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# Less is more

## The beneficial effects of short-term dietary restriction



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Disclosure:  
“I feel like a stange duck in the bite”



www.naturalnews.com/043124-dandelion\_cancer\_growth\_health\_benefits.html

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## Dandelion has unsuspected health benefits such as inhibiting cancer cell growth

Wednesday, December 04, 2013 by P. Simard  
Tags: dandelion, cancer growth, health benefits

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(NaturalNews) So many people can't wait to get rid of them once they start growing on their lawn, since dandelions are often seen as unwelcome weeds. Some of you may also recall the Rolling Stones song named "Dandelion" that came out during the summer of 1967. It was possibly the last time that dandelion was truly put into the spotlight, but now hope has now grown.

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Health claims on food are ubiquitous



olijfolie-doodt-kankercellen-binnen-een-uur/

**scientias.nl** HOME NIEUWS

## Stofje in olijfolie doodt kankercellen binnen een uur

Geschreven door Caroline Kraaijvanger op 20 februari 2015 om 08:52 uur



Wetenschappers hebben ontdekt dat een stofje in olijfolie in staat is om kankercellen in een half uur tot een uur tijd dood te laten gaan. En dat zonder de gezonde cellen te beschadigen.

## The Bad, the Bold and the Bogus: Food Industry Health Claims to Watch Out For

*There are myriad ways packaged food companies mislead consumers through vague, false, meaningless health claims, and difficult to decipher nutritional panels.*

# Common sense



ARE YOU POURING ON THE POUNDS?



**DON'T DRINK YOURSELF FAT.**  
Cut back on soda and other sugary beverages.  
Go with water, seltzer or low-fat milk instead.

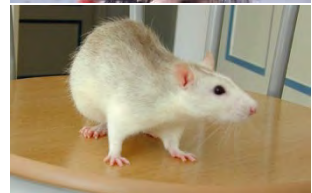
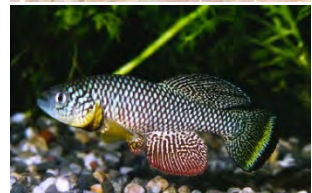
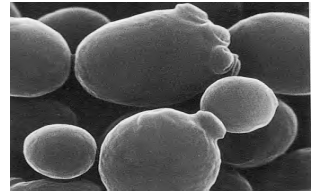
**NYC** Department of Health & Mental Hygiene  
Division of Field Operations

# Why are we interested in (less) food?

- **Dietary Restriction (DR)** is defined as a reduction in food intake without malnutrition
- **Long-term DR:**
  - Increased lifespan
  - Less cardiovascular disease
  - Lower incidence of diabetes mellitus
  - Lower incidence of malignancies
  - Increased resistance to oxidative stress

## Life-span extension by long-term DR:

- *Saccharomyces cerevisiae* (20-60%)
- *Caenorhabditis elegans* (10-35%)
- *Drosophila melanogaster* (20-30%)
- *Nothobranchius furzeri* (33-58%)
- *Mus musculus* (30-60%)
- *Rattus norvegicus* (30-60%)



# Long-term DR improves resistance against oxidative stress in the liver

40% CR, 6 months

*Resistance to paraquat toxicity*

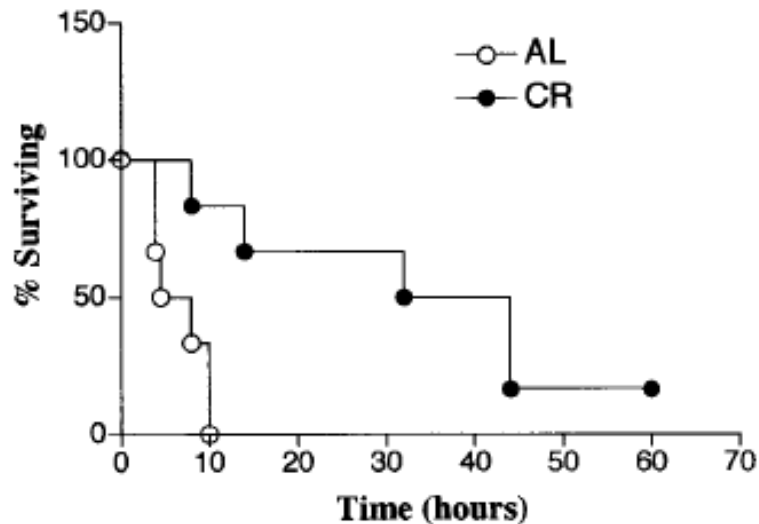
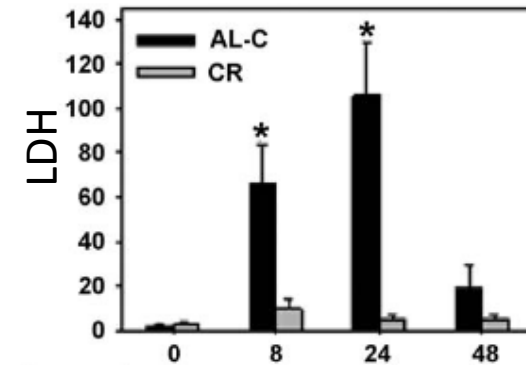
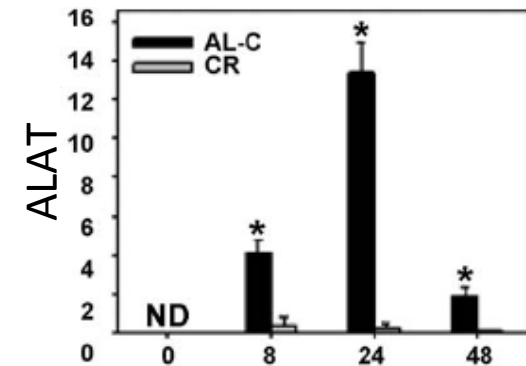


