

# Grapefruit and the Metabolic Syndrome

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Kinexum-Pennington Translational

Grand Rounds - 1/17/13

# The Grapefruit Diet

## “Fat-Burning Enzyme”

- The “Grapefruit diet” (also known as the Hollywood Diet) was originated in the 1930’s, became popular in the 1970’s and was reborn as the “10-day, 10-lb off” diet in the 1980’s
- It has been called the Mayo Clinic Diet, but has no connection to the Mayo Clinic
- Consists of hard-boiled eggs, green vegetables and melba toast with  $\frac{1}{2}$  grapefruit with each meal (585 kcal/d)

# Does Grapefruit Help Weight Loss?

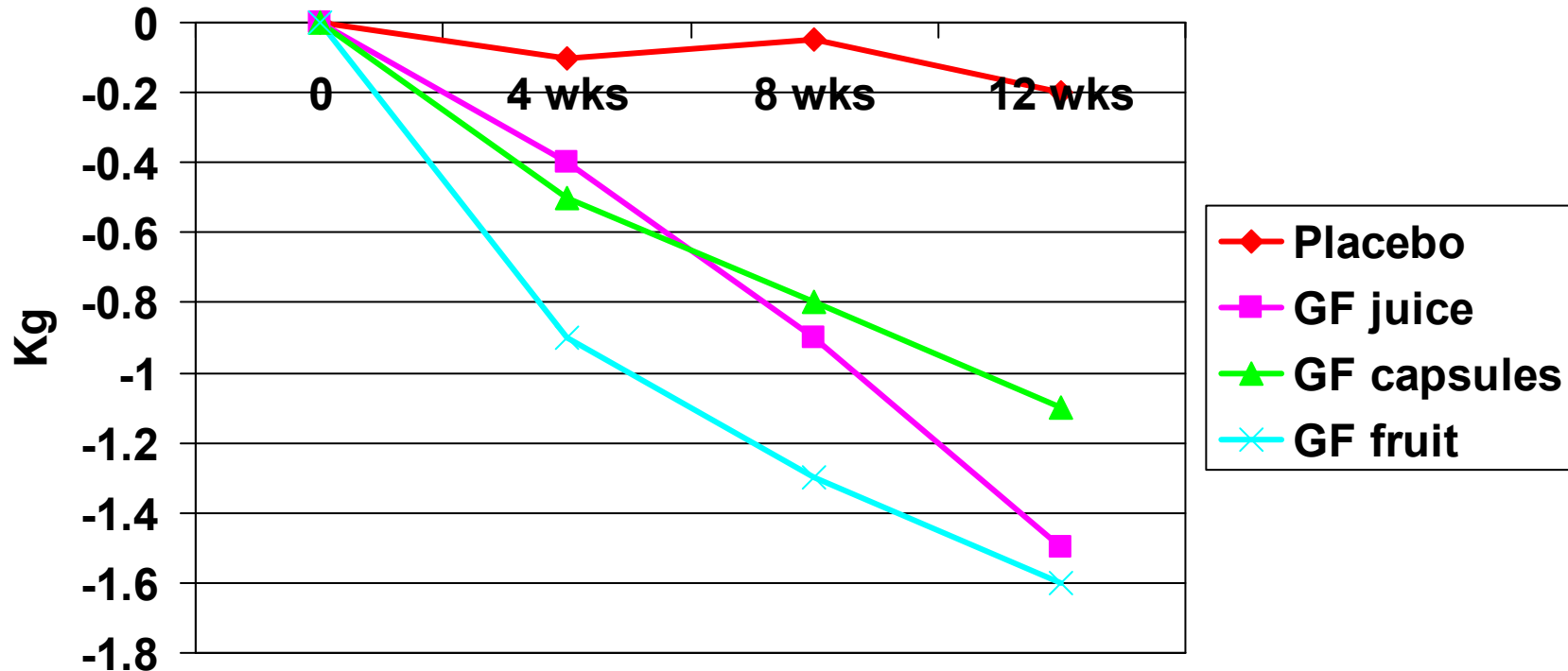
- Florida Citrus Growers funded a trial at Scripps Clinic with Pennington collaboration.
- 100 obese subjects were randomized to:
  - 1. 207ml apple juice and placebo capsule
  - 2. 207ml apple juice and Grapefruit capsules
  - 3. 237ml grapefruit juice and placebo capsule
  - 4. ½ grapefruit and placebo capsule
- Taken 3 times a day for 12 weeks

# Study

- Body Mass Index (BMI) 30 - 40 kg/m<sup>2</sup>
- Controlled hypertension ok
- No diabetes or cholesterol medications
- Continued their usual diet
- Walked 20-30 minutes 3-4 times per week
- Fasting chem panel 0 and 12 weeks
- Fasting & 2hr post 75gm glucose load - glucose & insulin.

