

Small molecules as geroprotectors

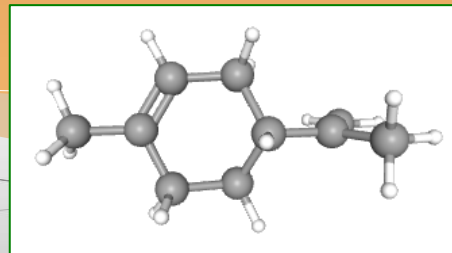


Patrizia A d'Alessio, MD PhD

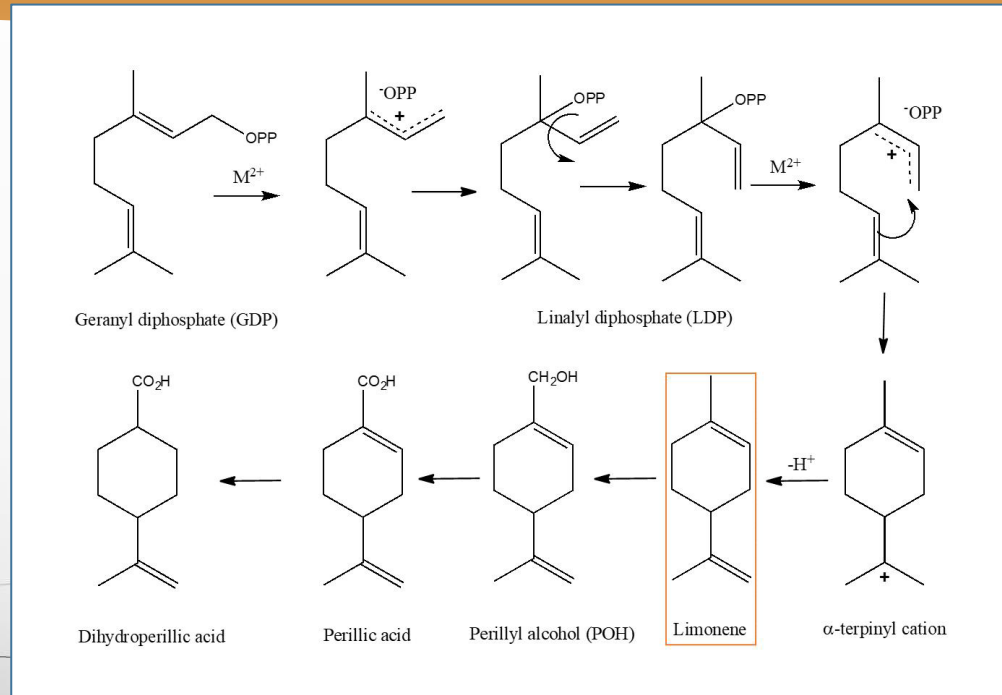
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Pr Dr University Paris Sud-11 and Genopole EVRY

« Small molecules » is what ?

- ◆ 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



2020-2022 Terpenoid « geroprotectors »



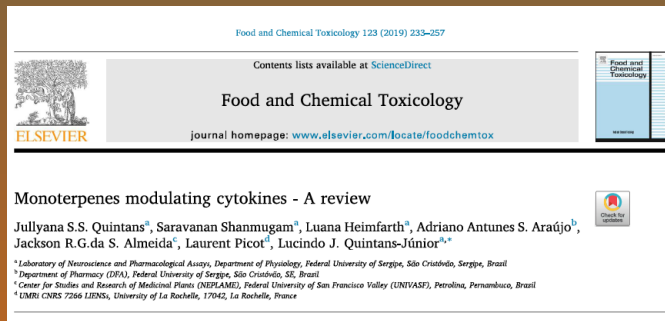
antioxidants



Review

Terpenoids as Potential Geroprotectors

Ekaterina Proshkina ¹, Sergey Plyusnin ^{1,2}, Tatyana Babak ¹, Ekaterina Lashmanova ¹, Faniya Maganova ³, Liubov Koval ^{1,2}, Elena Platonova ^{1,2}, Mikhail Shaposhnikov ¹ 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

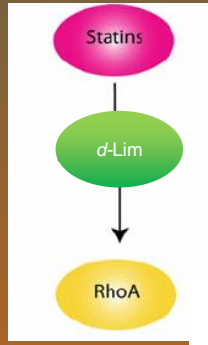
Patrizia A d'Alessio ¹ · · , Marie C Béné ², Chantal Menut ³