FIG. 10. Survival of mice fed a calorie-restricted diet and mice fed AL after challenge with the oxidizing agent paraquat. Six-month-old C57BL/6 mice fed a calorie-restricted diet and mice fed AL were injected intraperitoneally with paraquat at 70 mg/kg. Mice fed AL died significantly earlier than mice fed a calorie-restricted diet ( $P = 0.0048$ ).

*Sun et al. 2001*

40% CR, 8 months

*Resistance to paracetamol toxicity*



*Harper et al. 2006*

Long-term restriction of dietary intake:

- delays the aging process
- increases resistance to oxidative stress

***Long-term food restriction in humans not feasible***

Does short-term dietary restriction increase  
resistance to oxidative stress?

# Medically relevant oxidative damage

## Ischemia-reperfusion injury (IRI)

Temporary lack of blood flow in an organ transplant (ischemia)

Followed by reperfusion with blood in recipient

Oxidative stress → injury → inflammation → organ dysfunction

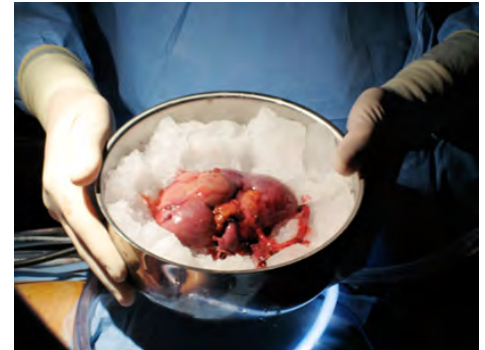
## Surgically induced IRI:

