

From Inflammaging to Intrinsic Capacity : a role for terpenoid geroprotectors

Patrizia A d'Alessio, MD PhD



INTERNATIONAL LONGEVITY SUMMIT
The Longevity and Biotech revolution in Africa:
Leveraging the dynamics of diversity, inclusivity, and innovation.

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Prof. Dr. Patrizia D'ALESSIO MD PhD
CEO AISA Therapeutics
Award Innovative Entrepreneurship Ministry of Research France.

23 -24 August 2023 | 26th South Hotel,
Cradle of Humankind Heritage Site,
Johannesburg, South Africa

For More Info :
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No conflict of interest

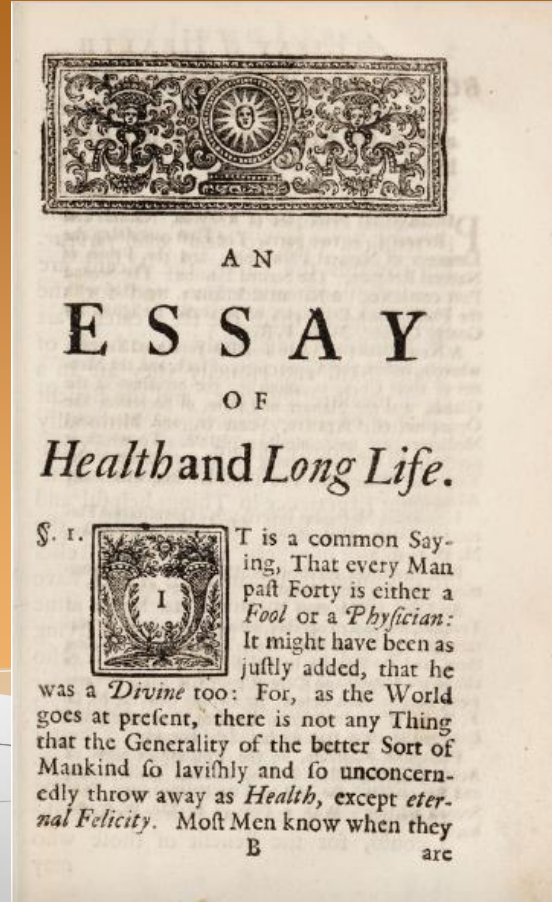
What will we be talking about?

- ◆ Starting from the « Inflammaging » concept
- ◆ Bio-guided research aimed at non toxic anti-inflammatory molecules
- ◆ « Small molecules » and Terpenoids
- ◆ Lowering pro-inflammatory cytokines (pre-clinical)
- ◆ RISTOMED EU FP7 **first in human study on « terpenoid geroprotectors »**
- ◆ Enhanced RISTOMED project integrating « Vitality » criteria

Iatromechanists British Enlightenment XVII-XVIII



Dr George Cheyne
(1671-1743)



In 1725 « An Essay
of Health and
Long Life »

2 *An ESSAY of HEALTH*

are ill, but very few when they are well. And yet it is most certain, that it is easier to *preserve* Health than to *recover* it, and to *prevent* Diseases than to *cure* them. Towards the first, the Means are mostly in our own Power. Little else is required than to *bear* and *endure*. But towards the latter, the Means are perplexed and uncertain; and for the Knowledge of them the far greatest Part of Mankind must apply to others, of whose Skill and Honesty they are in a great measure ignorant, and the Benefit of whose Art they can but conditionally and precariously obtain. A crazy Constitution, original weak Nerves, dear-bought Experience in Things helpful and hurtful, and long Observation on the Complaint of others, who came for Relief to this universal Infirmary, *BATH*, have at last (in some measure) taught me some of the most effectual Means of preserving Health and prolonging Life in those who are *tender* and *sickly*, and labour under *chronical* Distempers. And I thought I could not spend my leisure Hours better than by putting together the most general Rules for that Purpose, and setting them in the clearest and strongest Light I could, for the Benefit of those who may

« Most men know when they are ill, But very few when they are well. »

« And yet it is most certain, that it is easier to **preserve health** than to recover it and to **prevent diseases** than to cure them. »

Some centuries later chronic inflammation was identified as the main mechanism of aging

Review

> [Ann N Y Acad Sci. 2000 Jun;908:244-54. doi: 10.1111/j.1749-6632.2000.tb06651.x.](#)

Inflamm-aging. An evolutionary perspective on immunosenescence

[C Franceschi](#) ¹, [M Bonafè](#), [S Valensin](#), [F Olivieri](#), [M De Luca](#), [E Ottaviani](#), [G De Benedictis](#)

Inflammation that we **ache** about



Inflammation leads to **Common Chronic Diseases**



- ◆ Inflammation **that does not resolve** is at the basis of cancer, degenerative diseases and **CCD**.
- ◆ Inflammation **that does not resolve** is also the sign of **gut mucosal immunity impairment**.

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 stressful lives 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 immune and metabolic alterations that favour the appearance of ageing traits, researchers have pinpointed chronic (or silent) inflammation as a key factor. This status, which settles insidiously, is often not recognised as the source of odd palets, insomnia, mood changes or obsessive thoughts. Once acknowledged, three options can be chosen. The first is through medication, i.e. anti-inflammatory drugs that certainly relieve some symptoms but also come with unwanted side effects. The second involves taking care of the gut. Numerous signals are generated by constant brain-gut exchanges, also concerning the skin. A healthy gut depends on the action of microbiota, bacterial strains selected by healthy food. Among them, proper nutraceuticals have a place, especially if they are derived from natural products. Finally, a whole range of experiences, from mild exercise to social activities, engage the vagus nerve positively to establish a less-inflammatory, more efficient body status, able to cope smoothly with life's challenges.

