

**WHAT IS GOOD AND WHAT IS BAD FOR
YOU: THE ADVANTAGE OF AMBIGUITY.
THE CASE OF ALCOHOL AND WINE.**

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NUTRITIONAL EPIDEMIOLOGY

This branch of epidemiology studies the relationships between nutrition, health status and diseases.

The results are produced as “soft data” addressed to the identification of nutritional “risk factors” and “protective factors”.

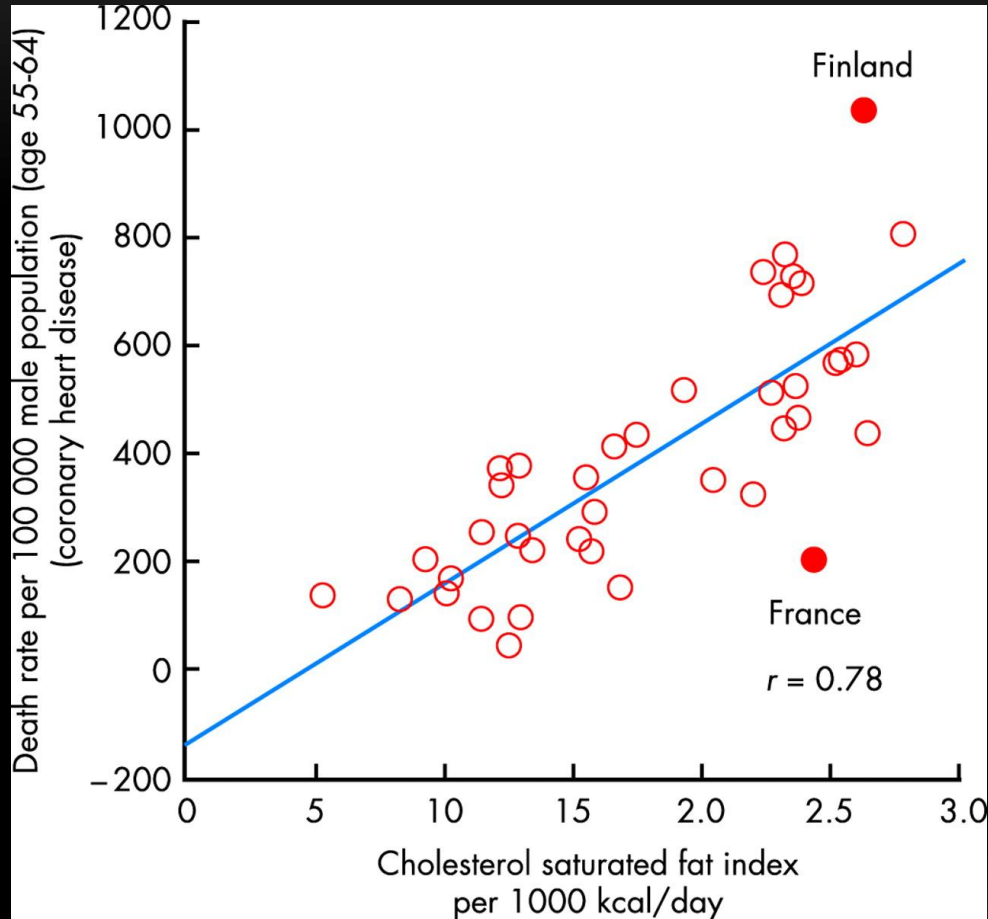
Sometimes the approach generates paradoxes

The divergence of a set of evidence from the “rule” descending from accepted bio-statistical analysis is often referred to as “**paradox**”.

The term describes an apparent contradiction when two events or concepts appear each-other incompatible although both being seemingly true.

The truth is not-dual and there must be an epistemological bias

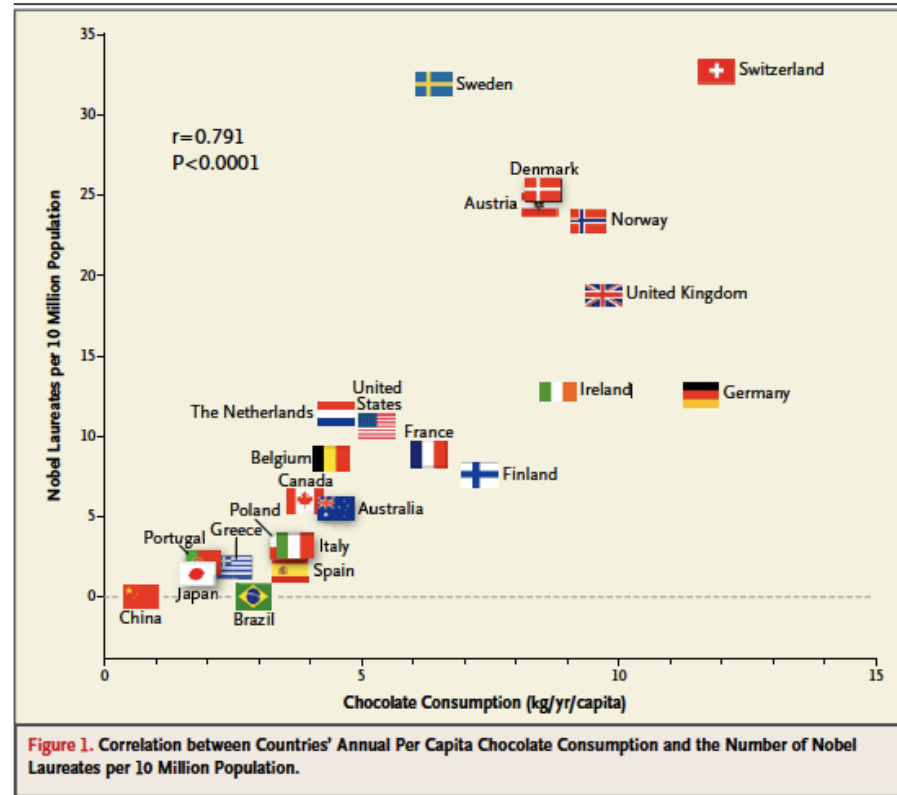
THE FRENCH PARADOX (RENAUD 1992)