- Cardiothoracic bypass surgery
- Liver resection
- Organ transplantation

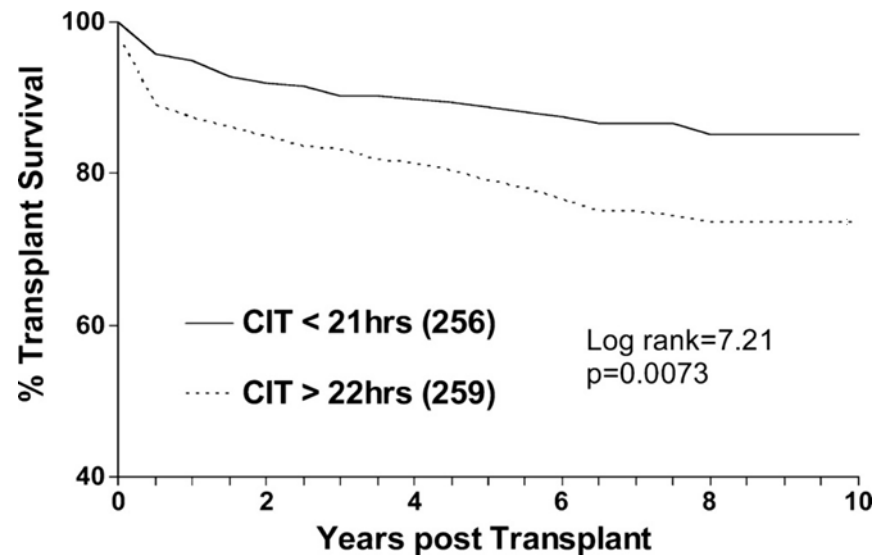
## Drug side effects

Paracetamol

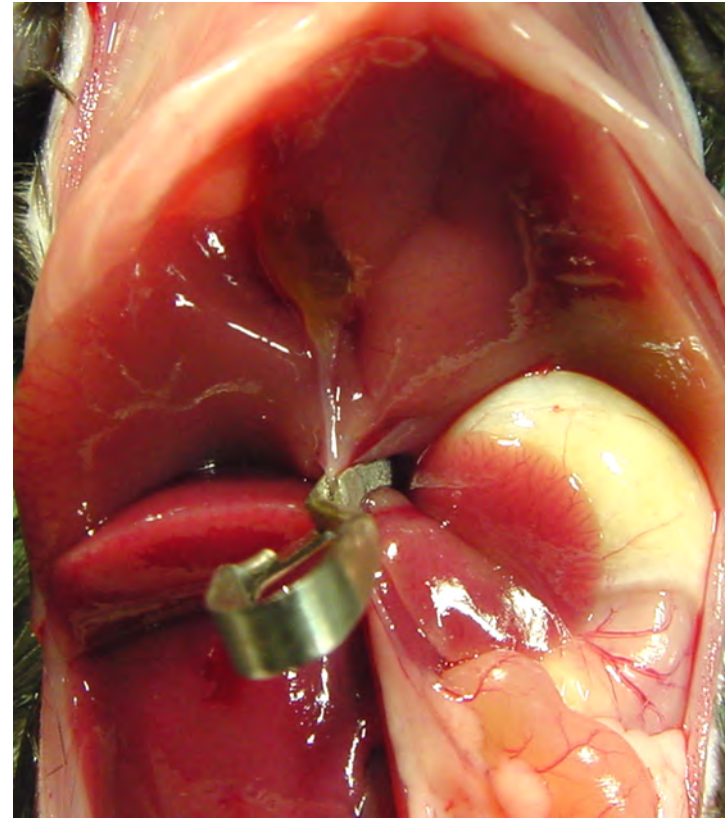
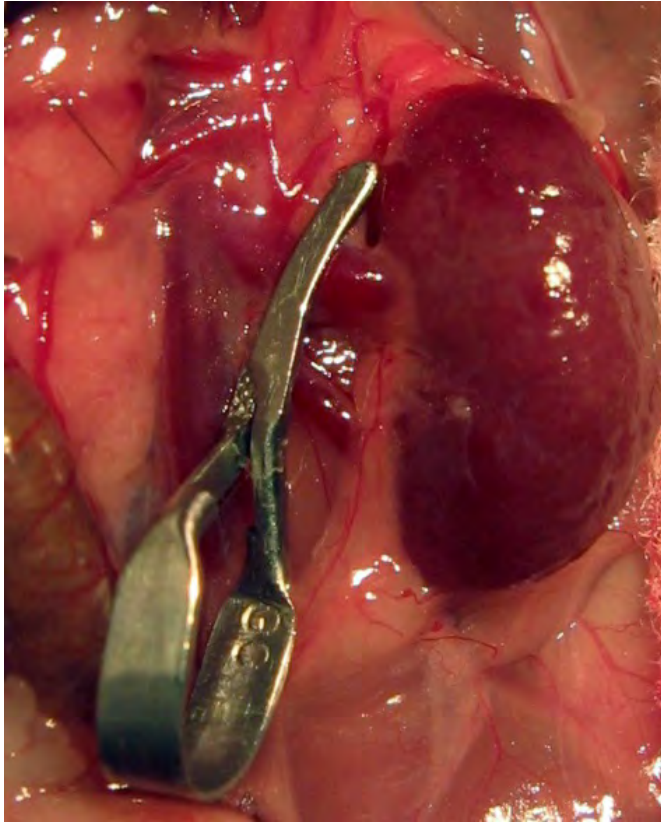
Chemotherapeutic drugs