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

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Previous Article

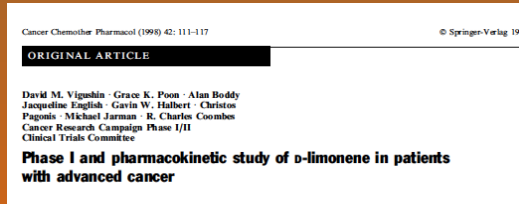
Mono- and di-terpenes in cancer



In 1997, a clinical trial in breast cancer identified the **maximal tolerated dosage (per os)** as $8\text{g}/\text{m}^2$ ($\sim 200\text{ mg}/\text{kg}$)



In 1994, Pamela Crowell, identified *d*-Limonene as an inhibitor of rho iso-prenylation,



◆ Pierre Potier



BIO-GUIDED RESEARCH identification **non toxic** anti-inflammatory molecule



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



✓ was also in **Citrus Sinensis peel extract** - same Genus, and as rich in d-Limonene



Institut des Biomolécules Max Mousseron



SENS 3 (2007) reversibility of inflammatory markers relevant to **cell senescence**

ICAM-1

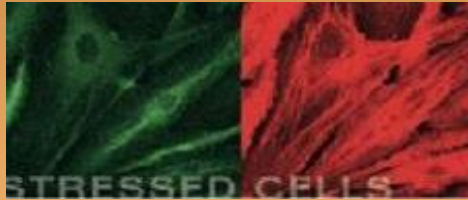
Actin

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

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

Innovative research award



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

allowed to pursue pre-clinical work on **non toxic** anti-inflammatory molecule,



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

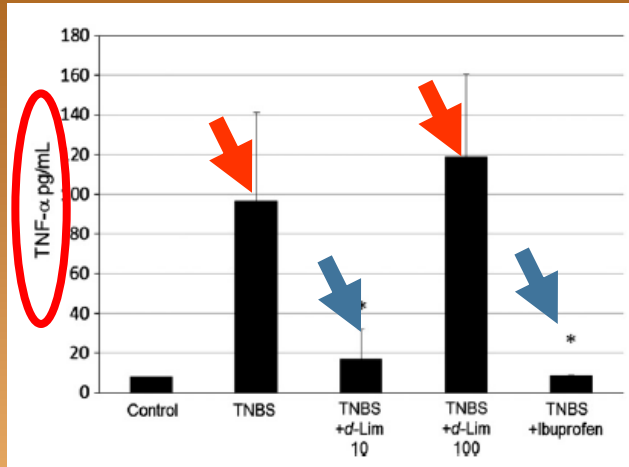
AISA can control the inflammatory facet of SASP

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

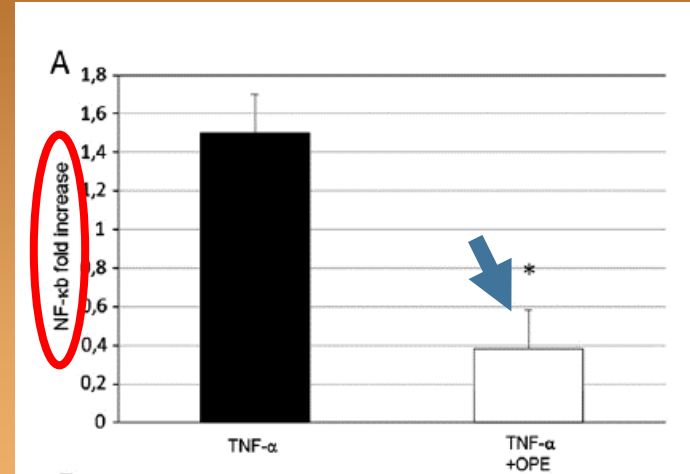
^a Genopole Entreprises, 4 rue Pierre Fossatine, 91058, Evry, France
^b Pôle Laboratoire Service d'Histologie Biologique CHU de Nantes, 9 Quai Moncousi, 44000, Nantes, France



In vitro PRE-CLINICAL results in colitis : decreased inflammatory cytokines & inhibition of **NF- κ B**



Ibuprofen effects comparable to **low-dose** *d*-Limonene



Anti TNF- α , IL-6, IL-1 β , IFN- γ effect
& Inhibition of transcription factor NF- κ B

