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Institute

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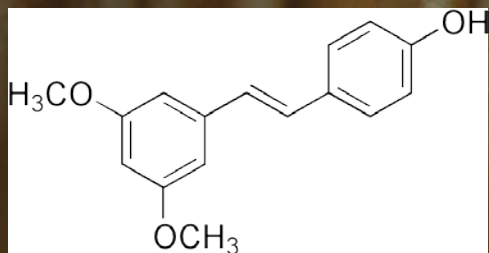
Bioactive polyphenols from wine grapes

Jeff Stuart
Biological Sciences
April 3, 2013

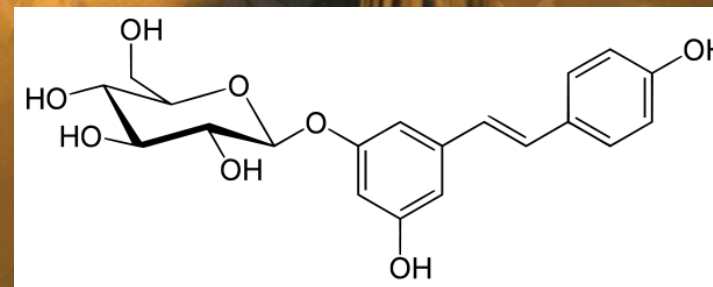
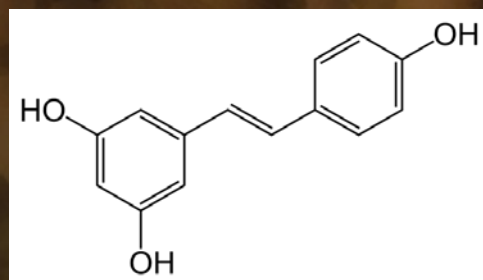


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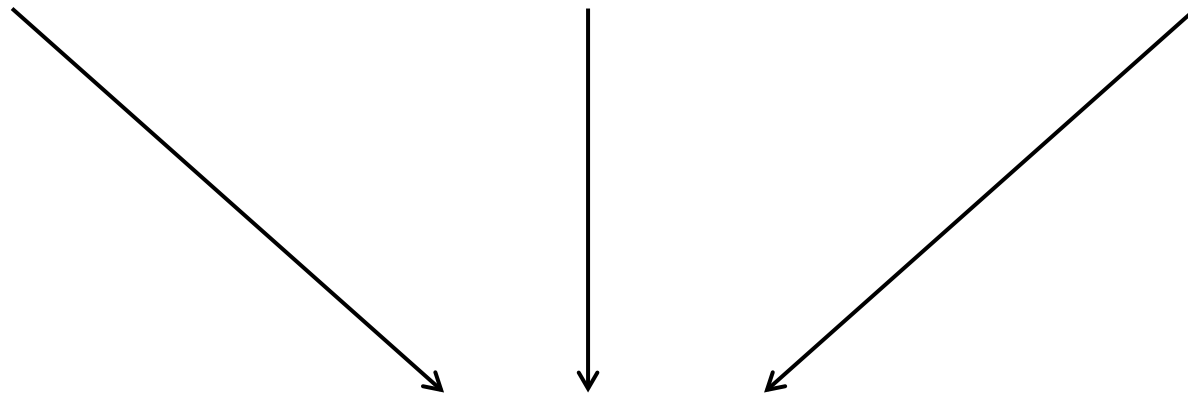
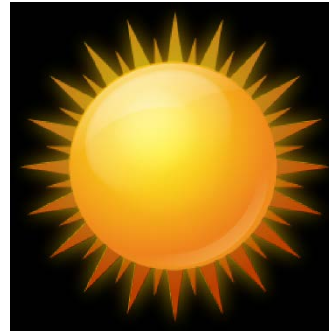
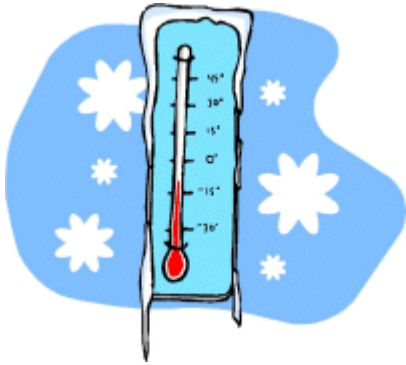


Ellen Robb
PhD candidate



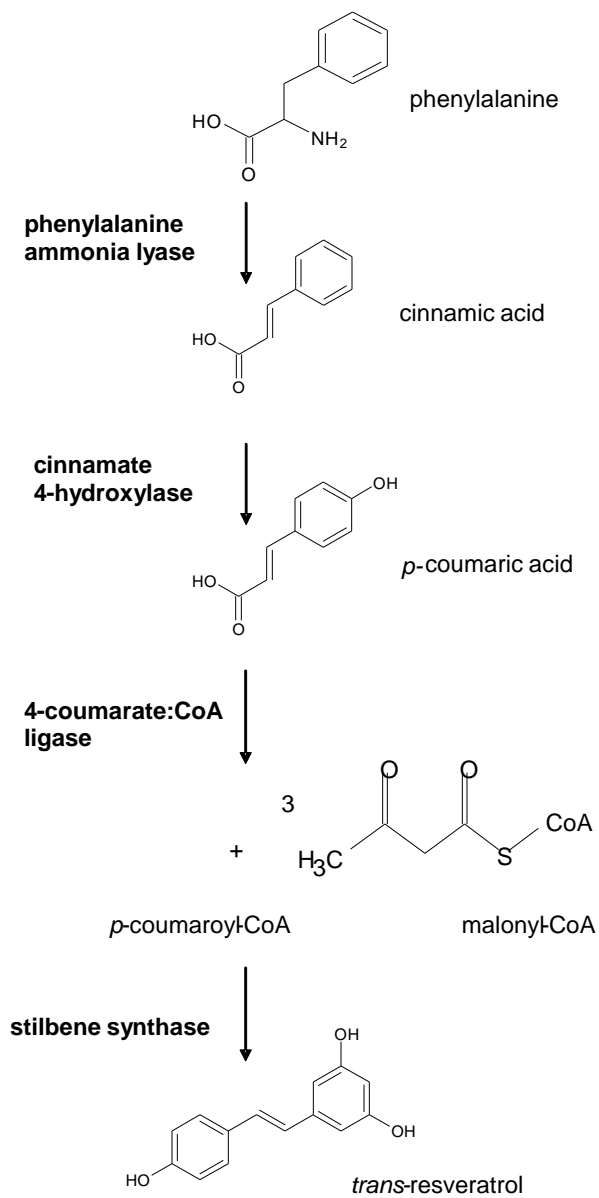
Friday, April 26

Stresses, both abiotic and biotic, stimulate phytoalexin synthesis in *Vitis vinifera*

