

Non-Toxic Anti-Inflammatory « Small molecules » to reverse organ-specific senescence

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ISOAD International Society on Aging and Disease

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Pr Dr University Paris Sud-11 and Genopole EVRY

Anti-Inflammatori Non Tossici

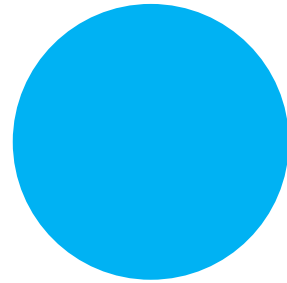
Ricerca & indicazioni cliniche

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Spezieria monastica
Abbazia di San Paolo fuori le Mura

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REVIEW ARTICLE

Salutogenesis and beyond

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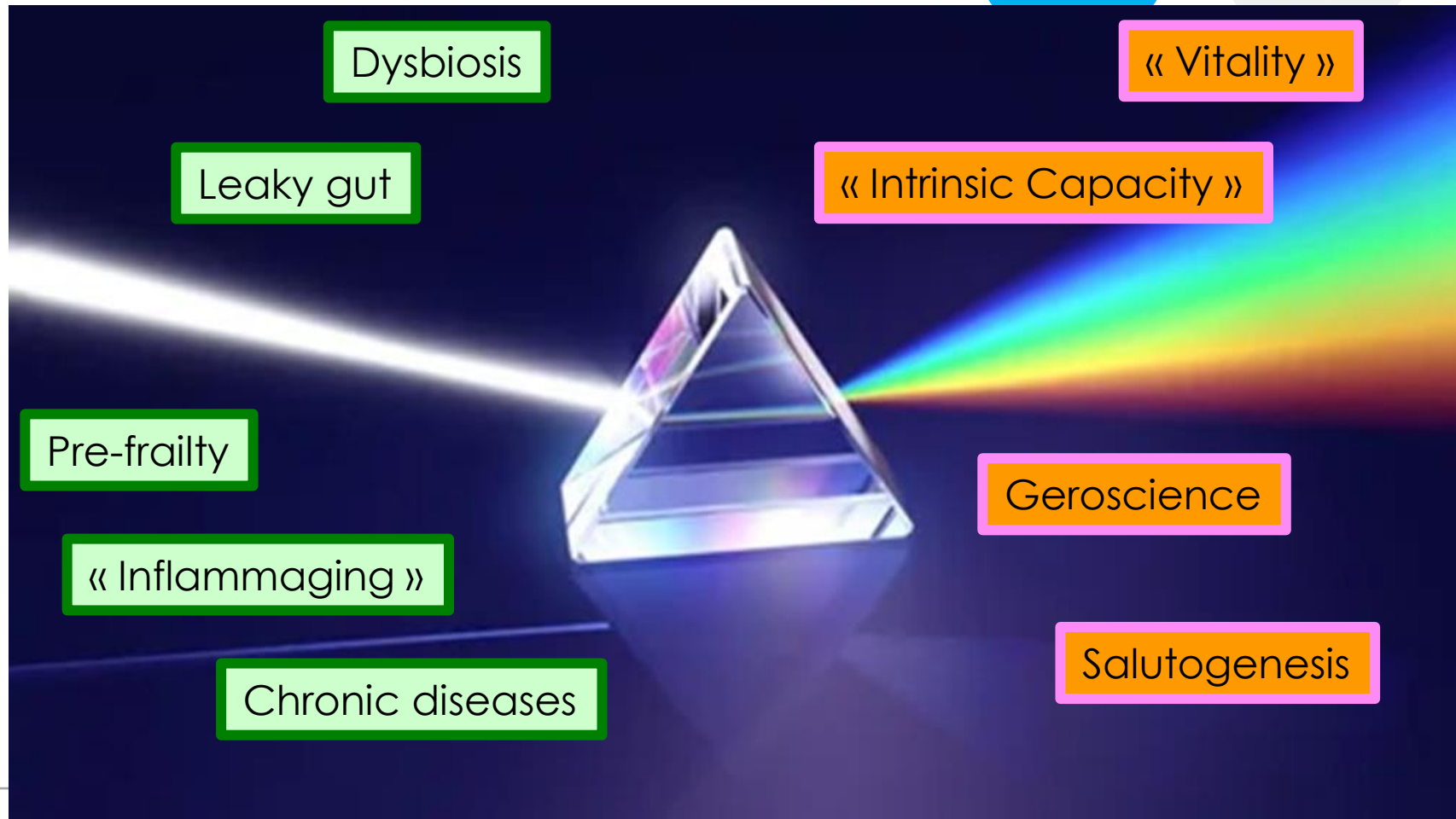
Email: patriz.dalessio@gmail.com

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

Il mitico Centauro trasmette al giovane **Asclepion la ricetta dell'immortalità** : un anti-infiammatorio non tossico ?

Di che cosa parleremo



Un **conundrum** d'interazioni

- ◆ Nutrizione / ruolo epigenetico della digestione
 - ◆ Potenziale neuroattivo del microbiota
 - ◆ Movimento e “grip test”
 - ◆ L'importanza della ricompensa e della **“resilienza”**
-



Iatromecanisti del XVII-XVIII secolo : l'importanza delle fibre per la **longevità**



Dr George 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 skin radiance.



A N
E S S A Y
O F

Health and Long Life.

§. I.



T is a common Saying, That every Man past Forty is either a *Fool* or a *Physician*: It might have been as justly added, that he was a *Divine* too: For, as the World goes at present, there is not any Thing that the Generality of the better Sort of Mankind so lavishly and so unconcernedly throw away as *Health*, except *eternal Felicity*. Most Men know when they
B are

2 *An ESSAY of HEALTH*

are ill, but very few when they are well. And yet it is most certain, that 'tis 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 forbear*. 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

An Essay of Health and
Long Life
by
Georges CHEYNE,
London 1725

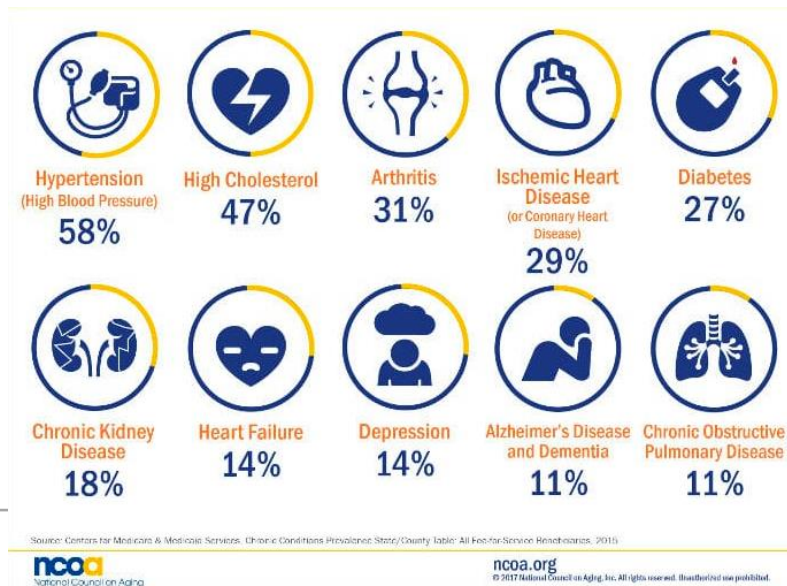
2 *An ESSAY of HEALTH*

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« 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. »