Life Sciences. **2013**;92:1151-1156

FOB on rodents: 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>

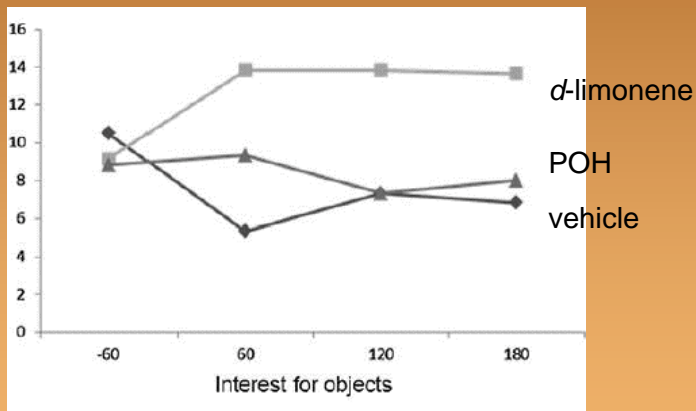


Pointing to

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

Mood modulation : pre-clinical / **clinical** RESULTS

Motivational effect in **rodents**



Mood modulation effect in **humans**

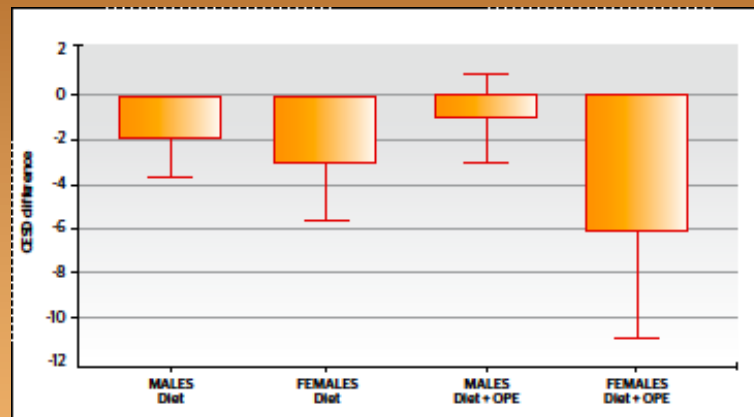


Figure 3 Gender partition and CES-D variation in diet versus diet plus OPE

Rejuvenation Res.
2014;17:145-149

PRIME **2012**; 30-37

In vivo PRE-CLINICAL in a wound healing model

Vehicle



d-Lim



POH



Strong 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

resulting in important tissue repair in a **dermatitis** model



Vehicle

TPA
lesion mim
for AD

TPA + *d*-Lim

TPA + POH



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

First in **human** observational study

INTERMEDIATE PSORIASIS



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D0

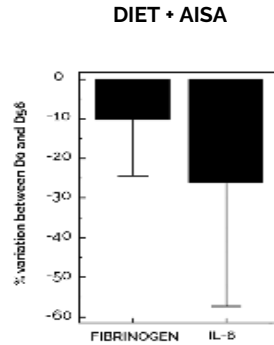
D45



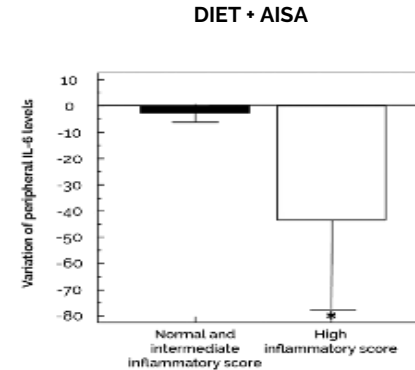
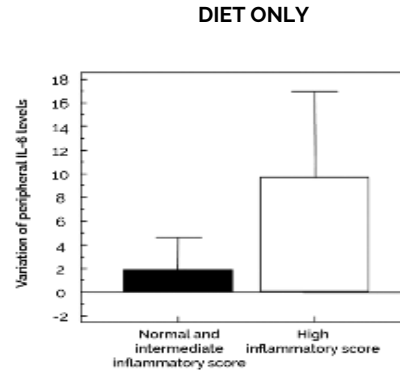
Global Journal of Dermatology & Venereology, 2015, 3, 1-4