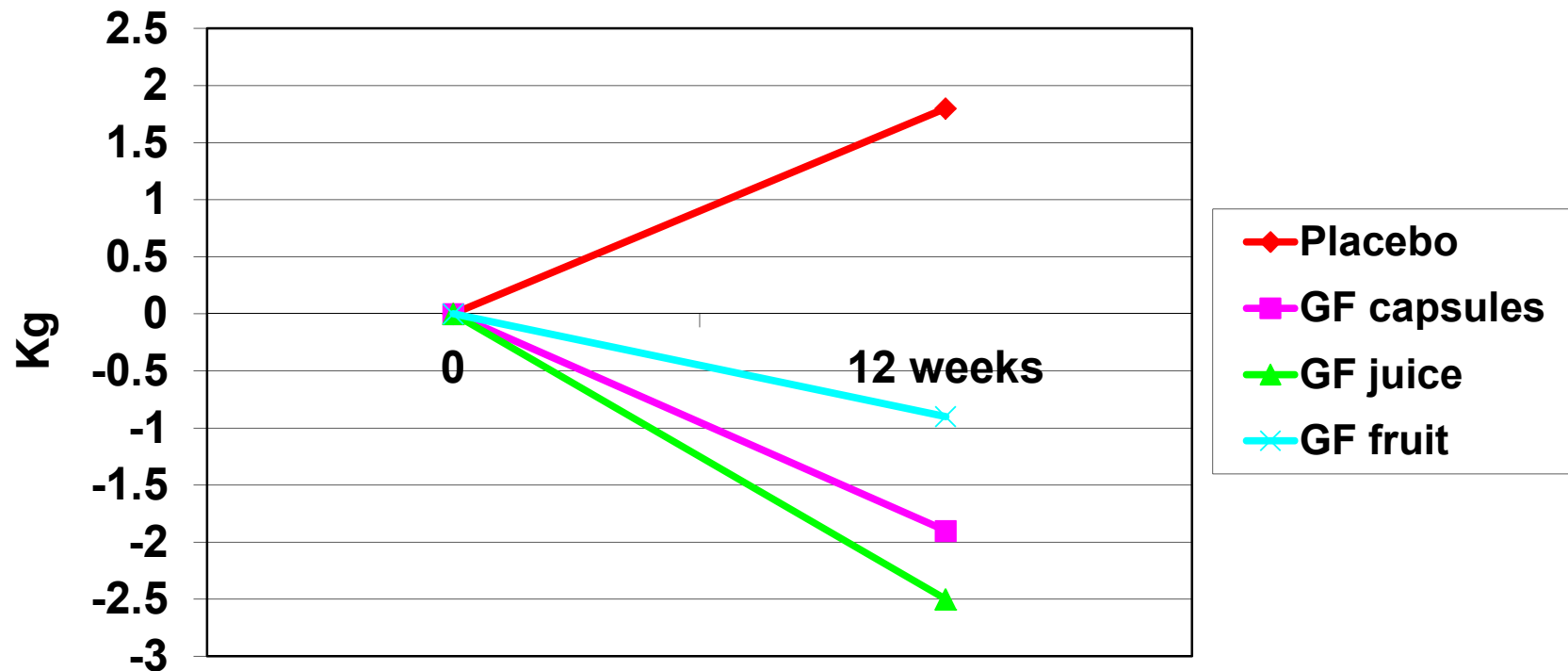
# Weight Loss with Grapefruit

Weight Loss: Grapefruit > placebo (p<0.05)