# A cold ischemia time (CIT) of >22 hours worsens kidney transplant survival

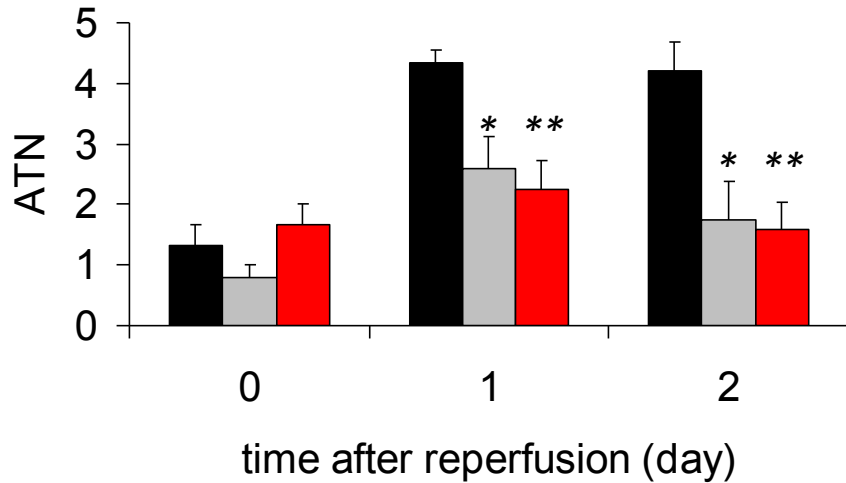


## MOUSE KIDNEY AND LIVER ISCHEMIA-REPERFUSION MODELS

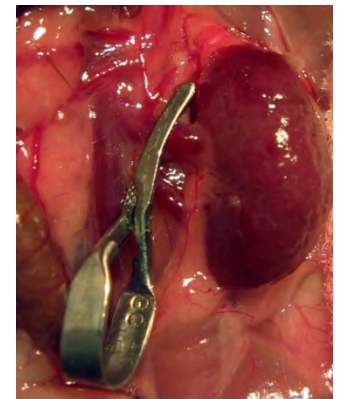
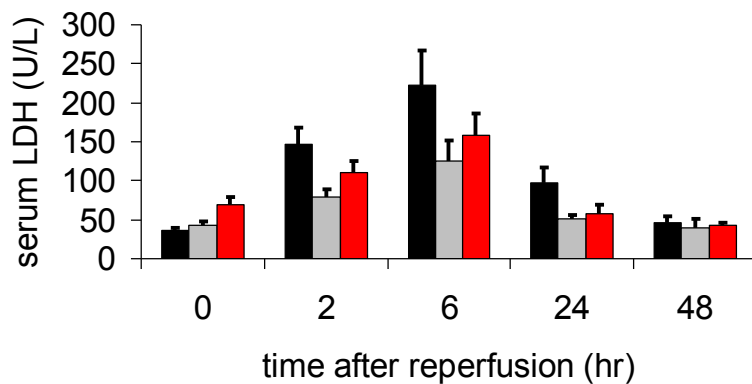
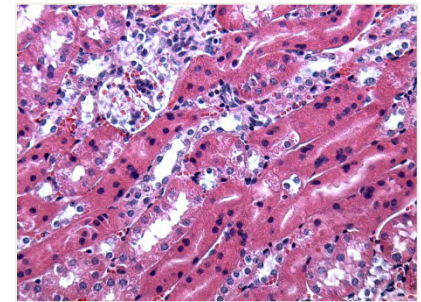
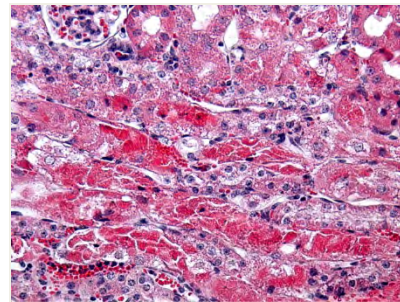


# Dietary restricted and fasted animals are protected against ischemia-reperfusion injury of the kidney

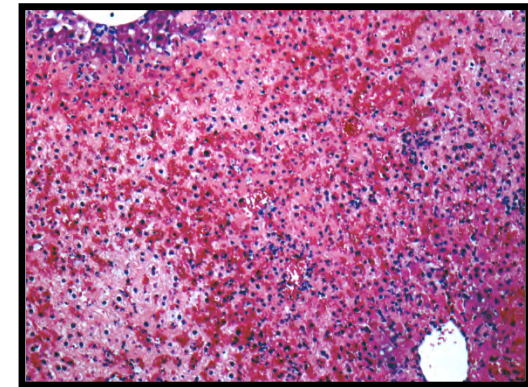
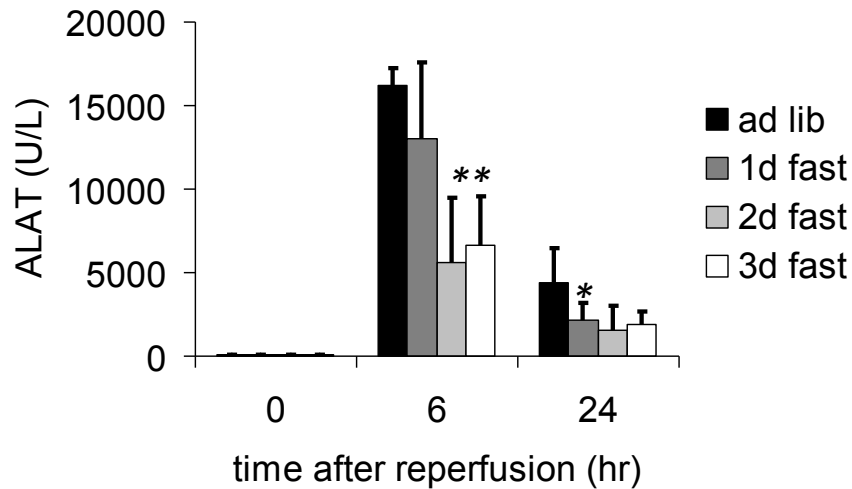
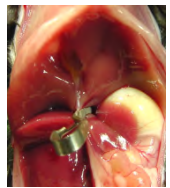
■ Ad lib ■ 30% DR ■ 3d fast