26 | September/October 2022 | prime-journal.com

Biomarkers

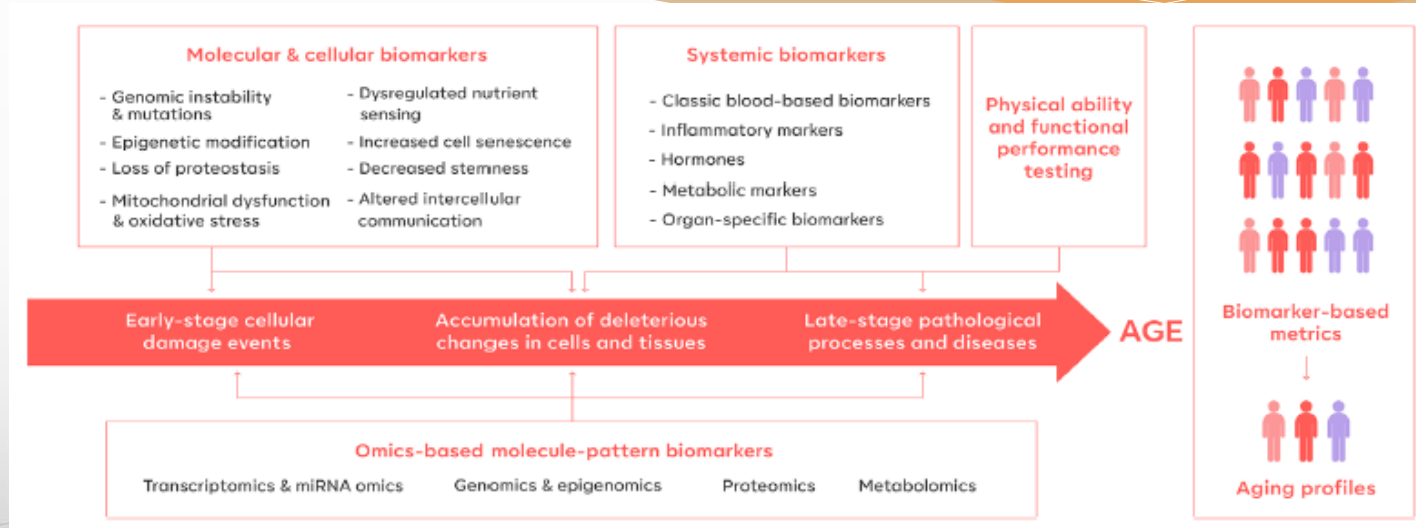
REVIEW

Proteomics

www.proteomics-journal.com

Aging Biomarkers: From Functional Tests to Multi-Omics Approaches

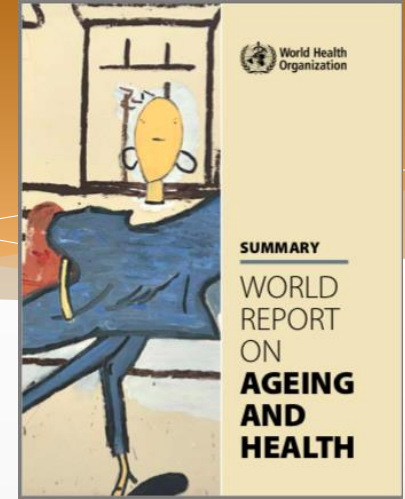
Ksenia S. Kudryashova, Ksenia Burka, Anton Y. Kulaga, Nataliya S. Vorobyeva,*
and Brian K. Kennedy*



◆ « When it comes to switch from biomarker-based metrics to the characterisation of aging **profiles** », ...

WHO 2015 : « Intrinsic Capacity »

- ◆ **Intrinsic capacity (IC)** has been proposed by the 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**.



Personal View

WHO working definition of vitality capacity for healthy longevity monitoring

Ivan Reutzmann*, Verónica Knopoff, Jat heeswaran Amuthavalli Thiyagarajan, Andrea Di Meier, John R Beard, Ellen Freiberger, Daniel Beldyk, Mylene Aubertin-Lehedir, Christopher Mikton, Matteo Cesari, Yuki Sumi, Theresa Diaz, Anshu Banerjee, on behalf of the WHO Working Group on Vitality Capacity†

Journal of Gerontology: Medical Sciences
c/o: J Gerontol A Biol Sci Med Sci. 2022, Vol. 77, No. 1, 94–100
<https://doi.org/10.1093/geron/glab225>
Advance Access publication August 3, 2021

OXFORD


Research Article

Intrinsic Capacity: Validation of a New WHO Concept for Healthy Aging in a Longitudinal Chinese Study

John R. Beard, MBBS, PhD,^{1,*} Yafei Si, MA,^{1,2,*} Zhixin Liu, PhD,^{3,4} Lynn Chenoweth, PhD,⁴ and Katja Hanewald, PhD^{1,2,*}

ARTICLES | VOLUME 12, 100284, AUGUST 2022

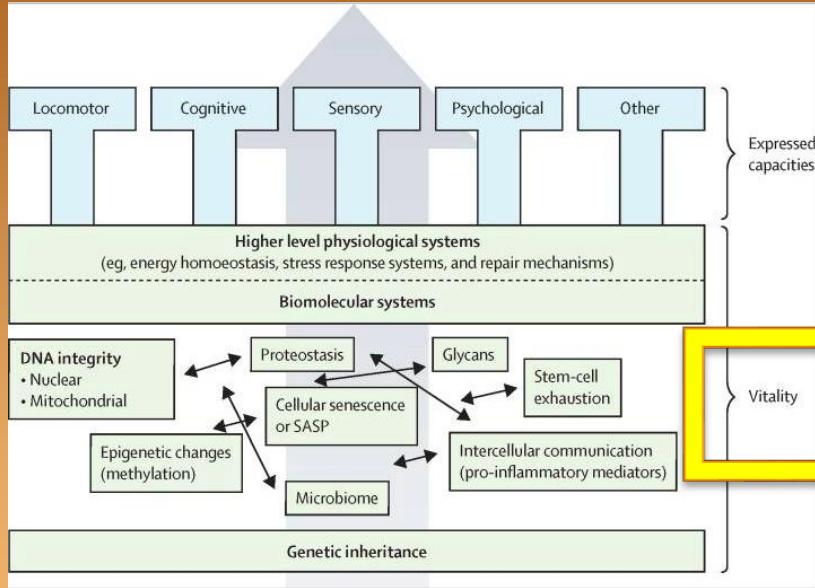
Validating intrinsic capacity to measure healthy aging in an upper middle-income country: Findings from the ELSI-Brazil