French do not die enough in respect the cholesterol and saturated fat intake

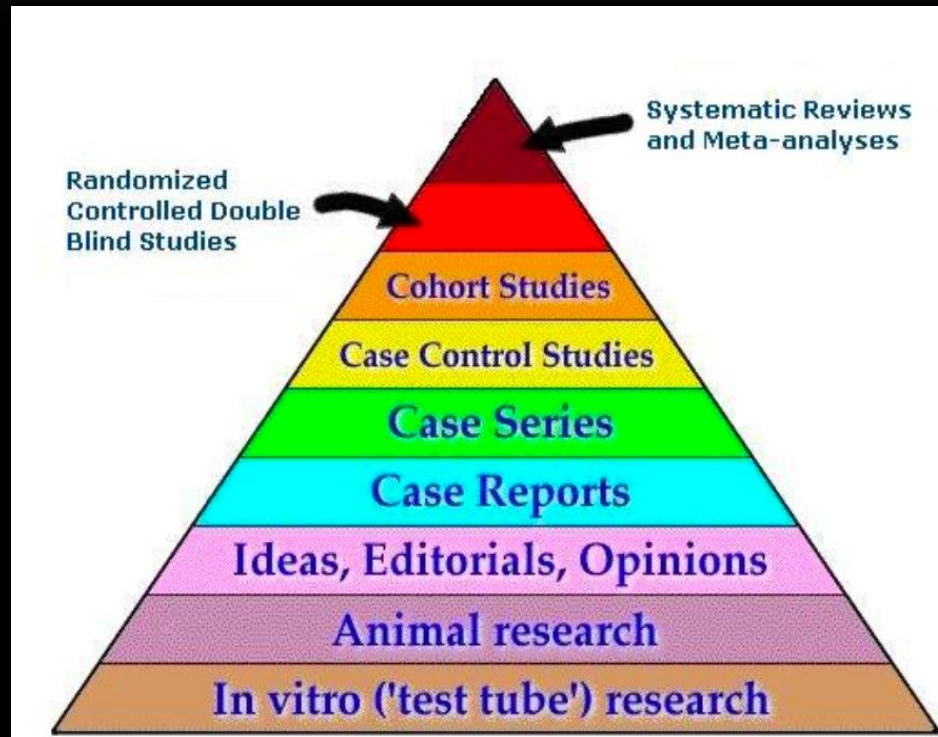
THE GERMAN PARADOX

(NEJM, OCT 10, 2012)



Germans did not get enough Nobel Prizes in respect the chocolate consumption

IN MEDICINE PARADOXES ARE OFTEN SOLVED WHEN
SOFT EPIDEMIOLOGICAL EVIDENCE
IS SUPPORTED BY **HARD** BIO-CHEMICAL EVIDENCE.
UNFORTUNATELY THIS IS ONLY RARELY THE CASE



We need more basic research

The case of beneficial effect of alcohol and wine

How come this “toxicant” that several people ask
for being banned, may be “healthy” for others?

How can we discriminate between what is bad
and what is good?

Since ancient times, wine has been considered the “healthiest of beverages”

" ..During meals drink wine happily, little but often.." and "...to avoid harming the body never drink between meals..." .

Arnoldo da Villanova (1253-1315) in the *Regimen Sanitatis Salernitani*

The 20th century brought a focus on alcohol *abuse*, and this led in the USA in the 1920s. to the **legal philosophy** of “Prohibitionism”

Fortunately, in the 1970s, the first rigorous epidemiologic studies began noting lower CHD rates among subjects who consumed some alcohol.

CHD MORTALITY IN THE FRAMINGHAM HEART STUDY, BY ALCOHOL INTAKE (1974) (PERCENT DEATHS OVER 24 YEARS IN MEN)

| | Alcohol consumption, drinks/day | | | | | |
|---------------|---------------------------------|-------|---------|---------|---------|------|
| | None | < 0.5 | 0.5-1.0 | 1.1-2.0 | 2.1-5.9 | 6.0+ |
| Non-Smokers | 16.3 | 14.8 | 14.6 | 7.8 | 5.7 | 7.4 |
| Heavy Smokers | 28.3 | 16.0 | 14.4 | 14.0 | 13.1 | 12.5 |

