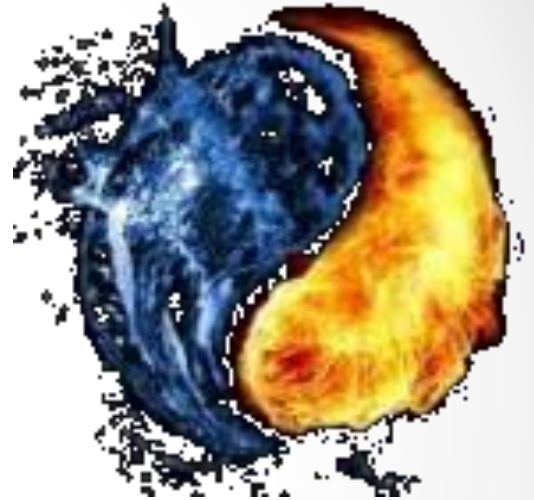


Geroprotector monoterpens : « small molecules » from pro-drugs to metabolites

Patrizia A d'Alessio, MD PhD
Rome 16-17 September 2023

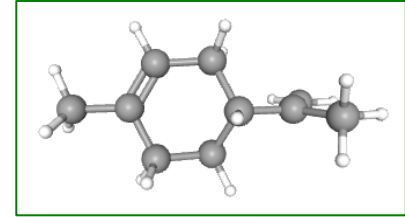


© copyright 2023 by Patrizia A d'Alessio
Pr Dr University Paris Sud-11 and Genopole d'EVRY



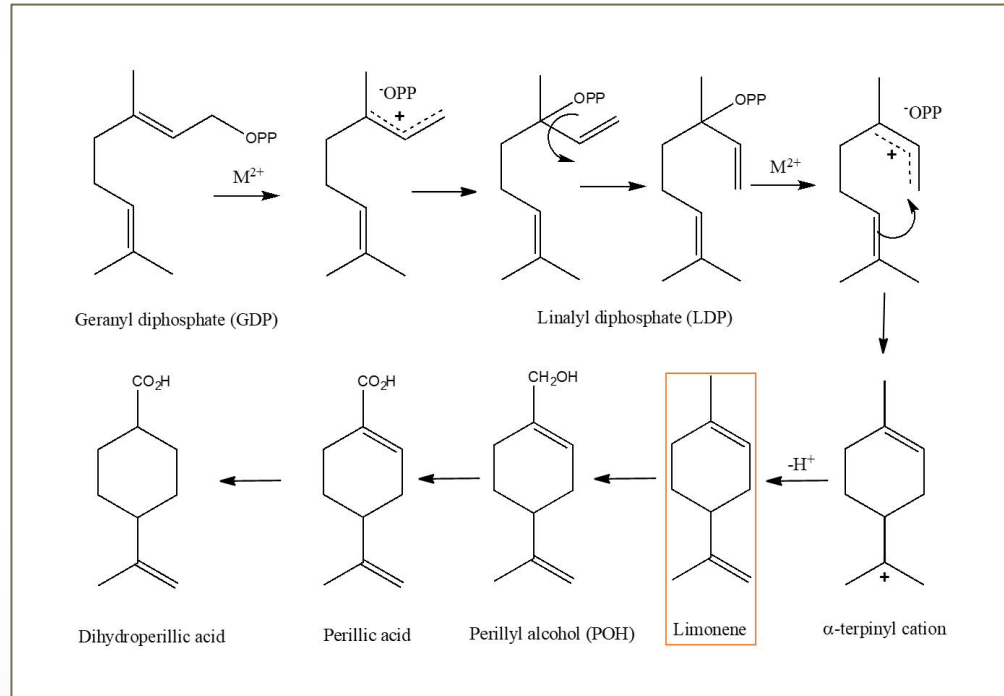
No conflict of interest

At the heart of plants' components are « small molecules »



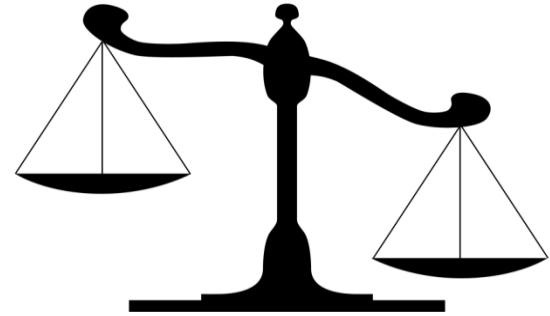
- ◆ Low molecular weight ($\leq 1\text{KDa}$) organic compounds involved in the regulation/modification of biological processes
- ◆ **Natural (or artificial)**, many have a beneficial effect against diseases.
- ◆ They can be administered orally and some **are excellent anti-inflammatory agents**.
- ◆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

The monoterpene *d*-Limonene and its metabolite Perillyl Alcohol (POH)



Potent « small molecules » !

Anti-inflammatory drugs are efficient but only on a fraction of the population

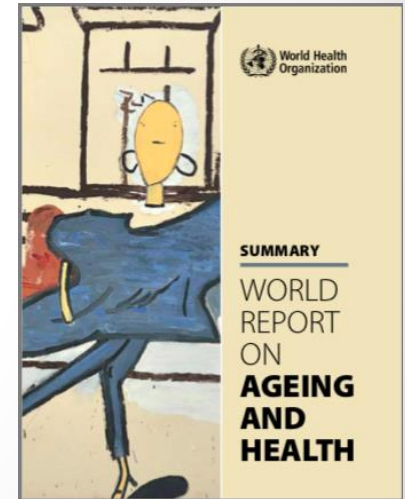


Only 25% responders !

AND SIDE EFFECTS

What will we be talking about?

