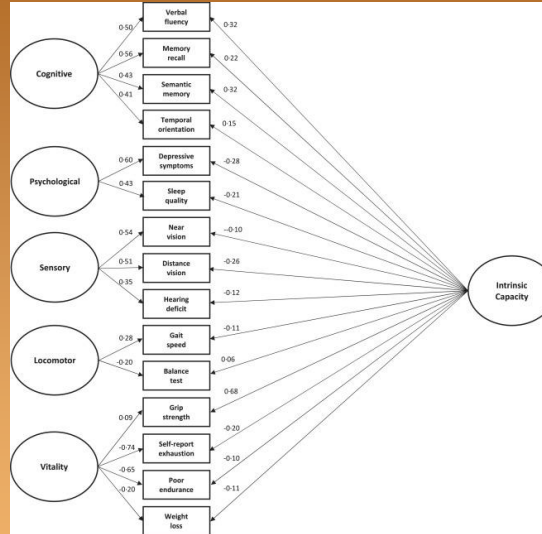
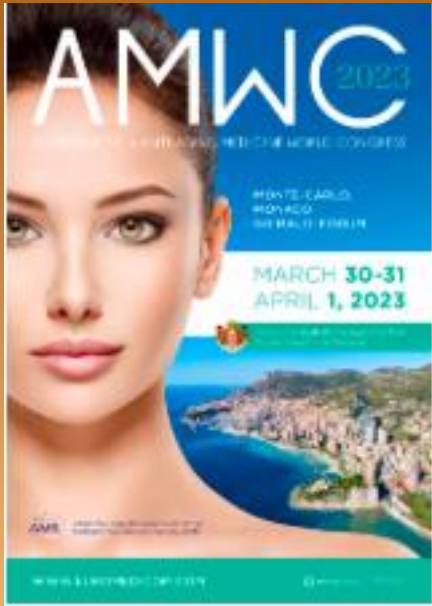


Nutraceuticals contribution

to healthspan



Patrizia A d'Alessio, MD PhD



No conflict of interest

Cometh aging challenging healthspan



In ancient times the food / skin link had already been observed



Dr Georges Cheyne
(1671-1743)

At the edge of the 17th – 18th century, **vegetarianism** became a treatment for **obesity and gout** for rich people consuming a lot of meat.

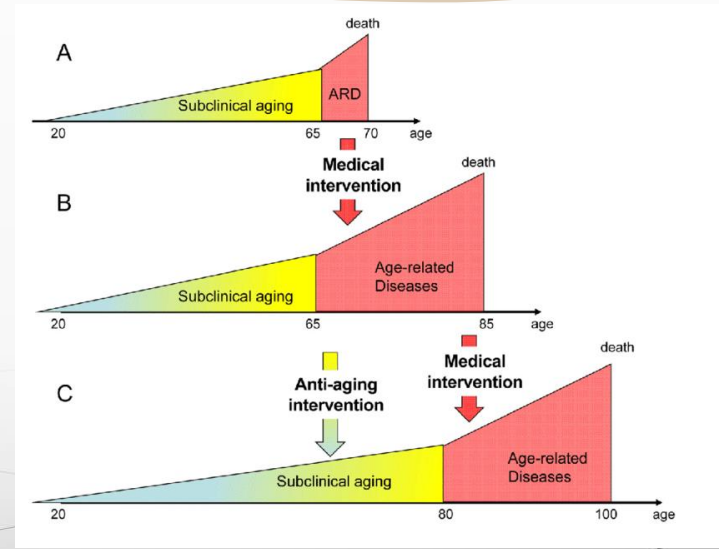
It turned out as a solution to **prevent wrinkles** and the fading of radiance of the skin.

Nutraceuticals

- ◆ The word “nutraceutical” is a “*portmanteau*” term, binding “nutrition” and “pharmaceutical”.
- ◆ A “nutraceutical” or “bioceutical” is a pharmaceutical alternative, **claiming physiological benefits**.
- ◆ These compounds are unregulated, assimilated to over-the-counter dietary supplements or food additives.