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

« Vitality » is the biomarker,



- 1/ **Expressed capacities** measurable by functional assessments
- 2/ **Underlying capacities** representing complex and dynamic of

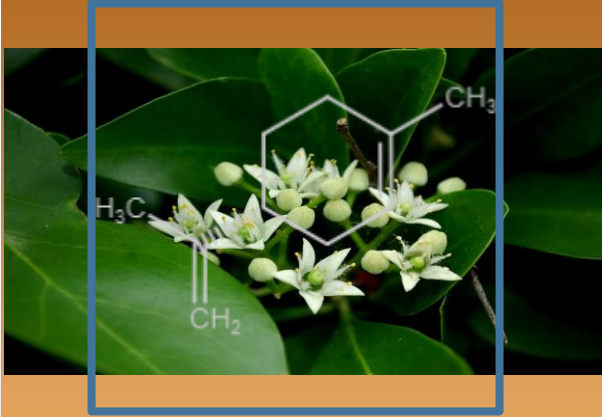
biological changes that occur with aging

« Changes in this underlying capacity might ultimately influence expression of the more overt capacities but may initially only be observable as basic **cellular or intracellular physiologic changes** » John R Beard et al.

Around 2000 we
started to look for
botanical
ingredients
contained in healing
plants

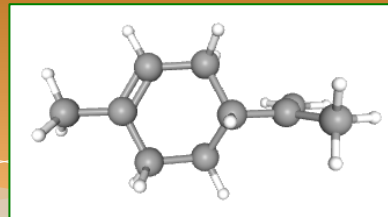


BIO-GUIDED RESEARCH aimed at the identification of a **non toxic** anti-inflammatory **molecule**



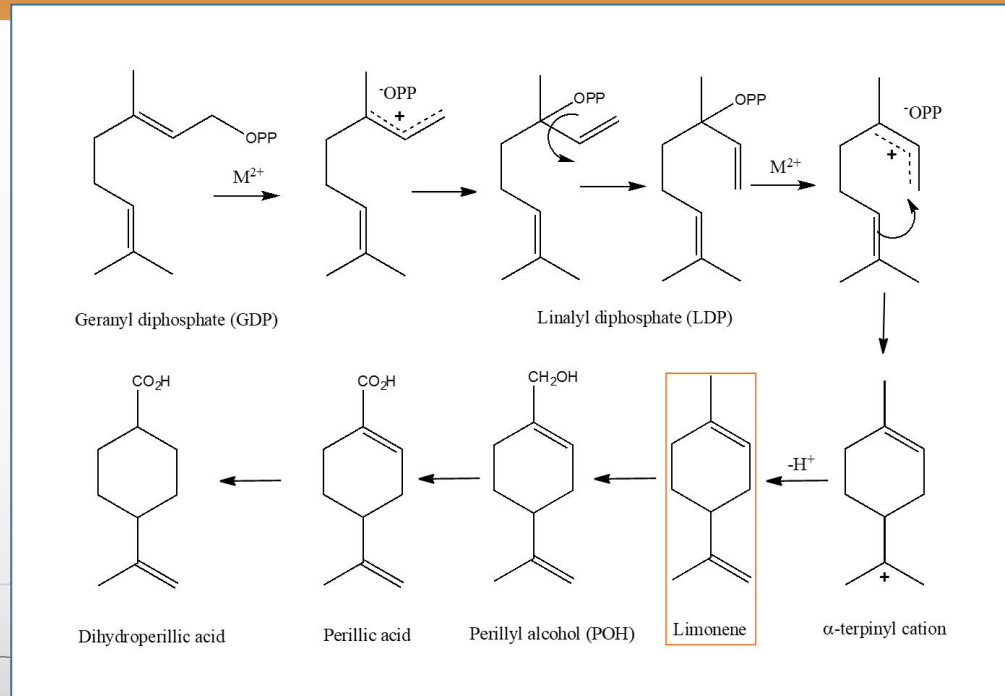
✓The monoterpene **d-Limonene** was the best **candidate** discovered in the *Halfordia kendack* healing plant in the Vietnam / China rain forest

At the heart of these different effects, « 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 molecule !