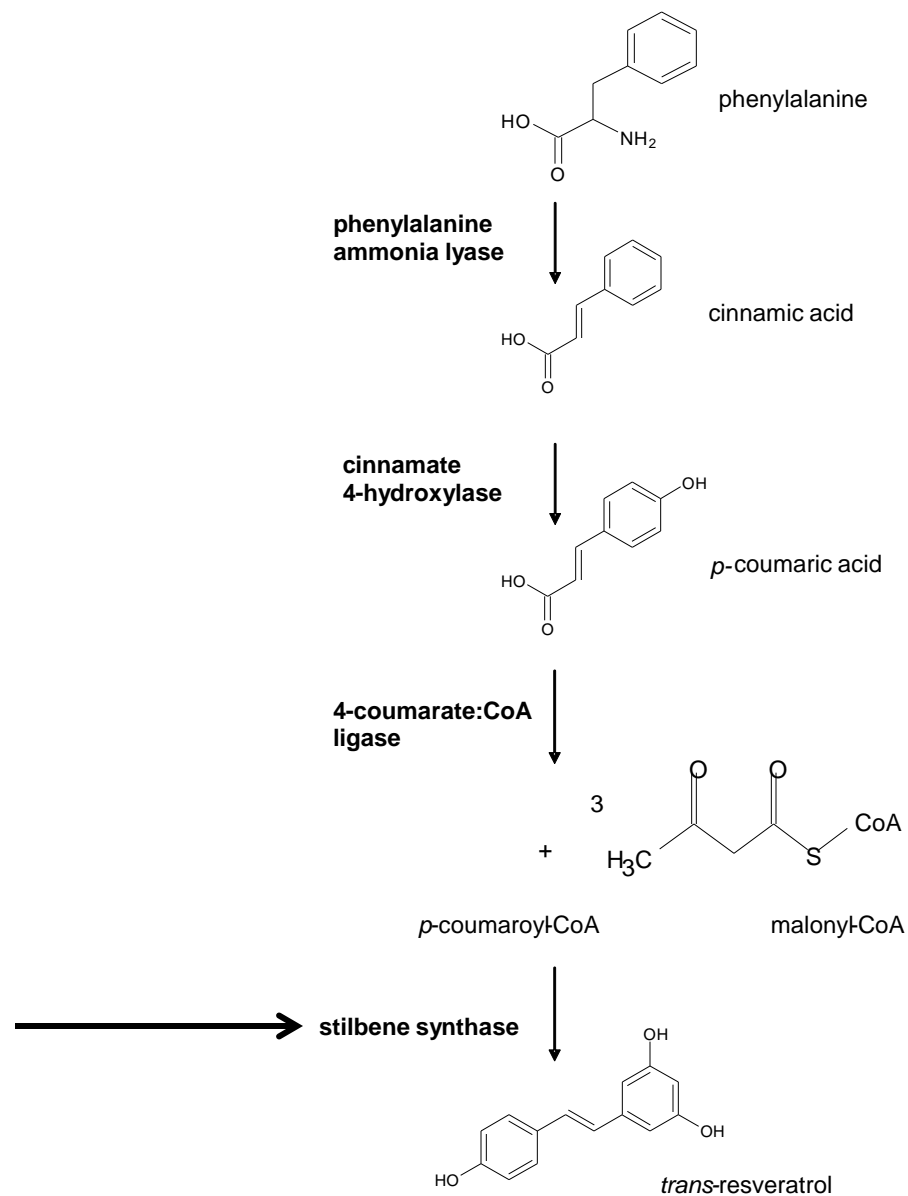


phytoalexins

trans-Resveratrol synthetic pathway



trans-Resveratrol synthetic pathway



trans-Resveratrol synthetic pathway

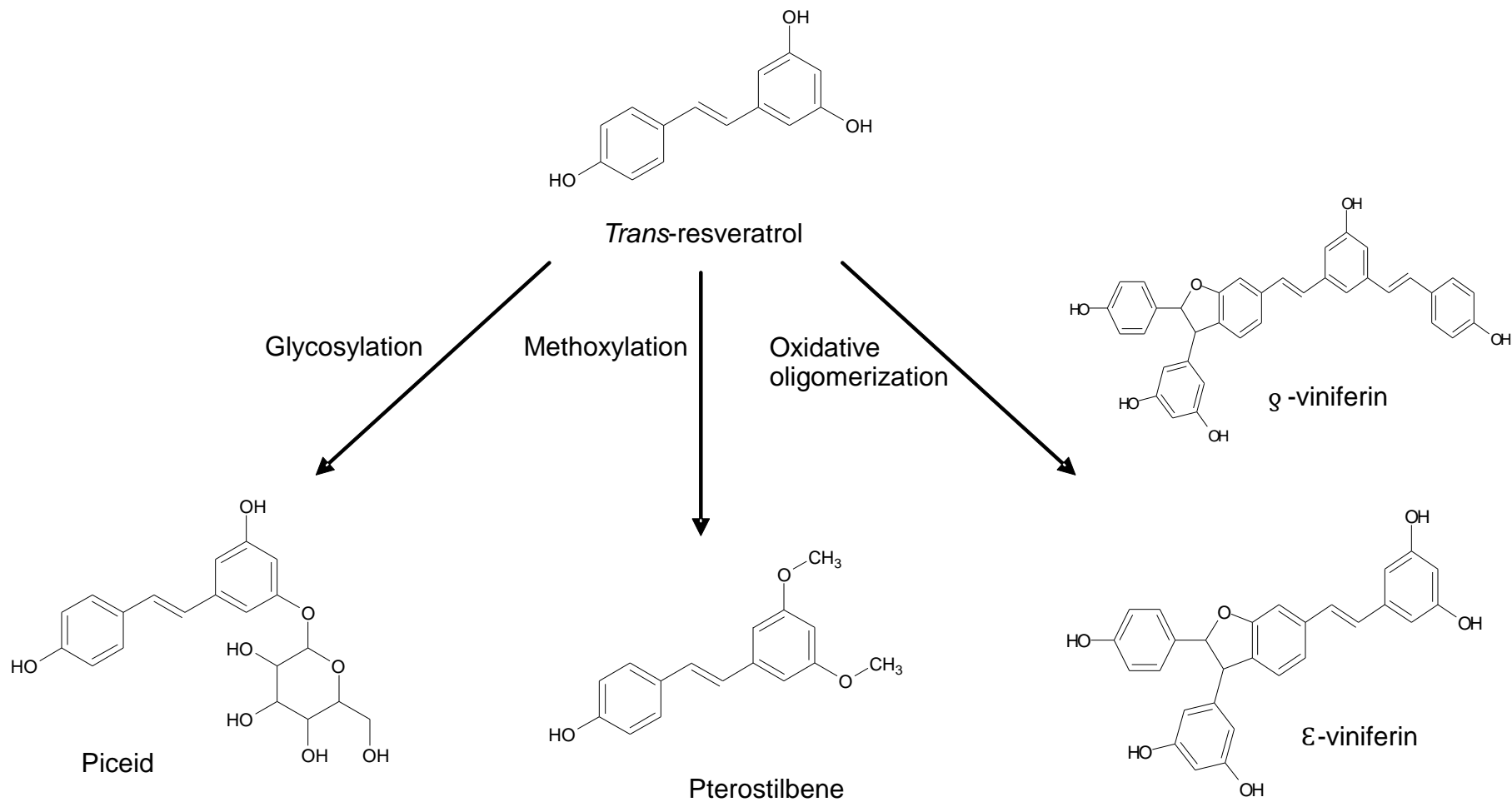
20-40 individual stilbene synthase genes have been identified in *Vitis vinifera*!