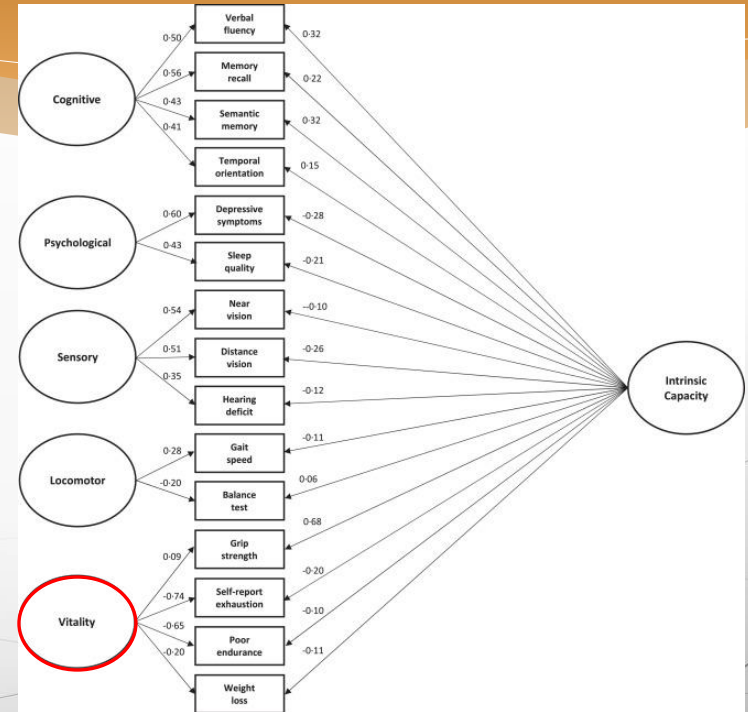
Nutraceuticals and healthspan

- ◆ **Nutraceuticals** may interfere with aging, in a way turning out to be beneficial for delaying health and beauty decay.
- ◆ To extend and enhance the part of a person's life considered in good health, « this is precisely the goal of **healthspan** ».



Healthspan & Intrinsic Capacity

- ◆ **Intrinsic capacity (IC)** has recently been proposed by the World Health Organization (WHO) as a multidimensional indicator of health,
- ◆ accounting for mental and physical capacities **that are crucial to older people to continue doing what they value most.**



ARTICLES | VOLUME 12, 100284, AUGUST 2022

Validating intrinsic capacity to measure healthy aging in an upper middle-income country: Findings from the ELSI-Brazil

Márlon J.R. Aliberti ¹ • Laiss Bertola ¹ • Claudia Szlejf • Déborah Oliveira • Ronaldo D. Piovezan • Matteo Cesari • et al.

Show all authors • Show footnotes

Open Access • Published: May 27, 2022 • DOI: <https://doi.org/10.1016/j.jana.2022.100284> • [Check for updates](#)

In order to achieve this goal we have to control inflammation



- ◆ because **inflammation** and its concomitant degradation of organ functions,
- ◆ together with the enhanced cell senescence it promotes, are **invisible**
- ◆ with the exception of depression, insomnia,
- ◆ decrease of youthful appearance, **mood and energy.**

INFLAMMATION: THE ARSENAL TO DELAY AGEING IN 2022

Patrizia A d'Alessio explains why she believes inflammation is the root cause of ageing symptoms and how it can be addressed

ABSTRACT
In our modern world, there is a paradox between our increased life expectancy and the increase in longevity. The latter should ideally be associated with healthy ageing, which is not always so easy to achieve. Trying to identify the complex interplay of metabolic alterations that underlie the development of ageing-related conditions have emerged chronic or silent inflammation as a key factor. This

status, which settles insidiously, is often not recognized as the source of red signs, rashes, rashes, mood changes or discomfort thoughts. Once acknowledged, there are various options for its treatment. The first is through medications, i.e. anti-inflammatory drugs that carefully relieve some symptoms. But to cope with chronic, site-specific inflammation, it is necessary to take care of the gut. However, signals are generated by constant brain-gut exchanges,

also concerning the skin. A healthy gut depends on the action of microbes, bacterial strains selected by healthy food. Among them, proper nutraceuticals have a place, especially if they are derived from natural products. Finally, a wider range of opportunities, from mild exercise to social activities, change the signs over periods to establish a new relationship's level between body status, able to cope smoothly with life's challenges.

BIO-GUIDED RESEARCH in search of a **non toxic** anti-inflammatory molecule



✓ ***d*-Limonene** best candidate among 2000 discovered in the *Halfordia kendack* plant in Viet / CN rain forest

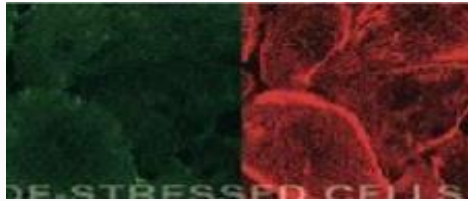


Reversibility of inflammatory markers relevant to cell senescence

ICAM-1

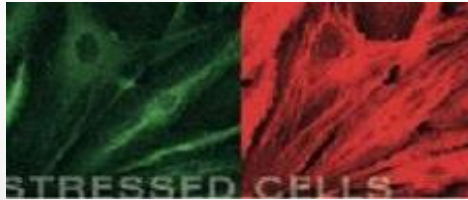
Actin

Normal



- ✓ Young cell's pre-stressed state with low adhesion molecule expression;

Activation by TNF- α



- ✓ Response to cytokine stimulation generates a senescent phenotype;