Anti-Inflammatory Senescence Actives **AISA** Inhibit adhesion molecules and actin cytoskeleton

ICAM-1

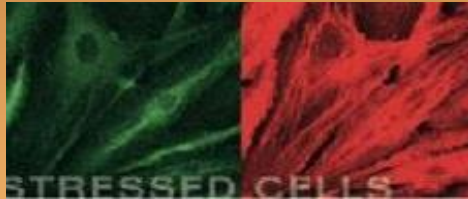
Actin

Normal



- ✓ Endothelial cells : low adhesion molecule and pre-stressed actin network

Activation
by TNF- α



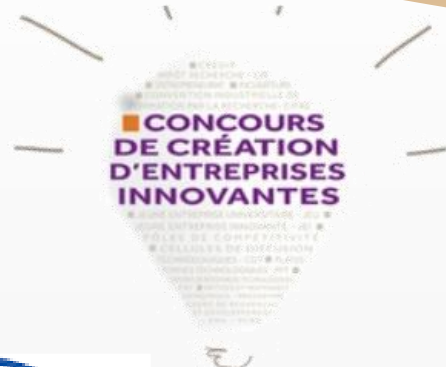
- ✓ Response to pro-inflammatory cytokine stimulation generates a senescent phenotype

Reset by
d-Limonene



- ✓ **80% reversibility** of adhesion molecules expression and actin stress fibers
- ✓ *d*-Limonene monoterpenene at 0.002% and 0.004% = micromolar concentrations

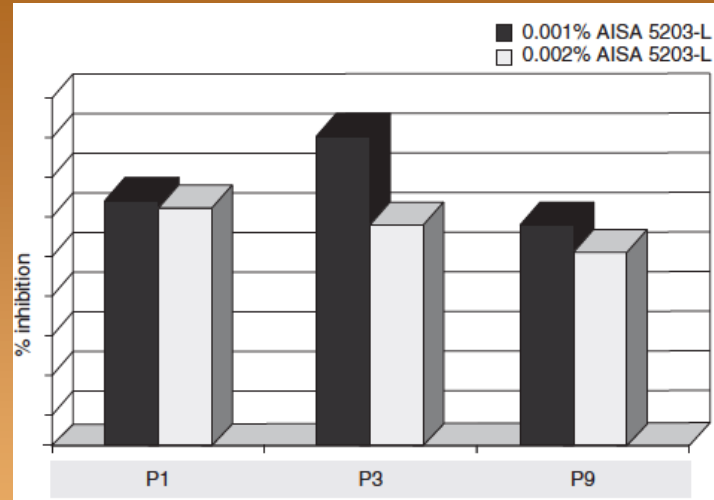
2005 national award for innovative research



Comprendre le monde,
construire l'avenir



2007 First results at SENS 3 conference



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

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

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

Mechanisms of Ageing and Development 136 (2007) 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

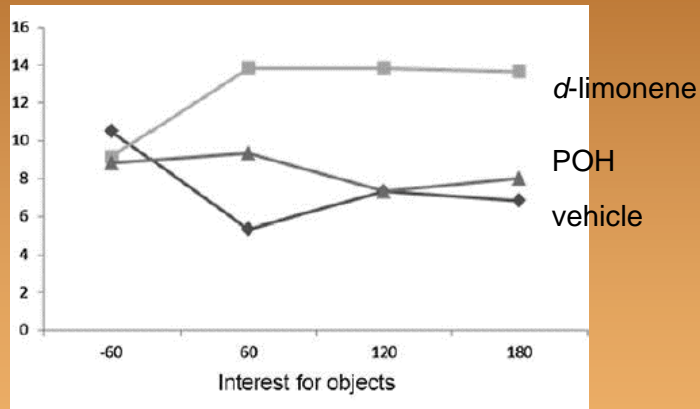
^a Centre de Biogéronte, 4 rue Marie Perle, 93156, Styr, France

^b Pôle Laboratoire Service d'Éthnologie Biologique CSU de Nancy, 9 Quai Maréchal, 54000, Nancy, France



Concomitantly, in a rodent stress model : **change in behavior** confirmed in humans

Motivational effect in **rodents**



Rejuvenation Res **2014**;17:145-149

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>

Mood modulation effect in **humans**

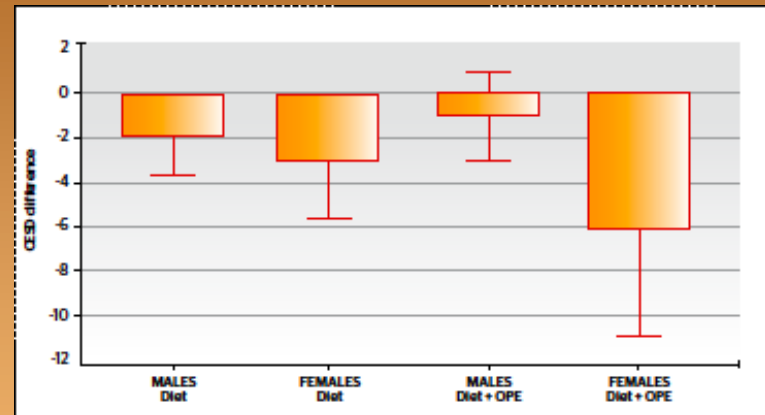


Figure 3 Gender partition and CES-D variation in diet versus diet plus OPE

PRIME **2012**; 30-37

D-Limonene decreases depression-like behavior and improves memory via an anti-neuroinflammatory mechanism under chronic restraint stress in rats

