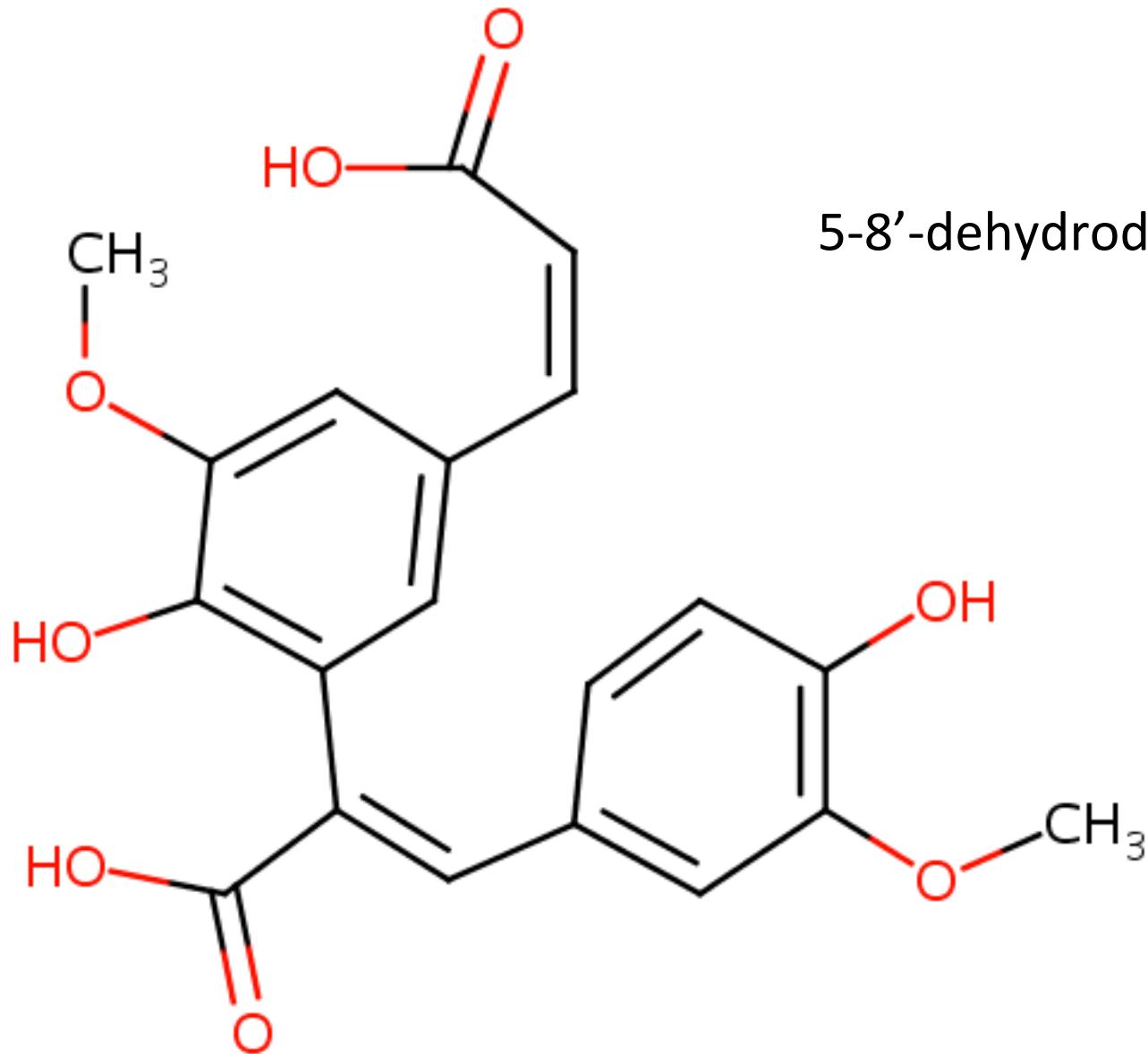


A chemogenomics approach defines novel food, chemical and genetic mediators of triglyceride homeostasis

Kenneth
Westerman

JEAN MAYER
USDA
HUMAN
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CENTER ON
AGING

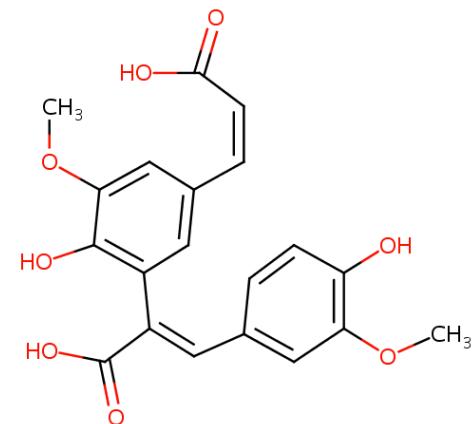
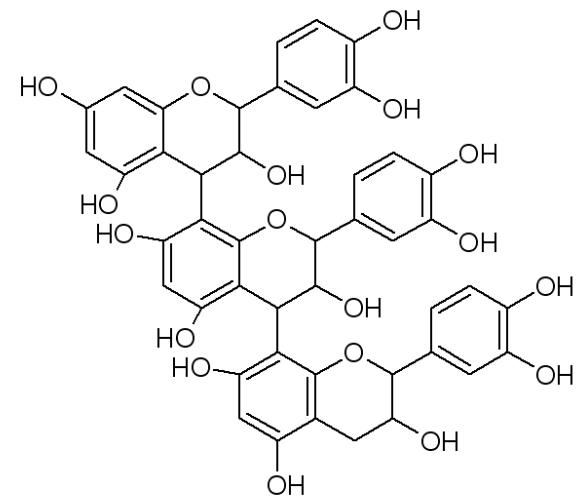
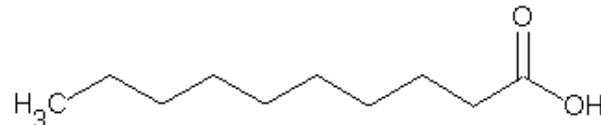
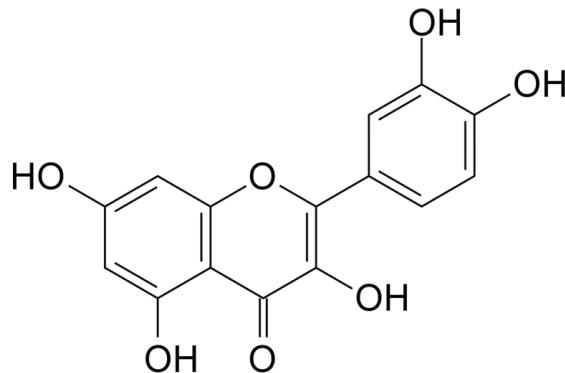
HN RCA



