

Small molecules for big aging, the discovery of terpenoids as geroprotectors:

the particular case of monoterpenes

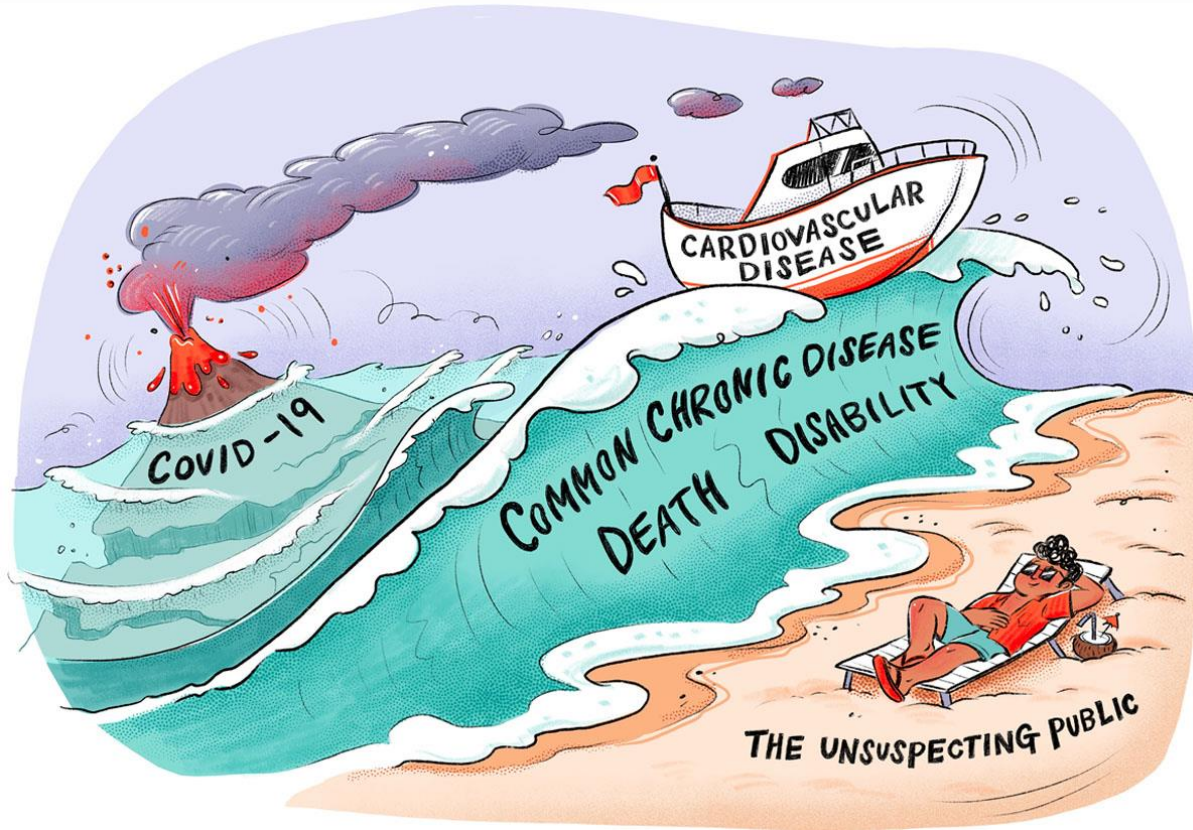
Pr Dr **Patrizia A d'Alessio**, MD PhD
Hematologist & Cell biologist

CEO



Covid-19 has allowed us to reassess chronic diseases

Something to do with aging?



Circulation

Avoiding the Coming Tsunami of Common, Chronic Disease

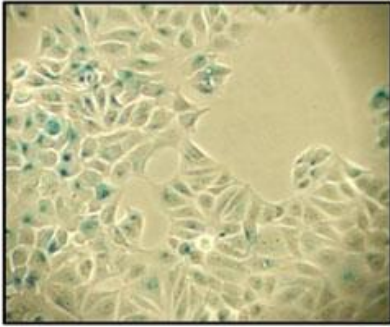
What the Lessons of the COVID-19 Pandemic Can Teach Us

Robert M. Califf

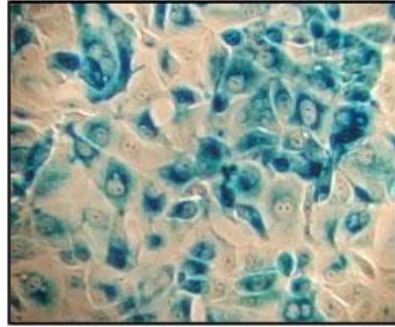
Originally published 6 Apr 2021 |
<https://doi.org/10.1161/CIRCULATIONAHA.121.053461> |
Circulation. 2021;143:1831–1834