MEHMET ALKANAT¹, Hafize Alkanat², and Arif Keskin³

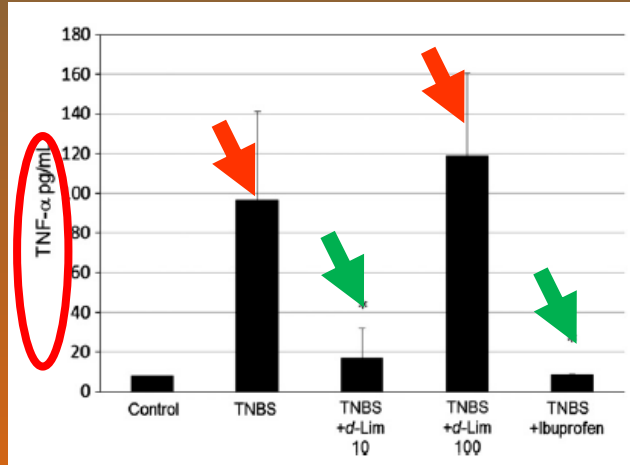
¹Giresun University Faculty of Medicine

²Giresun University

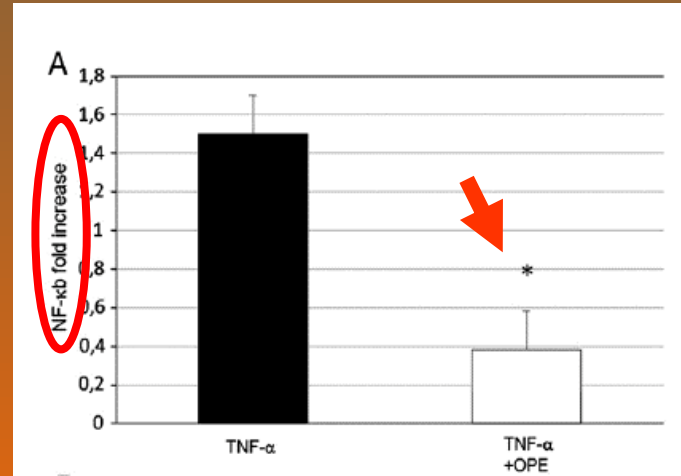
³Giresun Universitesi Tip Fakultesi

August 4, 2023

AISA *in vitro* PRE-CLINICAL colitis model : inflammatory cytokines inhibition transcription factor **NF- κ B**



Effect comparable to ibuprofen
for low-dose *d*-Limonene



Anti TNF- α , IL-6, IL-1b, IFN- γ effect
& inhibition of NF- κ B

AISA *in vitro* PRE-CLINICAL dermatitis model : inflammatory cytokines inhibition in a **wound healing model**

Vehicle



d Lim



POH



neo-angiogenesis inhibition

Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry, 2014, 13, 000-000

1

Skin Repair Properties of *d*-Limonene and Perillyl Alcohol in Murine Models

Patrizia A. d'Alessio^{1*}, Massoud Mirshahi², Jean-François Bisson³ and Marie C. Béné⁴

¹University Paris Sud-11 Biopark Campus Cancer, Villejuif, France; ²University Paris 6-Pierre et Marie Curie, Inserm E 9912, Paris, France; ³ETAP Research Centre, Vandoeuvre-lès-Nancy, France; ⁴Hematology, CHU & Nantes University, Nantes, France

Tissue repair in an auto-immune disease model



Vehicle

TPA
lesion mim
for AD

TPA + d-Lim

TPA + POH



TPA 12-O-Tetradecanoylphorbol-13-Acetate POH Perillyl alcohol

First in human study FP7 Capacities « Healthy aging by Nutrition »

Clinical Nutrition 35 (2016) 812–818



ELSEVIER

Contents lists available at ScienceDirect

Clinical Nutrition

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. Pryen ^e, Z. Charrouf ^f,
L. Valentini ^g, H. Lochs ^h, I. Bourdel-Marchasson ^{i,j,k}, C. Blanc-Bisson ^{i,j,k}, F. Buccolini ^l,
P. Brigidi ^m, C. Franceschi ^{a,n,o}, P.A. d'Alessio ^{p,*}