L'invecchiamento é principalmente causato da una infiammazione cronica definita "silenziosa"



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

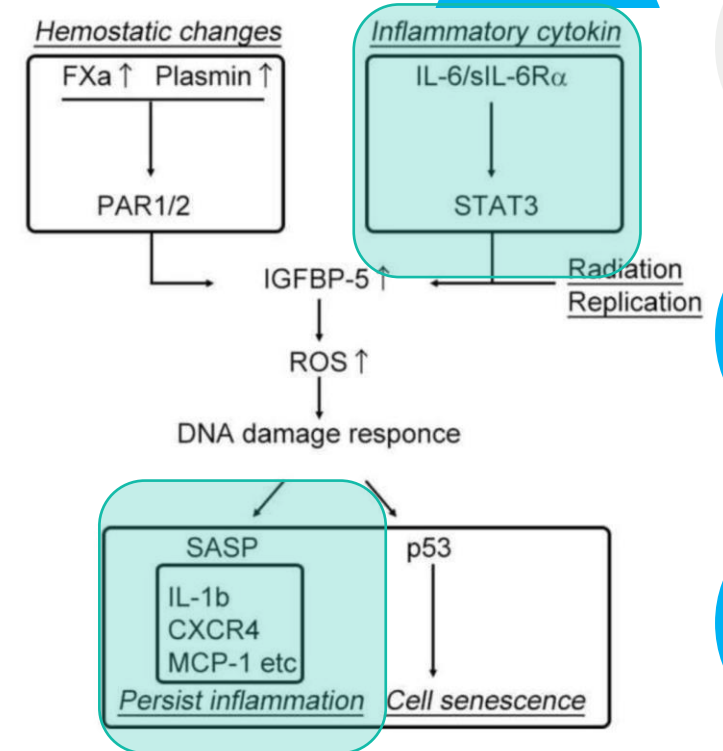
In our modern world, there is a paradox between our stressful lives and the increase in longevity. The latter should ideally be associated with healthy ageing, which is not always so easy to achieve. Trying to identify the complex immune and metabolic alterations that favour the appearance of ageing 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 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 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

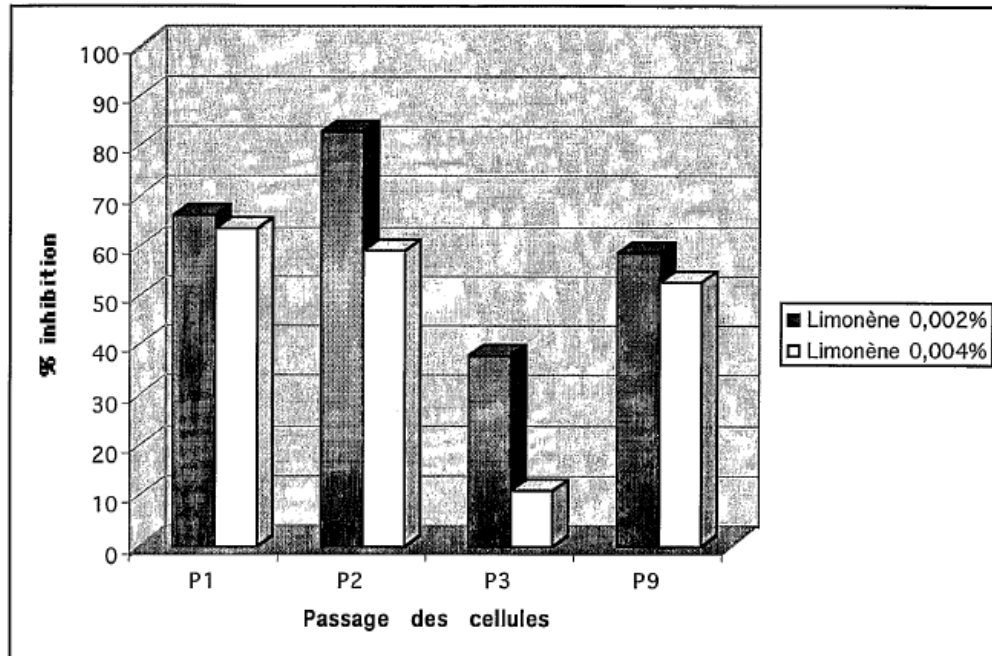
L'Inflamazione identificata meccanismo rilevante invecchiamento ma anche **senescenza cellulare**

- ❖ In contrast to young individuals, **aged individuals** have consistently elevated levels of inflammatory cytokines,
- ❖ especially interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α).
- ❖ *d*-Limonene is able to inhibit the secretion of IL-6 within the senescence-associated secretory phenotype (**SASP**).
- ❖ *d*-Limonene is also able to inhibit the secretion of IL-6 – IL-1 β , TNF- α , IFN- γ , LPS aso within animal and human organs.



d-Limonene as IL-6 lowering agent could contribute to control aging promoting inflammation as well as the secretory senescence process

Primo brevetto su ingredienti botanici capaci indurre reversibilità marcatori senescenza cellulare



(12) DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITÉ DE COOPÉRATION EN MATIÈRE DE BREVETS (PCT)

(19) Organisation Mondiale de la Propriété Intellectuelle
Bureau International



(43) Date de la publication internationale
10 novembre 2005 (10.11.2005)

PCT

(10) Numéro de publication internationale
WO 2005/105074 A2

Fonti: Bisson, J. F., Menut, C., & d'Alessio, P. (2008). Anti-inflammatory senescence actives 5203-L molecule to promote healthy aging and prolongation of lifespan. *Rejuvenation Research*, 11(2), 399-407.

Ricerca **BIO-GUIDATA** identifica molecole dagli estratti di piante capaci di indurre **reversibilità** marcatori infiammatori senescenza



- ◆ Il monoterpene *d*-Limonene/(*R*)-(+)-limonene si rivela il candidato
 - ◆ Scoperto nella pianta ***Halfordia kendack*** foresta vergine Vietnam / **Cina**
-

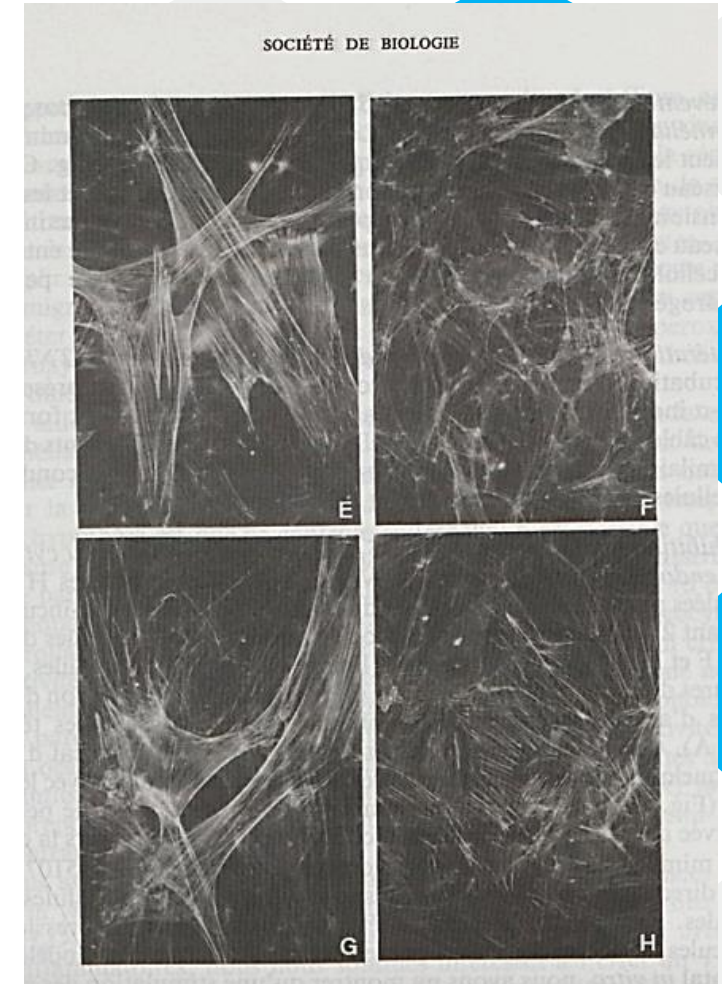
I modelli *in vitro* sulla “senescence indotta dallo stress” : reversibilità polimerizzazione delle fibre d’attina