# Grapefruit and Weight Loss with the Metabolic Syndrome

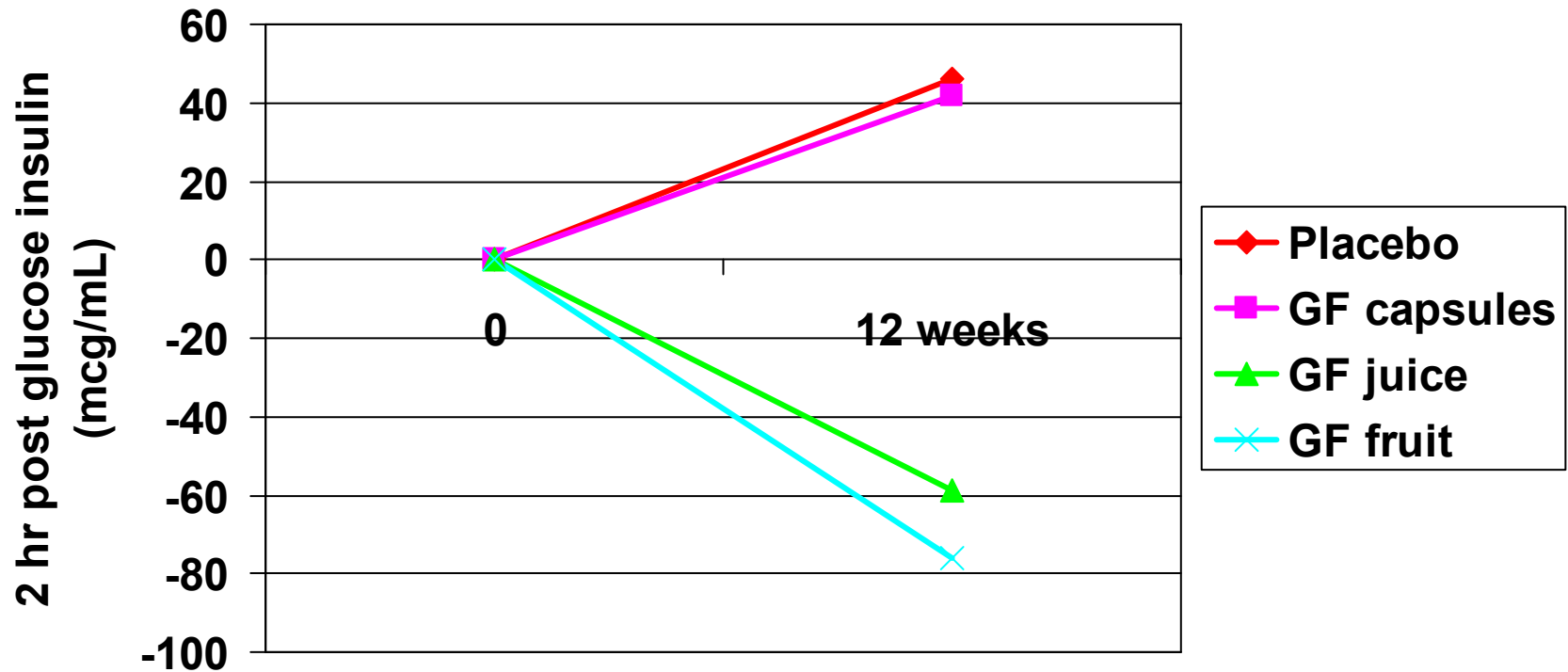
Wt loss: All greater than placebo (N=34, p<0.05)



Fujioka K et al. Journal of Medicinal Food, 2006

# Grapefruit Reduces Post-Glucose Insulin

2 hr pc glucose: grapefruit < placebo (p<0.04)



Fujioka K et al. Journal of Medicinal Food, 2006

# Grapefruit Inhibits Drug Metabolism Through Cytochrome P450-3A4 & 1A2

- Sedatives:
  - Alprazolam
  - Diazepam
  - Midazolam
  - Triazolam
- Hypertension medications:
  - Amlodipine
  - Diltiazem
  - Felodipine
  - Nicardipine
  - Nifedipine
  - Nisoldipine
  - Nimodipine
  - Verapamil
- Cholesterol medications:
  - Atorvastatin
  - Lovastatin
  - Simvastatin
- Itraconazole
- Tegretol
- Buspirone
- Carvedilol
- Cyclosporine
- Fexofenadine
- Losartan
- Quinidine
- Zoloft