ALMA MATER STUDIORUM
UNIVERSITA DI BOLOGNA
Prof. Claudio Franceschi

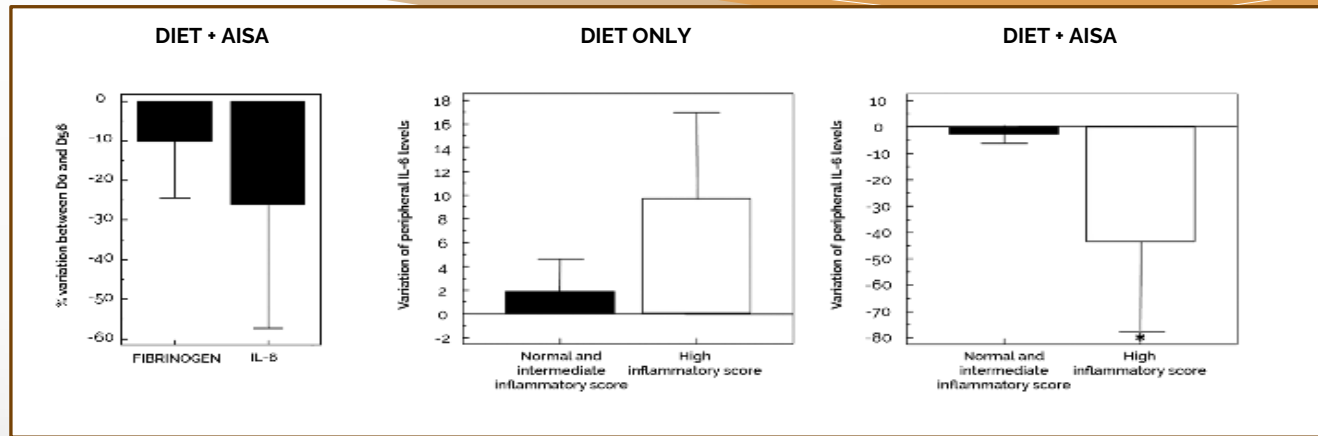
Clinical Nutrition 2016;35:812-818



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

Inflammation markers

Anti-IL-6 efficacy as food supplementation

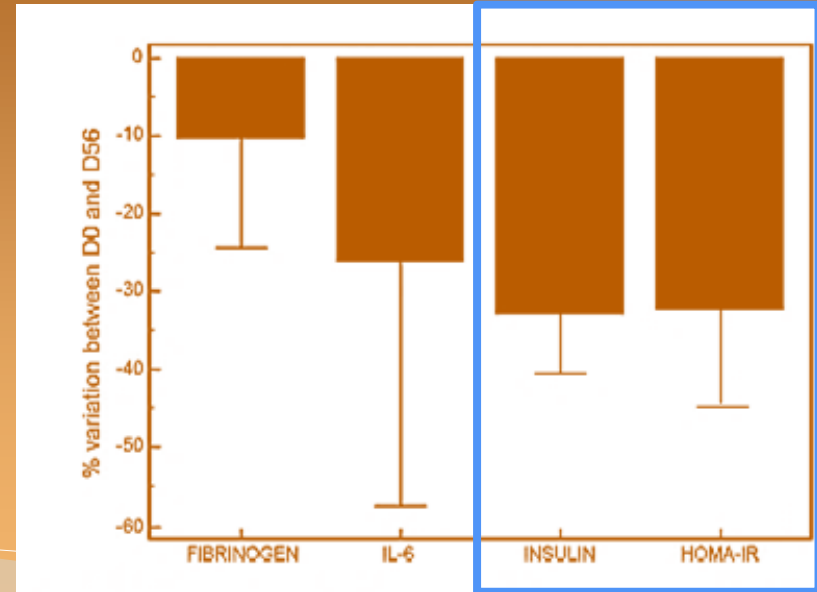


**Significant modifications of inflammation markers
(RISTOMED diet + d-Limonene) between D0 and D56.**

Biomarkers of cardio-metabolic syndrome, diabetes, thrombosis

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

* Homeostatic model assessment of insulin resistance HOMA-IR



Gut barrier repair

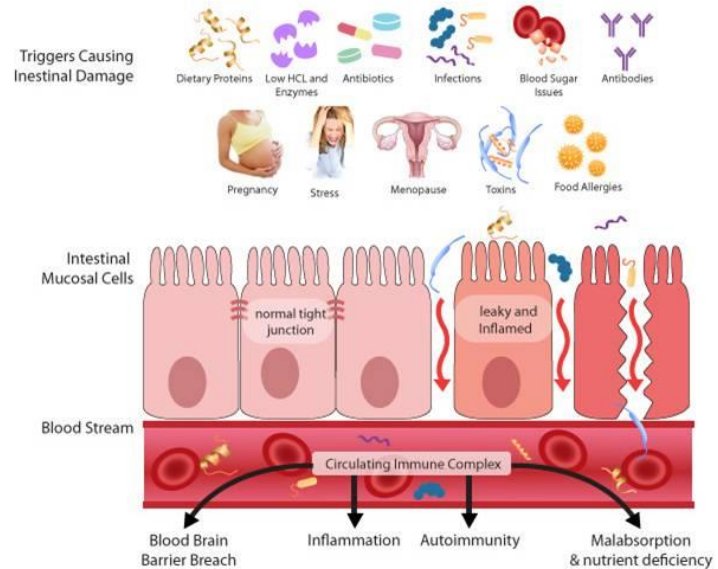


Table 1
OPE containing 95% of *d*-Limonene: effect on epithelial barrier function.

	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 resistance R_t.

Leaky Gut Syndrome



Consequences on microbiota

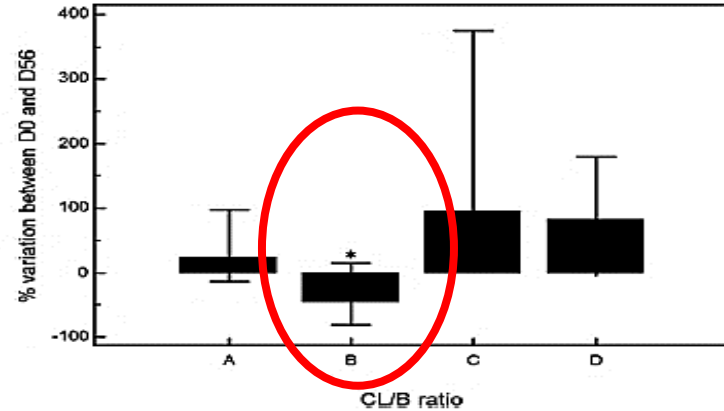
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microbiology

ARTICLES

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

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

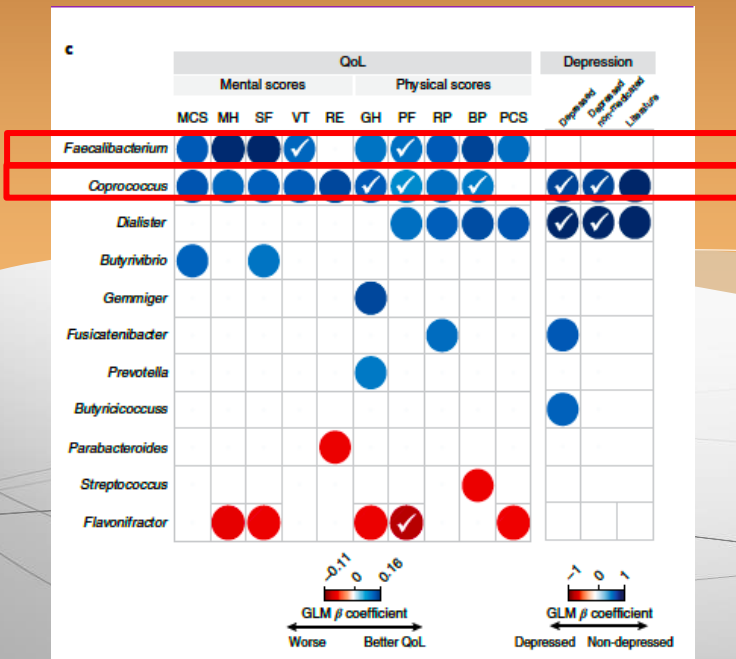
Mireia Valles-Colomer^{1,2}, Gwen Falony^{1,2}, Youssef Darzi^{1,2}, Ettje F. Tigchelaar³, Jun Wang^{1,2}, Raul Y. Tito^{1,2,4}, Carmen Schiweck⁵, Alexander Kurilshikov³, Marie Joossens^{1,2}, Cisca Wijmenga^{3,6}, Stephan Claes^{5,7}, Lukas Van Oudenhove^{7,8}, Alexandra Zhernakova³, Sara Vieira-Silva^{1,2,9}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