5-8'-dehydodiferulic acid

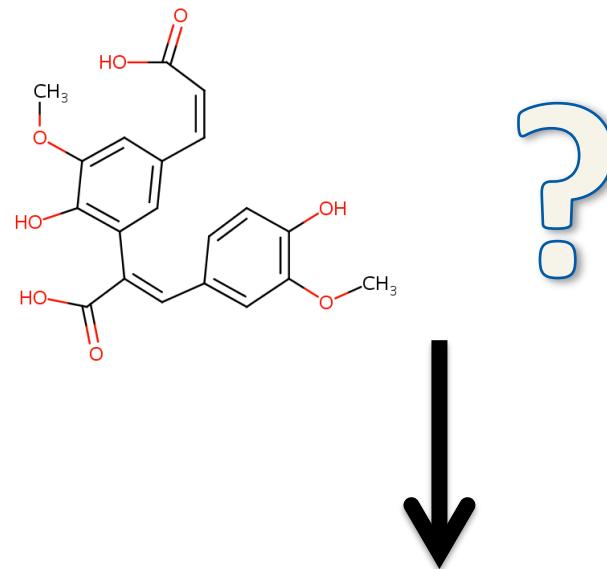
Food-based small molecules

- FooDB contains over 25,000 unique compounds; coffee alone contains over 2,000
- Incredible diversity, but low concentrations in foods



How can we gain information about these food chemicals in a *high-throughput* manner?

Take advantage of the wealth of drug information available!



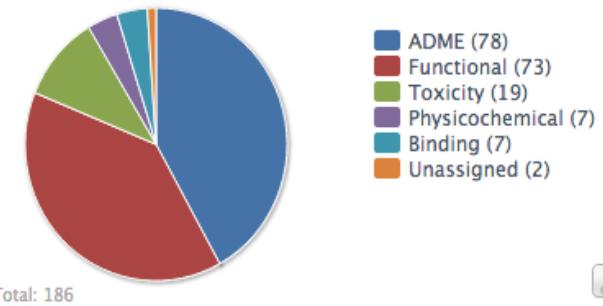
Mechanism of Action

Mechanism of Action	ChEMBL Target	References
GABA-A receptor; anion channel positive allosteric modulator	GABA-A receptor; anion channel	PubMed PubMed

Calculated Compound Parent Properties

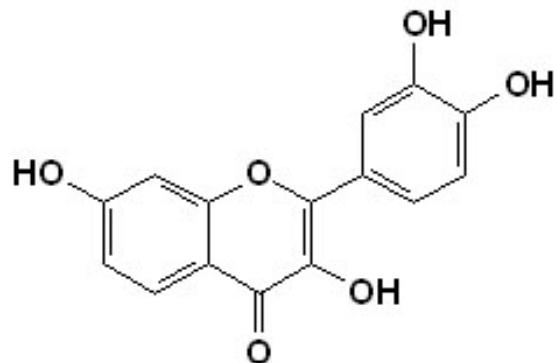
Mol. Weight	Mol. Weight Monoisotopic	ALogP	#Rotatable Bonds	Polar Surface Area	Molecular Species
286.7	286.0509	2.84	1	61.69	NEUTRAL