## Kidney damage

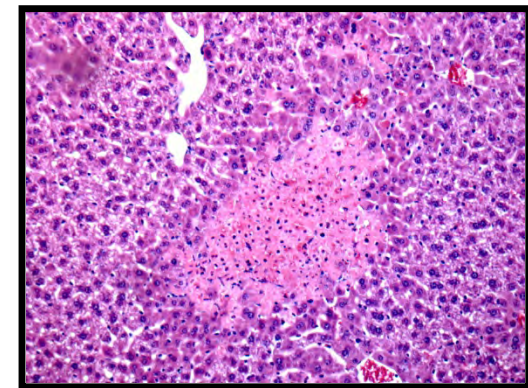
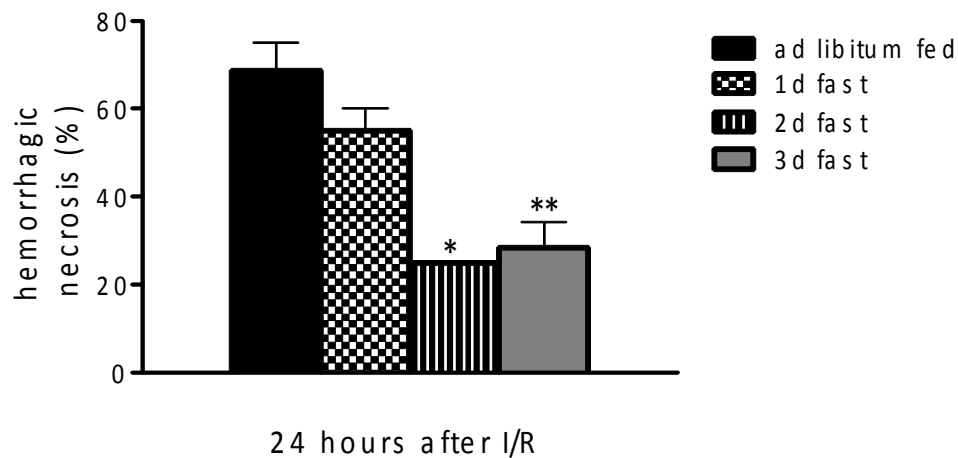


# Protection from ischemia reperfusion injury by fasting is not specific to the kidney



ad libitum fed

H&E 100x



72 hours fasted

Increased resistance to oxidative damage by dietary restriction is induced rapidly and may be tapped for clinically relevant stressors such as ischemia-reperfusion injury

How about other stressors?

## Short-term dietary restriction, cancer and chemotherapy

Potential benefits:

- Reduction of tumor growth
- Augmentation of irradiation effect
- Improved resistance to irradiation
- Protection against adverse side effects of chemotherapy
- Improved postoperative recovery



# Protection against adverse side effects of chemotherapy

Side effects of the chemotherapeutic drug Irinotecan are dose limiting

fatigue

hair loss

nausea

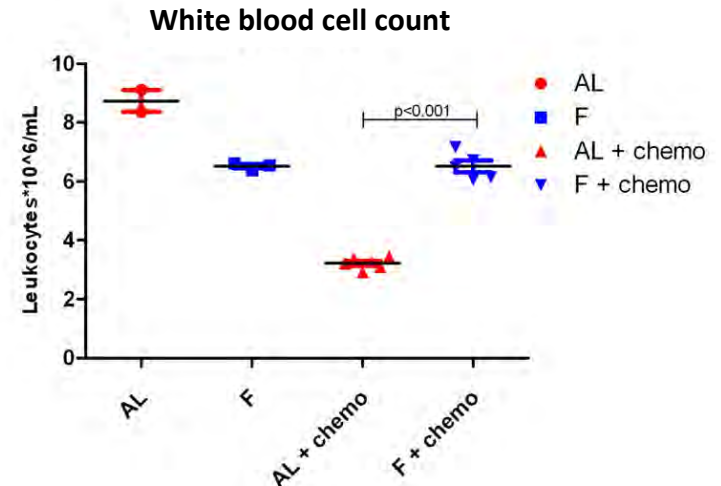
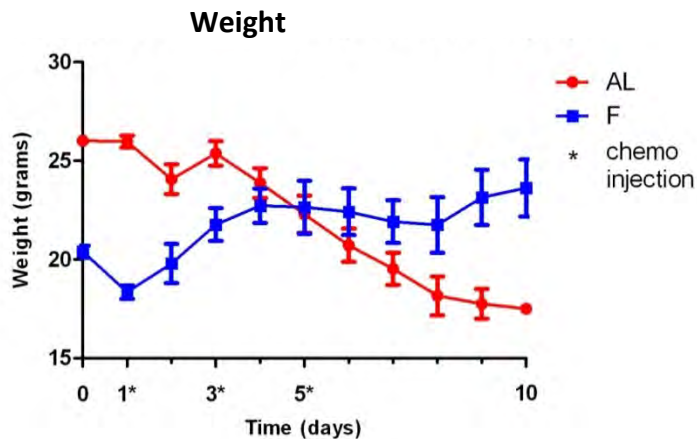
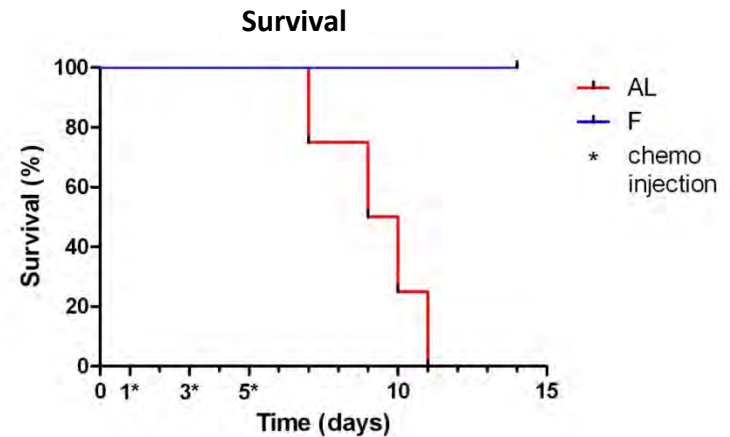
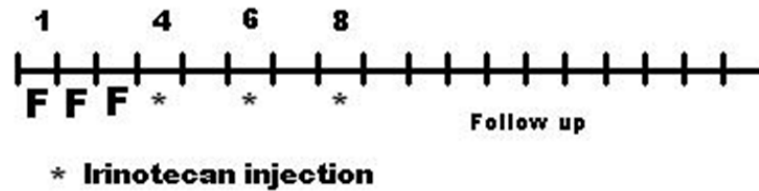
vomiting