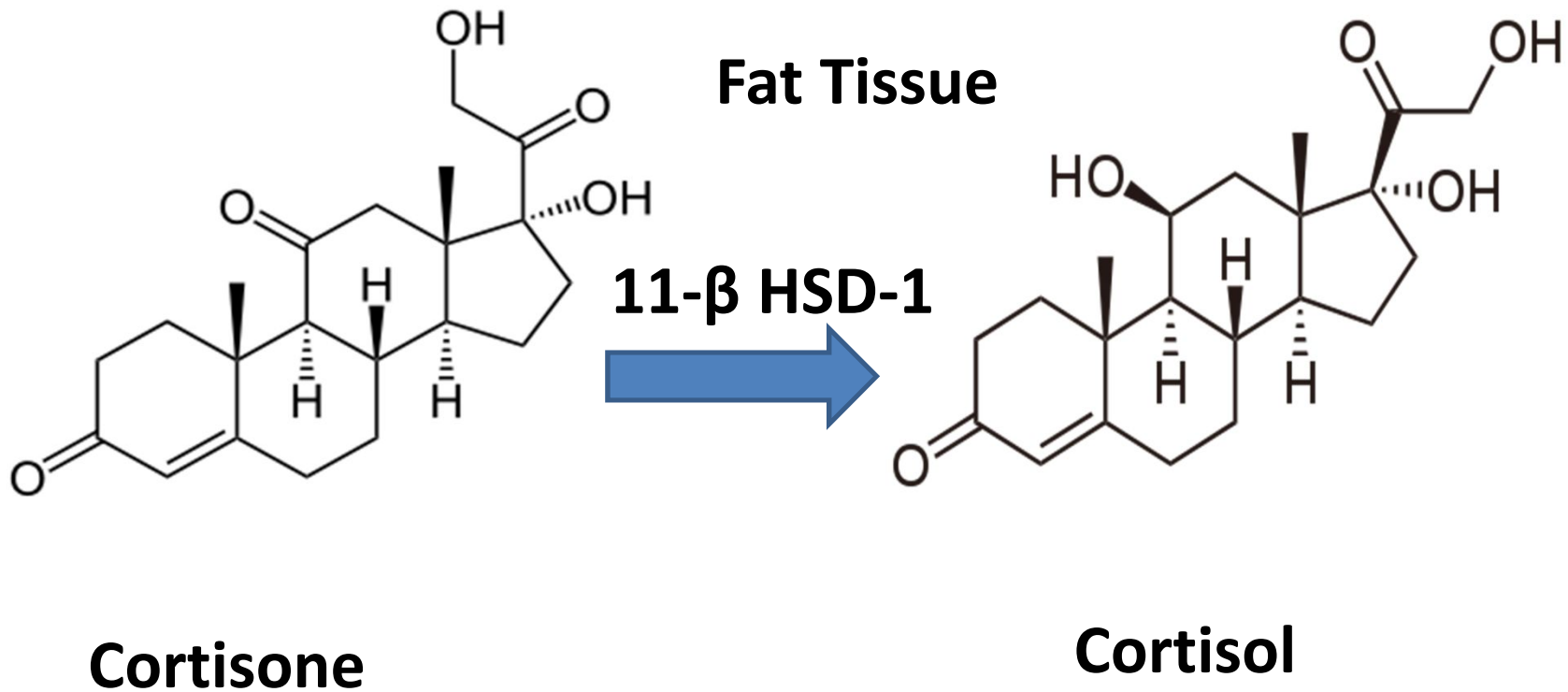
# Metabolic Syndrome

- The metabolic syndrome (insulin resistance, dyslipidemia, HTN and visceral obesity) resembles Cushing syndrome (high cortisol)
- Cortisol is normal in metabolic syndrome
- 11- $\beta$  hydroxysteroid dehydrogenase-1 (HSD-1) which converts inactive cortisone to cortisol in fat tissue is elevated in obesity
- Mice overexpressing 11 $\beta$ HSD-1 have metabolic syndrome and the KO resist it.