Reset by d-Limonene



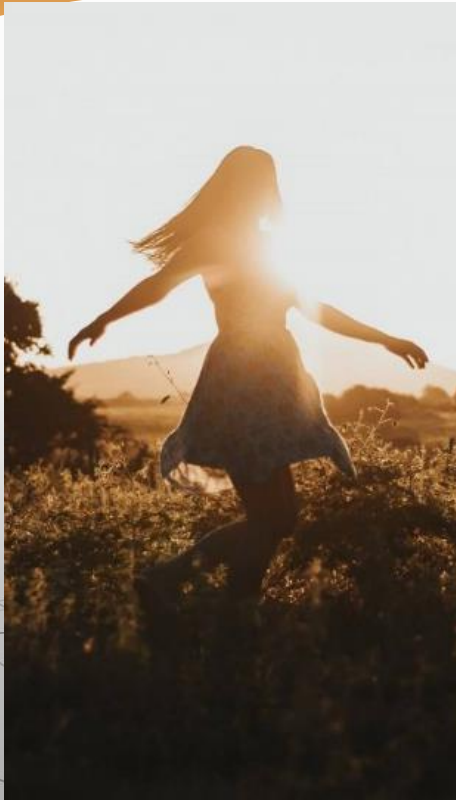
- ✓ **80% reversibility** of the process is possible with d-Limonene

REJUVENATION RESEARCH
Volume 11, Number 2, 2008
© Mary Ann Liebert, Inc.
DOI: 10.1089/rej.2008.0647

Anti-Inflammatory Senescence Actives 5203-L Molecule to Promote Healthy Aging and Prolongation of Lifespan

Jean-François Bisson,¹ Chantal Menut,² and Patrizia d'Alessio³

Anti-inflammatory / anti-aging effects are offered by nutritional ingredients

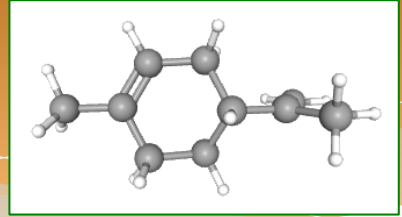


- ✓ The molecular complex identified in *Halfordia kendack* is also present in **Citrus Sinensis peel extract** (OPE)
- ✓ of the same botanical Genus, and as rich in d-Limonene
- ✓ It was named **AISA** standing for **Anti-Inflammatory Senescence Actives**



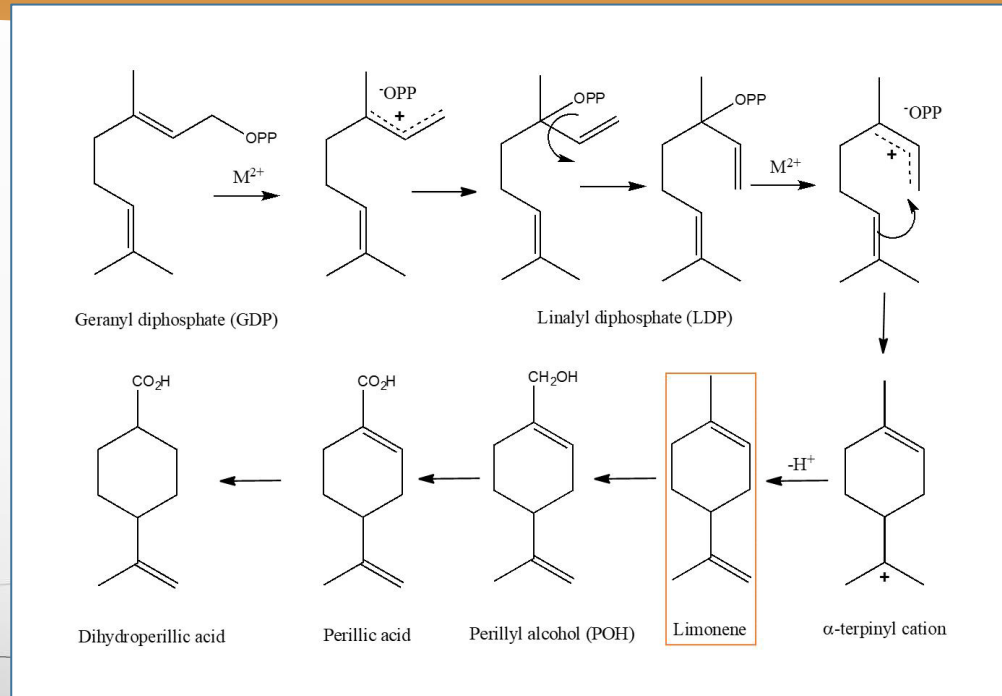
CONTRÔLÉ &
LABORÉ PAR
ASA-TECHNOLOGY

At the heart of plants and fruit components, are « small molecules »



- ◆ Low molecular weight ($\leq 1\text{KDa}$) organic compounds involved in the regulation/modification of biological processes
- ◆ **Natural** or **artificial**, many have a beneficial effect against diseases.
- ◆ They can be administered orally and some **are excellent anti-inflammatory agents**.
- ◆ They are considered different from biologics but may have similar effects.

d-Limonene and its metabolites



Potent small molecules!