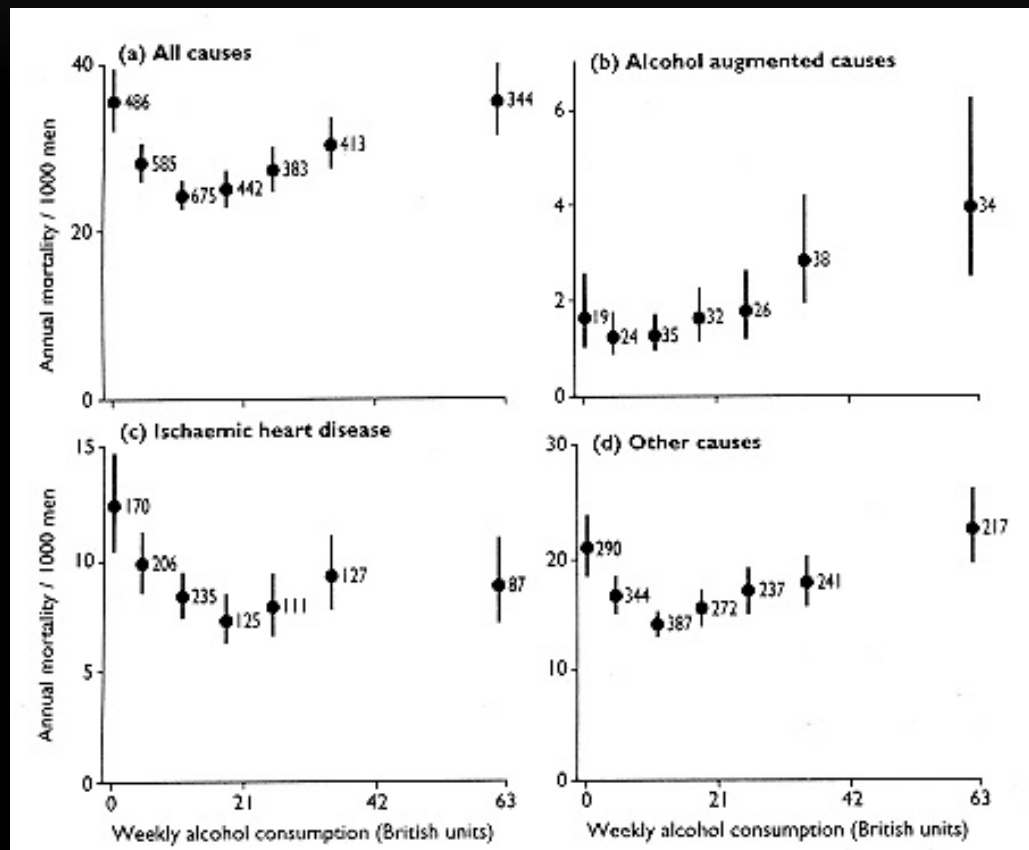
Recent high quality epidemiological studies confirm the evidence of a protective role of alcohol in CVD. Moreover, these data are in agreement with decrease of mortality for all-causes

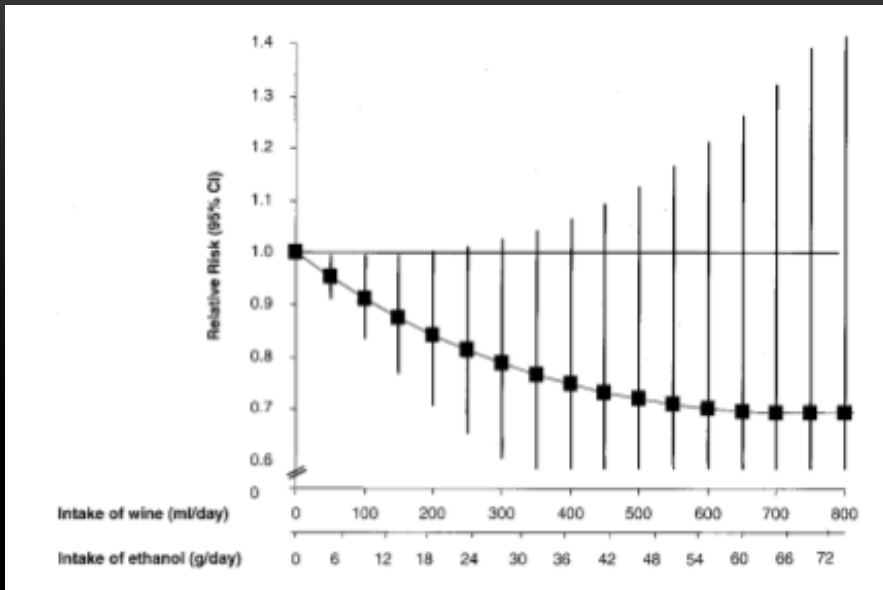
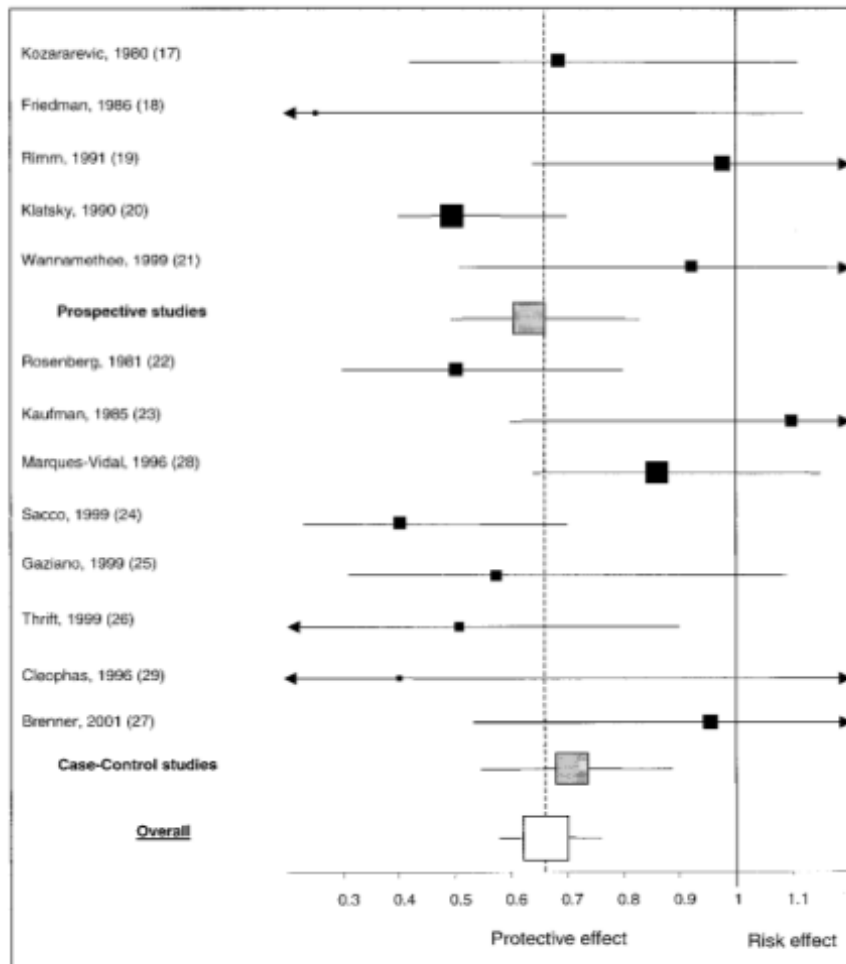
Finally...wine does it better !!