Inflammation markers



Anti-IL-6 efficacy as food supplementation

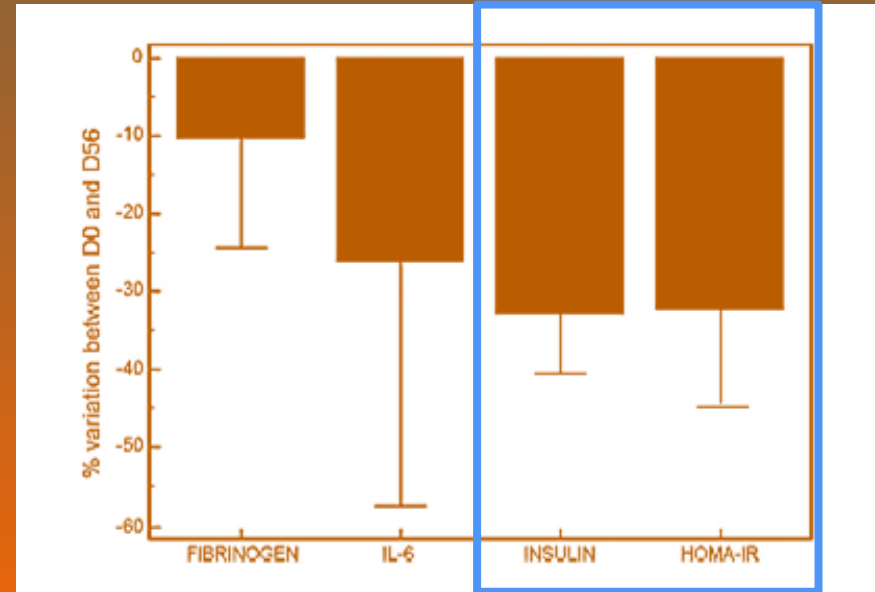


Significant modifications of inflammation markers (fibrinogen and IL-6) in moderate inflammation (RISTOMED diet + d-Limonene) between D0 and D56.

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 on gut barrier repair in a pre-clinical study

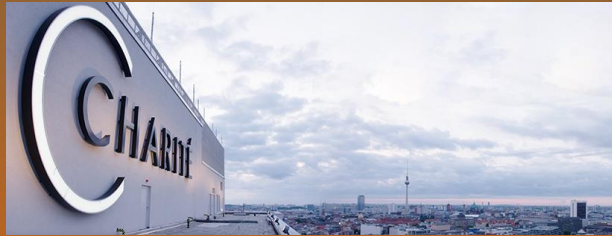
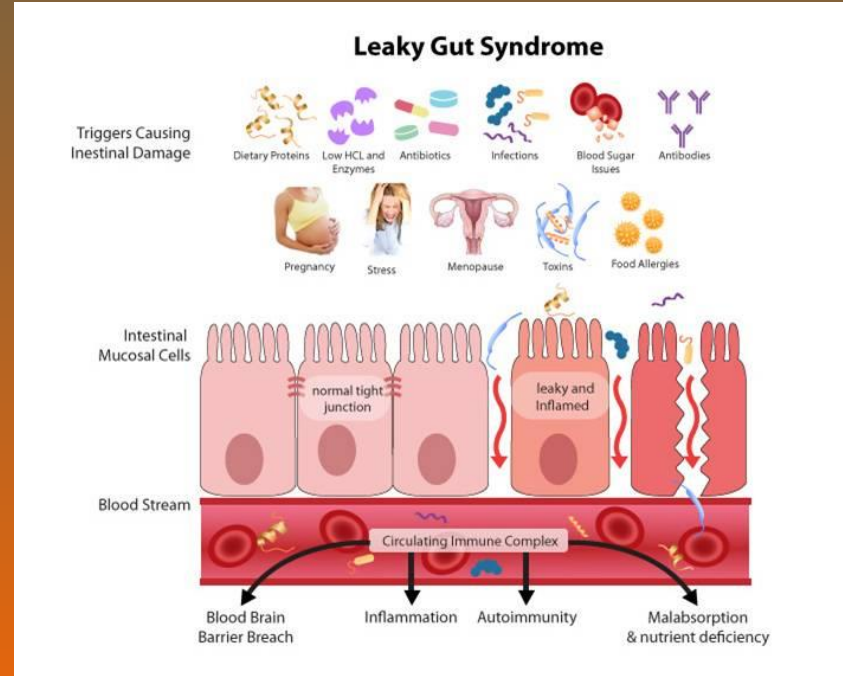


Table 1
OPE containing 95% of d-Limonene: effect on epithelial barrier function.