ChEMBL Assays for Compound CHEMBL568

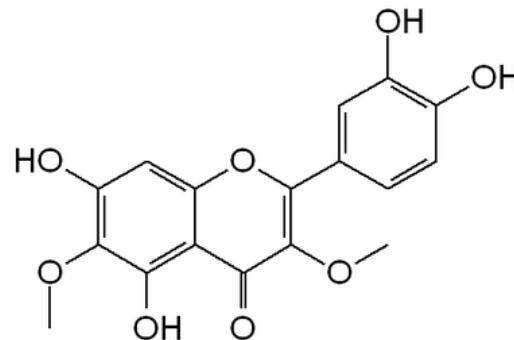


Sample ChEMBL drug “report card” excerpt

Chemical similarity may suggest similar bioactivity



Fisetin



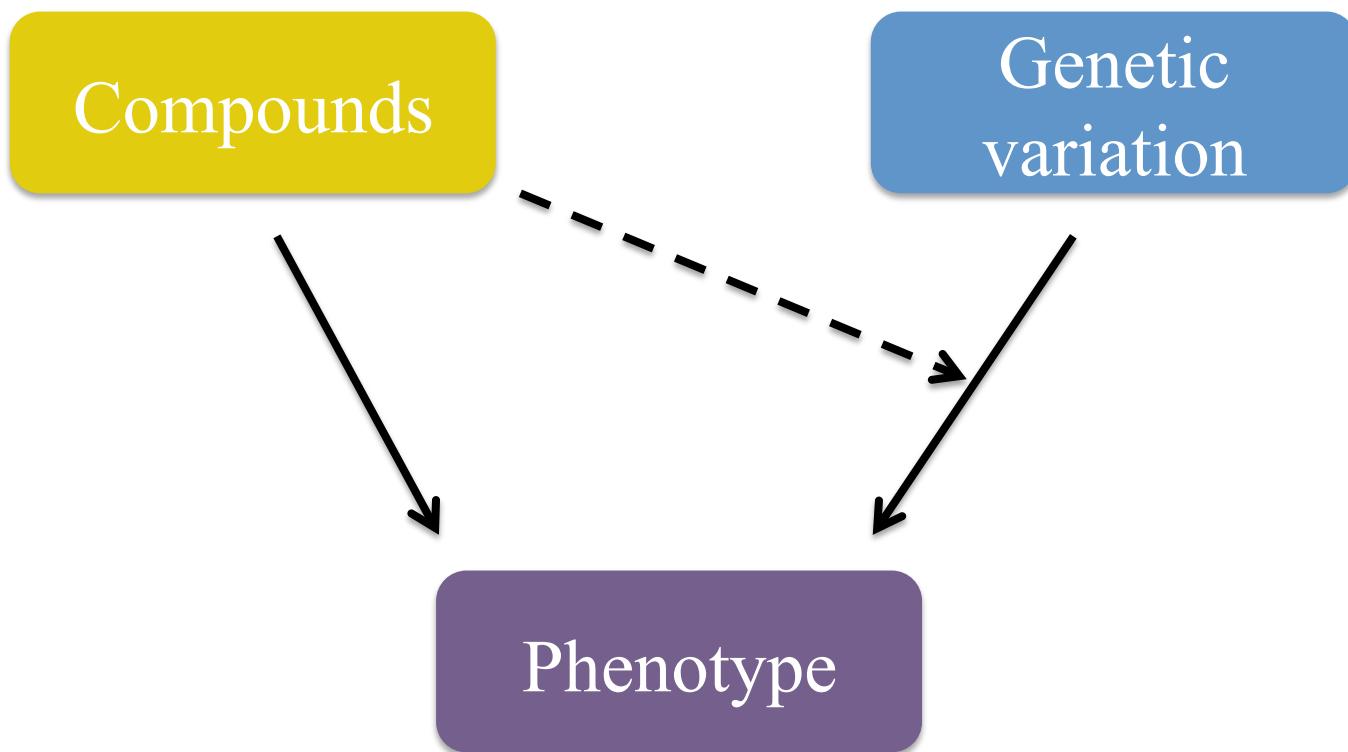
Axillarin

Tanimoto similarity score = **0.82**

- Comparison of chemical “fingerprints” generates a Tanimoto similarity score
- There is a certain association between chemical similarity and likelihood of similar bioactivity (estimates vary widely as to the strength of this correlation)