JUST FEW SELECTED EXAMPLES

Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors

Richard Doll, Richard Peto, Emma Hall, Keith Wheatley, Richard Gray

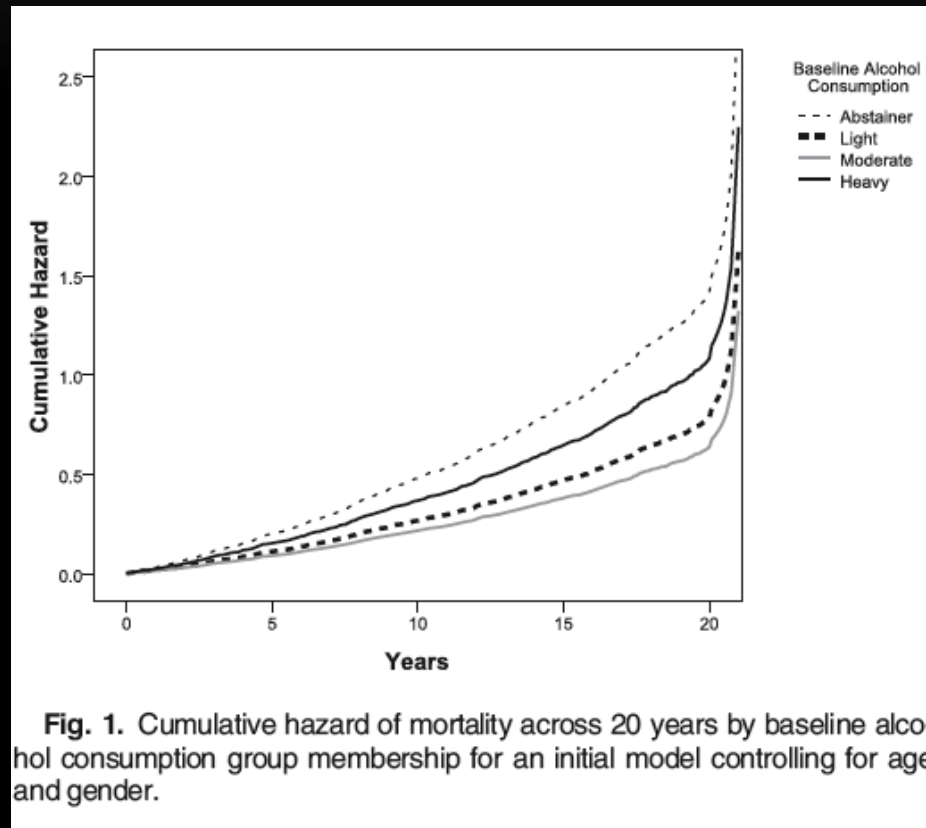




Meta-Analysis of Wine and Beer Consumption in Relation to Vascular Risk

Augusto Di Castelnuovo, MS; Serenella Rotondo, MS; Licia Iacoviello, MD, PhD;
 Maria Benedetta Donati, MD, PhD; Giovanni de Gaetano, MD, PhD

..AND EVENTUALLY THE CUMULATIVE HAZARD OF DEATH IS HIGHER FOR ABSTAINERS THAN FOR LIGHT, MODERATE AND ALSO HEAVY DRINKERS (MATHEMATICS SAYS)



The most recent evidence (Oct 2015)

Effects of Initiating Moderate Alcohol Intake on Cardiometabolic Risk in Adults With Type 2 Diabetes

A 2-Year Randomized, Controlled Trial

Yftach Gepner, MPH*; Rachel Golan, RD, PhD*; Ilana Harman-Boehm, MD; Yaakov Henkin, MD; Dan Schwarzfuchs, MD; Ilan Shelef, MD; Ronen Durst, MD; Julia Kovsan, MSc; Arkady Bolotin, PhD; Eran Leitersdorf, MD; Shoshana Shpitzen, MA; Shai Balag, MD; Elad Shemesh, MD; Shula Witkow, RD, MPH; Osnat Tangi-Rosental, BA†; Yoash Chassidim, PhD; Idit F. Liberty, MD; Benjamin Sarusi, MSc; Sivan Ben-Avraham, RD, MPH; Anders Helander, PhD; Uta Ceglarek, PhD; Michael Stumvoll, MD; Matthias Blüher, MD; Joachim Thiery, MD; Assaf Rudich, MD, PhD; Meir J. Stampfer, MD, DrPH; and Iris Shai, RD, PhD

Conclusion: This long-term RCT suggests that initiating moderate wine intake, especially red wine, among well-controlled diabetics as part of a healthy diet is apparently safe and modestly decreases cardiometabolic risk. The genetic interactions suggest that ethanol plays an important role in glucose metabolism, and red wine's effects also involve nonalcoholic constituents.

Alcohol consumption is associated with a lower incidence of acute myocardial infarction: results from a large prospective population-based study in Norway

■ K. Gémes¹, I. Janszky^{1,2}, L. E. Laugsand², K. D. László³, S. Ahnve¹, L. J. Vatten² & K. J. Mukamal⁴

From the ¹Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden; ²Department of Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway; ³Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; and ⁴Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

Conclusions. Light-to-moderate alcohol consumption was linearly associated with a decreased risk of AMI in a population in which abstaining from alcohol is not socially stigmatized. Our results suggest that frequent alcohol consumption is most cardioprotective and that this association is not driven by misclassification of former drinkers.