- ◆ Umbilical cord and organ specific endothelial cells – nearly non-dividing cells
- ◆ **Stressor panel** to induce replicative senescence
 - ◆ H₂O₂, pro-inflammatory cytokines, antibiotics, glucose & VitC cocktail, viruses, aso...
- ◆ **Heterogeneous organ-specific** senescence

> 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



> C R Seances Soc Biol Fil. 1996;190(2-3):289-97.

[Pharmacological modulation of alterations of endothelial cytoskeleton induced by hydrogen peroxide and by TNF- α]

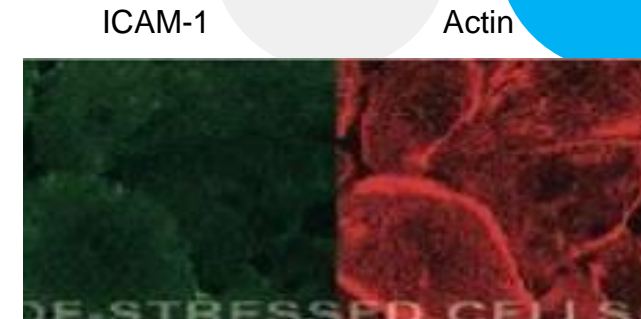
Marcatori infiammatori : aumento delle **molecole d'adesione** e co-localizzazione con le fibre d'attina ("**stress fibers**")

❖ **Young** cells pre-stressed state with **low** adhesion molecule expression

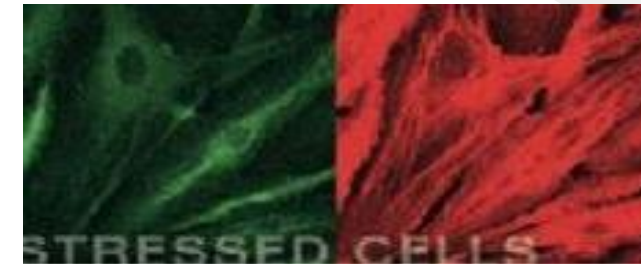
❖ Cytokine stimulation generating a inflammatory vs **senescent phenotype**

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

Normal



Activation
by TNF- α



Reset by
d-Limonene



Premio nazionale per la scoperta scientifica **innovante**

Brevetto quattro monoterpeni ad effetto reversibilità senescenza cellulare

Studi pre-clinici per definire “therapeutic window” e farmaco-cinetica

Primo studio sull'uomo EU call FP7 :
phase clinica 2A “trial” multicentrico



CONCOURS
DE CRÉATION
D'ENTREPRISES
INNOVANTES



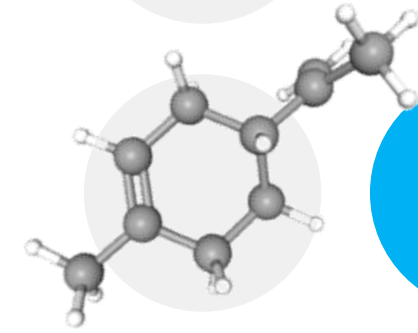
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MINISTÈRE DE
L'ENSEIGNEMENT
SUPERIEUR ET DE
LA RECHERCHE

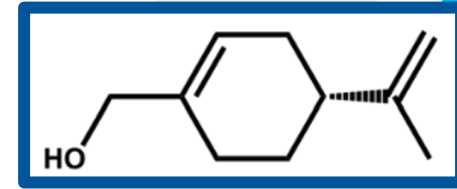


Nel cuore delle piante, i **terpenoidi sono delle** « small molecules » naturali



- ◆ 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.
-

Effetti anti-infiammatori dei monoterpeni per via **orale o topica**



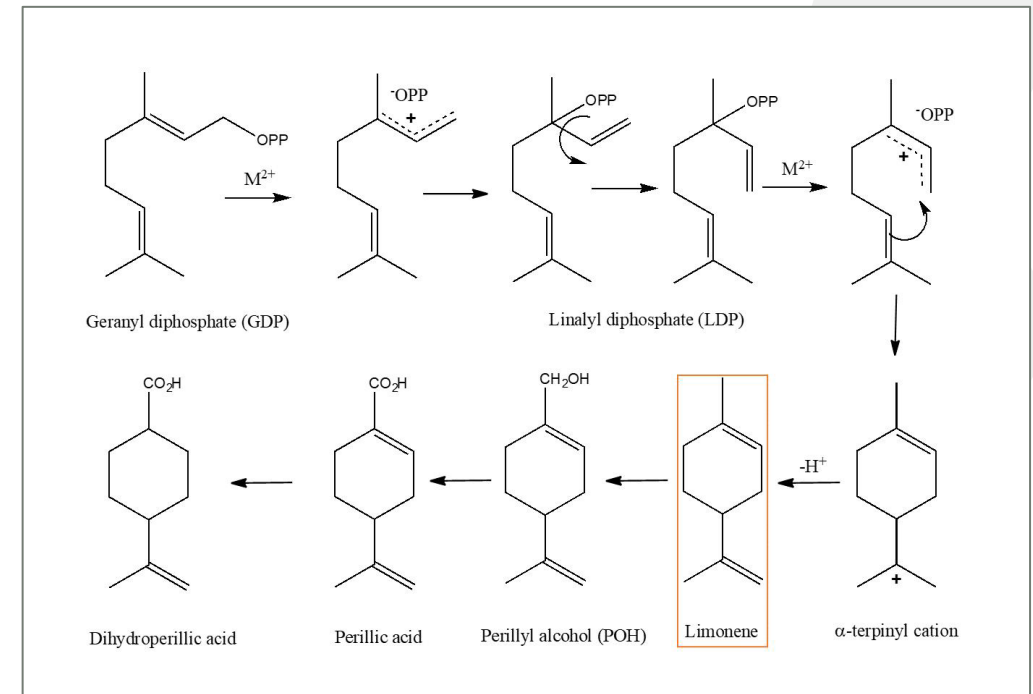
(R)-Perillyl alcohol

❖ Thanks to botanical *genus* the molecular complex identified in *Halfordia kendack* is also present in *Citrus sinensis* peel extract (OPE)

⑩ highlighting the effects of *d*-Limonene and its metabolite (R)-perillyl alcohol.

❖ A valuable strategy in aging prevention

⑩ based on a **non-toxic control** of the inflammatory reaction in the body.