Gene by environment interactions

- These compounds modify the relationship between gene variants and phenotype

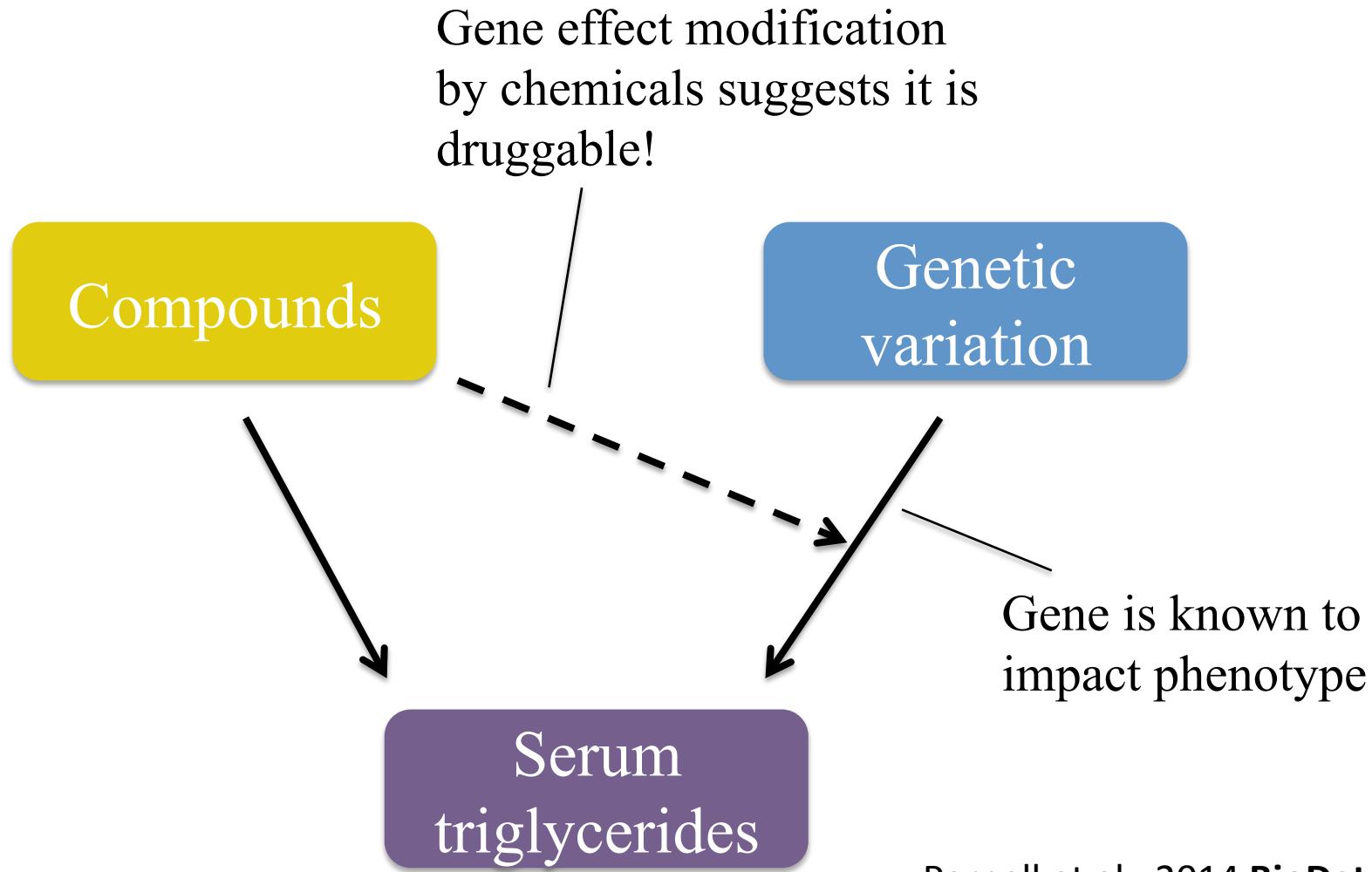


Objective

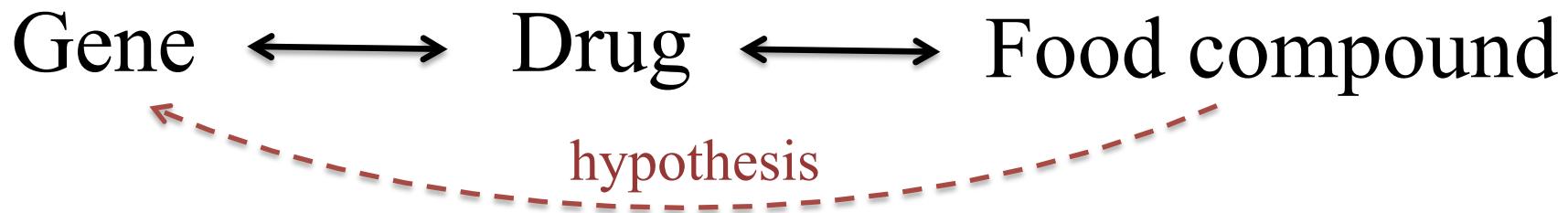
Develop a workflow to generate new GxE hypotheses and identify food compounds/foods that may have an impact on cardiometabolic phenotypes of interest

1. Select a gene set related to a phenotype of interest
2. Look for drugs that target those proteins
3. Generate a list of food compounds similar to those drugs

Gather triglyceride-based genes from CardioGxE gene set



Database relating TG-based drugs and food compounds



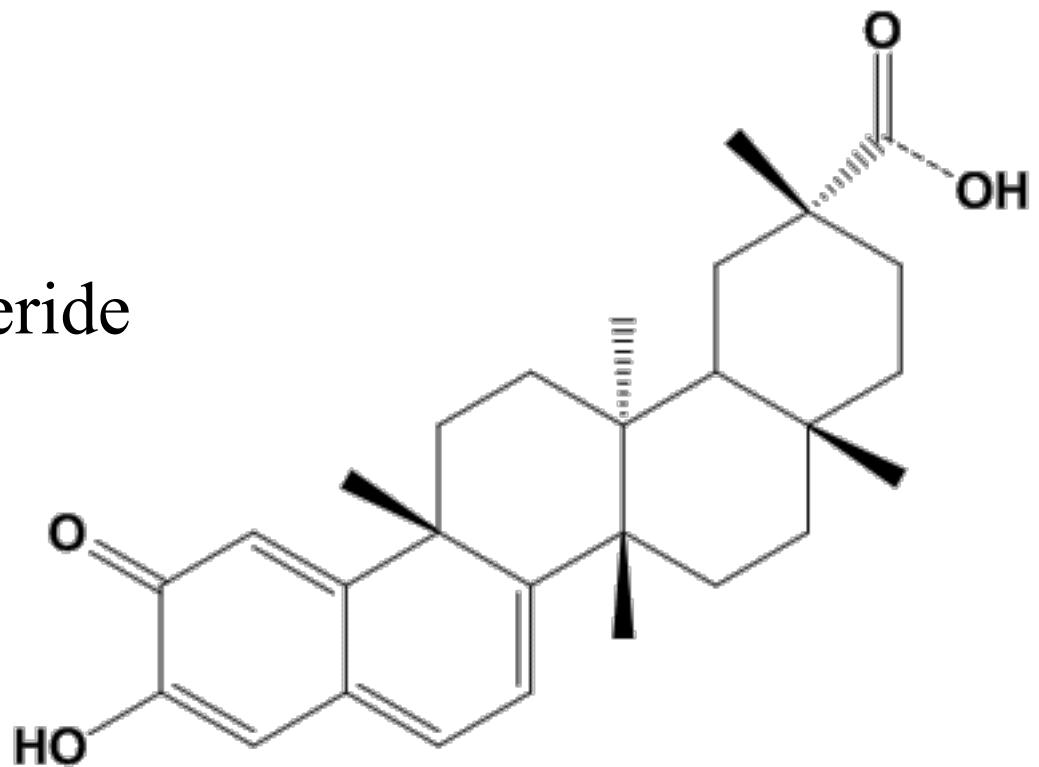
- 1/3 of the triglyceride GxE genes were able to be connected to food compounds
- Some of these links already have experimental evidence, some do not