IS THERE A TRUE BENEFICIAL EFFECTS OF ALCOHOL OR JUST A “BLACK SWAN” ?

EVIDENCE ON :

ALL CAUSE MORTALITY
CORONARY ARTERY DISEASE
STROKE
OSTEOPOROSIS
RHEUMATOID ARTHRITIS
OBESITY
DIABETES



For some reasons a kind of neo-prohibitionism emerges today leading to a paternalistic interpretation of selected epidemiological data

JUST FEW SELECTED EXAMPLES

Alcohol attributable burden of incidence of cancer in eight European countries based on results from prospective cohort study

BMJ 2011;342:d1584

Conclusions In western Europe, an important proportion of cases of cancer can be attributable to alcohol consumption, especially consumption higher than the recommended upper limits. These data support current political efforts to **reduce or to abstain from alcohol consumption to reduce the incidence of cancer.**

The latest news from across the WCRF network.

[View this email in your browser](#)



eNews



Three alcoholic drinks a day can cause liver cancer

Today, World Cancer Research Fund International publishes global research which finds strong evidence that consuming approximately [three or more alcoholic drinks a day causes liver cancer](#). The finding provides the clearest indication to date of how many drinks actually cause liver cancer.

Alcohol has virtually no discernible health benefits and claims that a glass of wine is good for the heart have been exaggerated, a study has concluded.

Researchers at University College London argue that studies suggesting that moderate drinkers are healthier rely on flawed comparisons with people who have given up alcohol, often because they are already sick.

Biomedical mechanistic aspects

THE ROLE OF PHYSIOLOGICAL RESPONSE TO METABOLIC CHALLENGE AND REDOX HOMEOSTASIS

Insights from ancient wisdom and molecular
medicine

The notion of disease as perceived by the Ayurvedic, Greek and Roman philosophy, and eventually acknowledged in its fundamentals by Hippocrates and Avicenna states that **the balance among the four humors of the body** (reminiscent of the four elements of the universe: air, fire, hearth and water) **determines the temperament of a person and his susceptibility to diseases.** What was missing for centuries was the real cause of the impairment of the equilibrium among “humors”.

In the modern view, the perturbation of the *milieu intérieur* (Claude Bernard) – we overlap today to the notion of **offset of homeostasis**- drives the susceptibility, initiation and progression of a disease



In analyzing the intimate nature of different diseases, we generally accept that imbalance between counteracting mechanisms must have taken place and that the pathological phenotype reflects the **altered homeostasis**.

Maintenance or re-establishment of homeostasis is the goal of preventive or therapeutic medicine

Inflammation and redox homeostasis

January 23, 2004

BUSH'S
MILITARY RECORDS
IS DISNEY MOUSETRAPPED?



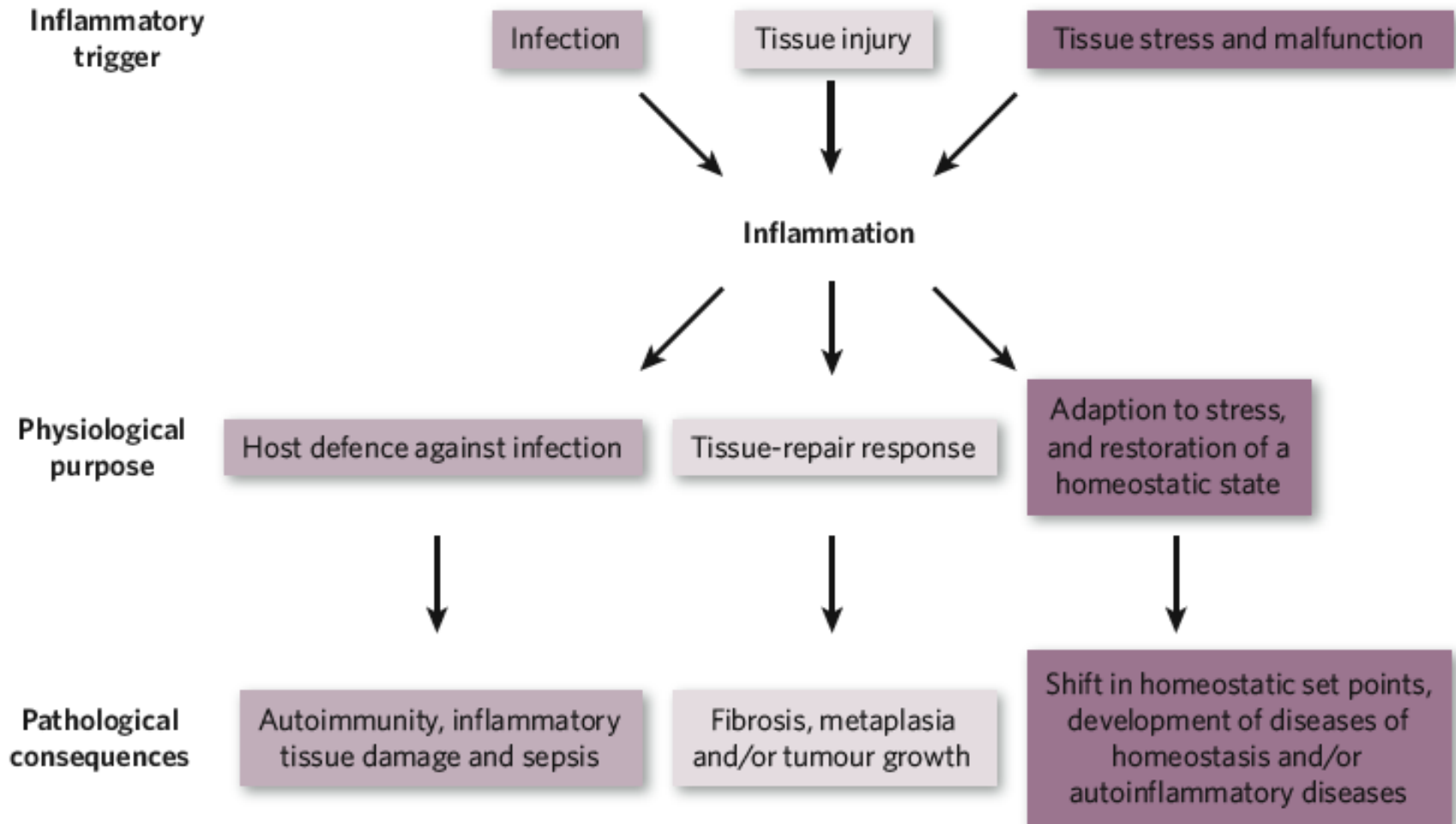
- The surprising link between **INFLAMMATION** and **HEART ATTACKS, CANCER, ALZHEIMER'S** and other diseases
- What you can do to fight it

