



A lemon A Day Keeps The Cancer Away

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WELLNESS



The Art & Science

of

Promoting Health

Preventing Diseases

Protecting from Health Hazards



THE UNIVERSITY
OF ARIZONA

Food as Medicine


Biomedical Nutrition Research

Improving Human Health through Innovative
Nutrition Interventions

Food's Natural Ability to Manage and Prevent
Chronic Disease




Why Use Food as Medicine ?

- Cheaper than pharmaceutical drugs
 - Offers variety
 - Completely able to be personalized
 - Low incidence of side effects
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Food as Medicine

People want to know the relationship between what they eat and health

Need for information about


- Antioxidants
 - Phytochemicals
 - Nutraceuticals
 - Nutrigenomics
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Antioxidants

Oxidation


- Natural process in the body
- Produces reactive substances known as free radicals that cause damage to cells

Antioxidants

- Natural components present in fruits and vegetables
 - Stabilizes free radicals before they cause harm
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Phytochemicals & How They Work

Non-nutritive plant chemicals that have protective or disease preventive properties

- Antioxidants
 - Antibacterial
 - Stimulation of detoxifying enzymes
 - Inhibit cancer cell proliferation
 - Hormonal action
 - Antidepressant
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Nutraceuticals

- Supplements made of isolated dietary compounds
- Fortified processed foods

Nutrigenomics

Genes load the gun, but environment pulls the trigger

Gene- Nutrition interaction

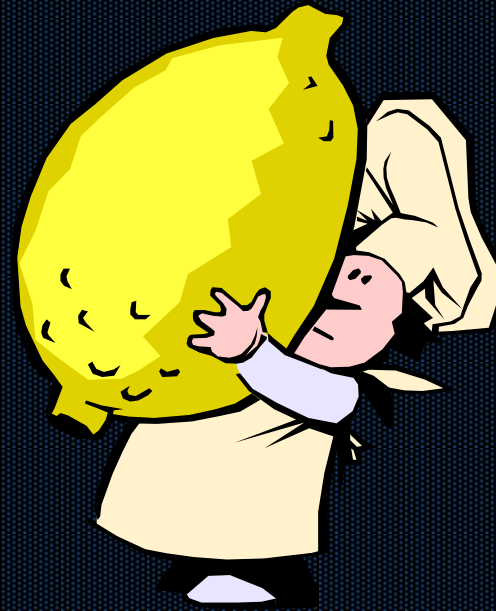
Study of how different foods may interact with specific genes to prevent chronic diseases



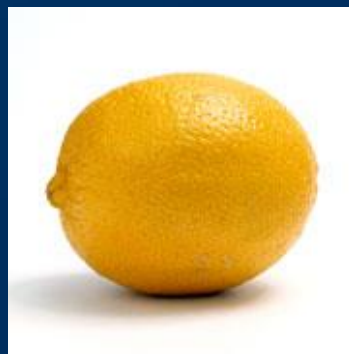
My Story



Citrus Peel, d-Limonene and Cancer Prevention



D-limonene content of citrus peel oil



Lemon: 75%
(γ -terpinene: 7.5%)