(C Parage et al 2012, Plant Physiol)

The resveratrol industry



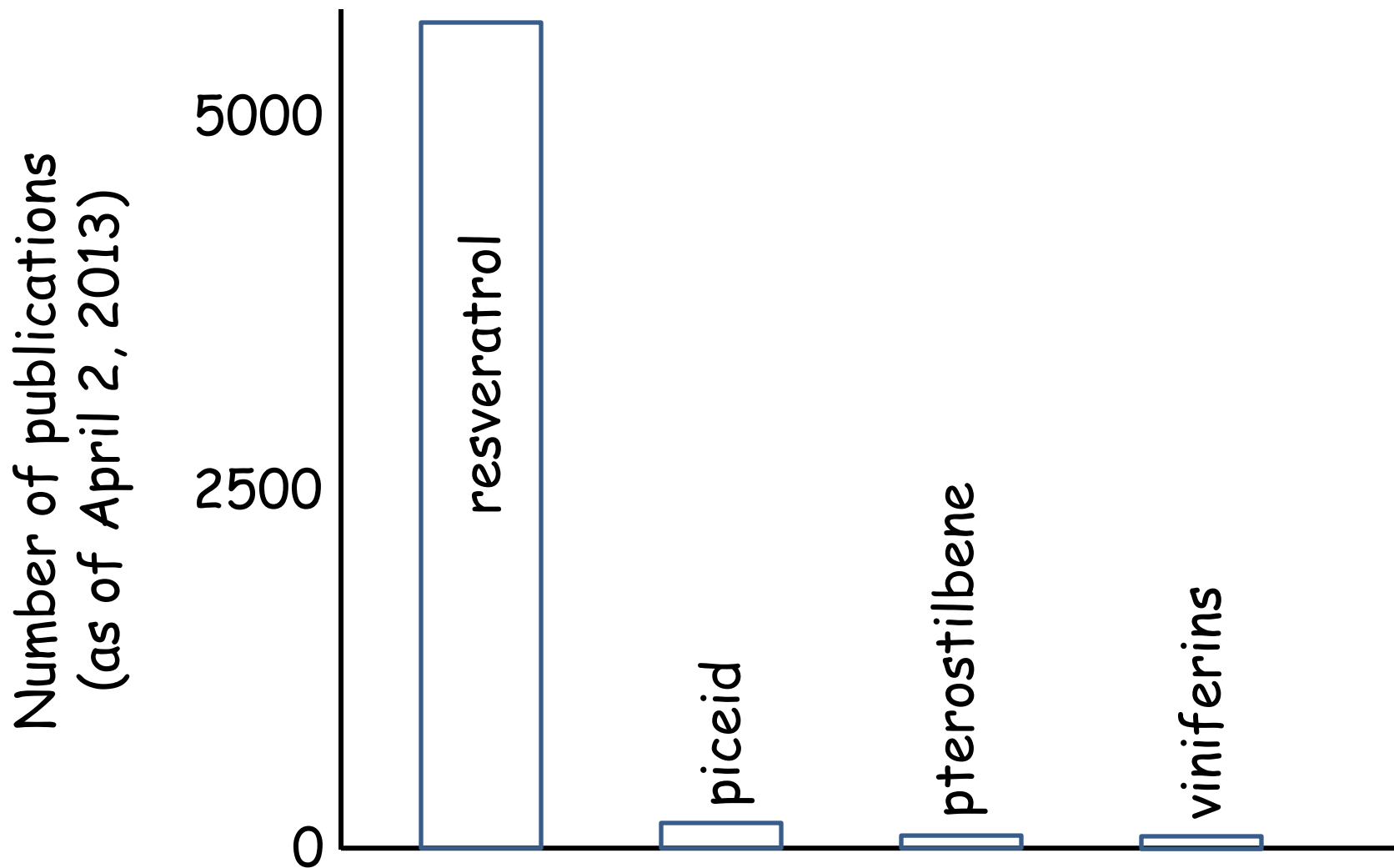
Further metabolism of resveratrol *in planta*



	0		2 dpi		6 dpi	
	Average	SD	Average	SD	Average	SD
<i>Trans</i> -piceid	ND	ND	ND	ND	2.7	0.4
<i>Trans</i> -resveratrol	ND	ND	ND	ND	5.7	3.6
Pallidol (ampelopsin H)	ND	ND	ND	ND	30.22	16.04
Ampelopsin D + quadrangularin A (1:1)	ND	ND	ND	ND	8.0	4.2
Isohopeaphenol	ND	ND	ND	ND	147.0	70.6
Ampelopsin H + vaticanol-C like isomer (ampelopsin H)	ND	ND	ND	ND	35.80	19.4
(+)- <i>E</i> - ϵ -viniferin	ND	ND	ND	ND	13.1	6.9
<i>Z</i> + <i>E</i> -miyabenol C (<i>Z</i> -miyabenol C)	ND	ND	ND	ND	10.5	2.9
<i>Z</i> + <i>E</i> - ω -viniferin (<i>E</i> - ω -viniferin)	ND	ND	ND	ND	9.5	2.7
α -viniferin	ND	ND	ND	ND	15.5	7.0
<i>E</i> - <i>cis</i> -miyabenol C	ND	ND	ND	ND	16.9	20.4
<i>Trans</i> -pterostilbene (<i>trans</i> -resveratrol)	ND	ND	ND	ND	6.0	4.0

ND, not detected.

Resveratrol has received far more attention from researchers than have its derivative molecules



Do resveratrol's derivatives its biological activities (in people)?

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Slows growth of cancer cells?

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Cardiovascular effects?

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Neuroprotective?

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Metabolic disease?

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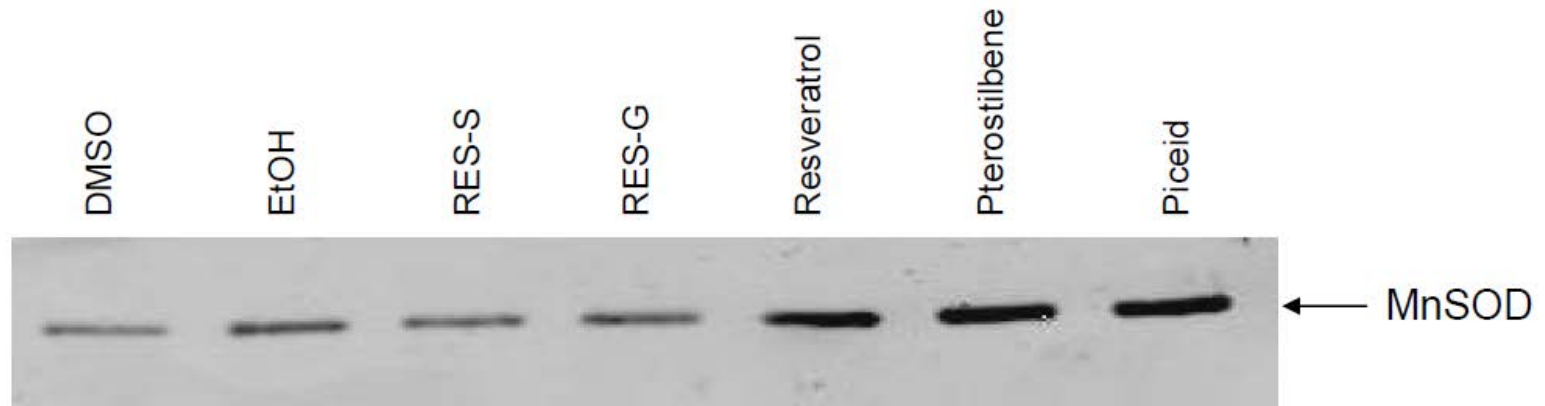
Do resveratrol's derivatives share its biological activities?

yes

Do the resveratrol derivatives share resveratrol's cellular mechanisms?