www.time.com/time/cover/012304/cover.012304.html

Inflammation is the elementary system of defense, indispensable for surviving since living matter is continuously challenged by agents perturbing its physiological functions.

When hit by a challenge an integrated biological system reacts to eliminate the challenge and repair the damage.

Both these events affect the homeostasis and the resolution of the pathological status passes through the re-establishing of the *quo ante* homeostasis. Failure of this results in a chronic degenerative disease (or cancer).



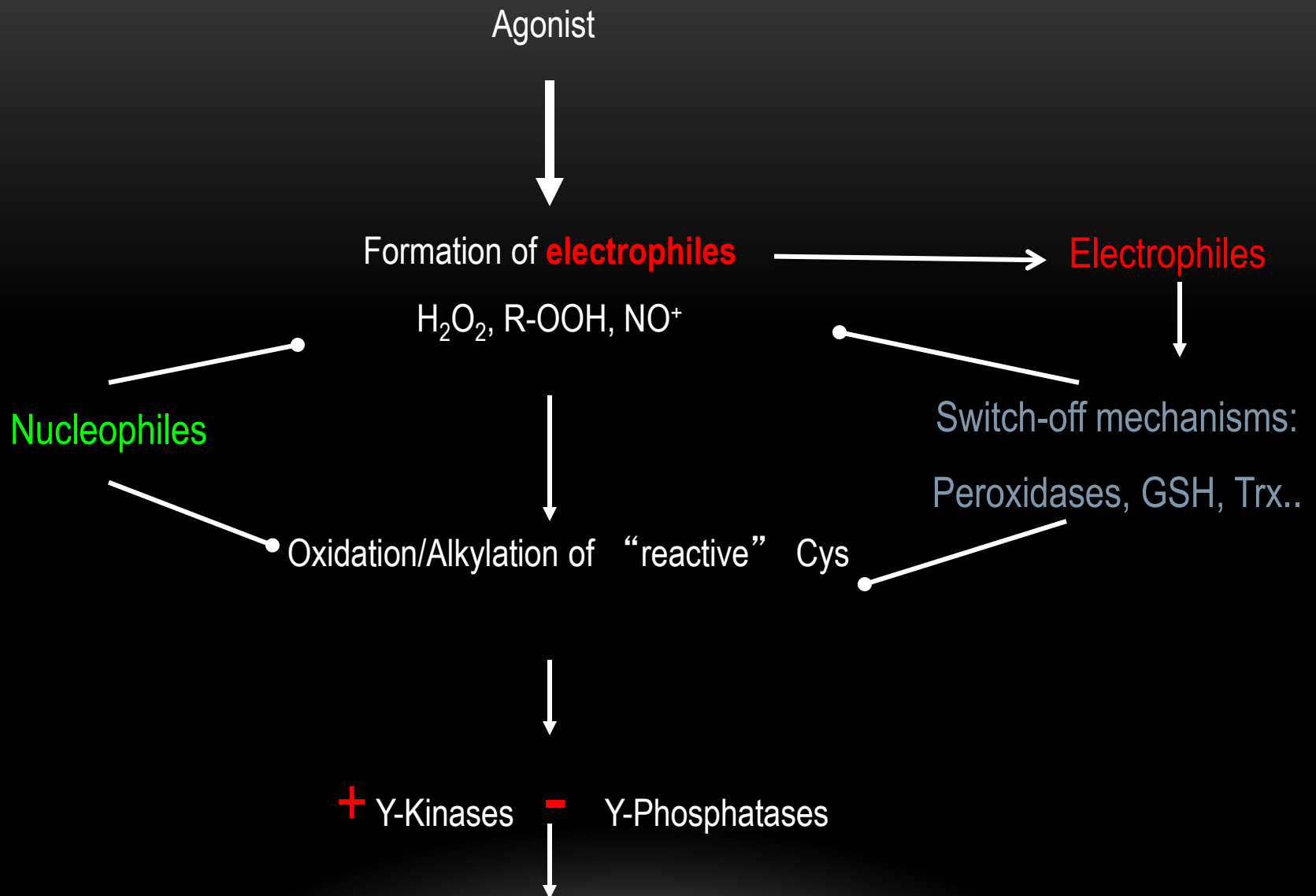