Orange: 95%

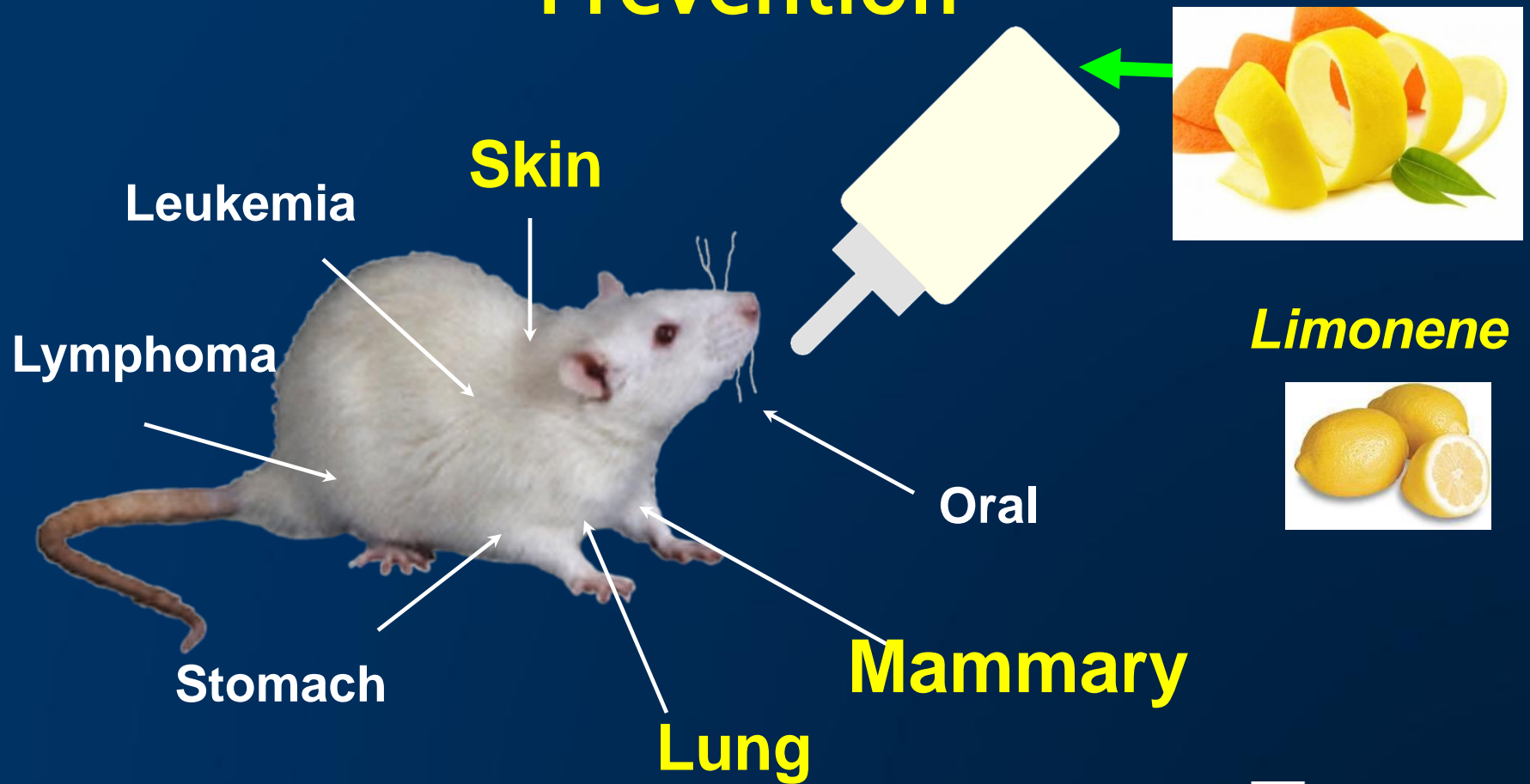


Kumquat: 97%



Mandarin: 87%
(γ -terpinene: 7.5%)

Limonene Intake and Cancer Prevention



D-Limonene: Mechanism of action

- **Immune-enhancing**
- **Anti-inflammatory**
- Anti-oxidant
- Cancer cell death
- Anti-hormone

Metabolism

- Pharmokinetic study in rats found 43% of d-limonene is available orally
- Not all d-limonene can be accounted for in blood serum metabolites
- d-limonene preferentially distributes to fatty tissues

Haitao Chen et al *Journal of Pharmaceutical and Biomedical Analysis* 17 (1998) 631–640

Pamela Crowell, et al. *Cancer Chemother Pharmacol* (1994) 35: 31-37.

Tumor Suppression in Humans



- Findings:
 - A **breast cancer** patient (maintained partial response for 11 months) on 13g/day
 - > 50% reduction in the size of supraclavicular lymphadenopathy
 - the widespread lytic bone metastases showed ↑ sclerosis associated with ↓ pain (after 3 months).
 - 3 patients with **colorectal** carcinoma had prolonged stable disease for longer than 6 months (800 mg or 1.6 g / day).

(Vigushin DM et al., Cancer Chemother Pharmacol, 42:111-17; 1998)

How about Cancer Prevention?

How much do we need?

Can we get it in our diet?