Il *d*-Limonene e le sue applicazioni terapeutiche

- ⑩ Anti-inflammatory
- ⑩ Anti-aging
- ⑩ Anti-stress and mood disorders



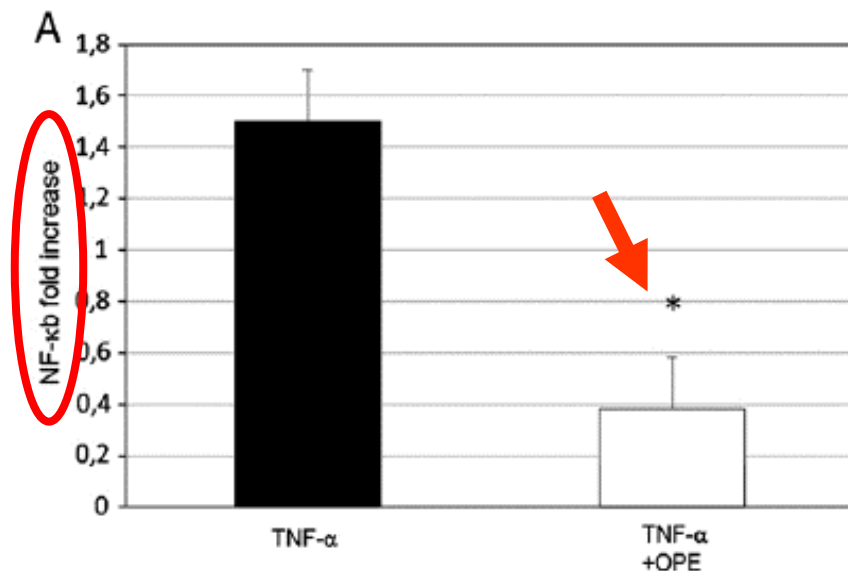
AISA Therapeutics domains

- ⑩ Antioxidant
- ⑩ Relief from heartburn
 - gastric acid neutralizing effect and support of normal peristalsis.
- ⑩ Dissolving cholesterol-containing gallstones
 - used clinically
- ⑩ **Anti-cancer properties**
 - *d*-Limonene and its metabolites impair tumor growth through inhibition of p21-dependent signaling and may induce apoptosis
 - **Inhibitor of farnesylation of rhoA₁**
- ⑩ Potential chemo-preventive and antineoplastic activities
- ⑩ Activation of aldehyde dehydrogenase
 - 3A1 (ALDH3A1), thereby decreasing aldehyde level.
 - Protection of salivary stem/progenitor cells (SSPCs) from toxic aldehydes.

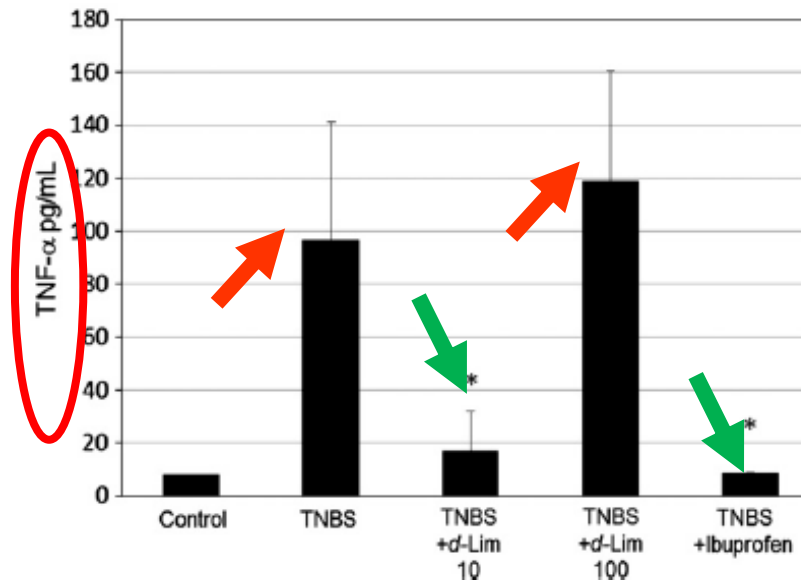


II *d*-Limonene come anti-Inflammatorio

- ❖ *In vitro* and preclinical validation of the mechanism of action in a **colitis model** : inhibition of inflammatory cytokines via impairment of transcription factor NF- κ B



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



Effect comparable to ibuprofen for low-dose
d-Limonene in a rat TNBS model (10 mg/kg)

TNBS = 2,5,6-trinitrobenzene sulfonic acid
(induced intestinal inflammation);

Terpenoidi anti-infiammatori nel « wound healing »

- ❖ Two murine models
 - ⑩ 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced dermatitis
 - ⑩ mechanical skin lesion.
- ❖ Assessment of the efficacy of *d*-limonene or POH applied topically
- ❖ Significant lower serum concentrations of IL-6 and TNF- α were observed in *d*-Limonene and POH-treated mice

Vehicle



D-Lim



POH



d-Limonene and POH demonstrate significant anti-inflammatory effects in murine dermal inflammation and wound-healing.

“Tissue repair” in modelli di auto-immunità



Vehicle

TPA*

TPA + *d*-Lim

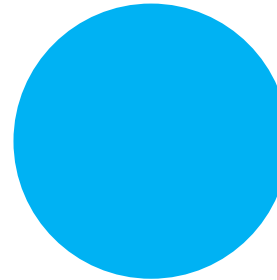
TPA + POH

**lesion mimicks
Atopic dermatitis**

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

“Case study” : applicazione terpenoidi anti-inflammatori nella **dermatite atopica** :

- ❖ Eczema worsened by repeated topic cortisol treatment
 - ⑩ High levels of zonulin / anti-food IgG
- ❖ Partial restoration after 10 days cure with anti-inflammatory terpenoids
- ❖ Additional benefit
 - ⑩ Gut barrier repair, with restitution of skin quality
- ❖ Visible mood amelioration
 - ⑩ **Rejuvenation effect**



Studio osservazionale nella psoriasi intermedia

Evoluzione positiva della « QoL »

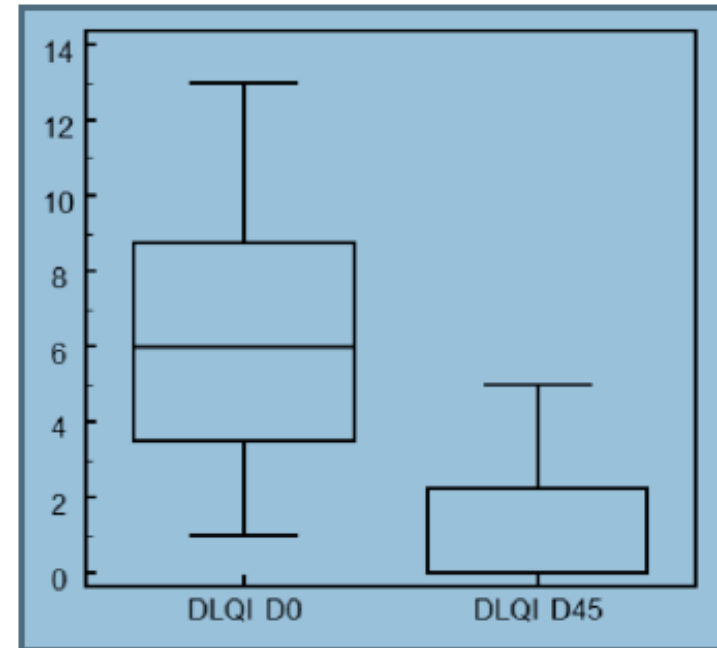


Figure 4: Evolution of Dermatology Life Quality Index.