CAUSES, AND PHYSIOLOGICAL AND PATHOLOGICAL CONSEQUENCES OF INFLAMMATION

MEDZHITOF 2008 NATURE, 454:428

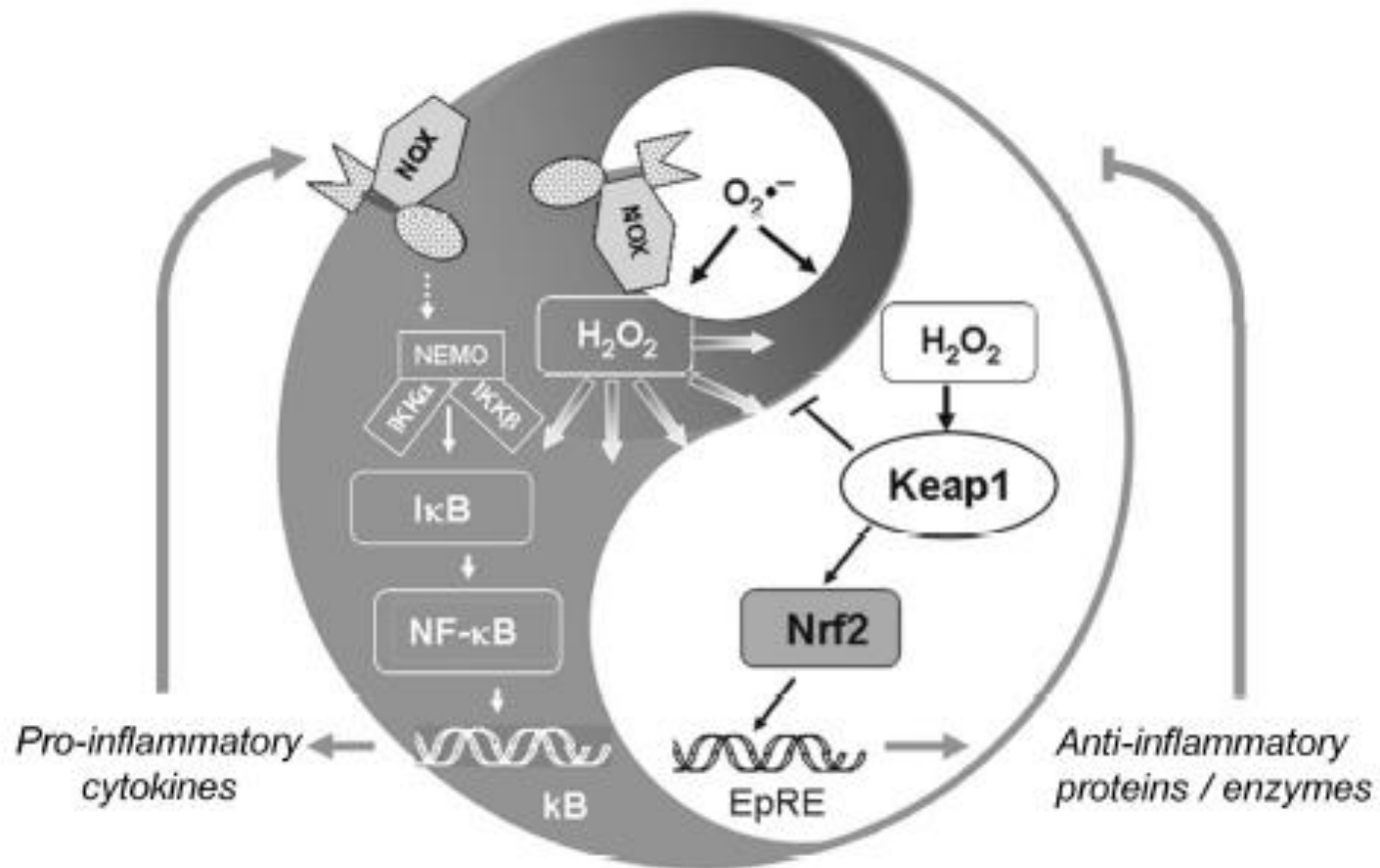
The triggers of inflammation (different challenges) use **electrophiles** (mainly hydroperoxides and species derived from them) in signaling pathways.

Redox homeostasis is re-established by a feedback activation of pathways increasing the **nucleophilic tone** (mainly thiols and related enzymes)

Large and continuous supply to cells of “metabolic energy” generates an inflammatory challenge leading to an homeostatic offset.



Activated enzymes and gene expression: **proliferation, survival, metabolism, angiogenesis....**