Method Verification -- Experimental

Drug: Celastrol

Gene target: TNF

Shown to lower triglyceride
levels in mouse, rat,
and rabbit models



Celastrol

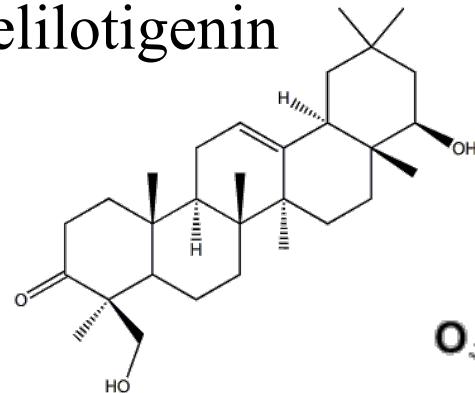
Kim et al., 2013 PLoS One

Zhu et al., 2014 Int J Clin Exp Med

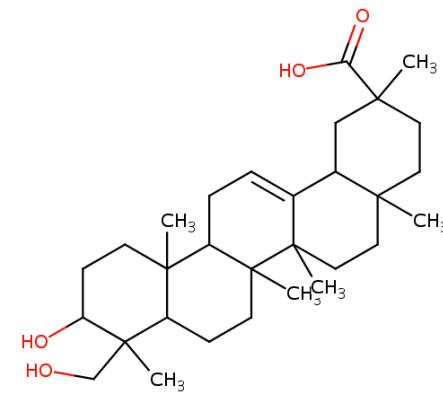
Wang et al., 2014 Eur J Pharmacol

Method Verification -- Experimental

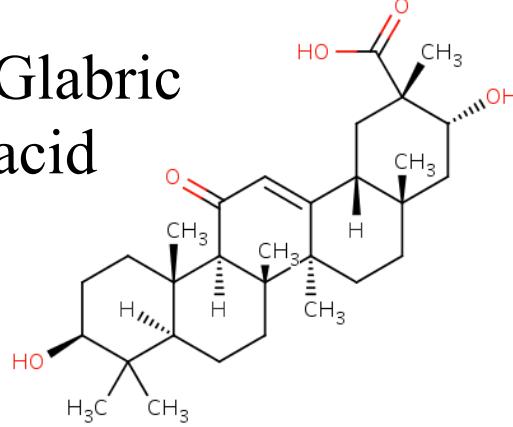
Melilotigenin



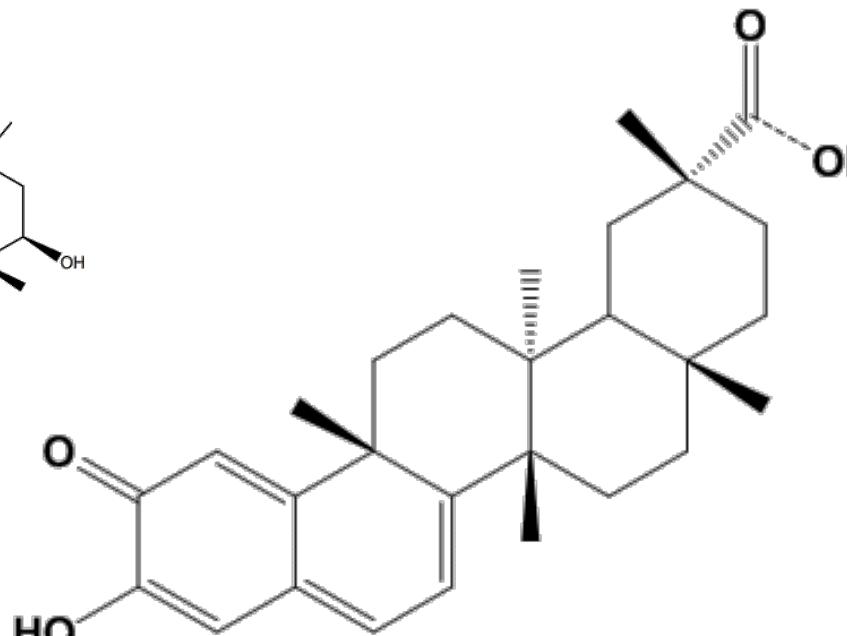
Azukisapogenol



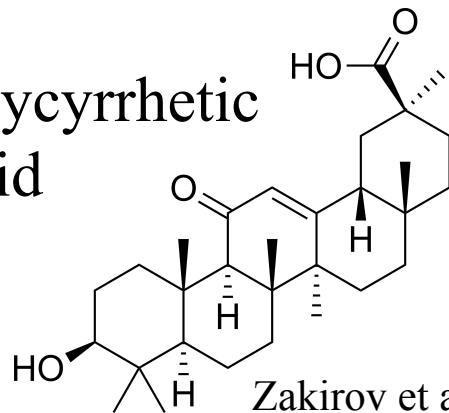
Glabric acid



Celastrol



Glycyrrhetic acid



Maruyama et al., 2008
J Clin Biochem Nutr
(azuki bean juice)