- ◆ Inflammation at the edge of chronic diseases vs aging
- ◆ Requiring a drug devoid of adverse effects
- ◆ 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 »** (clinical study)
- ◆ Enhanced RISTOMED project integrating NEW WHO criteria



Chronic « silent » inflammation has been identified as a mechanism of aging

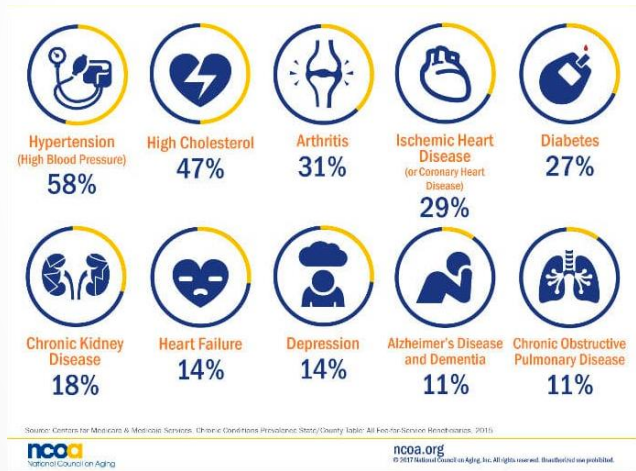
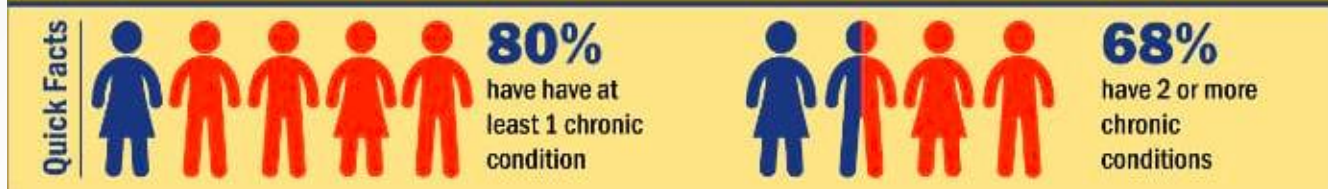
Review

> [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](#)

10 Common Chronic Conditions for Adults 65+



INFLAMMATION: THE ARSENAL TO DELAY AGEING IN 2022

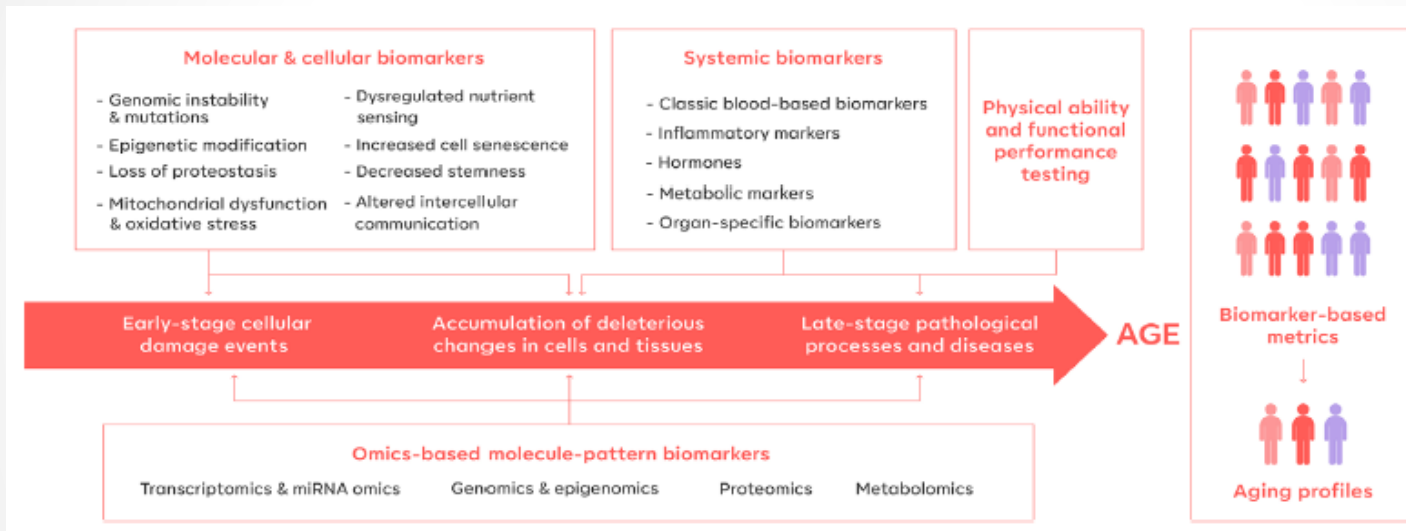
Patrizia A d'Alessio explains why she believes inflammation is the root cause of ageing symptoms and how it can be addressed

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, low-level inflammation as a key factor. This status, which settles insidiously, is often not recognised as the source of odd pains, insomnia, mood changes or obsessional 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 probiotics 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.