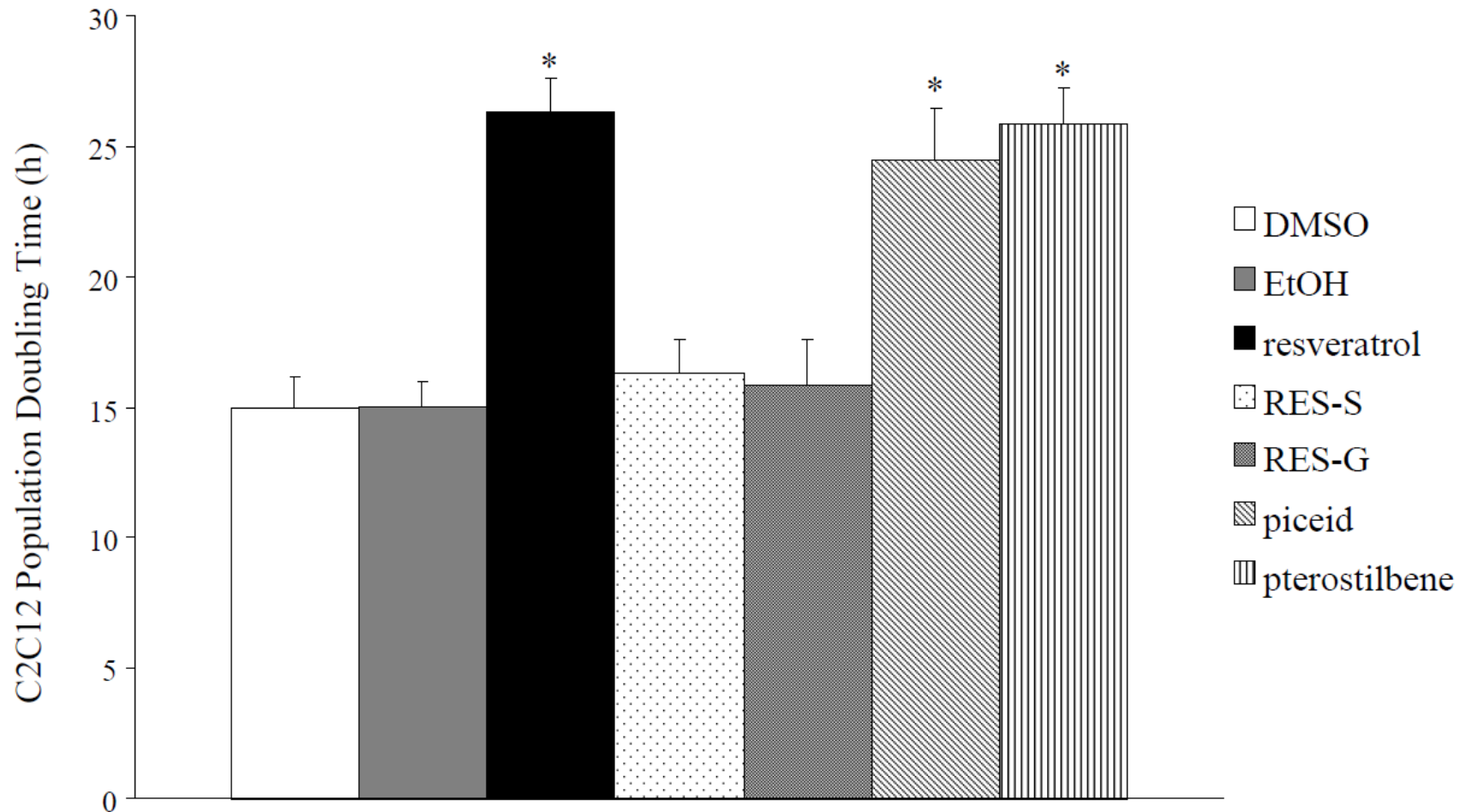


Pterostilbene and piceid have the same effect as resveratrol on cellular antioxidant systems



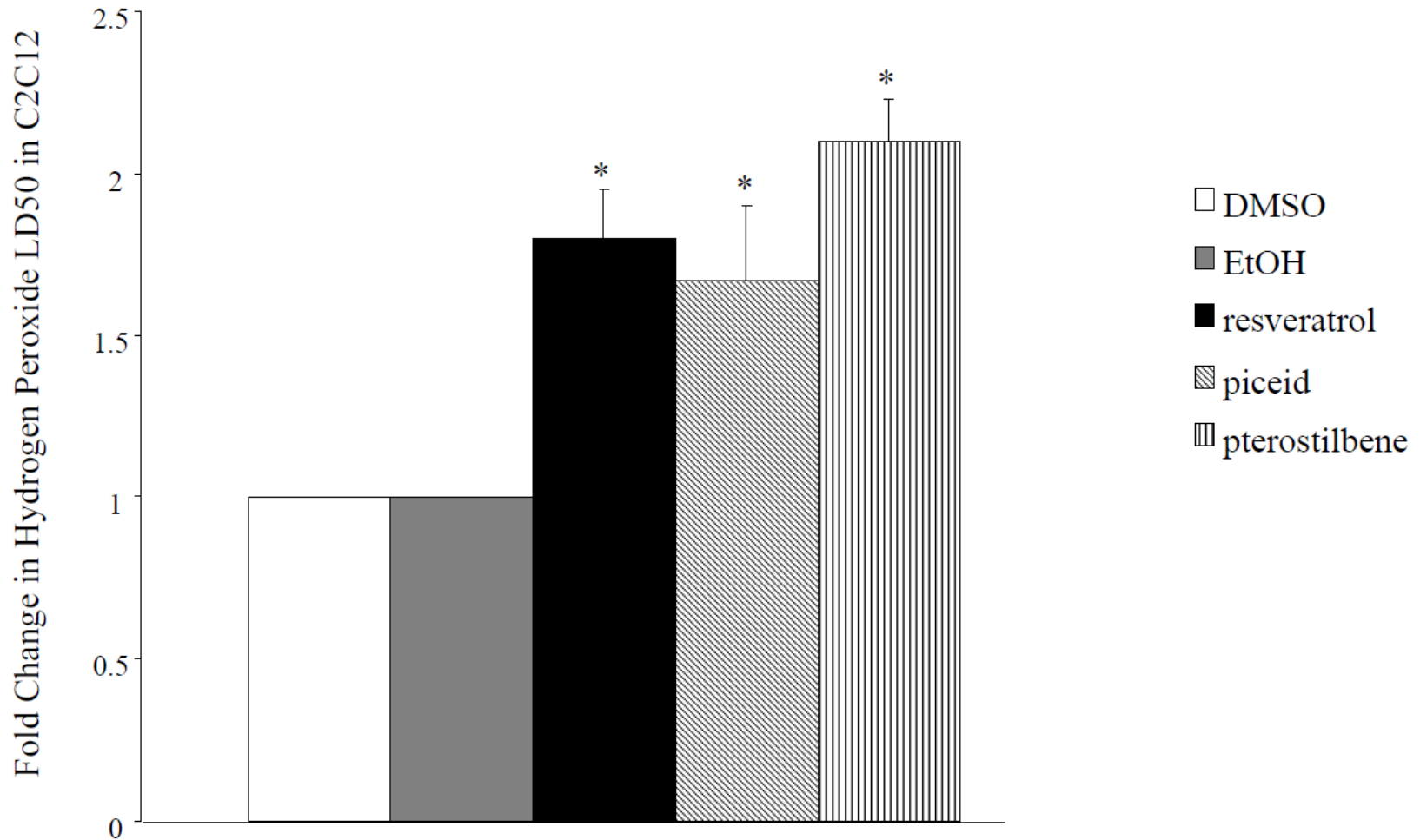
Robb and Stuart, unpublished

Pterostilbene and piceid inhibit cell proliferation similarly to resveratrol



Robb and Stuart, unpublished

Pterostilbene and piceid enhance cellular stress resistance similarly to resveratrol



Robb and Stuart, unpublished

Pterostilbene and piceid elicit very similar biological activities in people *in vivo* and have very similar cellular effects *ex vivo*

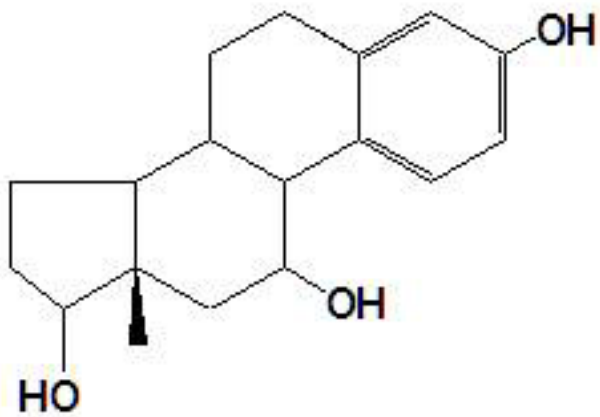
Pterostilbene and piceid elicit very similar biological activities *in vivo* and have very similar cellular effects

Why and How?