Markers to define senescence

Young cells



Senescent cells



β -galactosidase staining



« There are no *specific* senescence markers » Judith Campisi

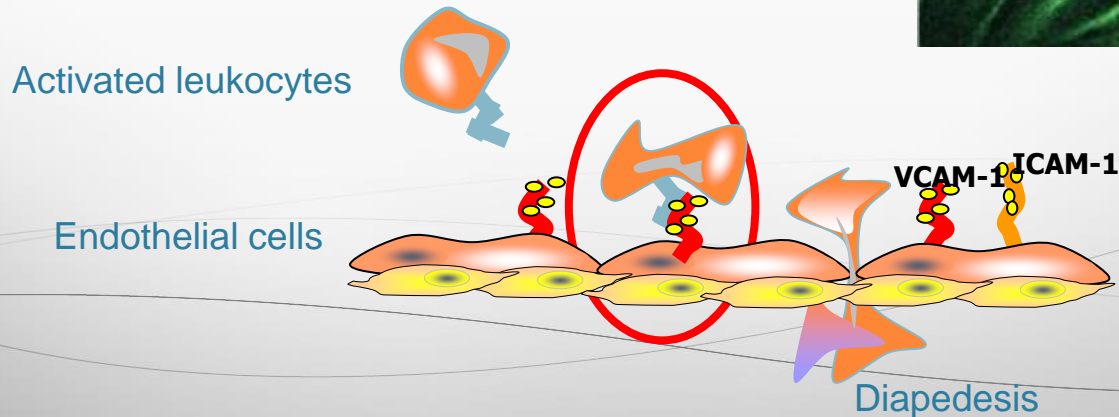
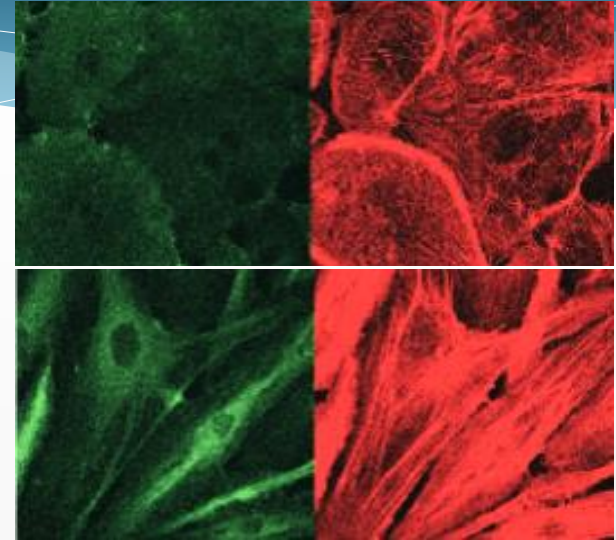
2017 ICOSA senescence meeting Paris Institut Pasteur



Our observations of markers to define senescence

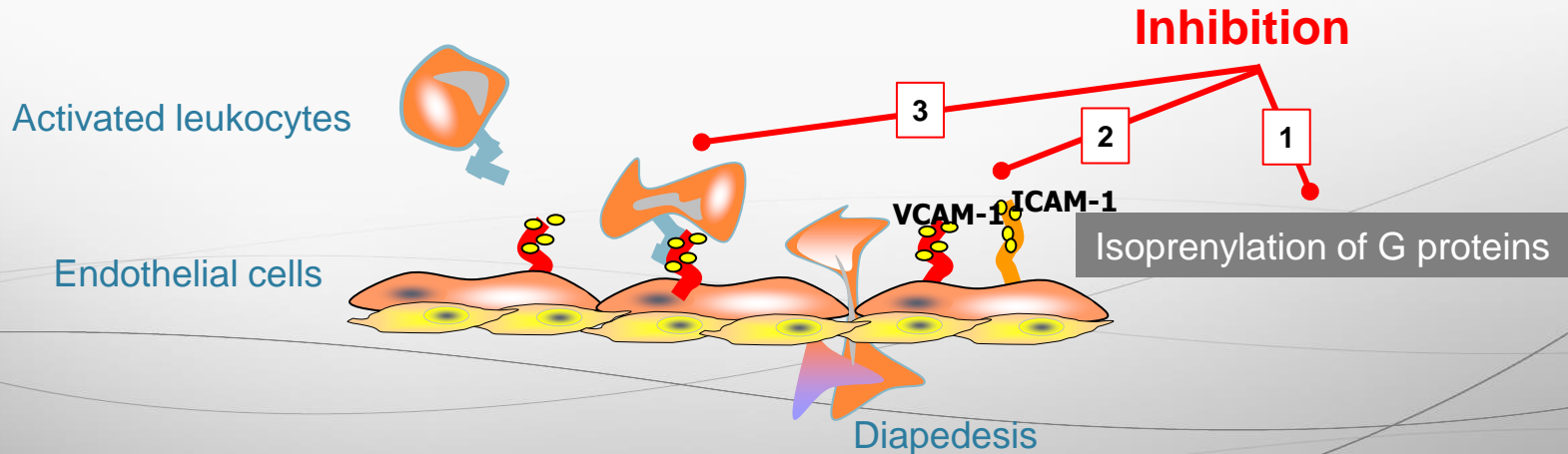
We defined senescence markers in endothelial cells :

- 1/ **over-expression** of ICAM-1, VCAM-1, selectins
- 2/ **polymerization of actin cytoskeleton**, stress fibers
- 3/ induced by circulating **pro-inflammatory cytokines**