La barriera intestinale e il microbiota **influenzano** **direttamente** lo stato di conservazione della pelle



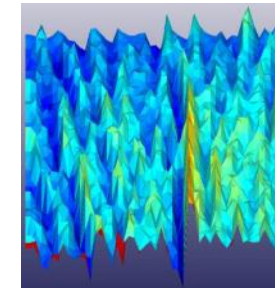
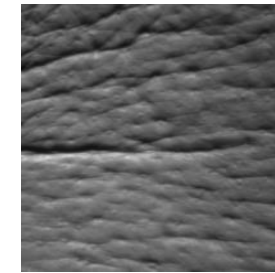
Day 0



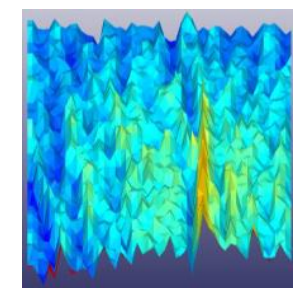
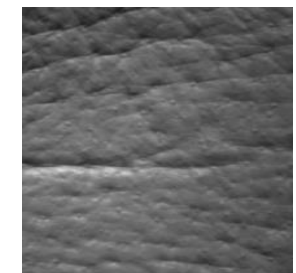
Day 56



Before



After



PRIME 2015;11:19-25

Life Sciences 92 (2013) 1151–1156

Contents lists available at SciVerse ScienceDirect

Life Sciences

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



Oral administration of *d*-Limonene controls inflammation in rat colitis and displays anti-inflammatory properties as diet supplementation in humans

Patrizia A. d'Alessio ^{a,*}, Rita Ostan ^b, Jean-François Bisson ^c, Joerg D. Schulzke ^d,
Matilde V. Ursini ^e, Marie C. Béné ^f

Nei « **mood disorders** » il α -Limonene svolge un ruolo endogeno interessante nei **> 40 anni**



aumento **dopamina**

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

Anti-Stress Effects of α -Limonene and Its
Metabolite Perillyl Alcohol

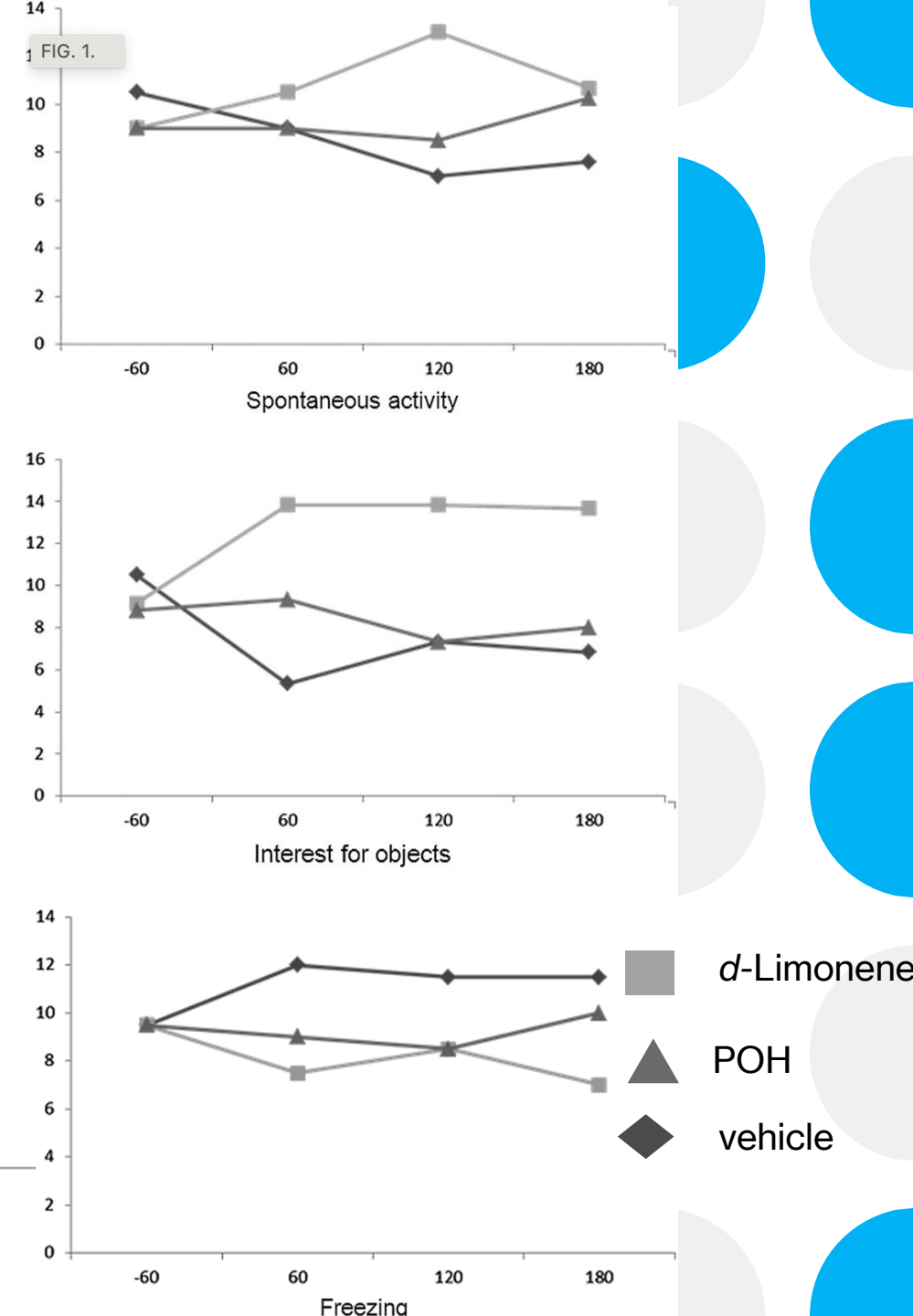
Patrizia A. d'Alessio,¹ Jean-François Bisson,² and Marie C Béné³