French National Innovative research award

Patent on monoterpene's effect on reversibility of cell senescence *in vitro* ...

allowed us to pursue pre-clinical work on **non toxic** anti-inflammatory molecules enhancing healthspan



Mechanisms of Ageing and Development 186 (2020) 111206

Contents lists available at ScienceDirect



Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

AISA can control the inflammatory facet of SASP

Patrizia A. d'Alessio^{a,*}, Marie C. Béné^b

^a Gsepole Biogerprises, 4 rue Pierre Fontaine, 91058, Evry, France
^b Pôle Laboratoires Service d'Histologie Biologique CHU de Nîmes, 9 Quai Moncaou, 44000, Nîmes, France



Working with ethologists in a stress model : a remarkable **change in behavior**



REJUVENATION RESEARCH
Volume 17, Number 2, 2014
© Mary Ann Liebert, Inc.
DOI: 10.1089/rej.2013.1515

Anti-Stress Effects of *d*-Limonene and Its Metabolite Perillyl Alcohol

Patrizia A. d'Alessio,¹ Jean-François Bisson,² and Marie C Béné³



Fukumoto S, Sawasaki E, Okuyama S, et al. (2006) Flavor components of monoterpenes in citrus essential oils enhance the release of monoamines from rat brain slices. *Nutr Neurosci* 9: 73–80. <https://doi.org/10.1080/10284150600573660>

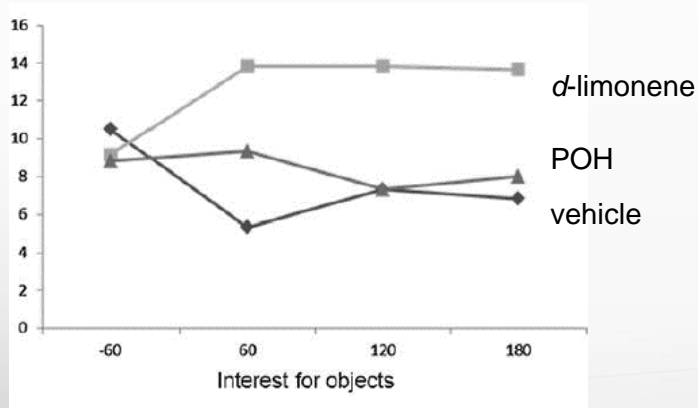


Pointing to

- ◆ activation of the **vagal tone**
- ◆ **dopamine** by *d*-Limonene

Mood modulation : pre-clinical / clinical results

Motivational effect in **rodents**



Mood modulation effect in **humans**

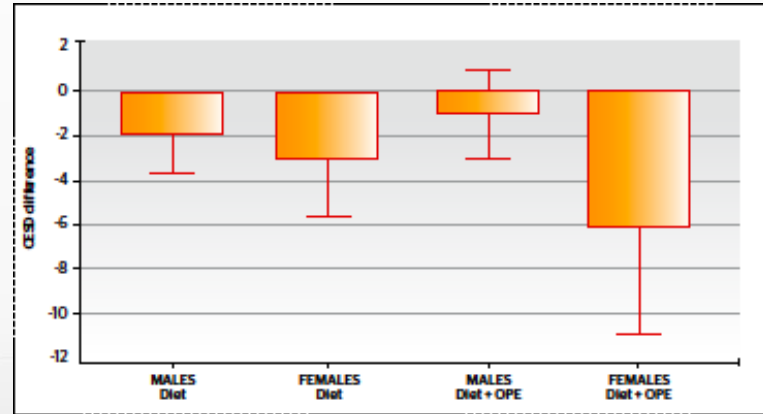


Figure 3 Gender partition and CES-D variation in diet versus diet plus OPE

Rejuvenation Res.
2014;17:145-149

PRIME 2012; 30-37

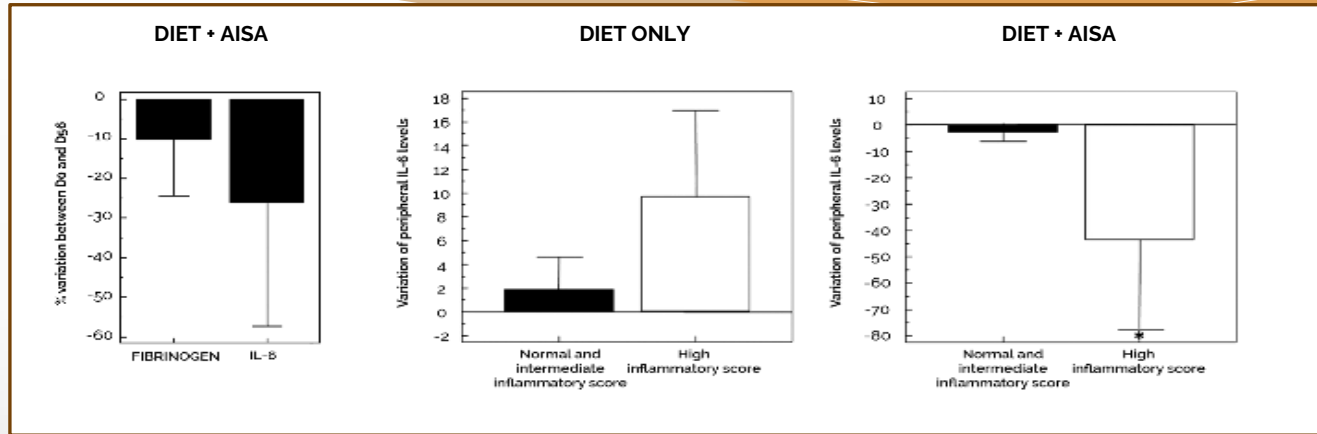
Oral administration in the first in human study « Healthy aging by Nutrition »