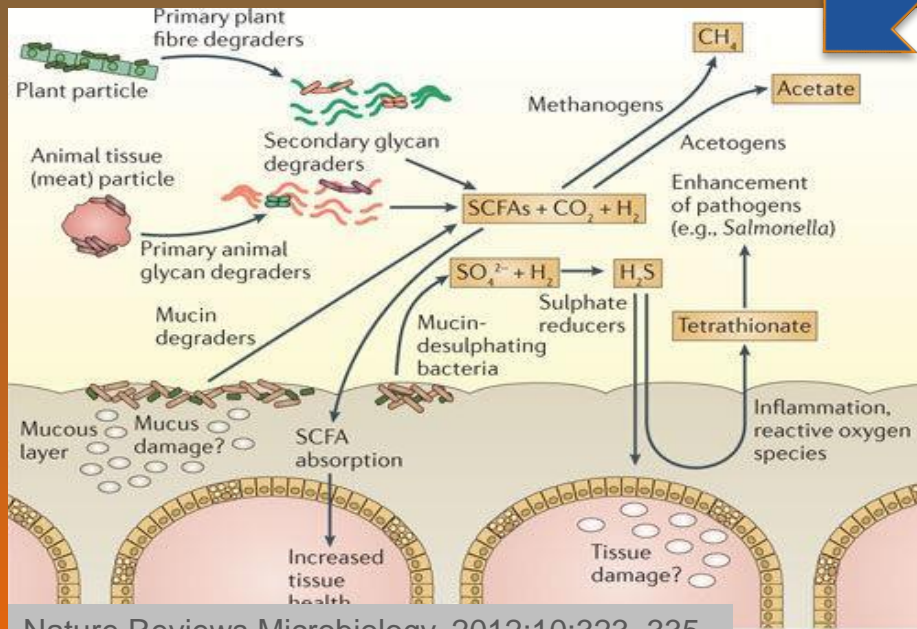
	Control	OPE			
		75 μ M	150 μ M	750 μ M	1500 μ M
R ^t	107 \pm 3%	106 \pm 4%	112 \pm 3%	132 \pm 3%	153 \pm 4%
n	9	6	6	6	6
p		n.s.	n.s.	<0.001	<0.001

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



Life Sciences **2013**;92:1151-1156

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



Nature Reviews Microbiology, 2012;10:323–335

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

produced by:
Bifidobacteria
Clostridii
Enterobacterium
Enterococcus
Ruminococcus
Roseburia

« 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

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}, I. Bourdel-Marchasson^{j,k,l}, C. Blanc-Bisson^{j,k,l}, F. Buccolini^j, P. Brigidi^m, C. Franceschi^{n,o,p}, P.A. d'Alessio^q

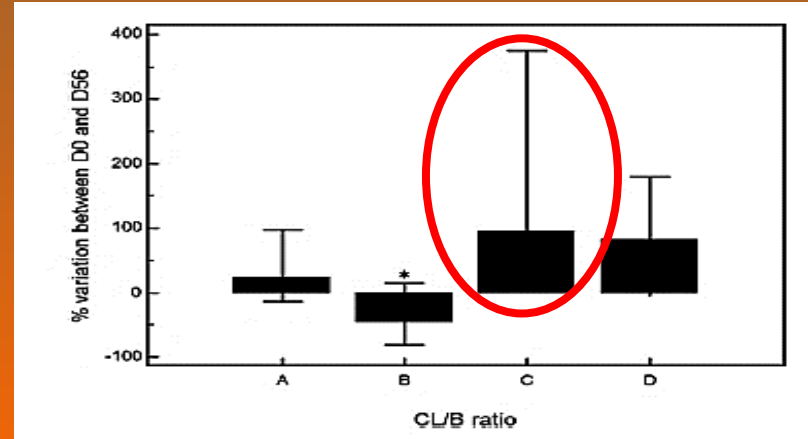
nature
microbiology

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. Tigchelaar¹, Jun Wang^{1,2}, Raul Y. Tito^{1,2,4}, Carmen Schiweck⁵, Alexander Kurilshikov³, Marie Joossens^{1,2}, Cisca Wijmenga^{3,6}, Stephan Claes^{1,7}, Lukas Van Oudenhove^{7,8}, Alexandra Zhernakova³, Sara Vieira-Silva^{1,2,9} and Jeroen Raes^{1,2,9*}