Monoterpen d-Limonene
modulates microbiota ratios
Clostridium cluster IV / *Bifidobacteria* ratio

« VITALITY » a matter of bacterial metabolites

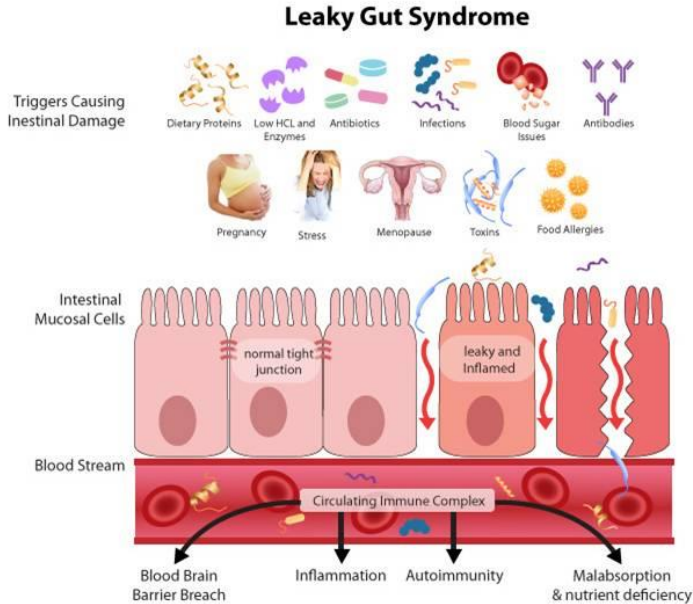
Faecalibacterium & **Coprococcus** for VITALITY, emotional well-being & social functioning



◆ **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.

Treating chronic inflammation by addressing gut barrier repair also brings amelioration of the skin



AESTHETIC FEATURE | INFLAMMATION | PRIME

THE GUT-BRAIN AXIS AND SKIN AGEING

Patrizia A 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 advances skin quality through three interconnected mechanisms: reaching from chronic inflammation that can damage the gut barrier function to the opportunity of organ-specific inflammatory healing in the gut and skin. But, it is a complex system. Inflammation, ageing and is related by these factors. Nutrition, however, may be an expected resource because of its ability to reduce systemic inflammation.

The skin participates in the gut-brain dialogue through the neuroendocrine system that has been established in the gut. Overall, chronic inflammation weakens the digestive system because of its ability to reduce intestinal permeability through autoantibodies. This ultimately affects the gut barrier function, a starting point for a generalized systemic 'leakage' of toxins, which can then be absorbed into the bloodstream. This leads to the production of organ-specific inflammatory and health issues. As a result, the help that can be brought by complete gut barrier healing through probiotics, neuro-peptide and botanicals, may be a key to improving skin quality by contributing to better information exchange, the ongoing exchange. There are two major organs that are so important to our health: the gut and the brain. The gut-brain axis is a complex system of events aimed at skin health and beauty. To summarize, because food intake activates complex signalling pathways, it plays a role in the dialogue between skin youth and its relationship with the gut.

The gut as a starting point

In order to better understand the gut-brain connection, it is necessary to consider the cause of food intake and the consequent signalling mechanisms. The role played by the brain and the gut in stress management, as stress probably alters the structure of the gut barrier and its composition to function resulting in dysbiosis. It is interesting to note that this complex system of events aimed at skin health and beauty. To summarize, because food intake activates complex signalling pathways, it plays a role in the dialogue between skin youth and its relationship with the gut.

In ancient times, and notably since the 17th and during the 18th century, dietary components have been observed to have specific effects on general health and skin quality. While Hippocrates first became a treatment for obesity and food, giving wealthy people consuming meat excessively. Dr George Chenier (1875-1943), who launched vegetarianism, was also beginning to consider it as a solution to speed wrinkles and lack of skin radiance. Today we know that specific food components of meat or vegetable intake play a role in skin communication. One of the best aspects of this dialogue is the contribution or preferential enhancement of specific microbiota strains developed to the digestion of



PATRIZIA ANNA D'ALESSIO, MD, PhD is an international expert on biological mechanisms of inflammation, aging and stress. She holds the position of Director, EVO France

small peptide delivery products

KEYWORDS
Skin care with challenge, stress management, chronic inflammation

Observational study in intermediate psoriasis

Dermatologic diseases depending on « leaky gut » and promoted by stress episodes – may benefit from gut barrier repair



D0

D45



SAPIENZA
UNIVERSITÀ DI ROMA

Case study ATOPIC DERMATITIS

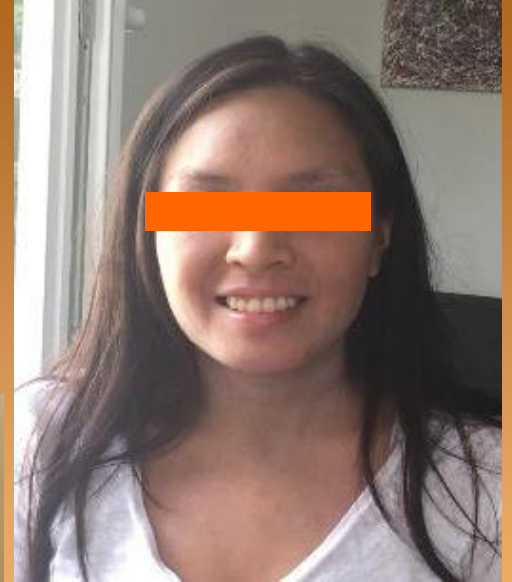
(eczema) worsened by repeated topic cortisol treatment

