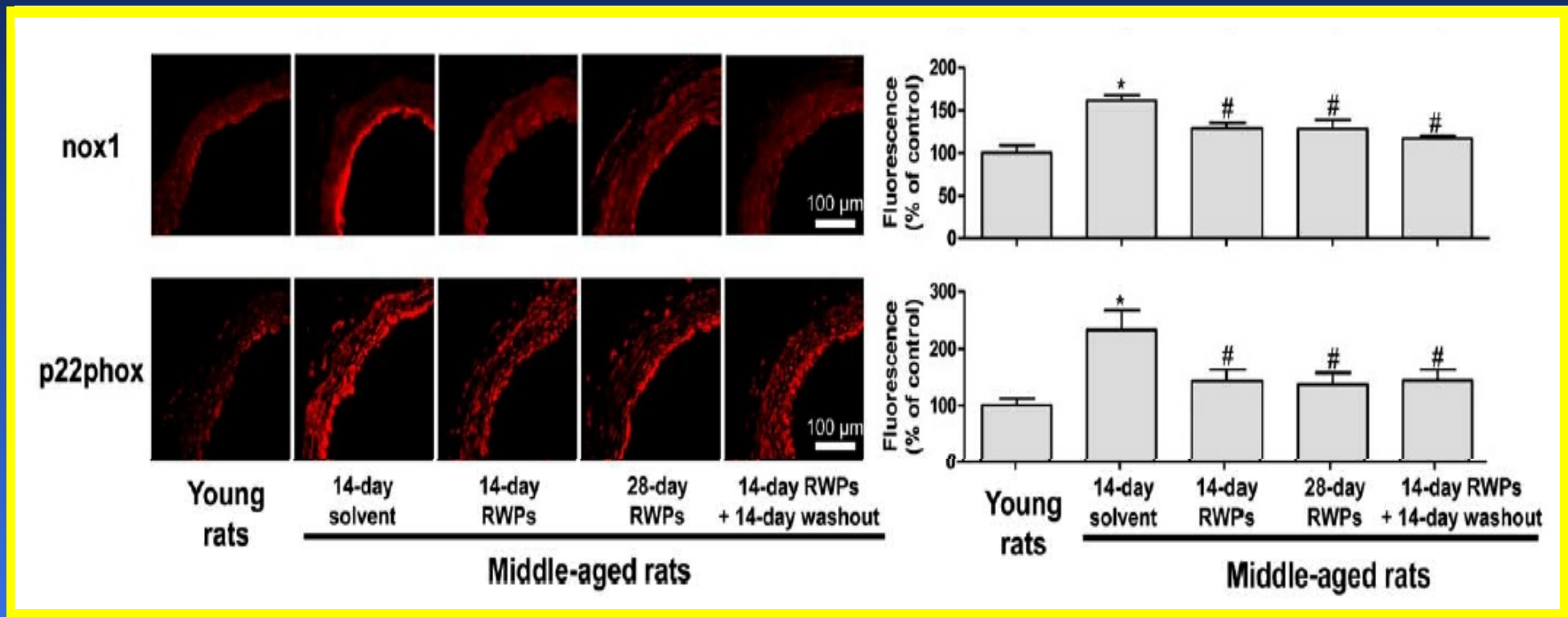
Vascular Oxidative Stress in Ageing

Mesenteric artery



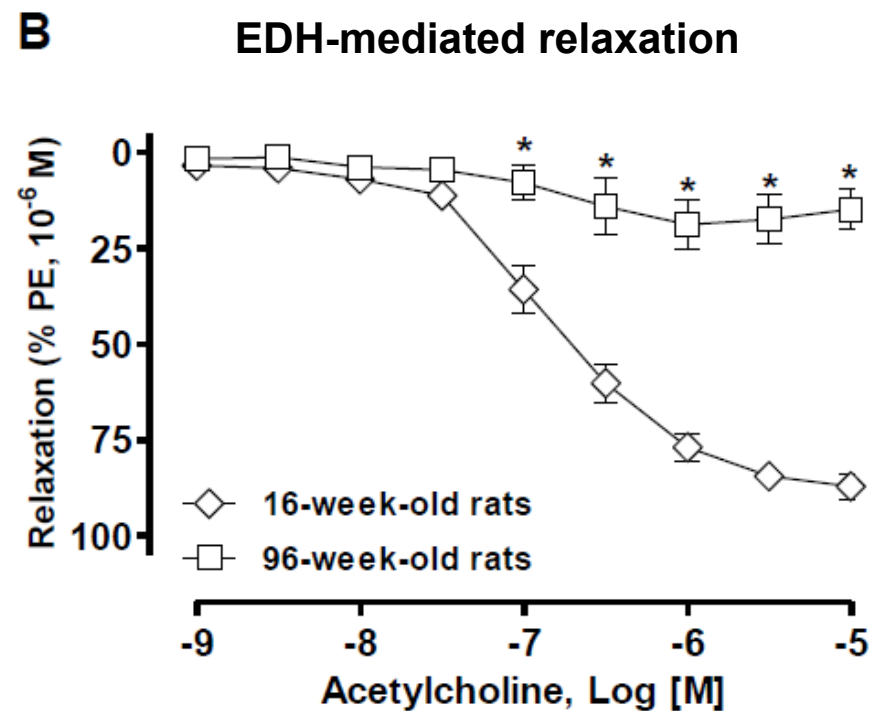
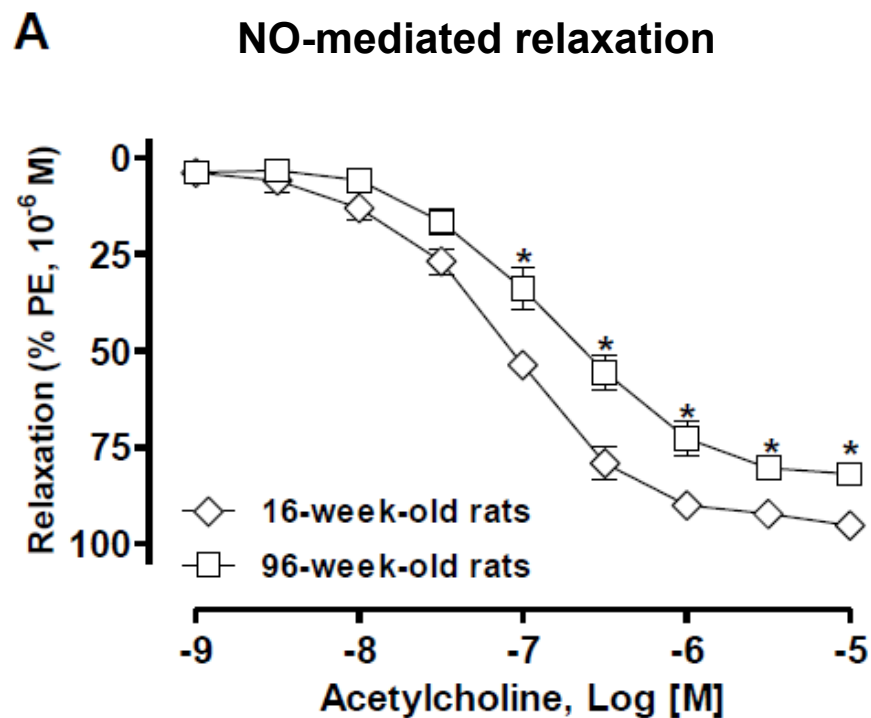
Vascular NADPH Oxidase subunits in Ageing

Mesenteric artery



Ageing-related Endothelial Dysfunction

Mesenteric artery



Ageing-related Endothelial Dysfunction