Small molecules monoterpene *d*-Limonene *reset* multi-system's body

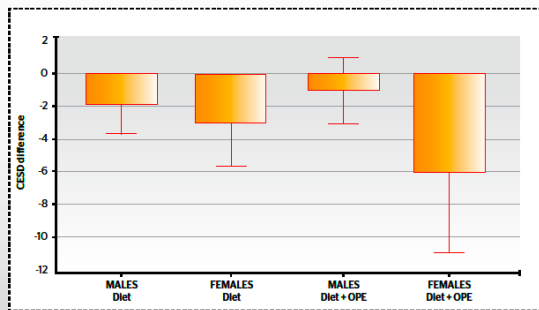
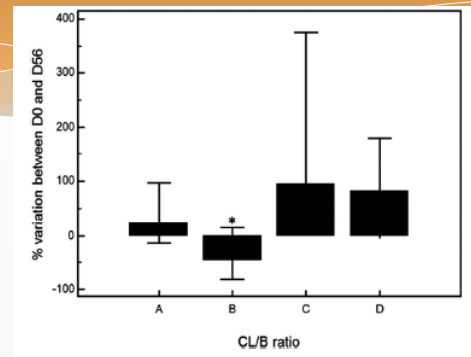


Figure 3 Gender partition and CES-D variation in diet versus diet plus OPE

Anti-inflammatory effect
enhances **dopamine**



Restoration of the gut barrier
fights **dysbiosis**

Useful to frialty ?

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** »
- ◆ anti-inflammatory bio-markers criteria should include **mucosal immunity compliance**

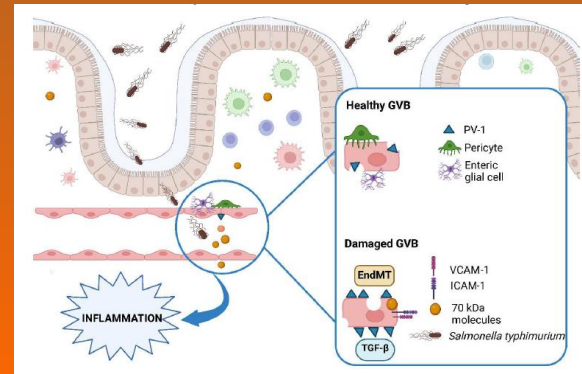


International Journal of
Molecular Sciences

MDPI

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

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



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



ASTHETIC FEATURE | INFLAMMATION | 149

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

WHAT WILL BE COVERED IN THIS ARTICLE? WELL, WE WILL discuss the relationship between the gut and the brain, the impact of the gut-brain axis on skin ageing, and the role of the gut-brain axis in skin ageing. We will also discuss the role of the gut-brain axis in skin ageing, and the role of the gut-brain axis in skin ageing.

KEYWORDS: Gut-brain axis, skin ageing, inflammation, oxidative stress, gut microbiome, gut-brain axis, skin ageing, inflammation, oxidative stress, gut microbiome, gut-brain axis, skin ageing, inflammation, oxidative stress, gut microbiome.

Abstract: The gut-brain axis is a bidirectional communication system between the gut and the brain. The gut-brain axis is a bidirectional communication system between the gut and the brain. The gut-brain axis is a bidirectional communication system between the gut and the brain.

Patrizia A. d'Alessio is a dermatologist and researcher in the field of skin ageing and inflammation. She is currently working on the role of the gut-brain axis in skin ageing and inflammation.

36 | July/August 2020 | primo-journal.com

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

WILEY **DERMATOLOGIC THERAPY**

REVIEW ARTICLE

Salutogenesis and beyond

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AISA Therapeutics, Villejuif, France

Correspondence

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Email: patriz.dalesio@gmail.com

Abstract

In the present hypothesis paper on paradoxes in preventive medicine, which also deals with the indolence 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



Patrizia A. d'Alessio is a dermatologist and researcher in the field of skin ageing and inflammation. She is currently working on the role of the gut-brain axis in skin ageing and inflammation.

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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