Aging Biomarkers: From Functional Tests to Multi-Omics Approaches

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

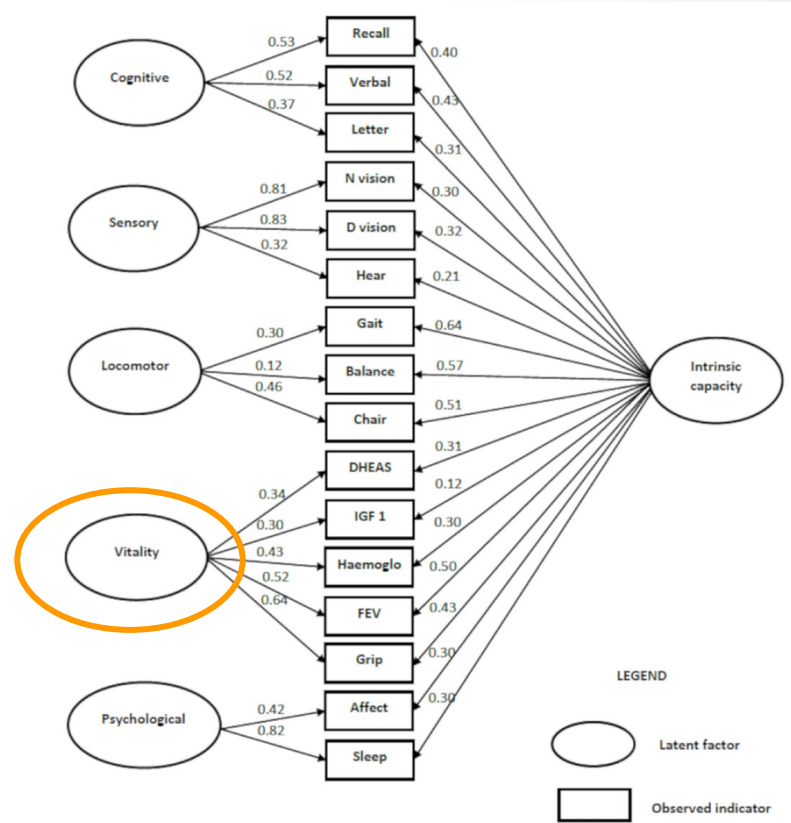
Biomarkers



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

WHO 2015 : « Vitality » as a component of « Intrinsic Capacity » (IC)

- ◆ **(IC)** a multidimensional indicator of health, accounting for mental and physical capacities that are crucial to older people to continue doing **what they value most**.



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,*} 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 Szejf, ¹ Déborah Oliveira, ¹ Ronaldo D. Plovezan, ¹ Matteo Cesari, ¹ et al.

Show all authors • Show footnotes

Open Access • Published: May 27, 2022 • DOI: <https://doi.org/10.1016/j.lana.2022.100284> • Check for updates



> [J Natl Cancer Inst.](#) 2001 Dec 19;93(24):1843-51. doi: 10.1093/jnci/93.24.1843.

Selective activation of cervical microvascular endothelial cells by human papillomavirus 16-e7 oncoprotein

R D'Anna¹, H Le Buanec, G Alessandri, A Caruso, A Burny, R Gallo, J F Zagury, D Zagury, P D'Alessio



Together with our academic partners, we started to look for native botanical ingredients contained in edible plants

BIO-GUIDED RESEARCH : identification of a **non toxic** anti-inflammatory molecule



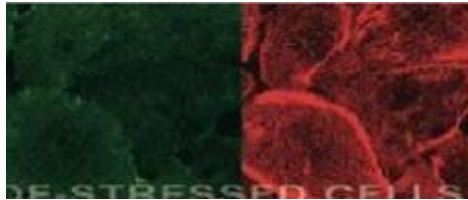
- ✓ The monoterpene **d-Limonene best candidate** discovered in the *Halfordia kendack* plant in Viet Nam / China rain forest

First step : reversibility of inflammatory markers relevant to **cell senescence**

ICAM-1

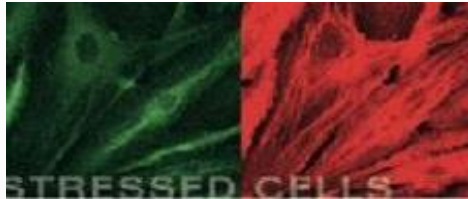
Actin

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

French National Innovative research award

Patent on monoterpene's effect on senescent cells reversibility *in vitro* ...



Followed by pre-clinical work to elucidate PK & define therapeutic windows

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

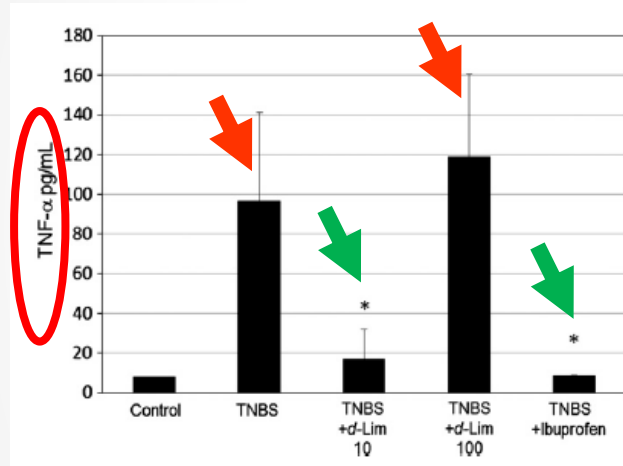
AISA can control the inflammatory facet of SASP

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

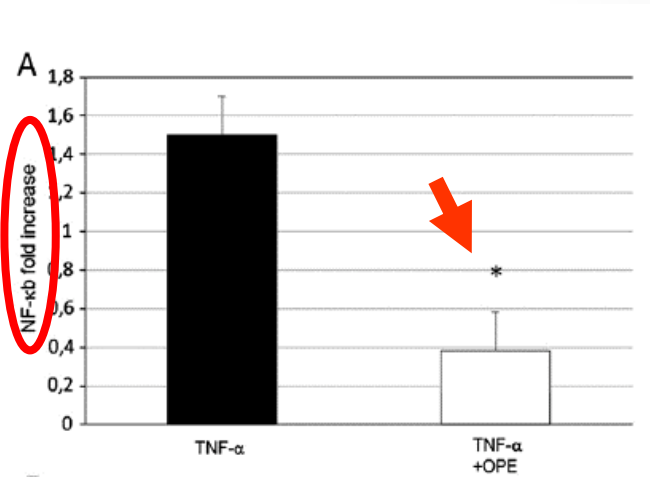
^a Genopole Bioprotéus, 4 rue Pierre Fontaine, 91058, Evry, France
^b Pôle Laboratoires Service d'Hématologie Biologique CHU de Nîmes, 9 Quai Moncaussu, 44000, Nîmes, France



Preclinical validation and mechanism of action in a colitis model : inflammatory cytokines inhibition via transcription factor **NF- κ B inhibition**



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



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

Life Sciences. 2013;92:1151-1156

AISA PRE-CLINICAL studies in skin : wound healing model and first distinction between **pro-drug and metabolite**