Our studies

- D-Limonene database
- D-Limonene Assessment tool (ACQ)
- Skin Cancer (SCC): 34% decrease risk
- Bioavailability
- Feeding study (lemonade)

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- Topical Study (cream)
 - Pre-surgery study (Pill)
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d-Limonene Database



Lemonade

d-limonene (mg/oz)

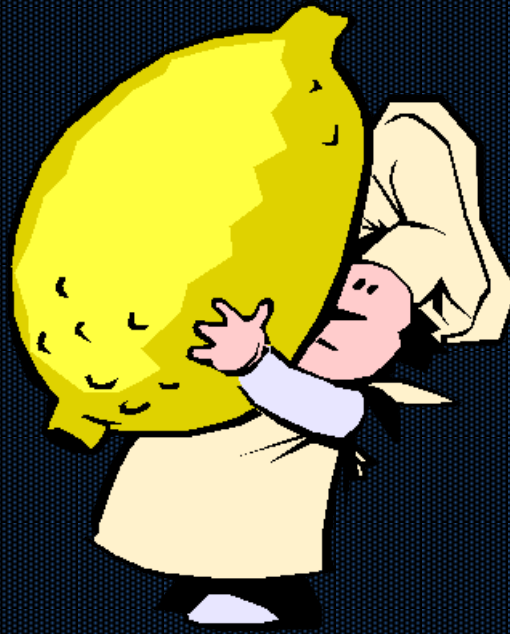
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- **Fresh (Mediterranean)** **15 – 31**
 - **Citrus juices in the market** **0 -2.8**
 - Sources, packaging, and preparation practices have major influences on d-limonene level.
 - Hakim et al., Journal of Food Compositions and Analysis 2000; 13 (4):329-336.

Citrus Study: Skin Cancer (SCC) 2000

- Adults (AZ) with the highest citrus juice intake (2 cups per day) were consuming **20- 50mg** d-limonene per day.
- Individuals reporting some citrus peel use (163/470) were consuming **60-100 mg** d-limonene per day
- No association between citrus fruits or juices and skin SCC
- The most striking feature was the protection associated with citrus peel consumption (**34%** decrease risk)

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- **Hakim et al., Nutrition & Cancer. 37 (2), 43-50, 2000.**
 - **Hakim & Harris BMC Dermatology , 1:3, August 2001**

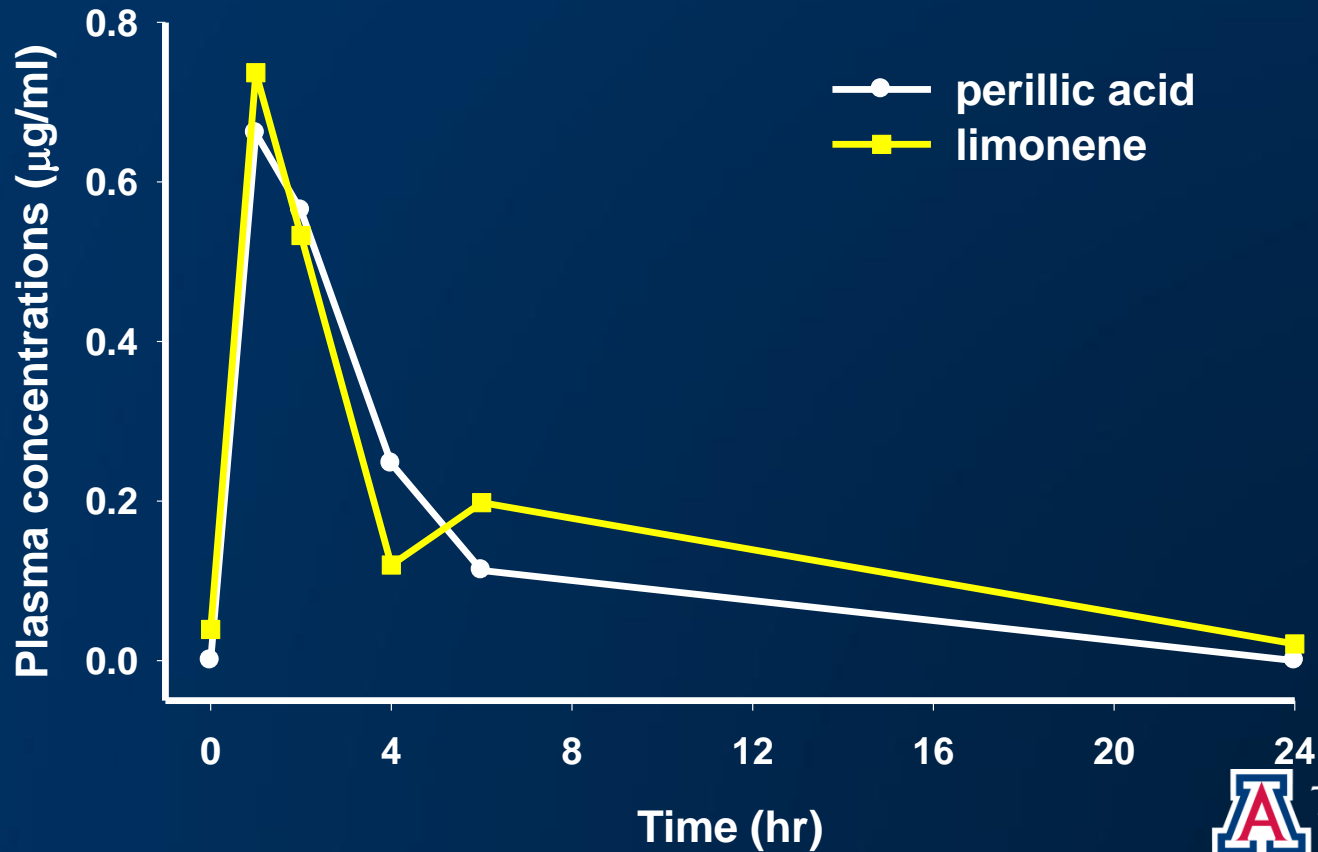
Bioavailability of Dietary d-Limonene "SEALS"