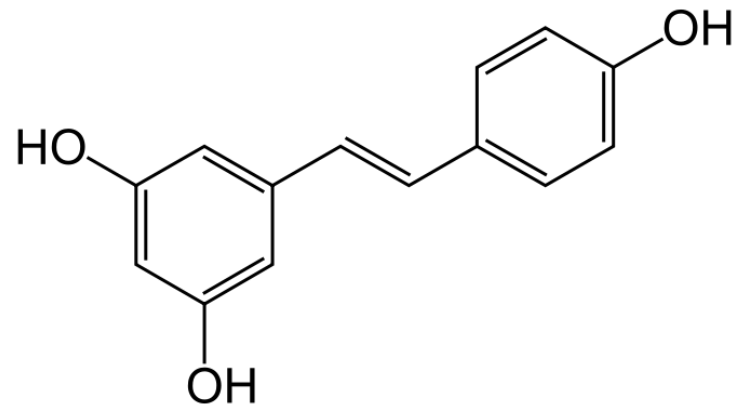
Pterostilbene and piceid elicit very similar biological activities *in vivo* and have very similar cellular effects

Do they stimulate the same signal transduction pathway?

Resveratrol has similar chemical structure to estrogen



17β-Estradiol

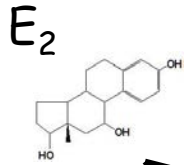


trans-Resveratrol

....and similar biological activities

Disease	Protection by resveratrol	Protection by estrogens
Atherogenesis	√	√
Hypertension	√	√
Ischemic stroke	√	√
Neurodegeneration	√	√
Cancer	√	Tissue specific
Obesity	√	√
Type 2 Diabetes	√	√

Many of estrogen's effects mediated by the 'classical' estrogen receptors ER α and ER β