Vehicle



d Lim



POH



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

TPA + *d*-Lim

TPA + POH

lesion mimicks
Atopic dermatitis



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

Observational study in intermediate psoriasis

INTERMEDIATE PSORIASIS



D0

D45



SAPIENZA
UNIVERSITÀ DI ROMA

Case study ATOPIC DERMATITIS

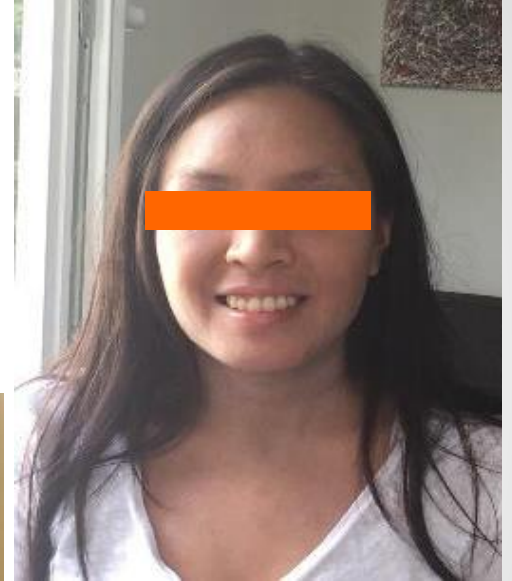
(eczema) worsened by repeated topic cortisol treatment

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

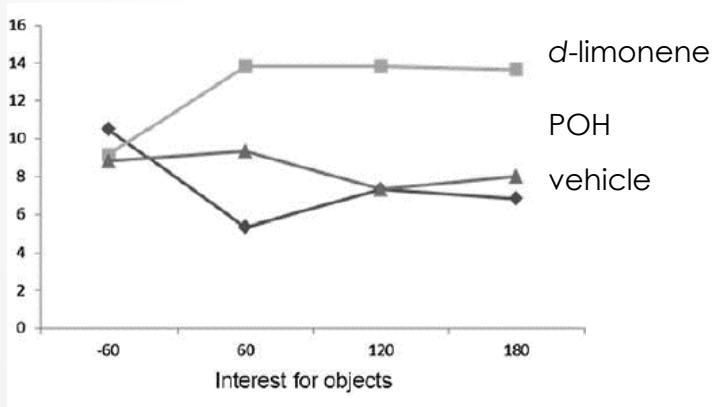
Visible **mood** amelioration
Rejuvenation effect



AISA PRE-CLINICAL studies on mood: FOB on **pro-drug and metabolite** effects

◆ activation of the **vagal tone**

Motivational effect in **rodents**



Mood modulation effect in **humans**

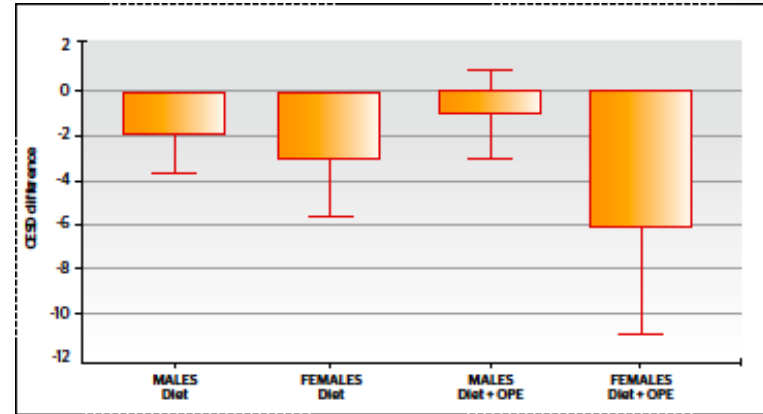


Figure 3 Gender partition and CES-D variation in diet versus diet plus OPE

Rejuvenation Res.
2014;17:145-149

PRIME **2012**; 30-37

Endogenous enhancer effect valuable from 40 ys on

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

Pointing to

◆ **dopamine increase** by *d*-Limonene

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>



Anti-inflammatory effects offered by monoterpenes administered orally or topically in animals



- ✓ were found back in **Citrus Sinensis peel extract (OPE)** of the same botanical Genus, as rich in *d*-Limonene;
- ✓ **AISA** standing for Anti-Inflammatory Senescence **Actives** was administered in human studies as soft gel capsules



Oral administration of a non toxic anti-inflammatory active : first-in-human study « Healthy aging by Nutrition » FP7 Capacities

Clinical Nutrition 35 (2016) 812–818



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



Diet vs Nutraceutical supplementation

collected early in the morning before (D0) and after the diet period (D56).

2.2. Diet

The RISTOMED diet was personalized by a dietician using the RISTOMED-Health dietary Services (www.ristomed.eu) [12]. Each participant received a personal login to the RISTOMED website, and was trained by a dietician to get the personalized diet from the web platform. Recipes and daily menus were formulated taking into account traditional and personal eating habits. The nutritional pattern was established in agreement with the current dietary recommendations for elderly people, specific attention being given to the intake of food compounds that can affect inflammation, oxidative stress and gut microbiota [i.e. Poly Unsaturated Fatty Acids – PUFA n-6/n-3 ratio – antioxidant vitamins (vitamin E, C and carotenoids) and minerals (zinc and selenium), polyphenols and soluble dietary fiber].

The RISTOMED diet provided ~15% of energy as proteins, 50–60% as carbohydrates and ~35% as lipids. The latter were 15–20% Mono-Unsaturated Fatty Acids (MUFA), provided by virgin olive oil, ~8% Saturated Fatty Acids (SFA) and ~7% PUFA with 0.5% α -linolenic acid and 2% linoleic acid. The daily recommended intake of uncooked Argan oil (25 mL), when required in the study arm, was given in partial replacement of an equal amount of extra-virgin olive oil. Dietary fiber intake was ~35 g/day with an insoluble/soluble fiber ratio of around 1:1, related to the prebiotic activity generally assigned to soluble fiber [16]. Polyphenols' intake was established at ≥ 400 mg/day (as phenolic acids plus flavonoids;

[17]). The intake of vitamins and minerals was referenced to the WHO program “Keep fit for life” [18]. The minimum water need for elderly people is 1–1.5 mL/kcal/day and it was recommended to use a calcium-rich water ($\text{Ca} \geq 150$ mg/L).