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
Prof. Claudio Franceschi

Inflammation markers

Anti-IL-6 efficacy as food supplementation



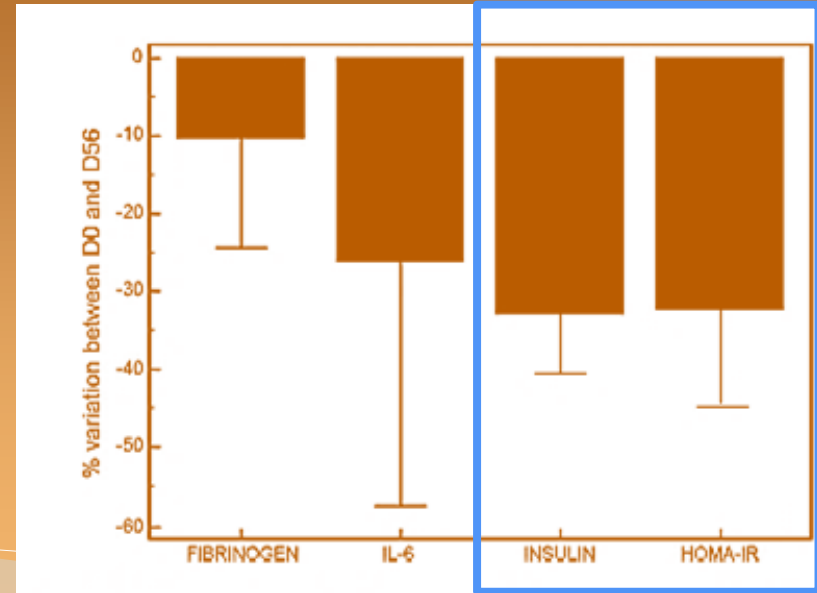
Significant modifications of inflammation markers
(fibrinogen and IL-6) in moderate inflammation (**RISTOMED**
diet + d-Limonene) between D0 and D56.



Bio-markers of cardio-metabolic syndrome, diabetes, thrombosis

Monoterpens target IL-6 and fibrinogen, but also insulin and **markers** of insulin resistance*

* Homeostatic model assessment of insulin resistance HOMA-IR



Clin Nutr. 2016;35:812-818.

d-Limonene and gut barrier repair in a pre-clinical study

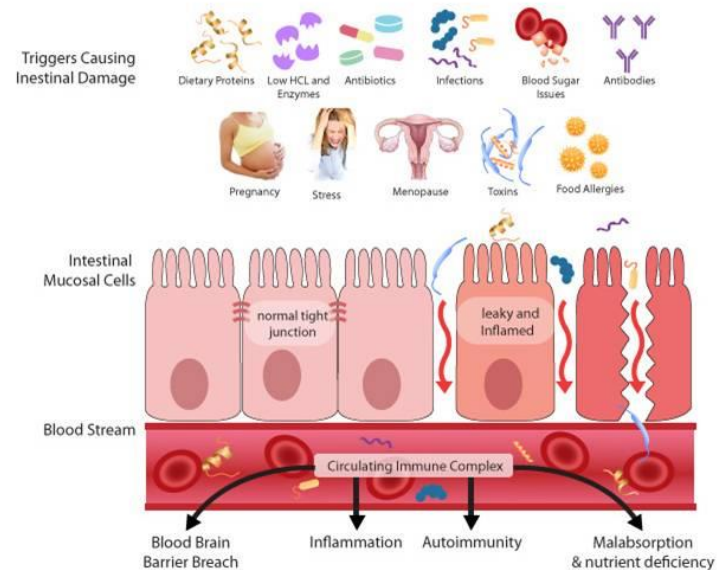


Table 1
OPE containing 95% of *d*-Limonene: effect on epithelial barrier function.