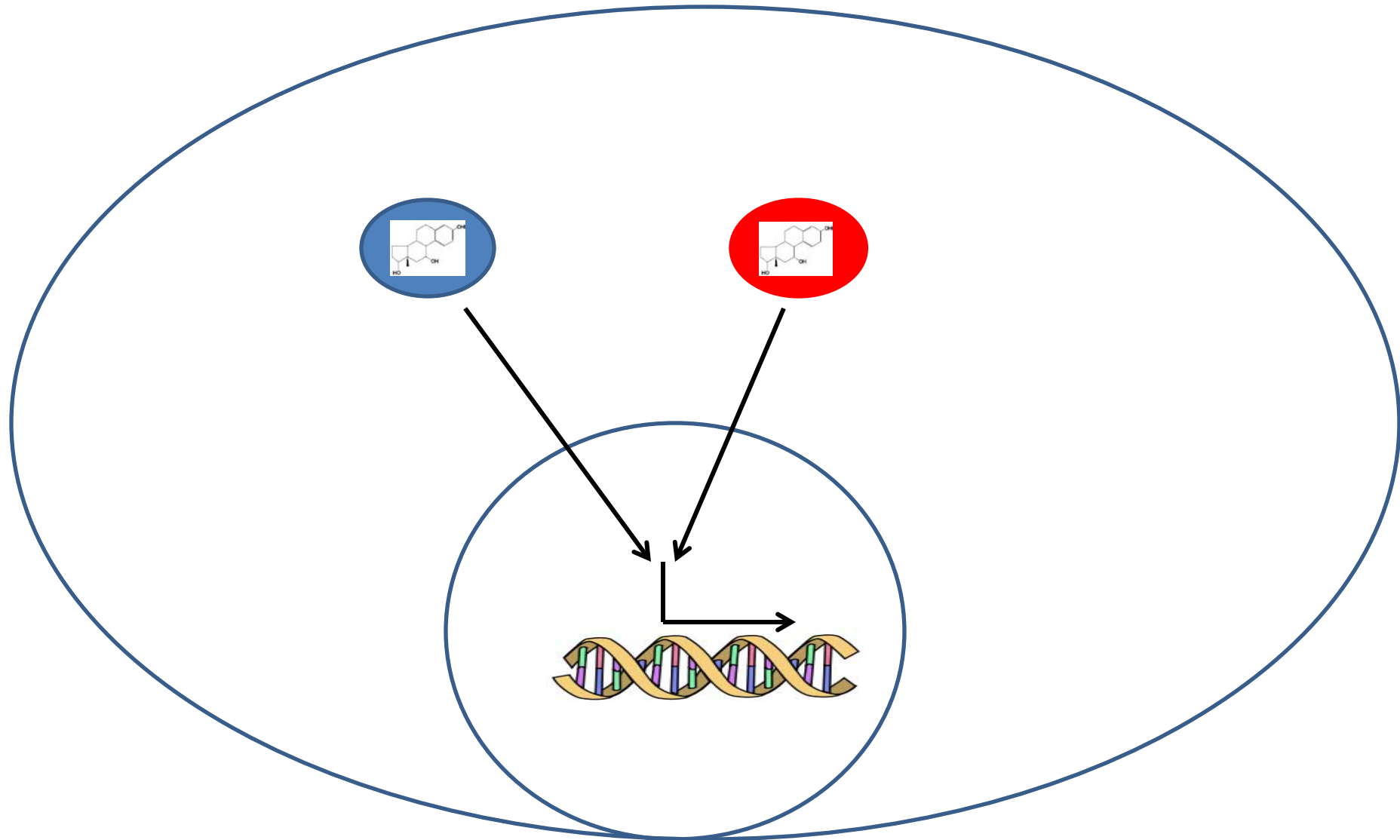


ER α

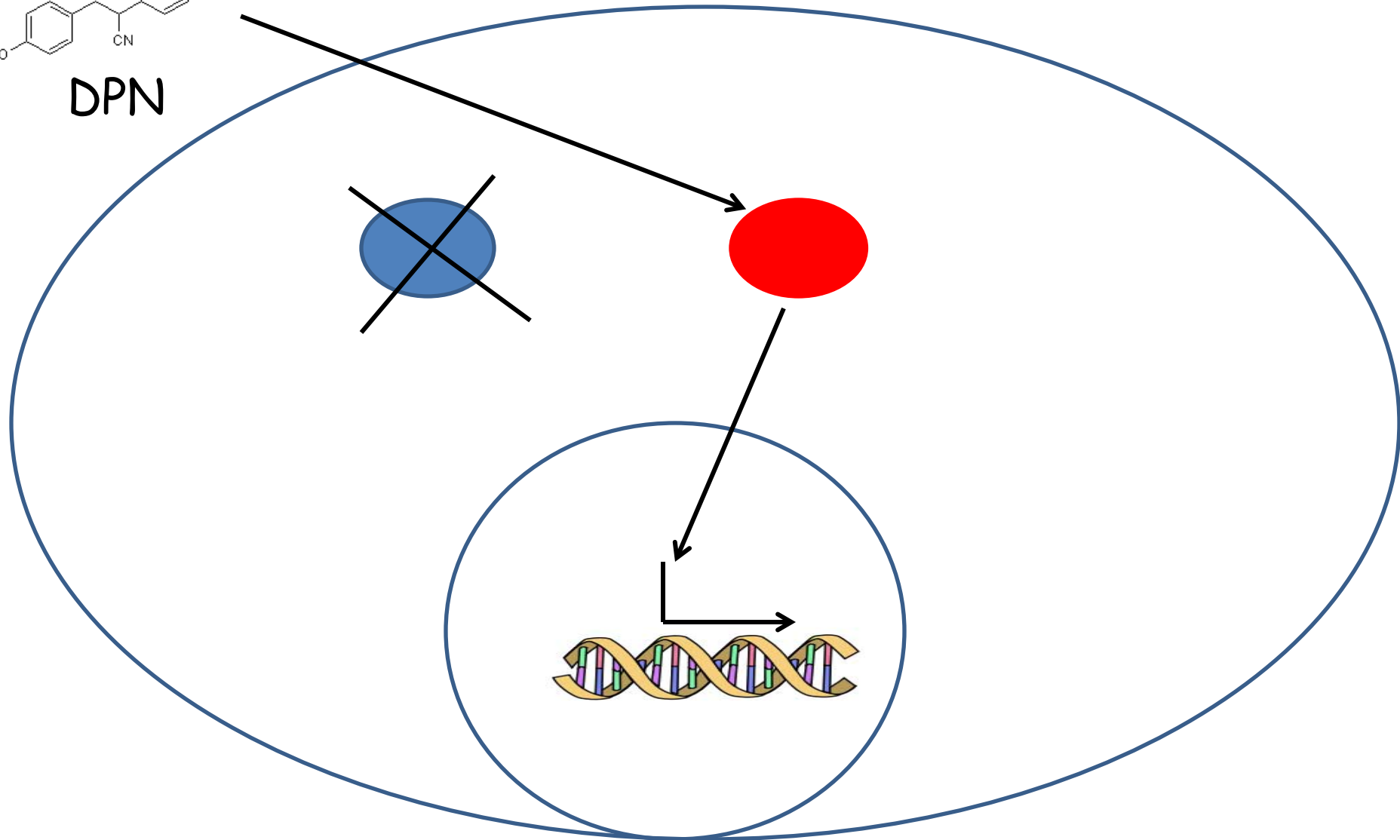
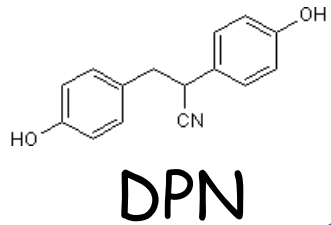
ER β



ER α and ER β regulate transcription of hundreds of genes

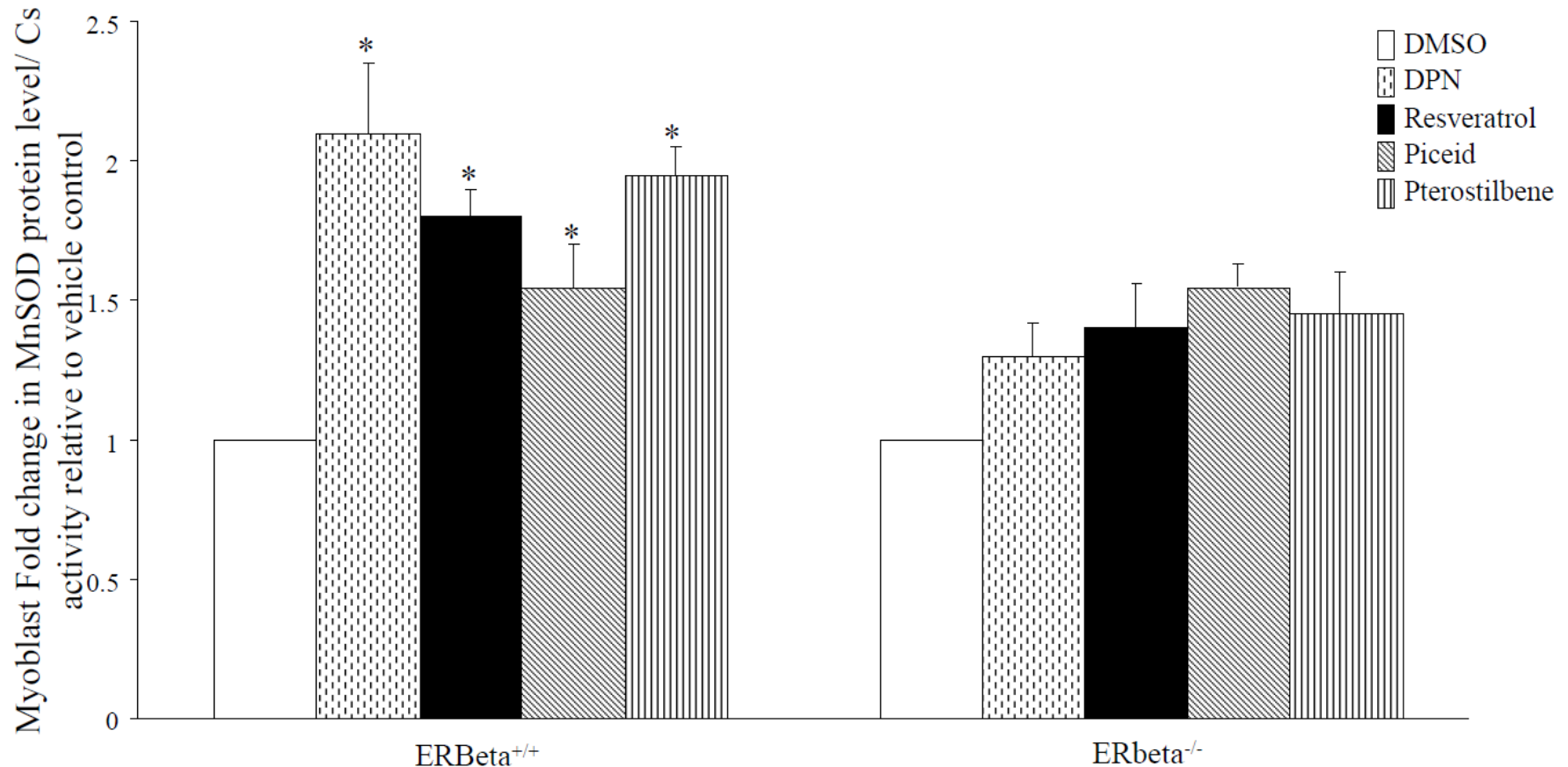


Drugs are available that specifically bind to and stimulate ER β (and not to ER α)