On the website, participants recorded their weight weekly and described the compliance to the diet and to the nutraceutical supplementation daily. After 2 and 6 weeks (D14 and D42) from the beginning of the intervention, the nutritionist/dietician contacted by phone each participant to verify his/her compliance to the diet and to the nutraceutical supplementation.

2.3. Nutraceutical supplementation

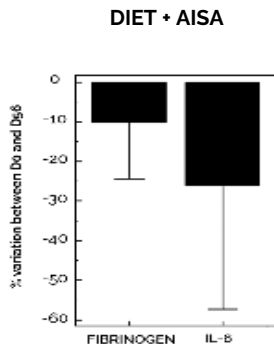
VSL#3 probiotic blend (ACTIAL Farmaceutica Lda) is formulated as a granulated powder of 112 billion lyophilized bacteria per capsule in defined ratios of 4 strains of *Lactobacillus* (*Lactobacillus paracasei*, *Lactobacillus plantarum*, *Lactobacillus acidophilus*, and *Lactobacillus delbrueckii* subsp. *bulgaricus*), 3 strains of *Bifidobacterium* (*Bifidobacterium longum*, *Bifidobacterium breve*, and *Bifidobacterium infantis*) and *Streptococcus thermophilus*. The product was administered orally, 2 capsules daily on an empty stomach with a glass of water.

The monoterpene AISA 5203-L (*d*-Limonene and its metabolites) extracted from orange peel was administered orally in soft gel capsules with a meal and a large glass of water. The daily number of soft gel capsules was established for each patient according to the recommended dose of 10 ± 1 mg/kg.

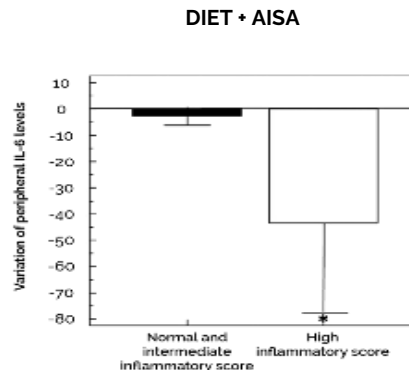
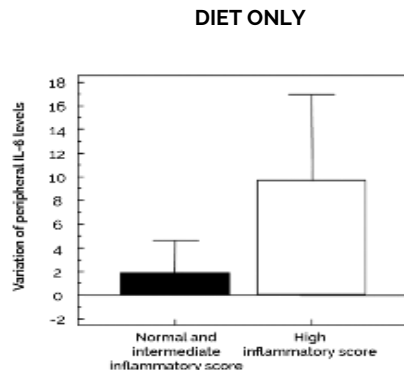
Argan oil, the extra-virgin oil obtained using a cold-pressed technique of kernels contained in the *Argania spinosa* fruit, was

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

Inflammation markers



Anti-IL-6 efficacy as food supplementation



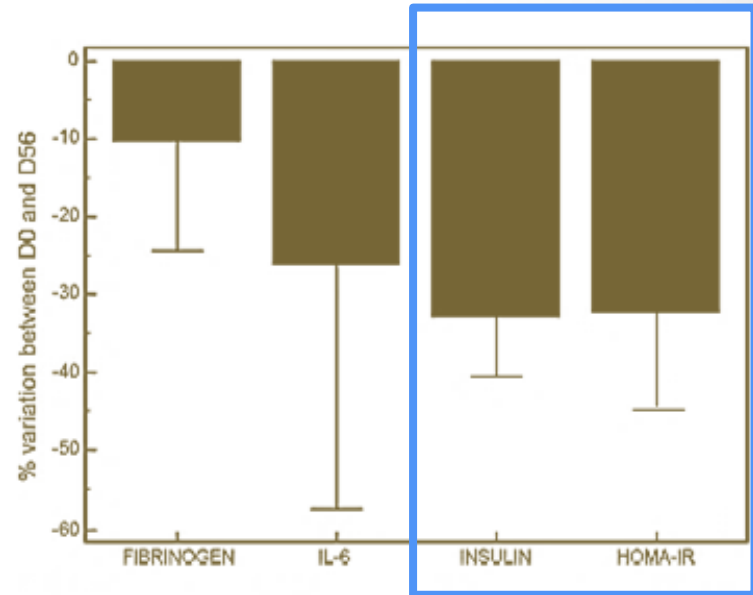
**Significant modifications of inflammation markers
(RISTOMED diet + d-Limonene) between D0 and D56.**