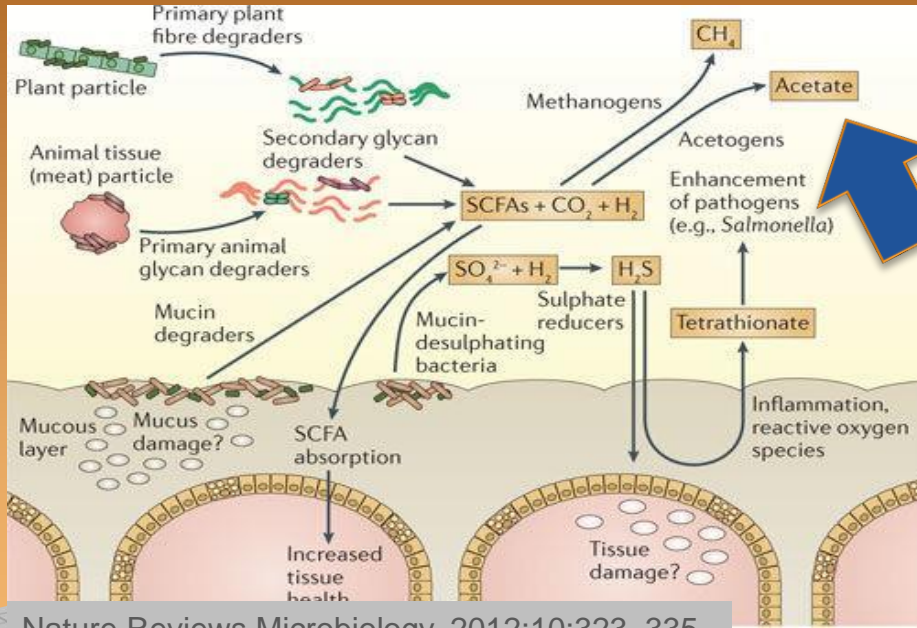
	Control	OPE			
		75 μ M	150 μ M	750 μ M	1500 μ M
R ^t	107 \pm 3%	106 \pm 4%	112 \pm 3%	132 \pm 3%	153 \pm 4%
n	9	6	6	6	6
p		n.s.	n.s.	<0.001	<0.001

Mesure of the electrical resistance (in $\Omega \cdot \text{cm}^2$) expressed as percentage of the initial restistance Rt.

Leaky Gut Syndrome



Monoterpenes address the gut-brain axis acting as pre-biotics (fibers)



Butyrate, **Propio-butyrate**,
Folate, Propionate

produced by:
Bifidobacteria
Clostridii
Enterobacterium
Enterococcus
Ruminococcus
Roseburia

Nature Reviews Microbiology, 2012;10:323–335

« The Gut-brain axis is relevant to skin aging ». d'Alessio PA
PRIME July 2020, Vol 10 Issue 4, 36-42

Gut barrier repair effects on microbiota

Monoterpenes modulate microbiota ratios

Clostridium cluster IV / *Bifidobacteria* ratio

Contents lists available at ScienceDirect

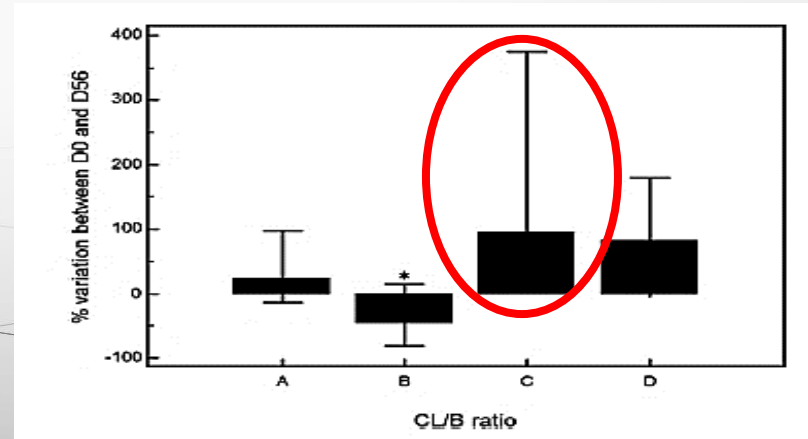
Clinical Nutrition

ELSEVIER journal homepage: <http://www.elsevier.com/locate/clnu>

Randomized control trials

Impact of diet and nutraceutical supplementation on inflammation in elderly people. Results from the RISTOMED study, an open-label randomized control trial*

R. Ostan^a, M.C. Béné^b, L. Spazzafumo^c, A. Pinto^d, L.M. Donini^d, F. Pryn^e, Z. Charrouf^f, L. Valentini^g, H. Lochs^h, J. Bourdel-Marchasson^{i,j,k}, C. Blanc-Bisson^{i,j,k}, F. Buccolini^l, P. Brigidi^m, C. Franceschi^{n,o}, P.A. d'Alessio^{p,*}



Vitality is a question of microbiota strains



nature
microbiology

ARTICLES

<https://doi.org/10.1038/s41564-018-0337-x>

The neuroactive potential of the human gut microbiota in quality of life and depression