Bioavailability of perillic acid following a single dose of Mediterranean-style lemonade

- Healthy males and females (n=7)
- Consumed 40 oz of Mediterranean-style lemonade (contained 600 mg d-limonene) with a light breakfast
- Blood samples collected up to 24 hrs post dose
- Samples analyzed by reversed phase HPLC

Mediterranean Lemonade (0.6 gm limonene)



Hakim et al (2002)

- Four-week feeding trial in healthy adults
 - Mediterranean-style lemonade as the source of d-limonene
 - 40 oz lemonade every day
- Pre- and Post-intervention fat biopsies

It took
10 years



D-Limonene levels (ng/g) after 600 mg/day for 4 weeks (2010)

Patient	Fat Cells	Plasma	Fat/Blood Ratio
101-4	7,297	152	47.99
102-4	13,578	105	129.42
103-4	9,045	225	40.26
104-4	24,289	217	111.69
105-4	40,044	230	174.30
106-4	9,171	224	41.01
107-4	15,822	257	61.45

Plasma and Tissue Levels of d-Limonene and its Metabolites in Humans (1998)

- Intratumoral levels in two breast cancer patients
- Dose 13 g/day in capsules

D-limonene	<u>tissue/plasma</u>
Patient 1	5.52
Patient 2	1.91

CONCLUSION

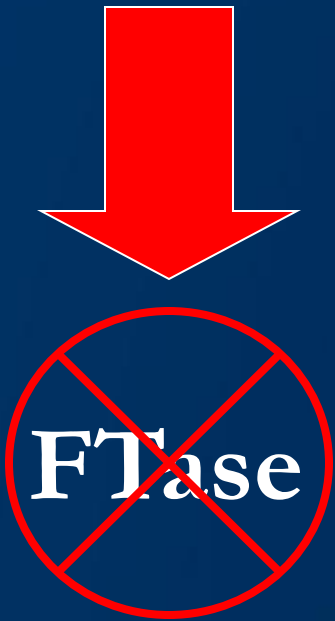
Limonene and its major metabolite are bioavailable following oral consumption of Mediterranean-style lemonade



Our studies

- D-Limonene database
- D-Limonene Assessment tool (ACQ)
- Skin Cancer (SCC): 34% decrease risk
- Bioavailability
- Feeding study (lemonade) 2000-2010
- Topical Study (cream) in 2012
- Pre-surgery study (Pill)

Pill or Lemonade?