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



d-Limonene and gut barrier repair in vitro study on enterocytes

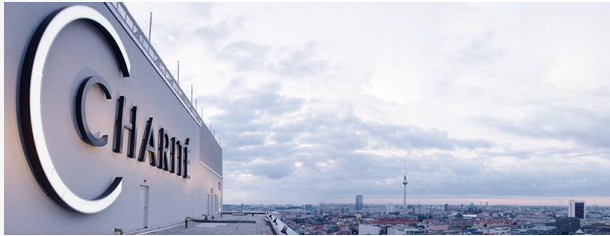
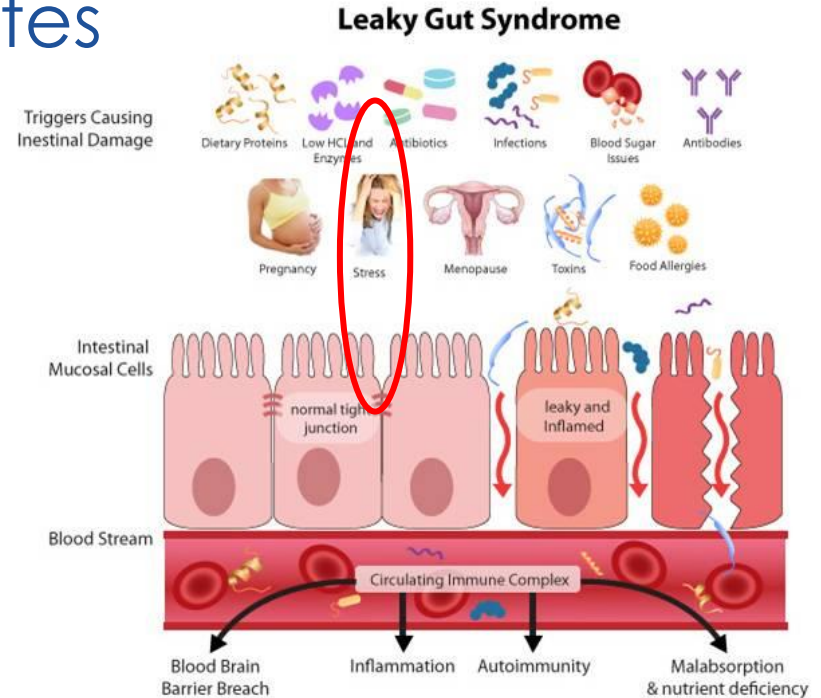


Table 1
OPE containing 95% of d-Limonene: effect on epithelial barrier function.

	Control	OPE			
		75 μM	150 μM	750 μM	1500 μM
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 .



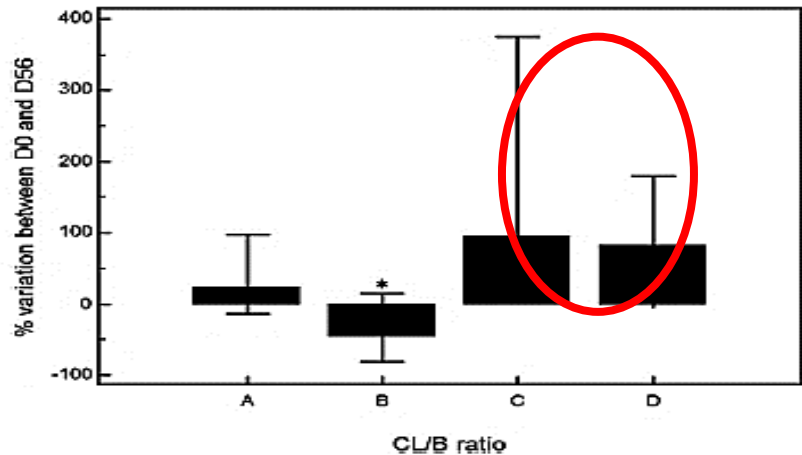
Life Sciences **2013**;92:1151-1156

Gut barrier repair effects on **microbiota**

Modulation of microbiota ratios
following administration of d-Limonene



Clostridium cluster IV / *Bifidobacteria* ratio



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

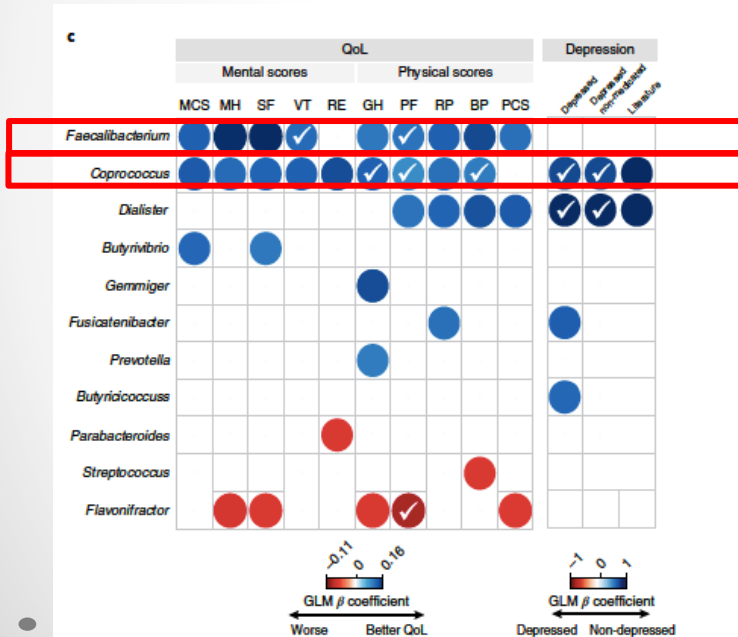
Mireia Valles-Colomer^{1,2}, Gwen Falony^{1,2}, Youssef Darzi^{1,2}, Ettje F. Tigchelaar³, Jun Wang^{1,2}, Raul Y. Tito^{1,2,4}, Carmen Schiweck³, Alexander Kurilshikov³, Marie Joossens^{1,2}, Cisca Wijmenga^{3,6}, Stephan Claes^{5,7}, Lukas Van Oudenhove^{7,8}, Alexandra Zhernakova³, Sara Vieira-Silva^{1,2,9} and Jeroen Raes^{1,2,9*}