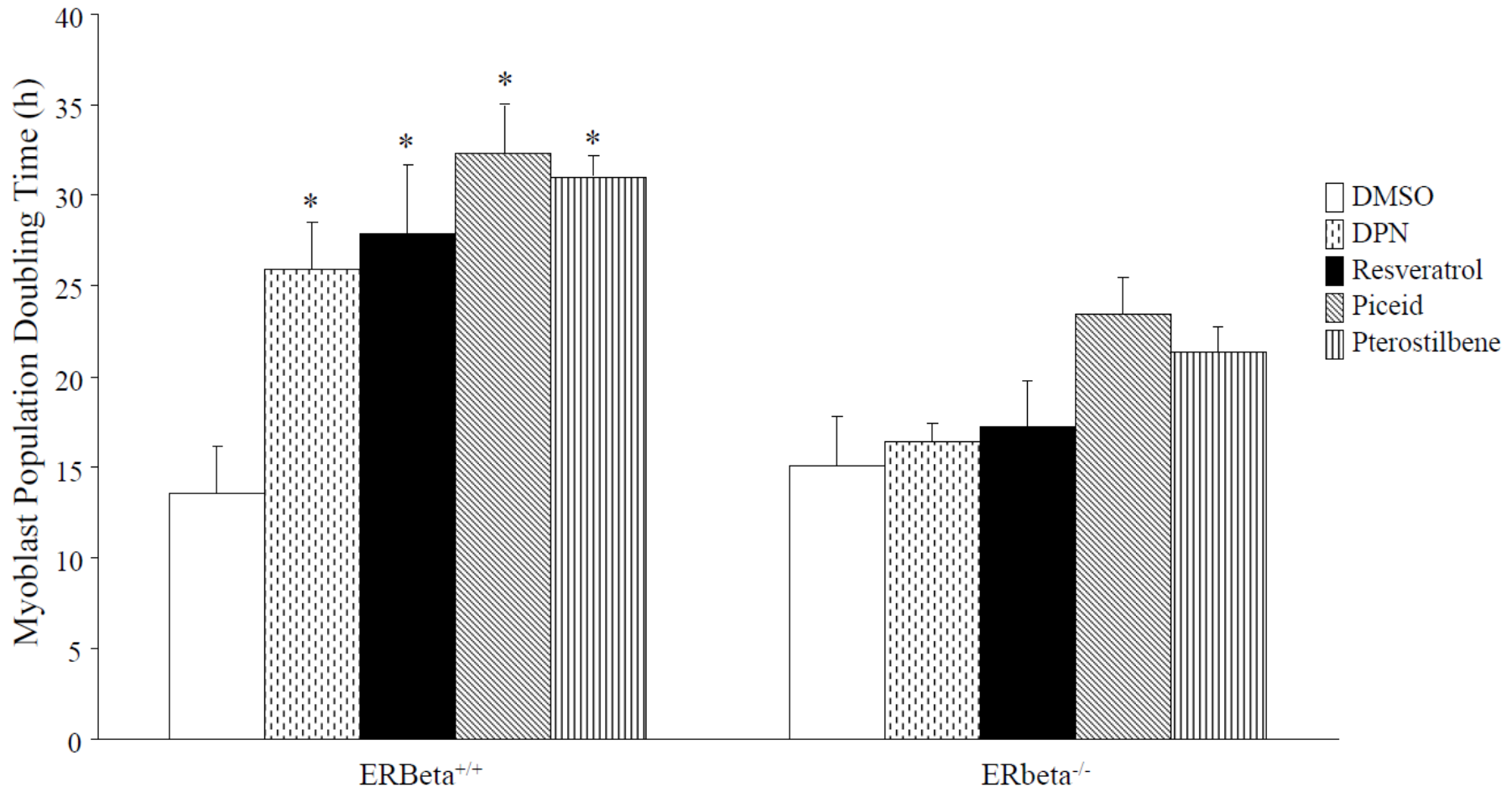


The cellular (and in vivo) effects of resveratrol, pterostilbene, and piceid can be reproduced using DPN and are reduced or abolished in ER β knockout cells

Induction of the intracellular antioxidant system is reproduced by DPN and blunted in the absence of ER β

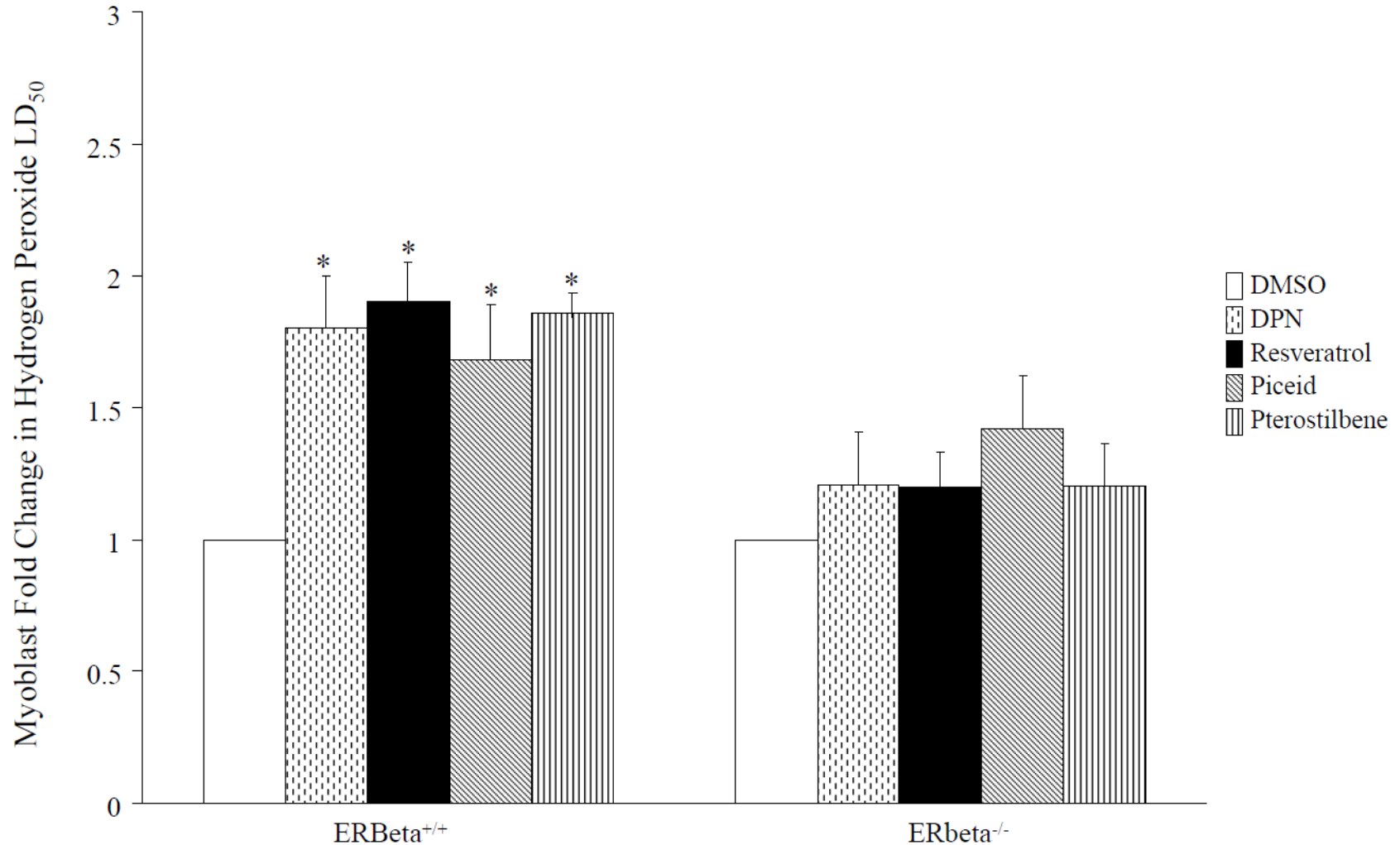


Cell proliferative growth is inhibited also by DPN and the effect is reduced in the absence of ER β