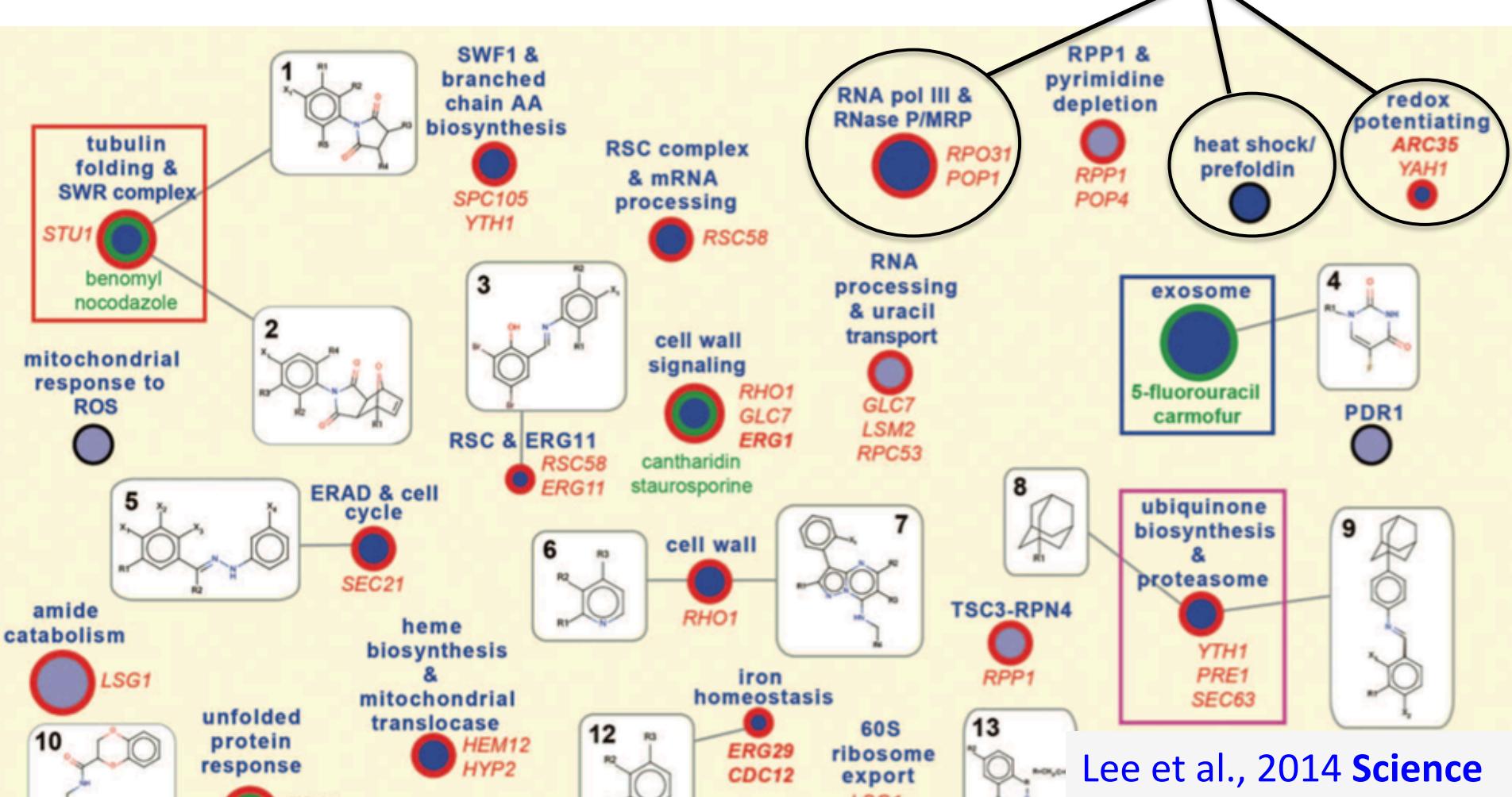
Experimentally
shown to lower TG!

Zakirov et al., 1996 **Eksp Klin Farmakol**

Method Verification – Yeast Dataset

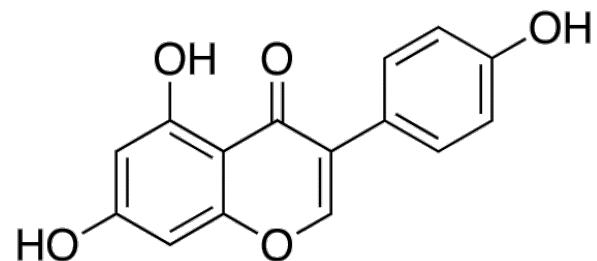
Chemical perturbation of haploinsufficient yeast cell lines

Fitness signatures



Method Verification – Yeast Dataset

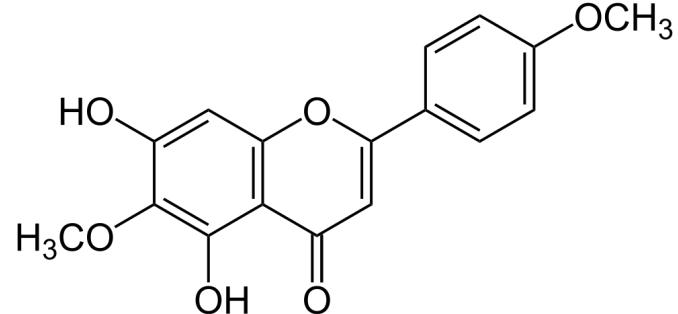
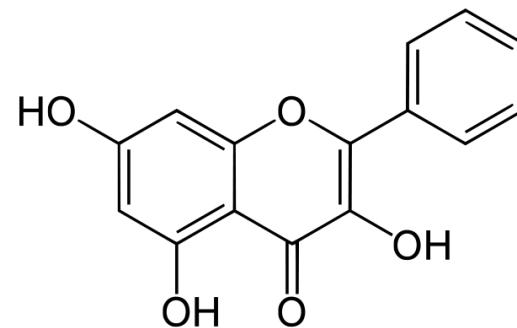
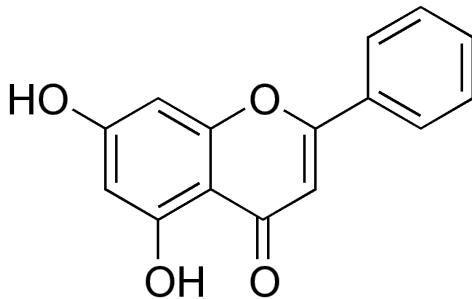
Drug: genistein (target: PPARG)



✓ 3 similar food compounds (chrysins, galangin, pectolinarigenin) found in one response