« VITALITY » a matter of bacterial metabolites

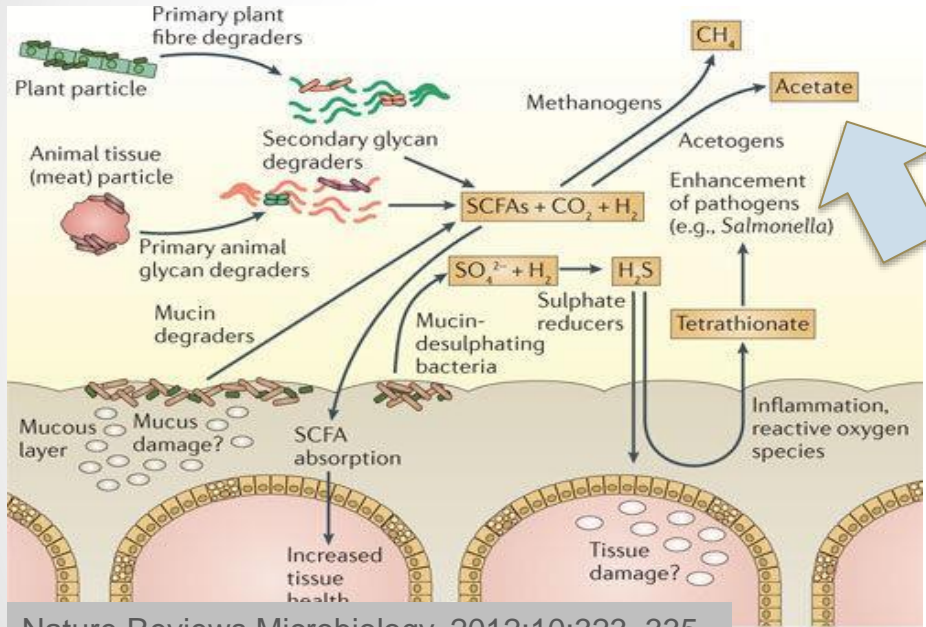
Faecalibacterium & **Coprococcus** for VITALITY, emotional well-being & Social functioning

◆ **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.



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



Nature Reviews Microbiology, 2012;10:323–335

Hydro-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

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,*} 

Food and Chemical Toxicology 123 (2019) 233–257

Contents lists available at ScienceDirect

Food and Chemical Toxicology

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

Monoterpenes modulating cytokines - A review

Julyana S.S. Quintans^a, Saravanan Shanmugam^b, Luana Heimfarth^c, Adriano Antunes S. Araújo^b, Jackson R.G.da S. Almeida^d, Laurent Picot^e, Lucindo J. Quintans-Júnior^{a,*}

^a Laboratory of Neuroscience and Pharmacological Assays, Department of Physiology, Federal University of Sergipe, São Cristóvão, Sergipe, Brazil
^b Department of Pharmacy (DFA), Federal University of Sergipe, São Cristóvão, SE, Brazil
^c Center for Studies and Research of Medicinal Plants (NUPRAM), Federal University of San Francisco Valley (UNIVASF), Petrolina, Pernambuco, Brazil
^d CNRS UMR 7266 LERINS, University of La Rochelle, 17042, La Rochelle, France

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 Bénédicte², 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

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

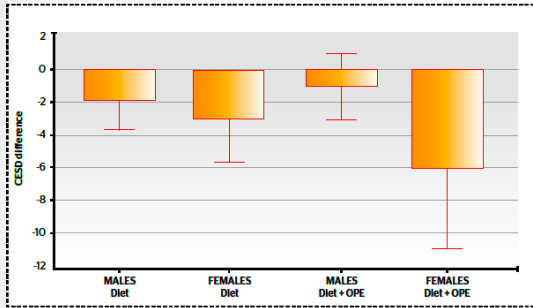
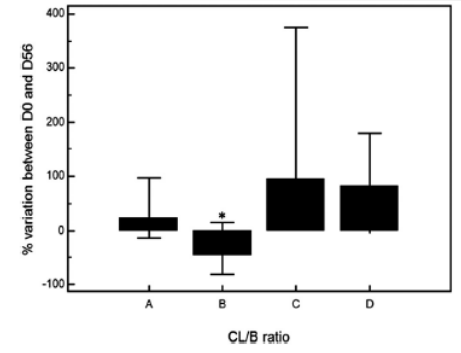


Figure 3 Gender partition and CES-D variation in diet versus diet plus OPE



Pro-drug effect

Anti-inflammatory effect enhances **dopamine**



Restoration of the gut barrier fights **dysbiosis**

POH-metabolite effect

The treatment of chronic inflammation involves repairing the **gut barrier** with amelioration of the skin

AE 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, whereby the gut health affects the skin, is a complex relationship involving the gut microbiome, the gut barrier function, the expression of epigenetic information, and the response to the whole body and health, by its composition of gut microbiome.

Chronic inflammation, both ageing and related to skin ageing, is an accelerated process because of signals by stress, epigenetic modification, the skin pathogenesis, the gut microbiome, and the gut barrier function. The gut microbiome, the gut barrier function, and the gut-brain axis are interconnected. Chronic inflammation, the gut microbiome, and the gut barrier function are interconnected. The gut microbiome, the gut barrier function, and the gut-brain axis are interconnected. The gut microbiome, the gut barrier function, and the gut-brain axis are interconnected.

WHAT WILL BE COVERED IN THIS ARTICLE? WELL, WE WILL discuss the relationship between the gut and the brain, if the dialogue between the gut and the brain is terrible, the progressive deterioration of our skin is clearly progressive and therefore, unavoidably accelerated. In simple terms, we are constantly observing the outcomes of our gut-brain relationship, and we cannot avoid the impression that our skin is losing its flame.

Let us begin with anatomy: one of the brain's corners, the skin, but of the connections between the two strategic organs that determine outcomes for general health as well as specific functionalities of the skin. Indeed, the anatomical gut-brain link is ensured by the vagus nerve, whereas the functional gut-brain link relies on the gut microbiome and its signaling.

Bidirectional communication channels are therefore activated continuously between the gut and the brain. Endocrine, sensorine, and inflammation-related signals generated by the gut microbiota and their specialized cells affect the brain, by turn, the brain can influence the microbial composition and functions via endocrine and immune mechanisms. Gut bacteria such as *lactobacillus*, *staphylococcus*, *staphylococcus* are present in the brain as well as in the gut. However, their release appears to be regulated by the gut flora in the brain. Moreover, antibiotic and immune-releasing bacteria have also been described in the gut. In other words, an individual's quality of life (QoL) and the feeling of well-being (WELL-BEING) would seem to be dependent on the gut's intrinsic machinery than the secretion of the brain neurotransmitters.