**Immune-
enhancing**

Anti-hormone


**Anti-
inflammatory**

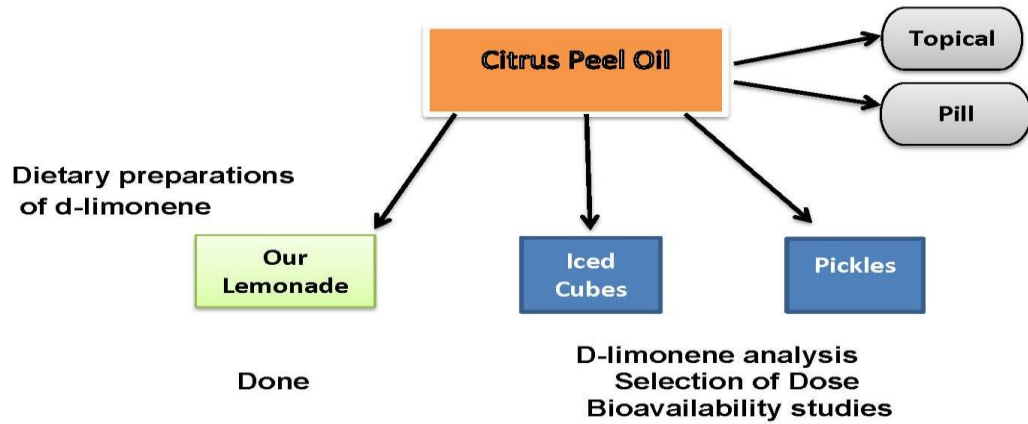
Apoptosis



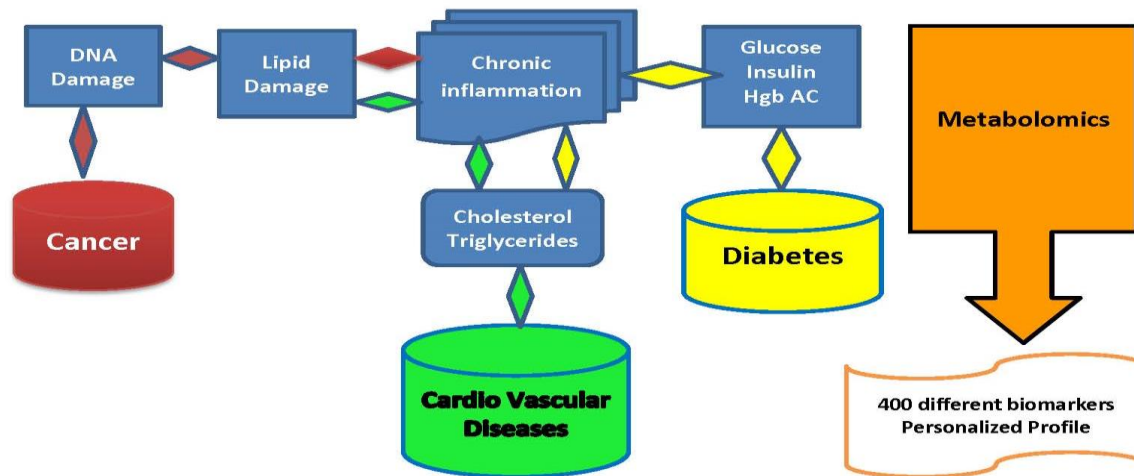
Antioxidant

Anti Diabetic Role

- Administration of D-limonene to **diabetic rats** for 45 days caused a significant reduction in the levels of lipid damage and an increase in the activities of antioxidant enzymes
 - Dietary d-limonene alleviates insulin resistance and oxidative stress-induced liver injury
 - It has insulin secretory and slimming effects (very beneficial to type 2 diabetics)
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Dietary Feeding Interventions
Different designs (amount and duration)
Biomarkers of different chronic disease (Diabetes, Cancer, CVD)

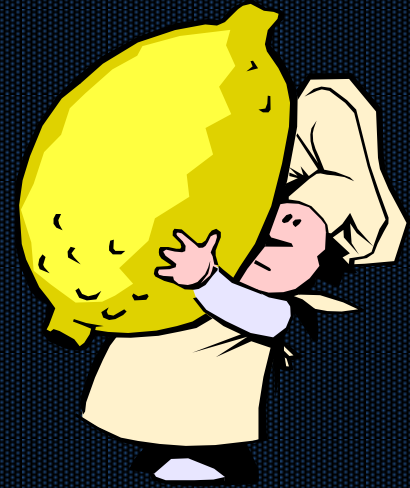


Research Goal

Ice cubes; Pickles; Drops; (\$15k)
Anti-diabetic effect (\$350K)

Dissemination Goal

Interactive Web site (\$25K)



Thank You
Questions ?