Robb and Stuart, unpublished

Cellular stress resistance is stimulated by DPN and abolished in absence of ER β

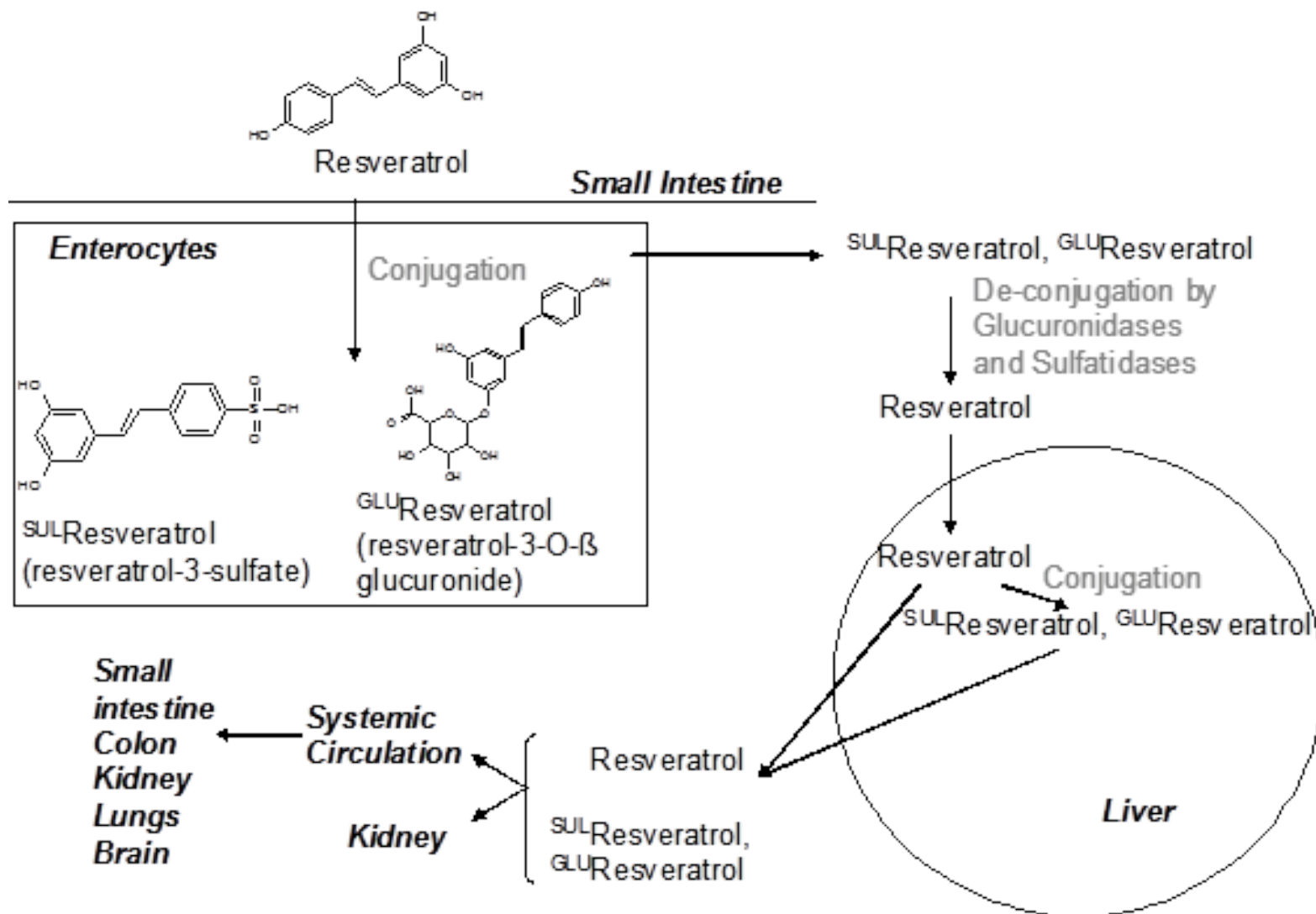


Resveratrol, pterostilbene, and piceid appear to work through the same pathway: $ER\beta$

Resveratrol, pterostilbene, and piceid are working
through the same pathway: ER β

Are pterostilbene and piceid 'better' than resveratrol?

Pterostilbene and piceid have better bioavailability *in vivo* than resveratrol





An opportunity!



Summary

Phytoalexins are molecules produced by stressed grapevines that are present in grapes and in wines fermented in the presence of grapes

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Resveratrol, pterostilbene, and piceid are all phytoalexins

Although resveratrol is the best characterized, many of its effects in people and in isolated cells can be replicated using pterostilbene or piceid.

Summary

Resveratrol, pterostilbene, and piceid stimulate ER β to generate some of their beneficial effects.

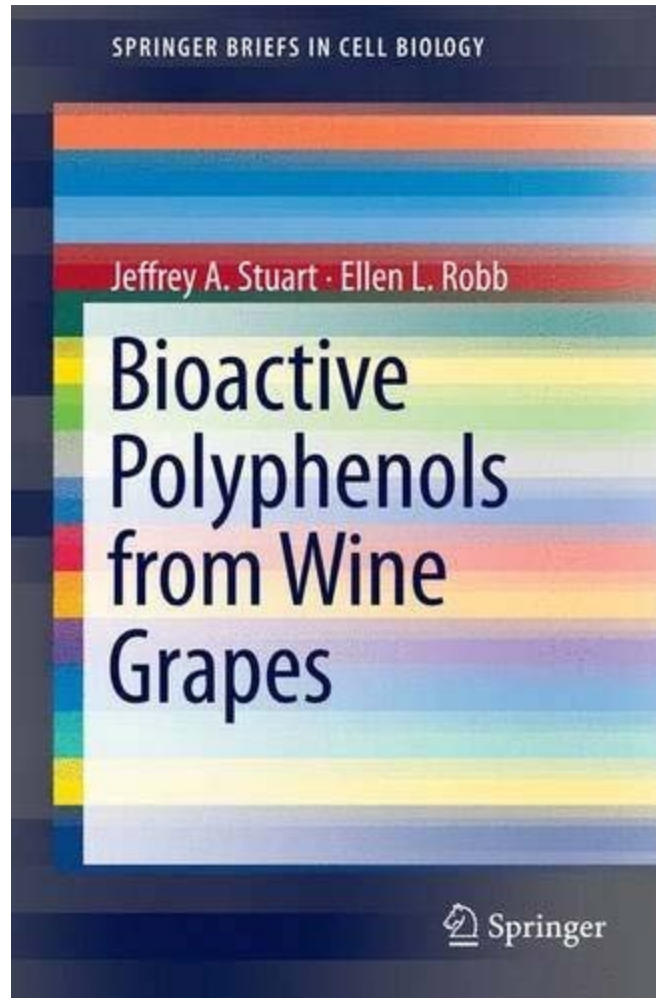
Other ER β agonists being developed to treat post-menopausal symptoms: MF101; phytoestrogen formulations

There is very little research data available for some other resveratrol derivatives that we know are also present in grapes - do they also stimulate ER β ?

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The way forward



The way forward

Detailed experimental determination of grapeskin
phytoalexins' effects

both alone and in combination

both ex vivo and in vivo

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Better understanding of how grape growing and storage practices, fermentation methods, affect stilbene levels in grapes (e.g. organic growing methods)

The way forward

Detailed experimental determination of grapeskin phytoalexins' effects

both alone and in combination

both ex vivo and in vivo

Better understanding of how grape growing and storage practices, fermentation methods, affect stilbene levels in grapes (e.g. organic growing methods)

Capture the full value of grapeskins, which may currently be considered waste in the process

Acknowledgements:



MINISTRY OF RESEARCH AND INNOVATION
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