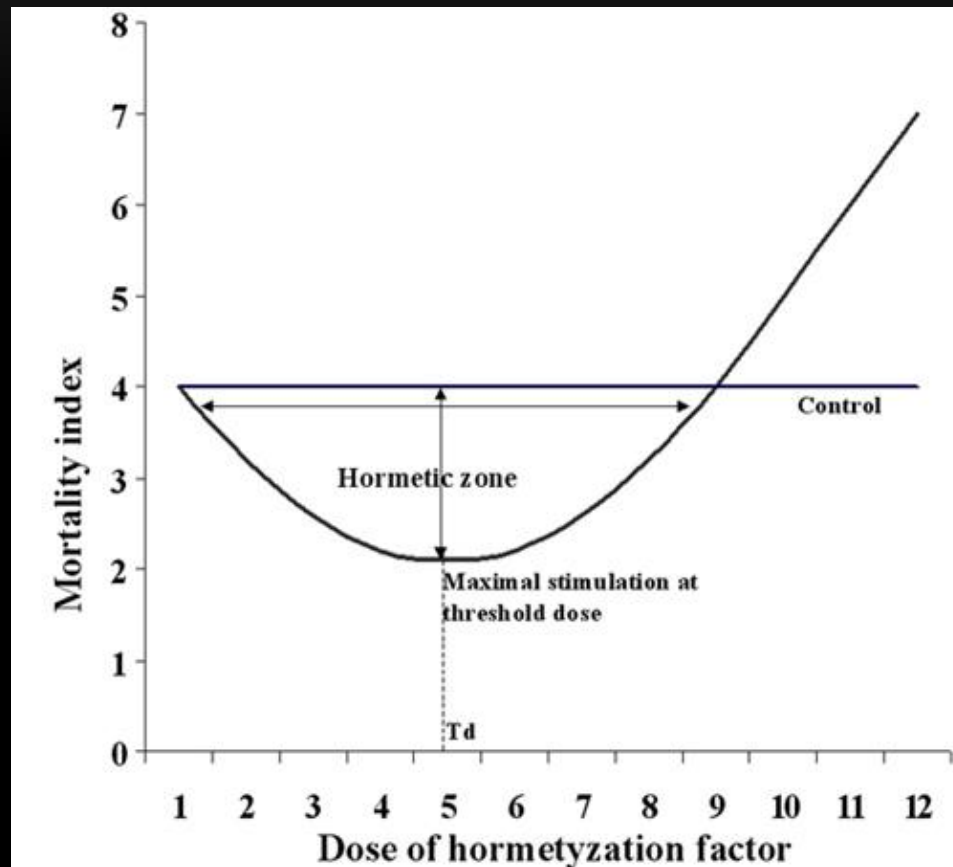


Redox feedback: NF-κB vs Nrf2

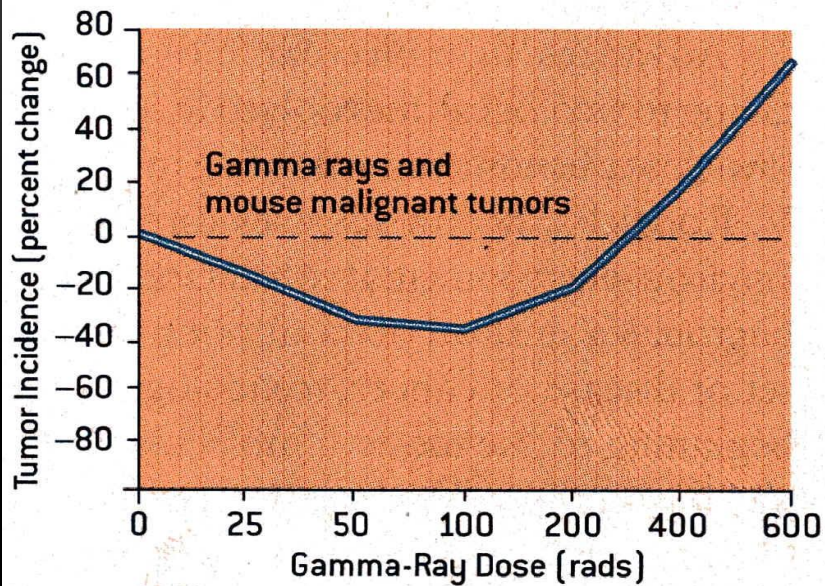
Nutritional “antioxidants” and para-hormesis

How do nutrition impact on redox status and
thus on inflammatory response ?

HORMESIS IS THE POSITIVE OUTCOME OF ADAPTIVE MECHANISMS



small (moderate) doses of a toxic compound -such as alcohol- can be health protecting when assumed in correct amount



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Nietzsche's Toxicology

Whatever doesn't kill you might make you stronger

By [Rebecca Renner](#) | August 18, 2003 | 0



Friedrich Nietzsche
1844-1900

The fact that the intake of a food component is good or bad for you is just matter of dose (Paracelusus)

Mild stimuli activate defense systems and metabolic flexibility.

Among hormetic stimuli there are: fasting, exercise, temperature, ethanol, xenobiotics and drugs such as metformin and statins, and finally also frank poisons as dioxin

PARA-HORMESIS

We name **para-hormesis** the mechanism by which non toxic nutritional compounds activate the cellular antioxidant defense system mimicking toxic electrophiles.

This is the case of nutritional “antioxidants”

How do nutritional antioxidants impact of health?



Fruit, vegetables and wine are the major sources of nutritional nucleophilic antioxidants

However, phenolic antioxidants generate by autoxidation electrophiles that activate the EpRE (ARE) complex eventually producing endogenous nucleophiles and the related enzymes.

In the frame of redox signaling this increases the nucleophilic tone that dampens the pro-inflammatory pathways

We suggest that the concepts of 'Nucleophilic Tone and 'Para-Hormesis' represent a paradigm shift in our understanding of the physiological mechanisms of action of nutritional antioxidants, from free radical scavengers to stimuli for the regulation of protective defense and repair systems.

**How Do Nutritional Antioxidants Really Work:
Nucleophilic Tone and Para-Hormesis Versus Free
Radical Scavenging *in vivo***

Henry Jay Forman, Kelvin J. A. Davies and Fulvio Ursini
FRBM 2013

A PARA-HORMETIC MECHANISM ACCOUNTS FOR HEALTH PROMOTION EFFECT OF FOODS CONTAINING “ANTIOXIDANTS” (FRUITS, VEGETABLES AND WINE!)

They activate when oxidized, the endogenous antioxidant system that operates a feedback regulation of the inflammatory pathways.

This is a major contribution to the maintenance of redox homeostasis and prevents the excess of reaction to different stimuli.

ACTIVATORS OF PARA-HORMESIS



Why wine is better than spirits



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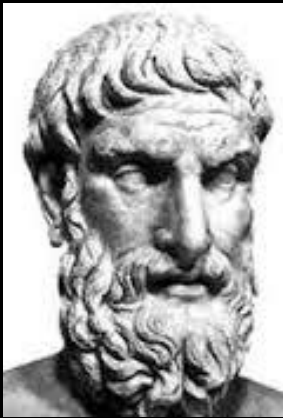
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Hormetic effect

Para-hormetic effect

The health is protected when challenges are efficiently neutralized escaping from excess in either side. By living in peace with our internal and external environment, adopting *aurea mediocritas* (moderation) we will achieve **ἀταραξία** (tranquillity, and seemingly a better health). Just an anticipation of the Claude Bernard physiology from the ethical phylosophy of Epicurus and Horace



342-270 BC



65-8 BC

Wine contributes to the maintenance of homeostasis by buffering the trend to an offset of the redox steady-state between pro and anti-inflammatory pathways

The wine, in this perspective, is not just a food protecting our health, but, remarkably, it does it in an ethical way.