diarrhea

low blood counts



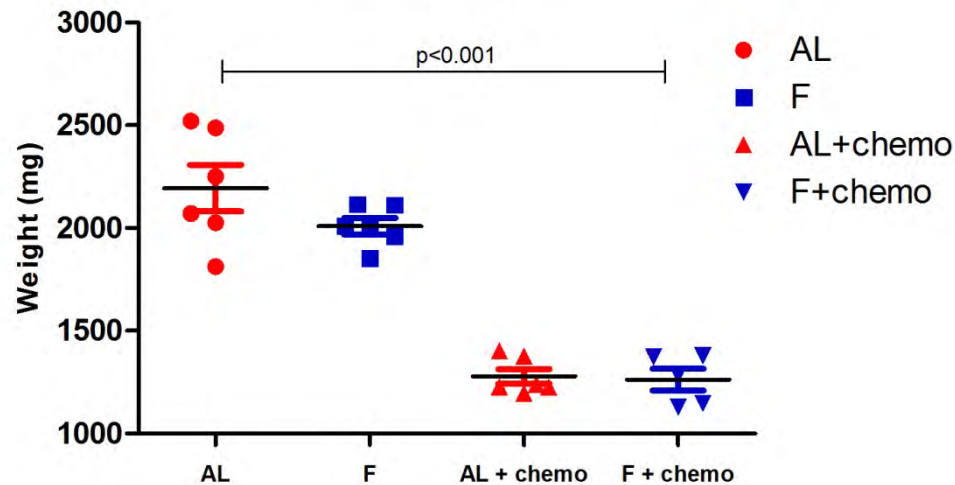
# 3 days fasting protects mice against a lethal dose of Irinotecan



- Fed group: weight loss, diarrhea, reduced mobility, ruffled coat, hunched back posture, leukopenia
- Fasted group: weight gain, no adverse side effects

# But how about the anti cancer effect of Irinotecan in fasted mice?

Tumor weight in mice with coloncarcinoma treated with Irinotecan



# Towards clinical application

- Composition
- Time
- Adherence



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## Products - **ChemoLieve™**



L-Nutra's first diet to nutritionally manage disease stems from 15 years of research at USC. It

### CHEMOLIEVE™



L-Nutra's first line of products stems from 15 years of research at the USC Longevity Institute, one of the world's leading centers for research on aging and its translation into human interventions that optimize longevity and healthspan. It was largely motivated by the request of many patients who wanted to take advantage of the potential beneficial effects of fasting during cancer treatment but were unable to fast and forego any all meals or and snacks.



# Calorie restriction trial

- Feasibility and safety of a preoperative diet
- Effects on postoperative recovery

## Pre-operative dietary restriction is feasible in live-kidney donors

van Ginhoven TM, de Bruin RWF, Timmermans M, Mitchell JR, Hoeijmakers JHJ, IJzermans JNM. Preoperative dietary restriction is feasible in live kidney donors. Clin Transplant 2011; 25: 486–494. © 2010 John Wiley & Sons A/S.