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>

Il complesso *d*-Limonene – POH as come **trattamento anti-stress**

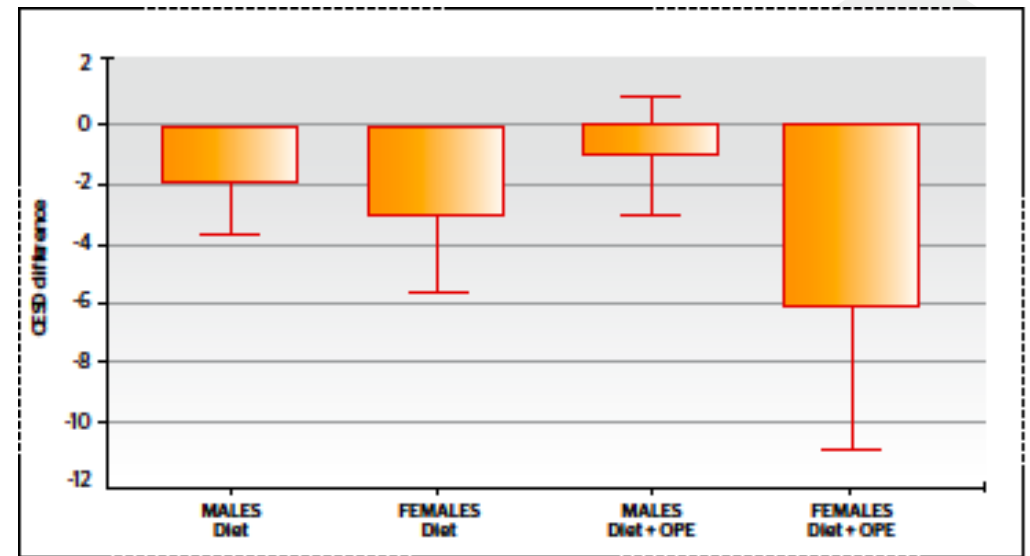
- ❖ *d*-limonene or POH to rats submitted to non-pathologic mild stress conditions.
- ❖ 3 studies performed:
 - ⑩ spontaneous activity
 - ⑩ interest for objects
 - ⑩ freezing
- ❖ Substantial changes in **movement** parameters as well as **motivational** aspects revealed the influential effect of *d*-Limonene on the emotional aspects of stress.

Fonte : d'Alessio, P. A., Bisson, J. F., & Béné, M. C. (2014). Anti-stress effects of *d*-limonene and its metabolite perillyl alcohol. *Rejuvenation research*, 17(2), 145-149.



Il d-Limonene come **trattamento anti-stress** e “mood disorders” nella **donna**

- ❖ It is well recognized that inflammation contributes to the development of depression with gender differences (2 fold).
- ❖ Orange peel extract (OPE) given as food supplementation
 - ⑩ high amount of d-limonene >95%, dose 10mg/kg
 - ⑩ 56 days
- ❖ Mood modulation effect in humans
- ❖ Healthy 65–85-year-old subjects enrolled in the Ristomed study with high inflammatory scores.
- ❖ Significant decrease of peripheral IL-6 levels associated with a statistically clear effect on depressive mood.



CESD: Center for Epidemiologic Studies Depression

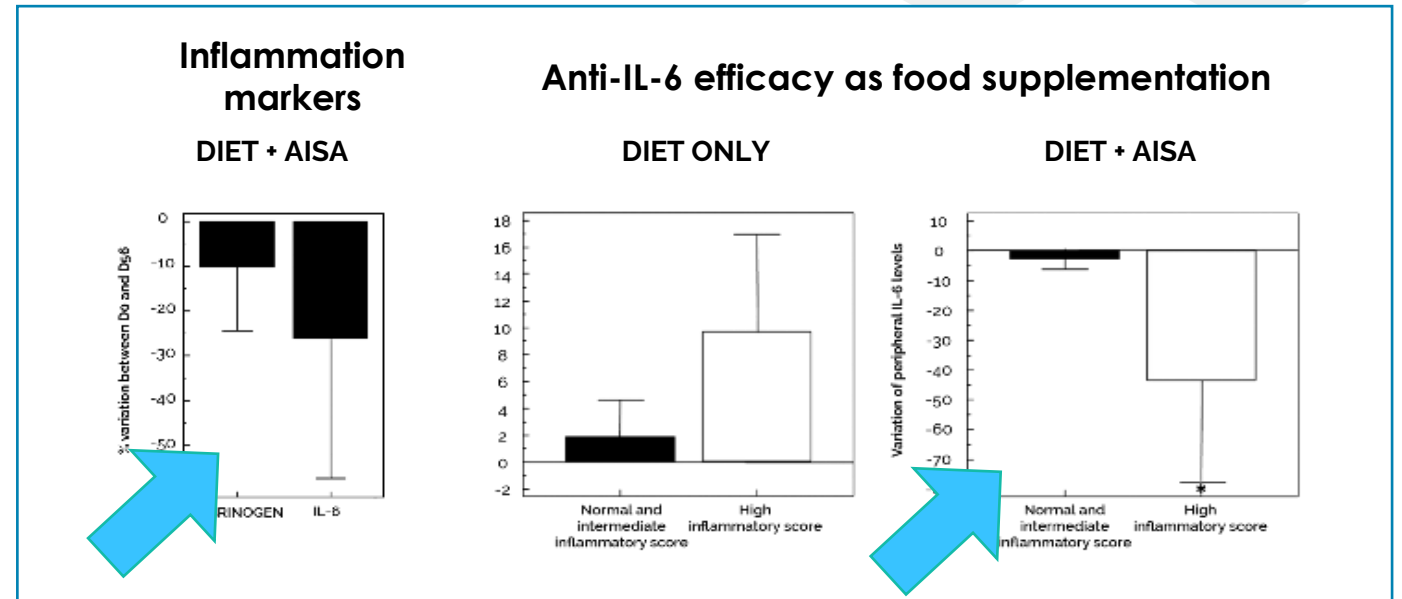
Reference: D'Alessio et Al. Prime 2012; 30-37

Gender effect : although the results are not statistically significant, the Ristomed study demonstrated that OPE was more efficient in subjects with an initially high inflammatory status and depression scores in women.

Lo studio RISTOMED

❖ The RISTOMED study enrolled in a first in human trial **138 healthy elderly individuals (age range 65–85 years)** in three countries.

- ⑩ Comparison of 3 groups with a dietary program supplemented with soft gel capsules containing OPE (N = 31) or without supplementation (N = 30).
- ⑩ Analysis at day 1 and day 56.



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

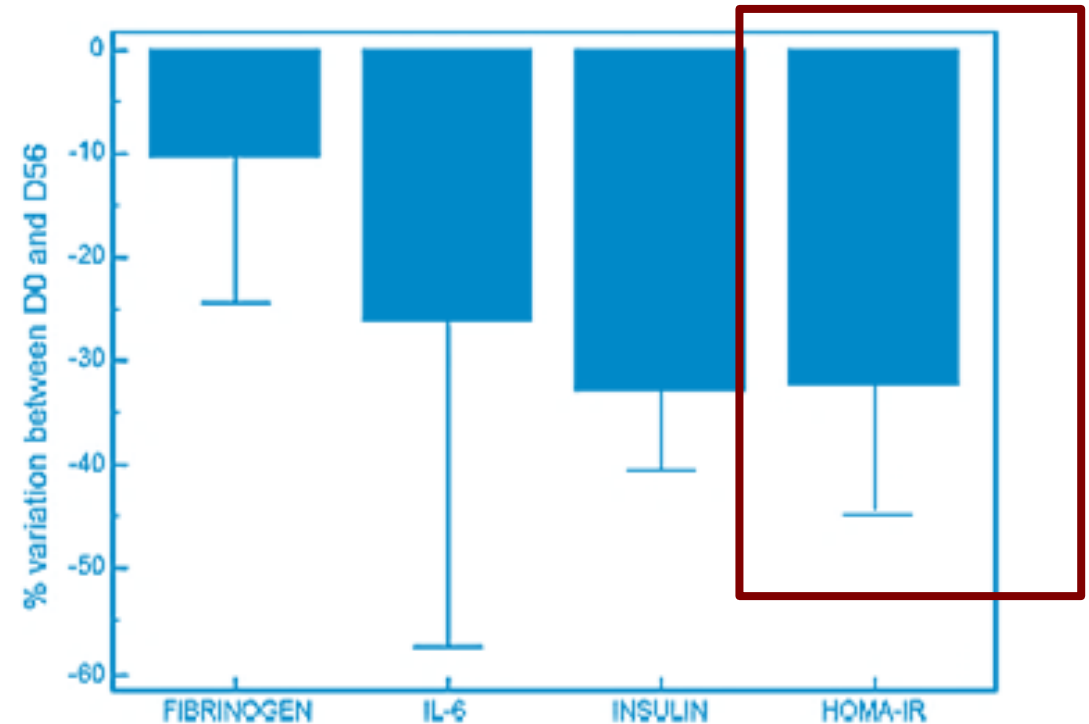


1. pronounced anti-inflammatory effects of *d*-Limonene *in vitro*, in a model of colitis and dermatitis
2. as dietary supplement in humans could be worthwhile in **multimodal anti-inflammatory therapy concepts**