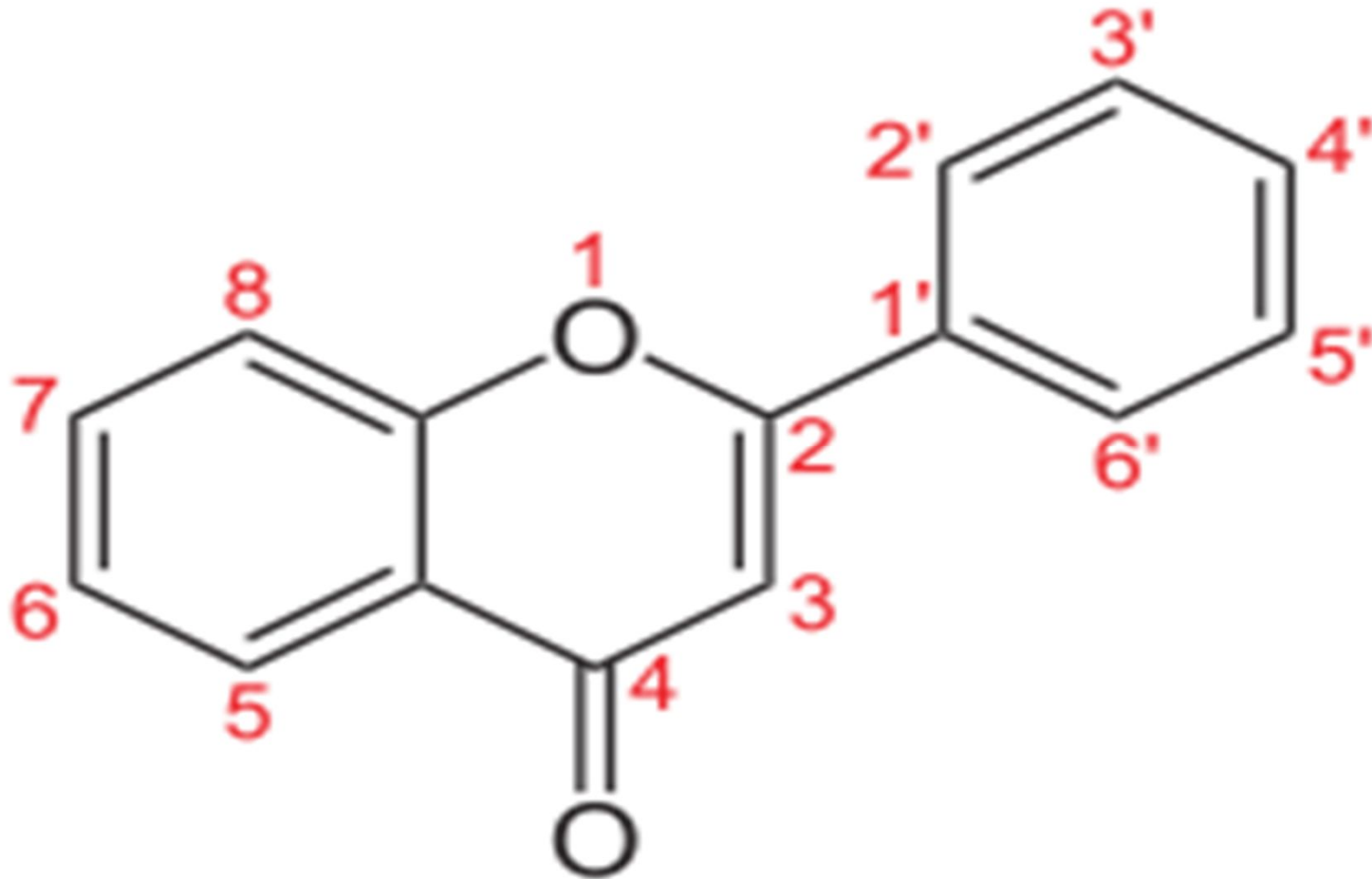
# Grapefruit Diet - Potential Mechanism

- The citrus bioflavonoids, including grapefruit, contain a flavanone-glycoside called naringin
- Naringin is converted to the flavanone naringenin by gut bacteria
- Flavanones inhibit 11-beta hydroxysteroid dehydrogenase-1 selectively
- 11-beta hydroxysteroid dehydrogenase-2 acts in the kidney increasing aldosterone to cause fluid retention and HTN (licorice).