Tessa M. van Ginhoven<sup>a</sup>, Ron W.F. de Bruin<sup>a</sup>, Marijke Timmermans<sup>b</sup>, James R. Mitchell<sup>c\*</sup>, Jan H.J. Hoeijmakers<sup>c</sup> and Jan N.M. IJzermans<sup>a</sup>

## Dietary Restriction Modifies Certain Aspects of the Postoperative Acute Phase Response

Tessa M. van Ginhoven, M.D.,<sup>\*</sup> Willem A. Dik, Ph.D.,<sup>†</sup> James R. Mitchell, Ph.D.,<sup>‡,1</sup> Marja A. Smits-te Nijenhuis, B.Sc.,<sup>†</sup> Conny van Holten-Neelen, B.Sc.,<sup>†</sup> Herbert Hooijkaas, Ph.D.,<sup>†</sup> Jan H. J. Hoeijmakers, Ph.D.,<sup>‡</sup> Ron W. F. de Bruin, Ph.D.,<sup>\*,2</sup> and Jan N. M. IJzermans, M.D., Ph.D.<sup>\*</sup>

*<sup>\*</sup>Department of Surgery; <sup>†</sup>Department of Immunology; and <sup>‡</sup>Department of Genetics, Erasmus MC, Rotterdam, The Netherlands*

The Protein and Calorie restriction Trial

## PROTECT Study

Effects of a preoperative protein and caloric restricted diet on postoperative recovery and genomic changes in healthy (kidney donation) and unhealthy (bariatric surgery) individuals undergoing surgery

# Self reported compliance

- Erasmus MC:
  - Scandishake 8/10 (80%)
  - Nutridrink 4/10 (40%)
- Maasstad:
  - Scandishake\* 12/18 (67%)
  - Nutridrink 9/10 (90%)

# Self reported adverse effects

## Scandishake:

■ 50%:

- Hunger
- General discomfort
- Bad taste

## Nutridrink:

■ 70%:

- Hunger
- Bad taste
- Diarrhea
- Nausea

# Why broccoli sprouts?

Practical limitations to dietary restriction fuel the search for “dietary restriction mimetics”

Broccoli, like dietary restriction, is able to extend lifespan!

Genes Nutr (2013) 8:439–448  
DOI 10.1007/s12263-012-0330-6

RESEARCH PAPER

**Longevity in the red flour beetle *Tribolium castaneum* is enhanced by broccoli and depends on *nrf-2*, *jnk-1* and *foxo-1* homologous genes**

Stefanie Grünwald · Julia Stellzig · Iris V. Adam · Kristine Weber · Sarai Binger · Michael Boll · Eileen Knorr · Richard M. Twyman · Andreas Vilcinskas · Uwe Wenzel



Can broccoli consumption mimic the effects of dietary restriction and fasting?