Bio-marcatori della sindrome cardio-metabolica, diabete e trombosi

- ❖ The monoterpene *d*-Limonene targets IL-6 and fibrinogen, but also insulin and markers of insulin resistance*

* Homeostatic model assessment of insulin resistance
HOMA-IR



Il *d*-Limonene agente riducente i bio-marcatori dell'invecchiamento

Riparazione della barriera intestinale e modulazione delle « ratio » microbiota

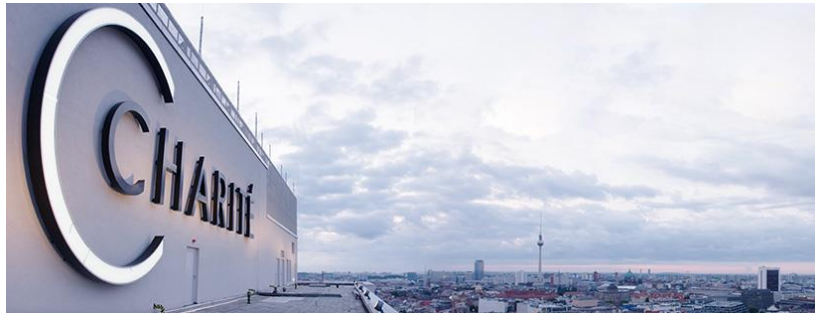
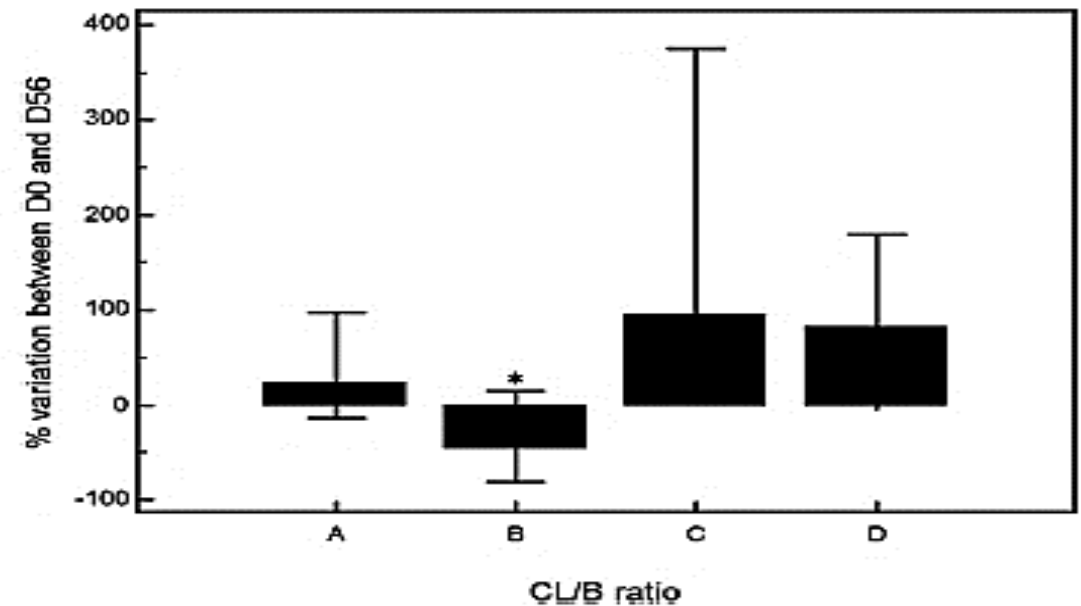


Table 1
OPE containing 95% of *d*-Limonene: effect on epithelial barrier function.

	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.

Clostridium cluster IV / *Bifidobacteria* ratio



Modulazione della « **VITALITA** »

OMS e nuovi criteri del « healthy aging » 2015, Matteo Cesari

- ◆ The World Health Organization (WHO) has proposed a novel concept, « **intrinsic capacity** » (IC),
- ◆ refers to the combination of one's physical and mental abilities.

The IC framework comprises cognition, mobility, psychological, « **Vitality** », and sensory functions.

Review > [Lancet Healthy Longev.](#) 2022 Nov;3(11):e789-e796.
doi: 10.1016/S2666-7568(22)00200-8.

WHO working definition of vitality capacity for healthy longevity monitoring

Ivan Bautmans ¹, Veerle Knoop ², Jotheeswaran Amuthavalli Thiyagarajan ³, Andrea B Maier ⁴, John R Beard ⁵, Ellen Freiburger ⁶, Daniel Belsky ⁷, Mylene Aubertin-Leheudre ⁸, Christopher Mikton ⁹, Matteo Cesari ³, Yuka Sumi ³, Theresa Diaz ¹⁰, Anshu Banerjee ¹¹; WHO Working Group on Vitality Capacity

Comment > [J Gerontol A Biol Sci Med Sci.](#) 2022 Jan 7;77(1):91-93.
doi: 10.1093/gerona/glab318.

What Is Intrinsic Capacity and Why Should Nutrition Be Included in the Vitality Domain?

Matteo Cesari ^{1 2}, Ritu Sadana ¹, Yuka Sumi ¹, Jotheeswaran Amuthavalli Thiyagarajan ¹, Anshu Banerjee ³

Affiliations + expand

PMID: 35015816 DOI: 10.1093/gerona/glab318

« **Intrinsic capacity** » (IC): indicatore multidimensionale della salute

« **VITALITY** »

Capacità mentali e fisiche cruciali per gli anziani per « **continuare a fare cio' a cui tengono di più** » (« **what they value most** »).



Figure 1. Bifactor CFA model of intrinsic capacity. CFA = confirmatory factor analysis.