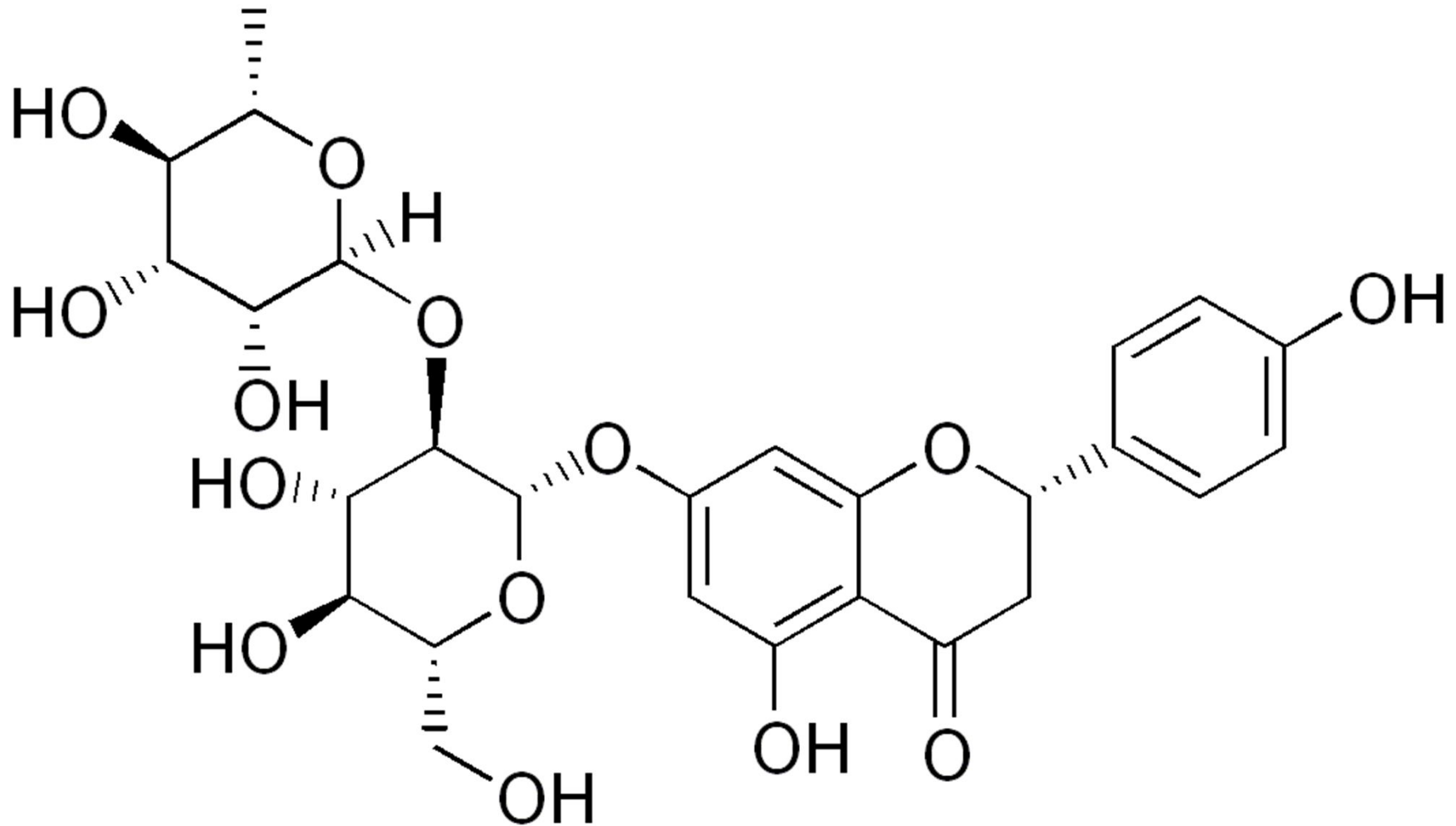
# 11-Beta HSD-1 in Fat Tissue



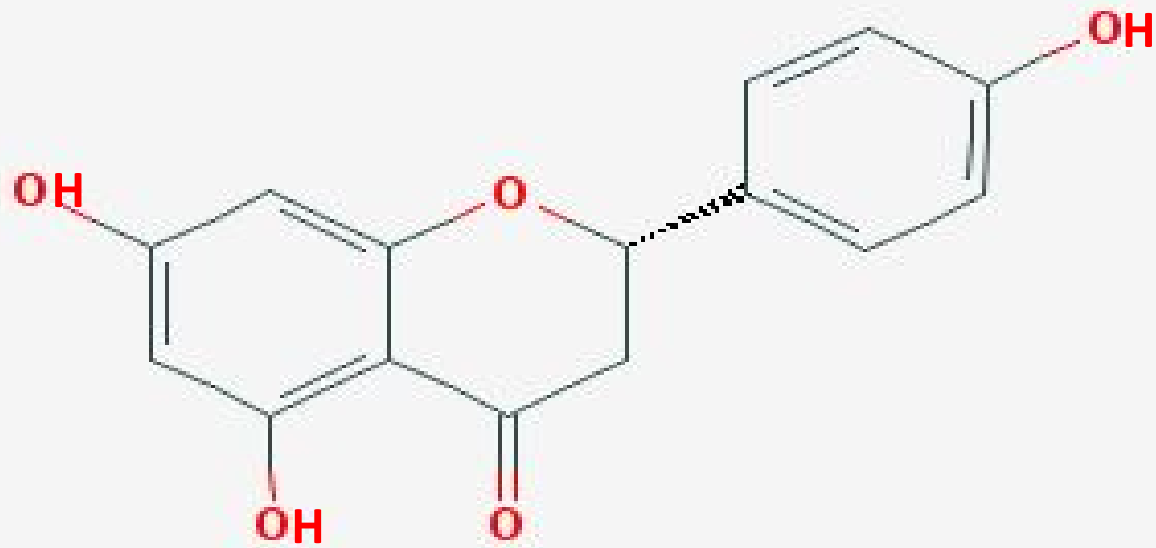
# Flavanone



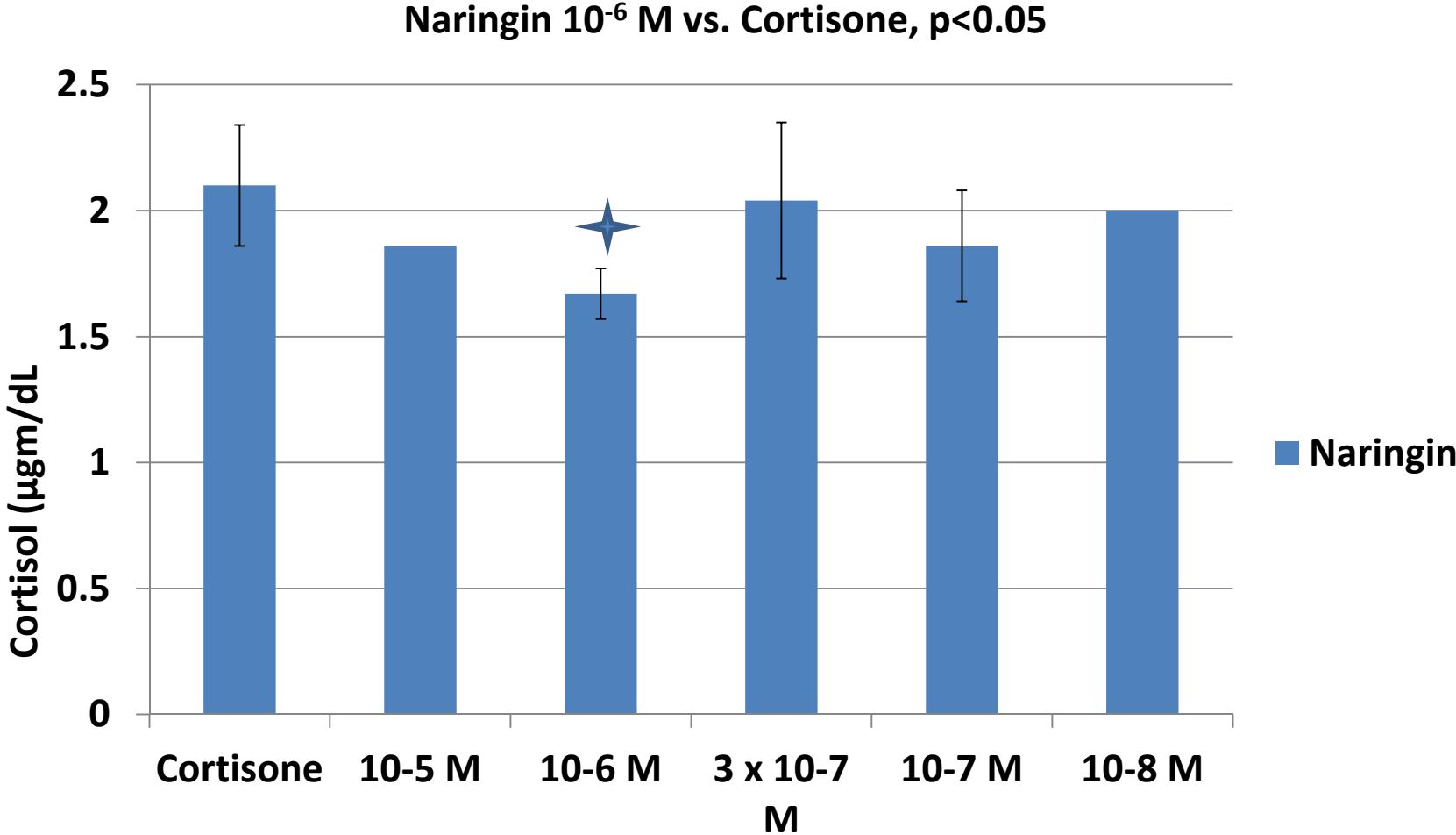
# Naringin – A Flavanone Glycoside



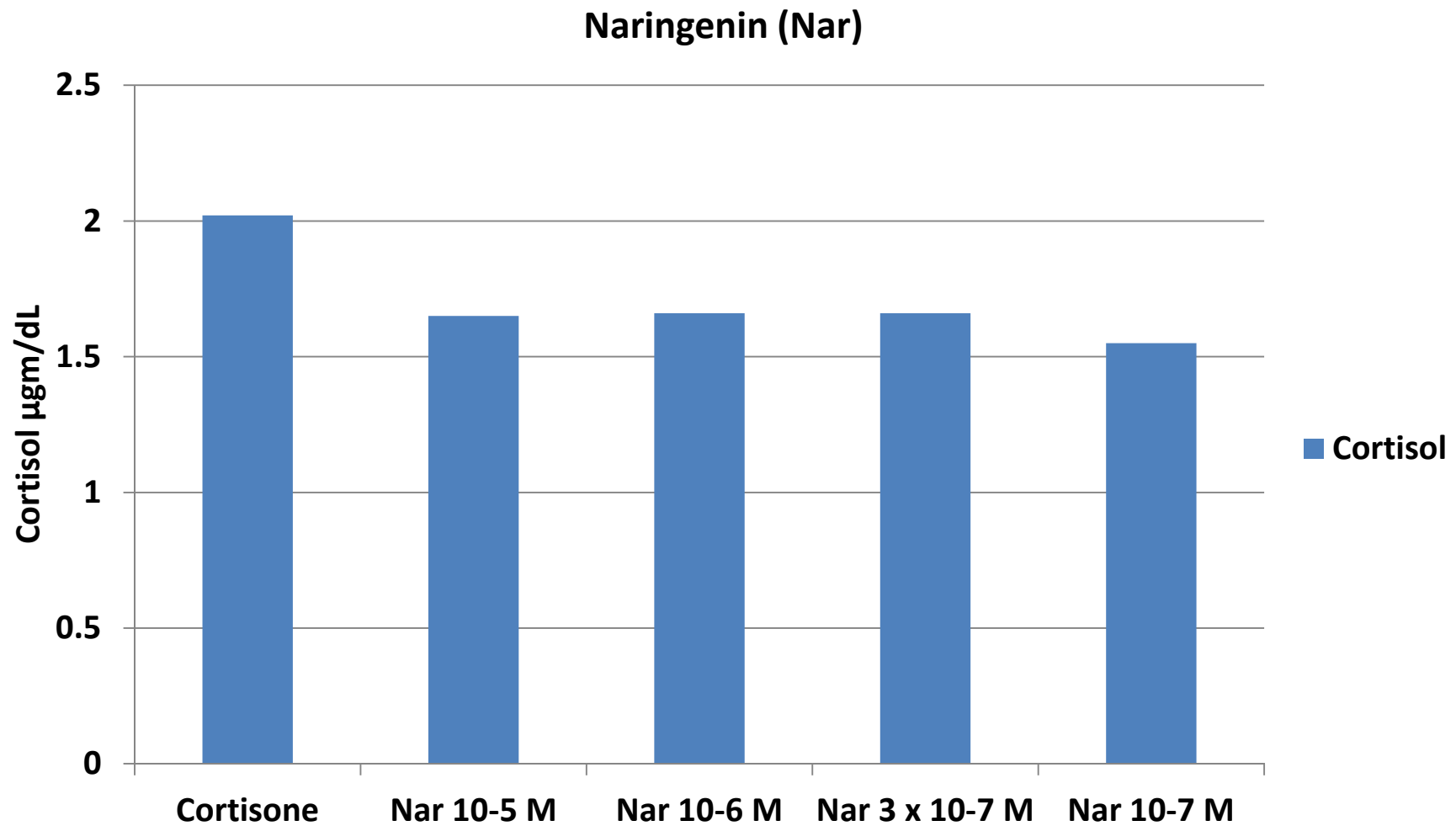
# Naringenin



# Naringin Inhibits 11 $\beta$ HSD-1 at 10<sup>-6</sup> M



# Naringenin Inhibits $11\beta$ HSD-1





# Making a Product

- Naringin and Naringenin are poorly soluble
- Solution: steviol glycosides (SG) have significant solubilizing properties (Sweetener sold as Truvia)
  - SG solubilized >50 small lipophilic molecules in >20 chemical classes
  - Solubility increased by a minimum of 2-fold (amiodarone) to as high as a million-fold (propofol)
- Mechanism of action: in aqueous media SG forms drug-SG nano-particles – likely nano-micelles - averaging 5-10 nm in diameter.
- Patents: LSU has filed 3 patent applications to protect this discovery