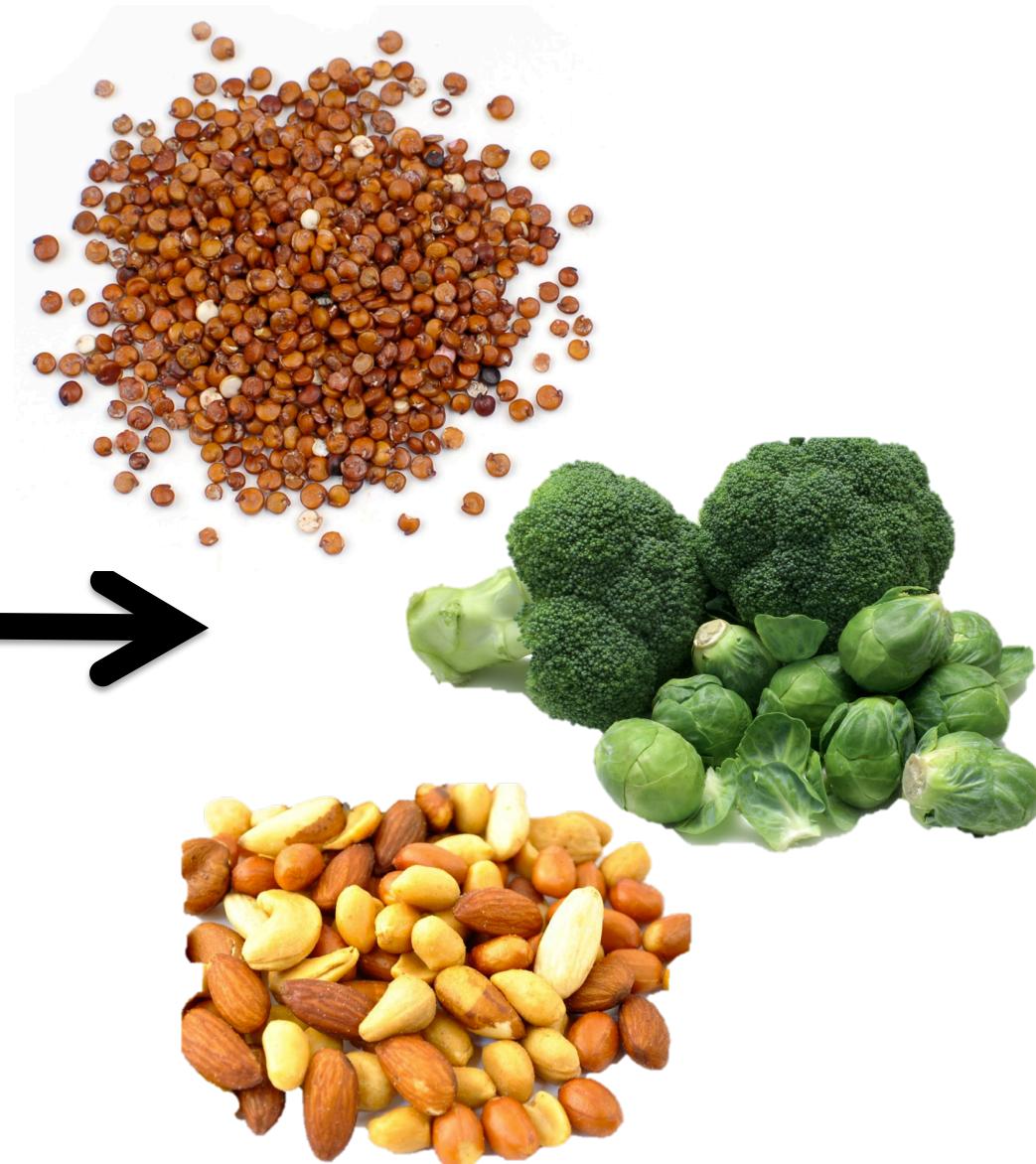
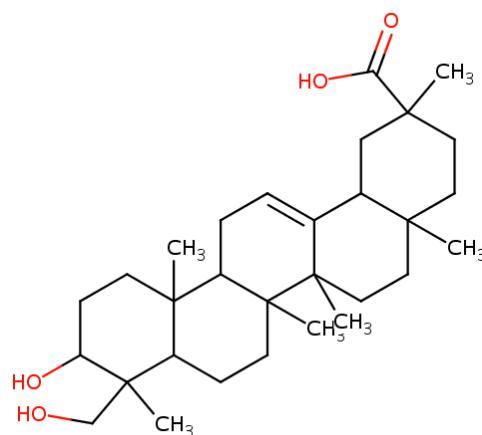
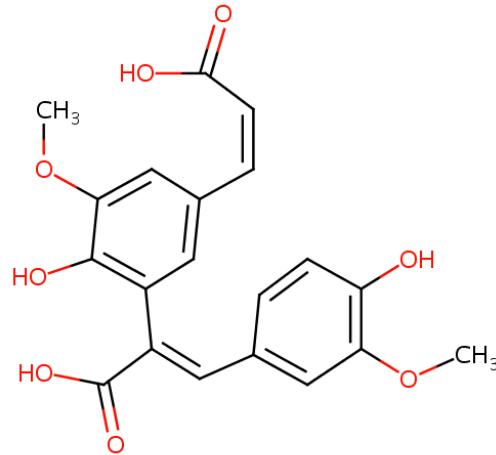
signature: **RPP1 & pyrimidine depletion**