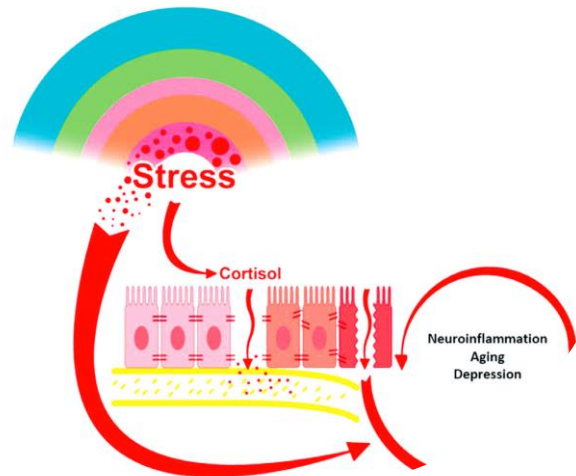
- The issue of food intake and the consequent signaling by neurotransmitters
- The role played by the brain and the gut immune system in stress management, an stress profoundly alters the structure of the gut barrier and can compromise its function resulting in leakage.
- How long the visible side of this complex sequence of events relevant to skin health actually is.

To summarize, because food intake activates complex signaling pathways, a place that is the starting point between skin and gut health is the relationship with the gut.

The gut as a starting point
to succeed times, and notably since the 1970s and during the 1980s century, dietary components have been observed to have specific effects on general health and skin quality alike. Vegetarianism became a treatment for obesity and psoriasis, wealthy people consuming meat excessively. Dr George Chenoy (2007, 2013), who had been a vegetarian, was also migrating from meat to a substantial weight loss and lack of skin redness. Today we know that specific food components (meat or vegetables intake) affect skin composition. One of the first steps of the dialogue is the treatment or prevention/enhancement of specific constitutive factors dependent to the digestion of



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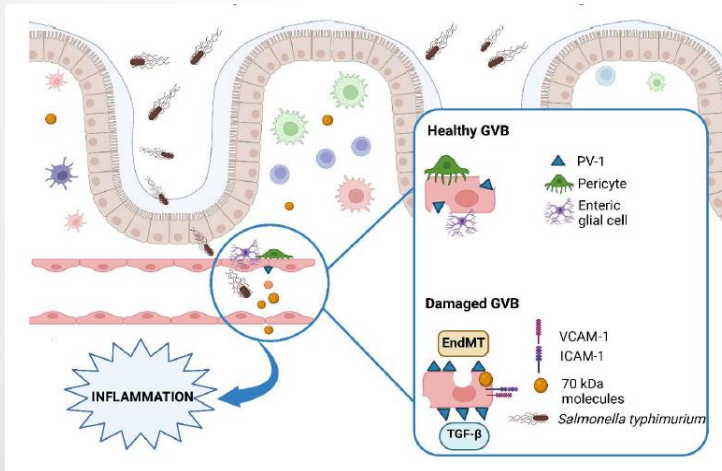
Anti-inflammatory effects offered by monoterpenes administered orally or topically

- ✓ The molecular complex identified in *Halfordia kendack* also present in **Citrus Sinensis peel extract** (OPE) is highlighting the effects of *d*-Limonene and its metabolite POH:
- ✓ representing a valuable strategy in aging prevention - based on the control of the inflammatory reaction in the body



Redefining inflammatory markers relevant to aging

◆ mucosal immunity compliance



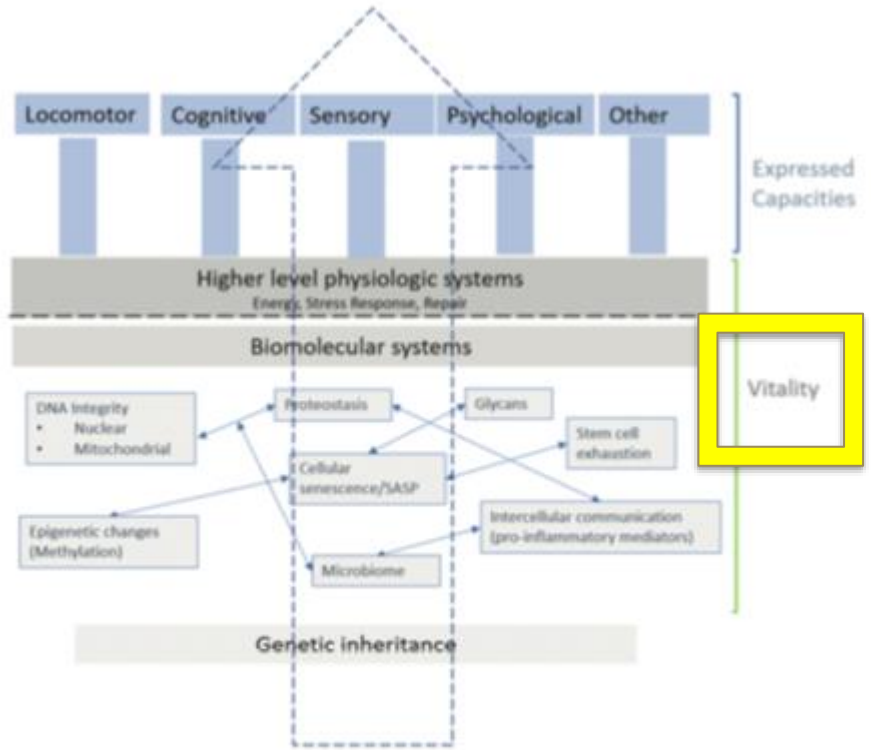


Figure 5. Schematic diagram of intrinsic capacity (16).

Vitality is the invisible biomarker,

yet measurable !

- ◆ Positive grip test
- ◆ Stress resilience

The Centurion transmitting to young Asclepion the recipe for immortality :


was it a non-toxic anti-inflammatory brew ?

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REVIEW ARTICLE

Salutogenesis and beyond

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THERAPY

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



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Thank you for your attention Questions & Credits



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