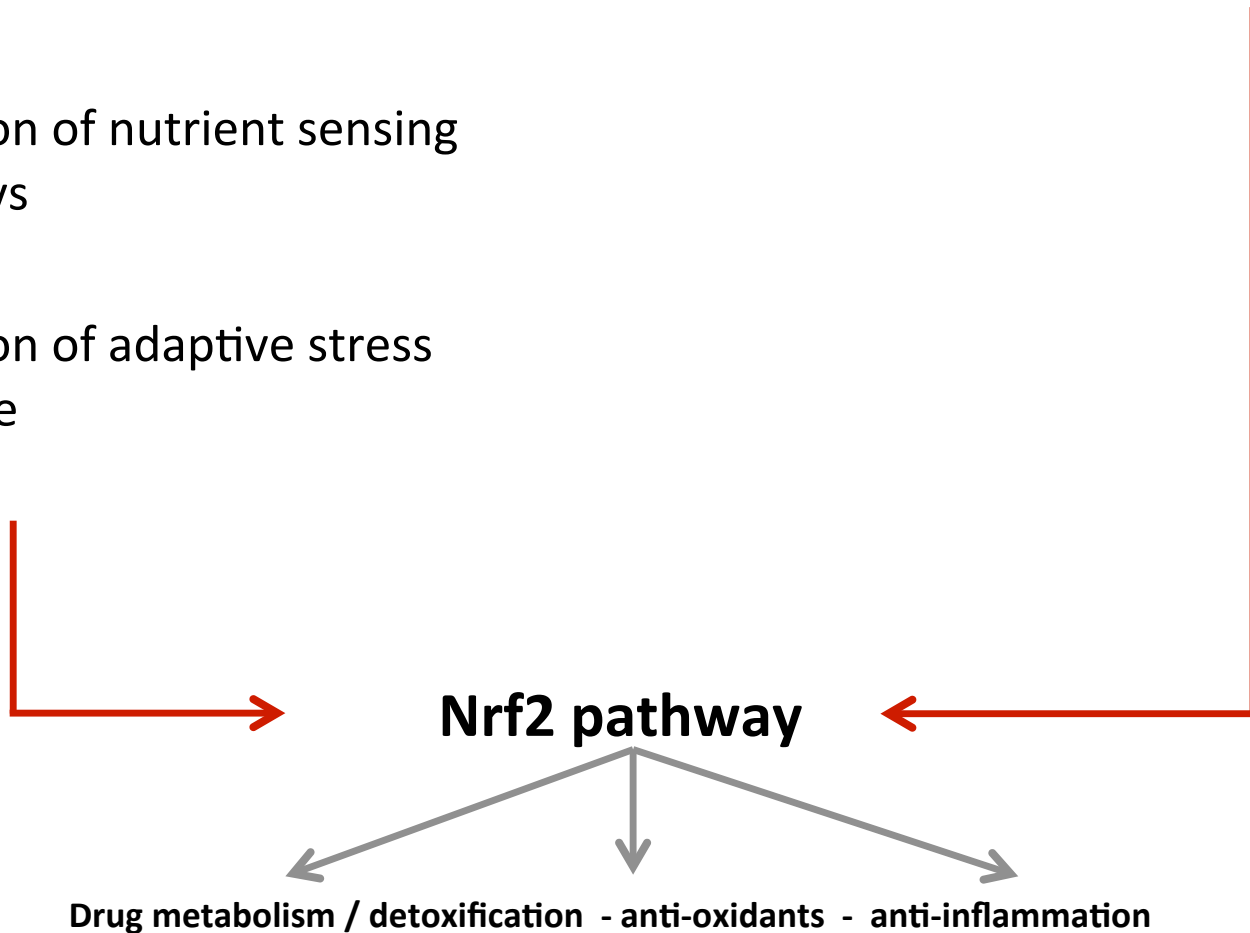
# Theoretical considerations

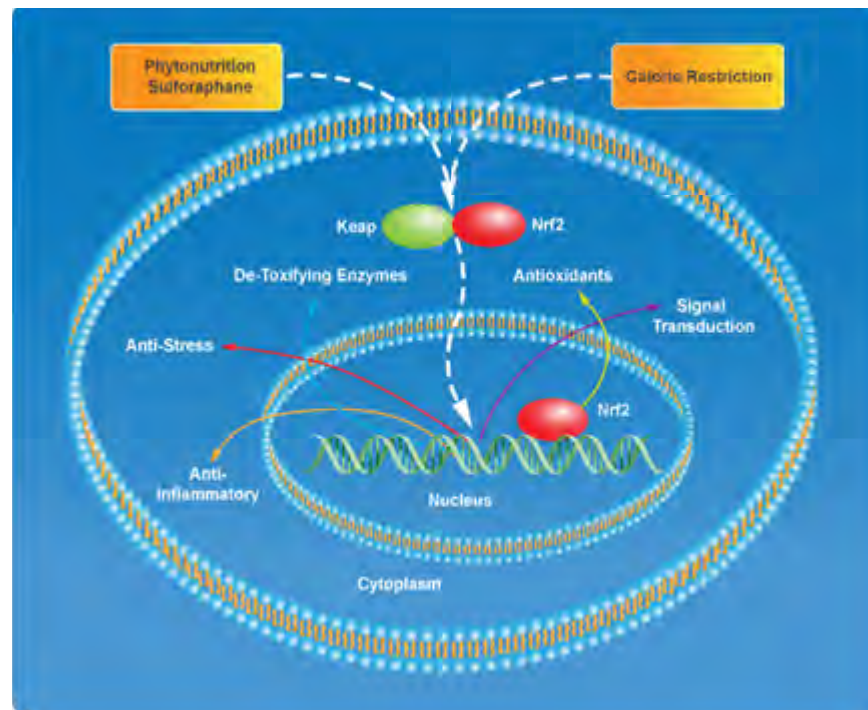
## Dietary restriction

Activation of nutrient sensing pathways

Activation of adaptive stress response

## Broccoli - Sulforaphane





# **The effects of pre-operative broccoli cress consumption on the response to surgery and on postoperative recovery**

AIM:

- To investigate whether a broccoli cress enriched diet induces a protective response in patients undergoing surgery.

## The effects of pre-operative broccoli cress consumption on the acute phase response after surgery and on postoperative recovery

- **Study population:**

40 healthy people (>18 years) who are listed to undergo kidney donation at the Erasmus Medical Center.

- **Intervention:**

Two patient groups. Broccoli enriched diet (8 gram of broccoli cress) or control (8 gram of lettuce, no *Brassicaceae* in diet) during 5 days before surgery.

**Main study parameter:**

Acute phase response by measurement of leukocytes, C-reactive protein and IL-6, TNF- $\alpha$ , IFN- $\gamma$ , IL-10 in blood.

- **Secondary parameters:**

The Nrf2 mediated stress response will be measured in kidney tissue.

Well-being and postoperative recovery with the help of standardized questionnaires (VAS, MFI-20, SF-36, EuroQol and work related scores).

# Take home

- Short-term dietary restriction and fasting protect against medically relevant stressors
- Activation of the Nrf2 pathway is important in inducing this protection
- Sulforaphane-precursor containing vegetables may induce similar protective effects
- Do these rapidly induced effects predict long-term health benefits?