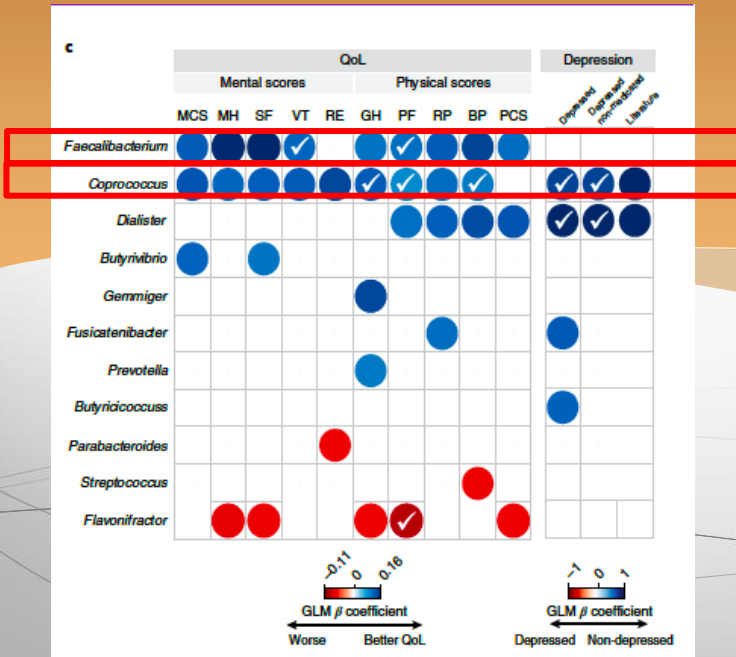
Mireia Valles-Colomer^{1,2}, Gwen Falony^{1,2}, Youssef Darzi^{1,2}, Ettje F. Tigchelaar³, Jun Wang^{1,2}, Raul Y. Tito^{1,2,4}, Carmen Schiweck⁵, Alexander Kurilshikov³, Marie Joossens^{1,2}, Cisca Wijmenga^{3,6}, Stephan Claes^{5,7}, Lukas Van Oudenhove^{7,8}, Alexandra Zhernakova³, Sara Vieira-Silva^{1,2,9} and Jeroen Raes^{1,2,9*}



Increased health span through a healthy microbiota?

QoL could thus be a MATTER of bacterial metabolites

Faecalibacterium & **Coprococcus** for
VITALITY, emotional well-being & Social functioning



◆ **Faecalibacterium** and **Coprococcus**, among the producers of **propiobutyrate**, are associated to good QoL

◆ **Coprococcus** spp are decreased in case of depression even after correction for the effects of anti-depressants.

The small molecule monoterpene *d*-Limonene *resets* body multi-systems

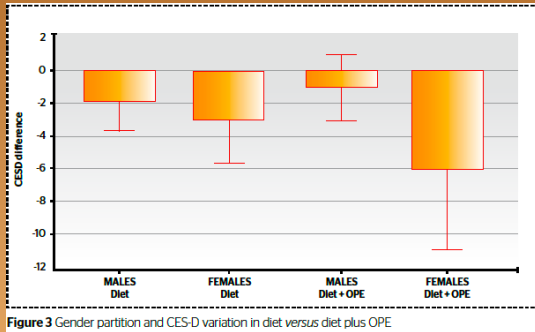
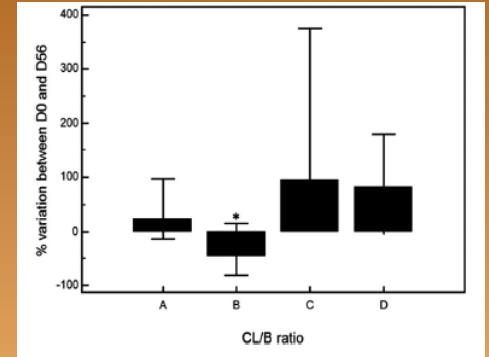


Figure 3 Gender partition and CES-D variation in diet versus diet plus OPE



Anti-inflammatory effect enhances **dopamine**



Restoration of the gut barrier fights **dysbiosis**

2020-2022 Terpenoid « geroprotectors »






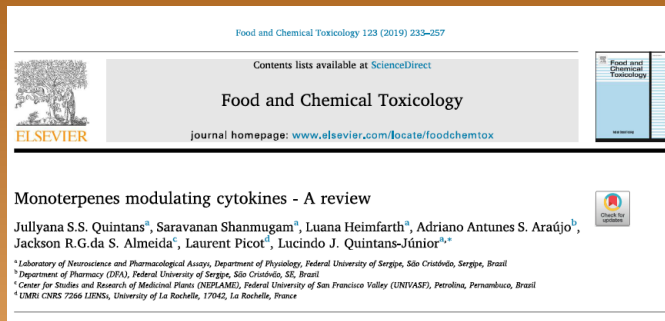
antioxidants



Review

Terpenoids as Potential Geroprotectors

Ekaterina Proshkina¹ , Sergey Plyusnin^{1,2} , Tatyana Babak¹, Ekaterina Lashmanova¹, Faniya Maganova³, Liubov Koval^{1,2}, Elena Platonova^{1,2}, Mikhail Shaposhnikov¹ and Alexey Moskalev^{1,2,*} 



AIMS Molecular Science

2022, Volume 9, Issue 2: 46-65. doi: 10.3934/molsci.2022003

Research article

d-Limonene challenging anti-inflammatory strategies

Patrizia A d'Alessio¹ , Marie C Béné², Chantal Menut³

1. AISA Therapeutics, University Paris Sud-11 and Genopole, Evry, France
2. Hematology Biology, CHU de Nantes & Inserm 1232 CRCINA, Nantes, France
3. IBMM, Univ Montpellier, CNRS, ENSCM, Montpellier, France

Received: 12 November 2021 | Revised: 09 January 2022 | Accepted: 07 April 2022 | Published: 20 April 2022

 Previous Article

Useful to health span ?