# SG-nanoencapsulated curcumin (ENCAP-CUR)



Figure 1. SG-solubilized curcumin in water solution can be spray-dried to SG-encapsulated powder and completely reconstituted in water. To make a 10 mM stock solution of curcumin, 16% w/v SG is needed compared to the same 10 mM stock by absolute DMSO.

# Advantages to the Solubilized Product

- SG is a food and so is citrus fruit. The peel of the fruit contains naringin too and the peel is used in food like marmelade jam. Orange peels are orange juice production waste.
- Solubility is essential to a product and other solubility systems (cyclo-dextrins) are drugs
- A medical food needs to be given under medical supervision, which is good for this product due to CYP-450 inhibition.

# Future Steps

1. Make extract of grapefruit, orange or lemon
2. Standardize the extract to its naringin and naringenin content.
3. Solubilize with SG and freeze-dry to powder.
4. Pharmacokinetic study of the powder testing the blood levels of naringin and naringenin over a range of doses to identify  $T_{max}$ ,  $C_{max}$  and half-life using Mass Spec at PBRC.

# Clinical Trial

- Once the optimal dose and frequency of dosing is established, one could use the oral dose of SG solubilized naringin that gave the same levels of naringin and naringenin that were optimal in the assay to inhibit 11-beta HSD-1 and compare against a placebo the effect on weight loss and insulin resistance in patients with the metabolic syndrome.

# Conclusions

- The solubilized standardized grapefruit extract at dose to optimally inhibit 11- $\beta$  HSD-1 may become a patent-protected medical food to treat metabolic syndrome with weight loss.
- Collaborators:
- Ken Fujioka – Scripps Clinic
- Zhijun Liu – LSU Ag Center