La « small molecule » monoterpene *d*-Limonene opera un resetting multi-sistemico

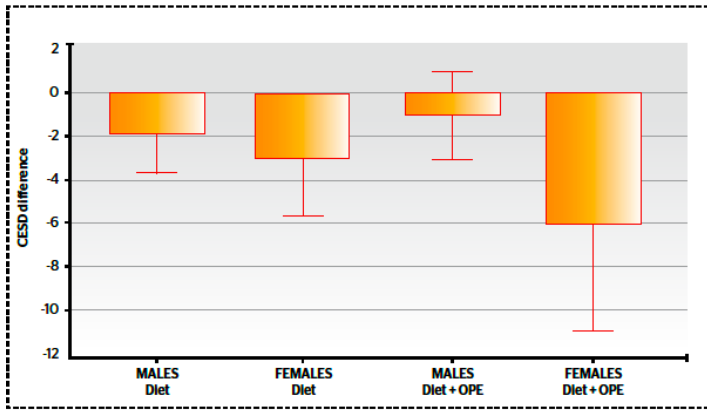
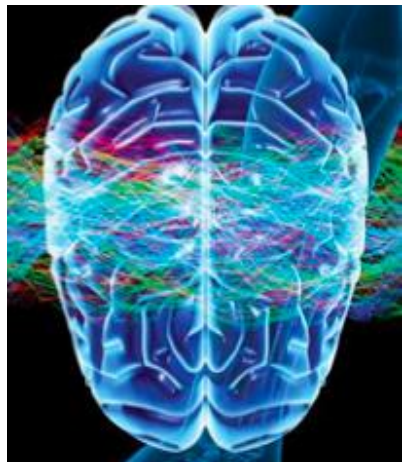
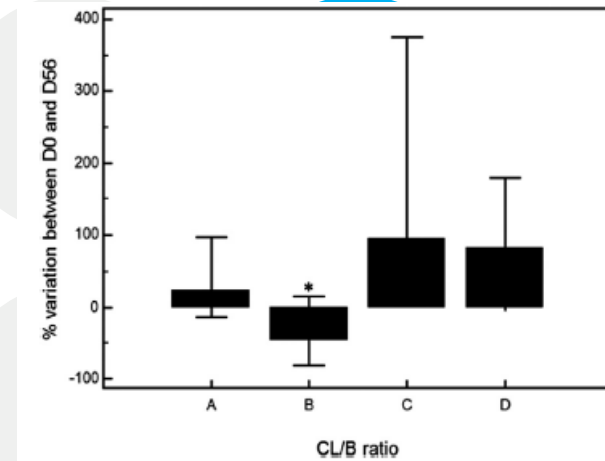
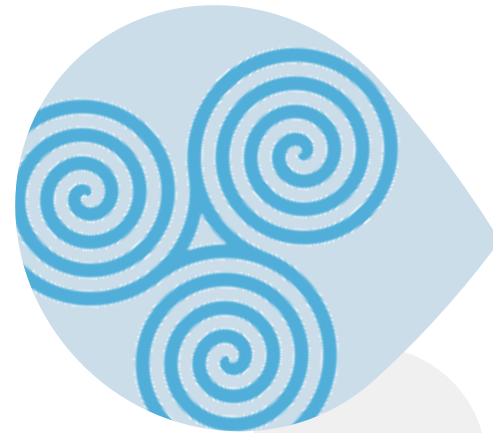


Figure 3 Gender partition and CES-D variation in diet versus diet plus OPE



d-Limonene
Pro-drug effect

Anti-inflammatory effect & enhancing **dopamine**



Restoration of the gut barrier fighting **dysbiosis**

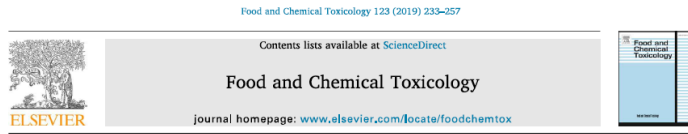
POH-metabolite effect

Ridefinizione dei marcatori del « healthy aging »



Review
Terpenoids as Potential Geroprotectors

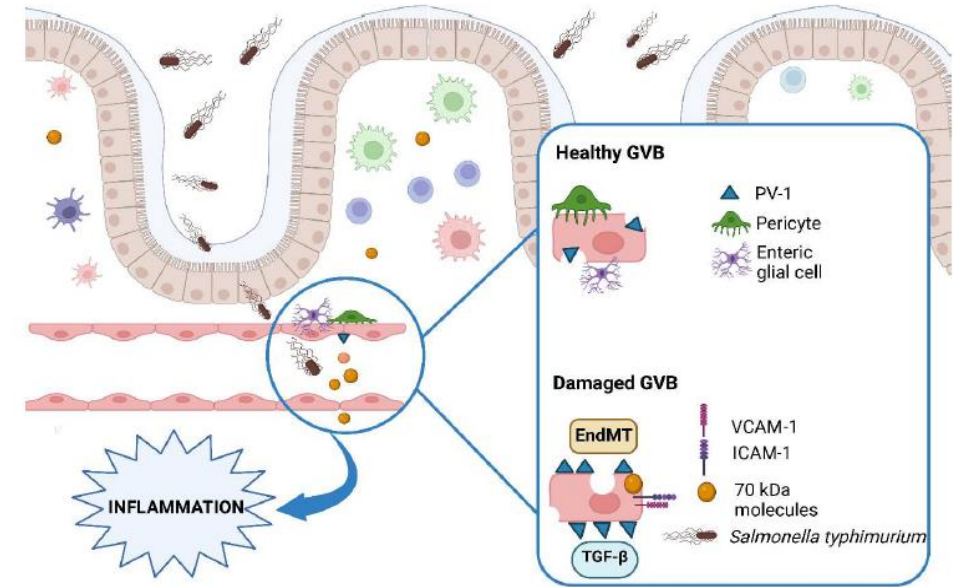
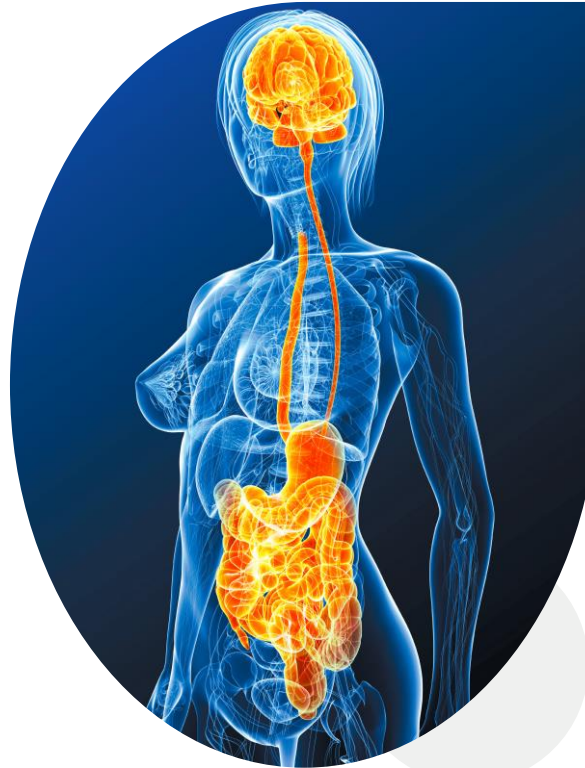
Ekaterina Proshkina ¹, Sergey Plyusnin ^{1,2}, Tatyana Babak ¹, Ekaterina Lashmanova ¹, Faniya Maganova ³, Liubov Koval ^{1,2}, Elena Platonova ^{1,2}, Mikhail Shaposhnikov ¹ and Alexey Moskalev ^{1,2,*}



Monoterpenes modulating cytokines - A review

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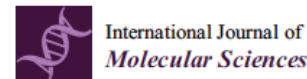
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d-Limonene challenging anti-inflammatory strategies

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

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

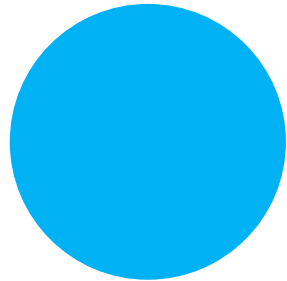
Terpenoidi
 « aeroprotettori »

Da RISTOMED e Terpenoidi Non Tossici alle « Small Molecules » : nuovi candidati farmacologici



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