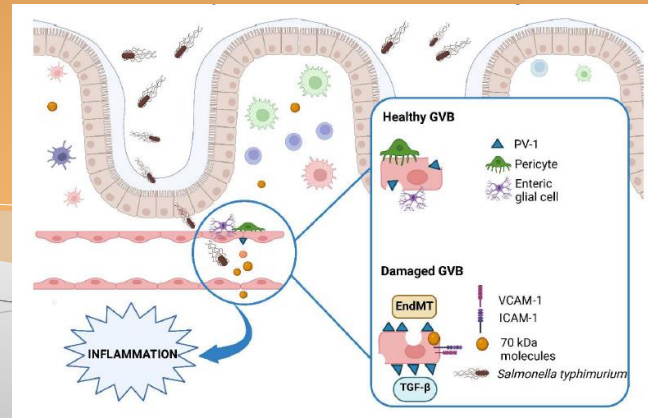
REVIEW

Proteomics
www.proteomics-journal.com

Ageing Biomarkers: From Functional Tests to Multi-Omics Approaches

Ksenia S. Kudryashova, Ksenia Burka, Anton Y. Kulaga, Nataliya S. Vorobyeva,*
and Brian K. Kennedy*

- ◆ « When it comes to switch from biomarker-based metrics to the characterisation of aging **profiles** »
- ◆ anti-inflammatory bio-markers criteria should include **mucosal immunity compliance**



International Journal of
Molecular Sciences



Review

The Gut-Vascular Barrier as a New Protagonist in Intestinal and Extraintestinal Diseases

Natalia Di Tommaso ¹, Francesco Santopaolo ¹, Antonio Gasbarrini ^{1,2} and Francesca Romana Ponziani ^{1,2,*}

- ◆ Aiming at longevity and increased healthspan includes frailty and pre-frailty issues
- ◆ Monitoring the propensity to develop diseases should include **gut-brain** issues



ESTHETIC FEATURE | INFLAMMATION | FINE

THE GUT-BRAIN AXIS AND SKIN AGEING

Patrizia d'Alessio explains how the gut-brain relationship can be the cause and possible solution to issues around inflammation and skin ageing

ABSTRACT
The gut-brain connection is an emerging field of research involving microbiome, nutrition, stress management that can modulate the gut barrier function, its permeability and its communication with the rest of the body and brain. In this comprehensive review, we discuss the role of the gut-brain axis in skin ageing and its potential as a target for skin care.

WHAT WILL BE COVERED IN THIS ARTICLE? WELL, WE WILL discuss the relationship between the visible and invisible in the dialogue between the gut and the brain in various, the progressive transformation of our skin in daily genotype and phenotype, and how they are affected by the gut-brain axis. We will also discuss the role of the gut-brain axis in skin ageing and its potential as a target for skin care.

KEYWORDS
Gut-brain axis, skin ageing, inflammation, microbiome, nutrition, stress management, skin care.

INTRODUCTION
The gut-brain connection is an emerging field of research involving microbiome, nutrition, stress management that can modulate the gut barrier function, its permeability and its communication with the rest of the body and brain. In this comprehensive review, we discuss the role of the gut-brain axis in skin ageing and its potential as a target for skin care.

CONCLUSION
The gut-brain axis is a complex system that involves the gut, the brain, and the rest of the body. It is a bidirectional system that can be affected by various factors, including diet, stress, and lifestyle. Understanding the gut-brain axis is crucial for developing effective skin care strategies.

Received: 6 August 2018 | Revised: 14 October 2018 | Accepted: 25 October 2018
DOI: 10.1111/dth.12783

REVIEW ARTICLE

Salutogenesis and beyond

Patrizia A. d'Alessio

Alisa Therapeutics, Villejuif, France

Correspondence
Patrizia A. d'Alessio, Biopark Campus, 11 rue de Pr Georges Mathé, 94807 Villejuif, France.
Email: patriz.dalesio@gmail.com

Abstract

In the present hypothesis paper on paradoxes in preventive medicine, which also deals with the indocility of biological functions, the following issues will be addressed. First, a definition of salutogenesis will be given, providing the origin of this notion of health preservation and disease prevention. Then, four paradoxes of the biology of health will be discussed. The first deals with the

WILEY **DERMATOLOGIC THERAPY**

The First Ristomed Consensus meeting



Thank you for your attention

Questions & Credits



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Consiglio Nazionale delle Ricerche
Institute of Genetics and Biophysics
Adriano Buzzati-Traverso