High levels of zonulin / anti-food IgG

Partial restoration after 10 days cure with **anti-inflammatory** terpenoids

Gut barrier repair, with restitution of skin quality

Visible **mood** amelioration
Rejuvenation effect



The « small molecule » *d*-Limonene and its metabolite POH *reset* body multi-systems

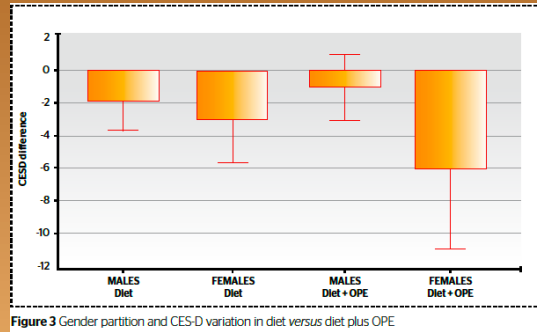
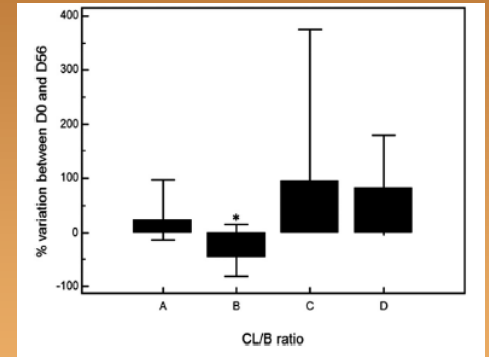
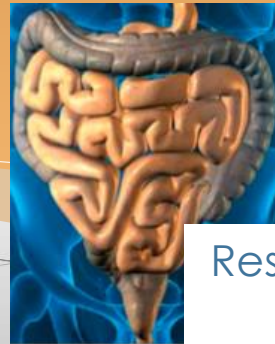


Figure 3 Gender partition and CES-D variation in diet versus diet plus OPE



Anti-inflammatory effect enhances **dopamine**



Restoration of the gut barrier fights **dysbiosis**

Anti-inflammatory supplements can address aging and prevent / cure chronic disease

- ✓ 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
- ✓ Anti-Inflammatory **Senescence** Actives



2020-2022 Terpenoid « geroprotectors »






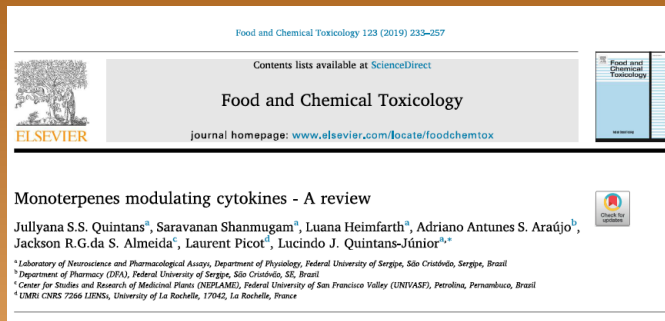
antioxidants



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

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2. Hematology Biology, CHU de Nantes & Inserm 1232 CRCINA, Nantes, France
3. IBMM, Univ Montpellier, CNRS, ENSCM, Montpellier, France

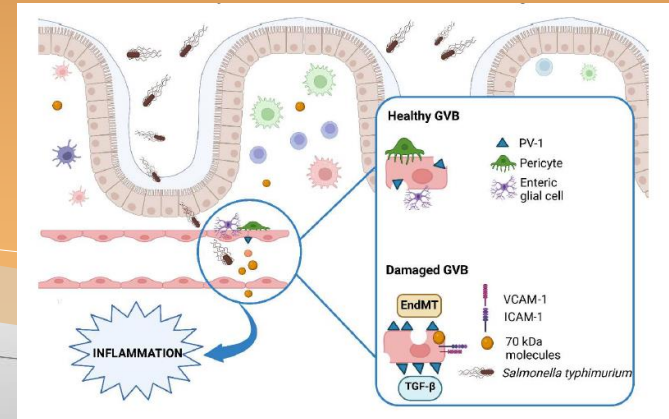
Received: 12 November 2021 | Revised: 09 January 2022 | Accepted: 07 April 2022 | Published: 20 April 2022

 Previous Article

Redefining markers



- ◆ To characterize « aging **profiles** »
- ◆ bio-markers criteria should include a **mucosal immunity compliance**
- ◆ In view the gut-vascular barrier as decision maker



The First Ristomed Consensus meeting



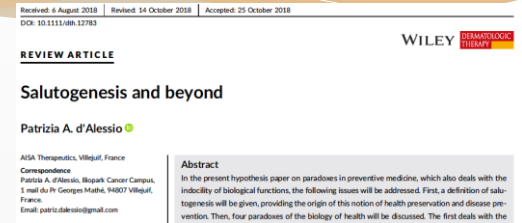
Moving to perspectives

- ◆ Launch an enhanced RISTOMED clinical study taking into account the Vitality Capacity criteria, in an **African population**.
- ◆ Reshape the EU research program « **Stress on Chips** » (2018) on stress resilience genetic background, in the African population.

Salutogenesis and AfroLongevity

As for the **AfroLongevity** specificity, the anti-inflammatory paradigm, from microbiota to neuro-inflammation, could be repositioned

- ◆ as Africans may embody **intrinsic longevity dynamics** due to active microbiota and important resilience scores, physical activity.
- ◆ Healthy longevity a universal concept could contribute to Afrolongevity.



Thank you for your attention Questions & Credits



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



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