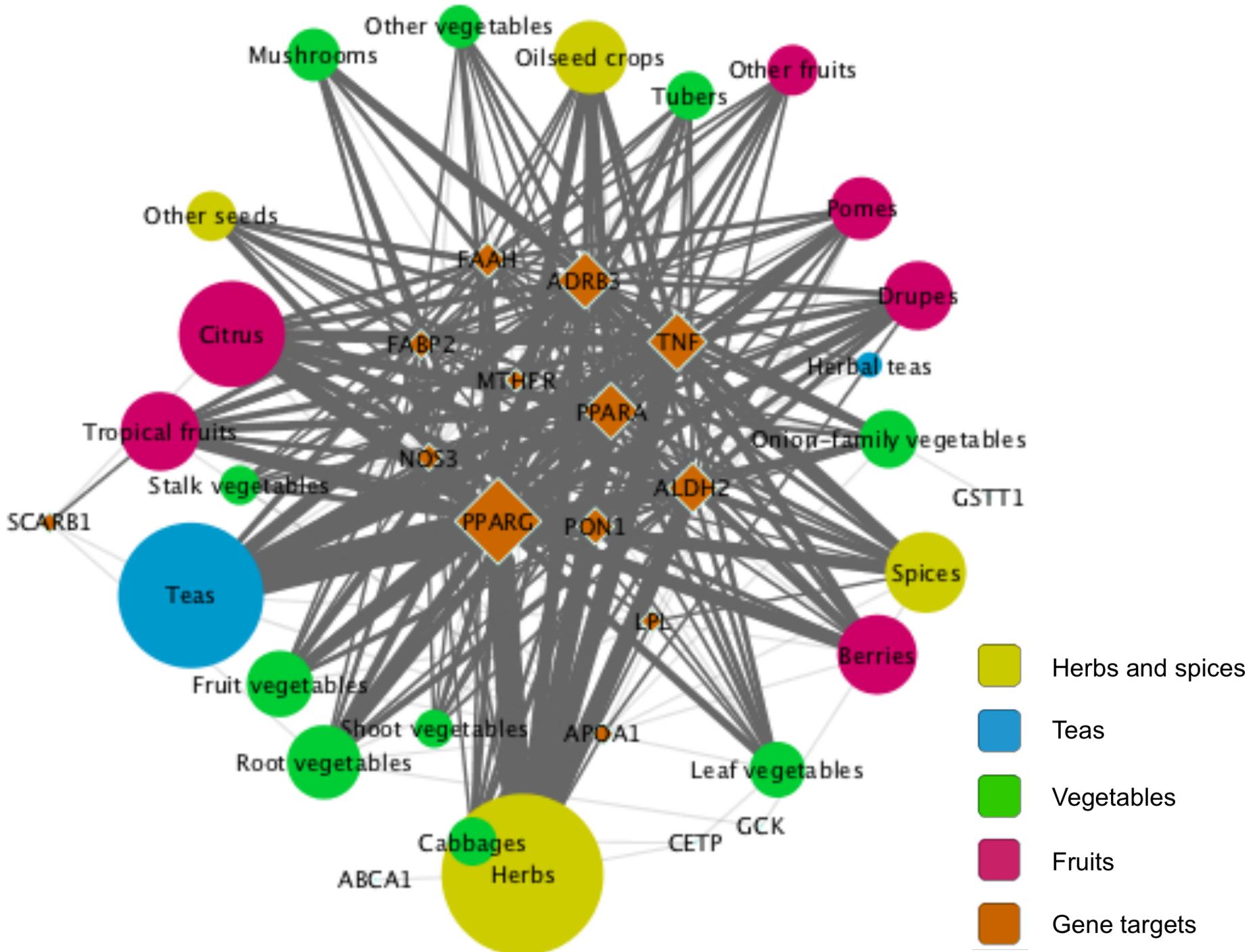
✓ Pyrimidine metabolism has been linked to serum lipid levels! (Le et al., 2013 J. Lipid Res.)



Le et al., 2013 J. Lipid Res.

Practical Implications





Future Directions – Similarity Threshold Optimization

Accuracy

Discovery



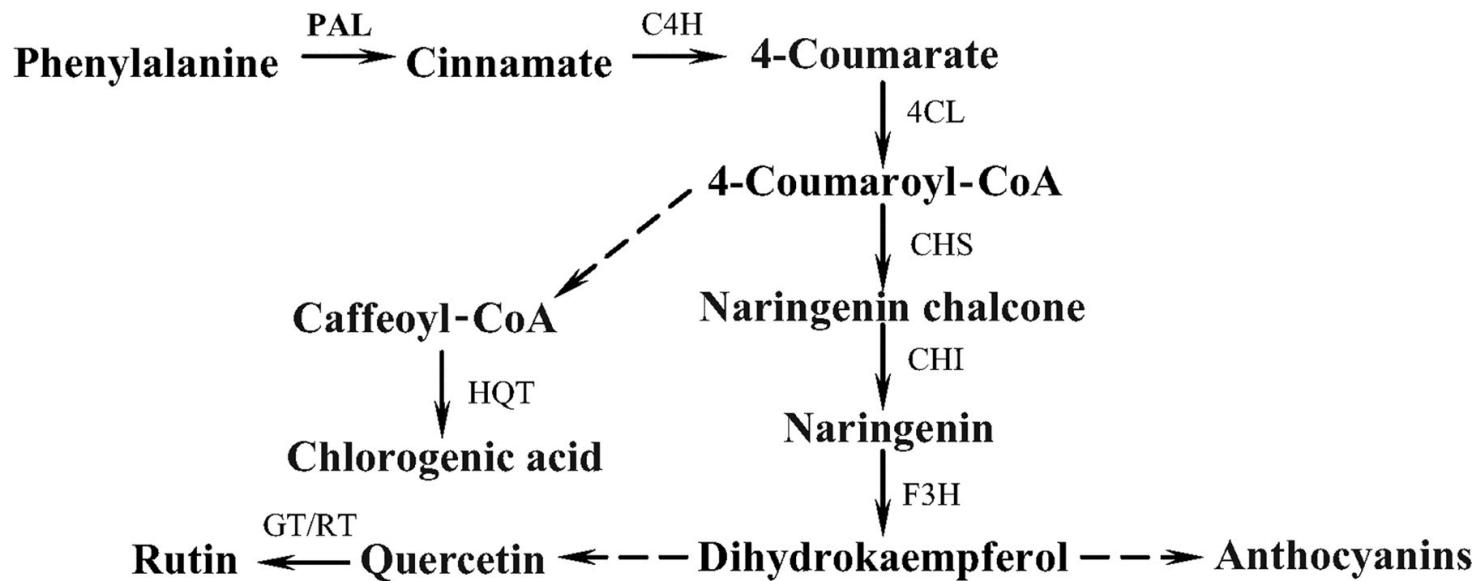
Future Directions – Food Compound “Ranking System”

How much effect is a given compound likely to have on triglyceride levels?

- Strength of its “partner” drug in modulating target protein activity
- Magnitude of effect of drug in clinical trials
- Level of chemical similarity with that drug

Future Directions

- New initial gene sets
 - Alternate cardiometabolic phenotypes
 - GxE genes for a specific environmental factor
- Incorporate human and microbial metabolites



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