Reverse expression of senescence markers

- 1/ Inhibition of adhesion molecules ICAM-1, VCAM-1, selectins
- 2/ Inhibition of actin cytoskeleton stress fibers polymerization
- 3/ inhibition of circulating pro-inflammatory cytokines





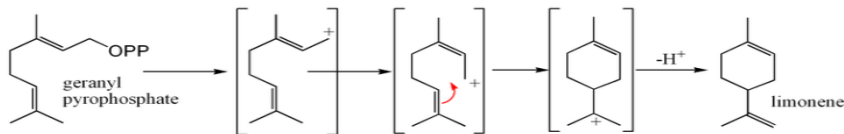
Bio-guided research

Some years of research on 100 plant extracts and
2000 molecules analyzed



- ◆ In collaboration with Pierre Potier (discoverer of Taxoter®), we identified anti-inflammatory anti-senescence monoterpenes....
- ◆ ...in the *Halfordia kendack* plant, collected yearly by ethno-botanists of Hanoi University (Vietnam).
- ◆ First patent on cell degeneration reversibility
- ◆ National award for innovative research

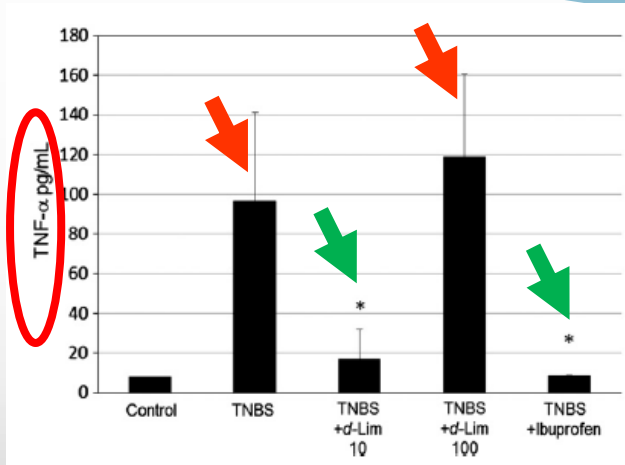




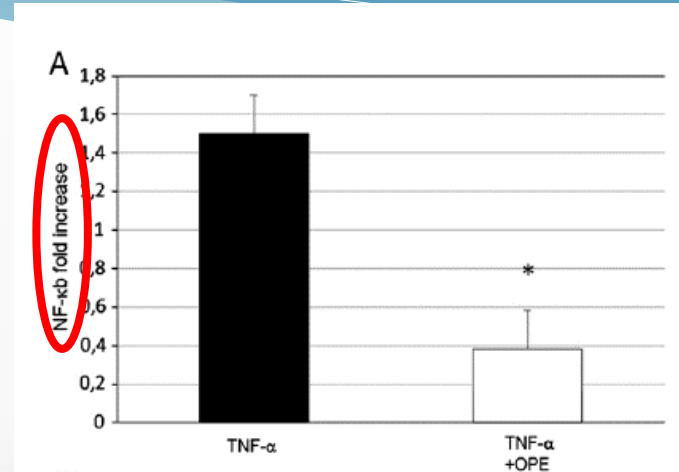
- ◆ From *in vitro* studies 2000-2004...
- ◆ ... to pre-clinical studies in rodents in gut, skin and stress FOB in 2007-2009...
- ◆ ...to first-in-human studies: RISTOMED EU project 2009-2013...
 - ◆ ..all confirmed the anti-inflammatory effect and QoL



Oral administration of *d*-Limonene controls inflammation in rat colitis



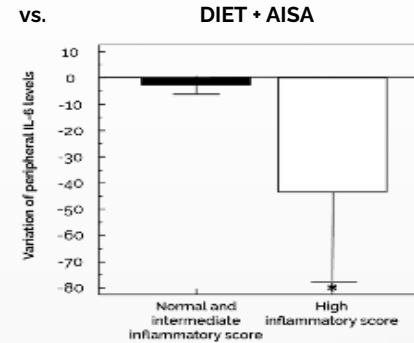
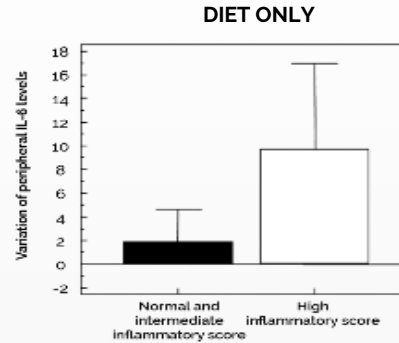
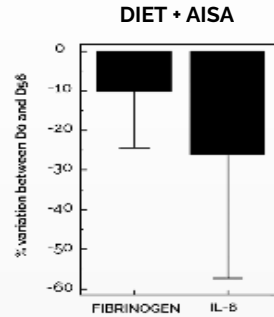
Effect comparable to ibuprofen
for low-dose *d*-Limonene



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

First in human RISTOMED EU study 140 patients

Inflammation markers



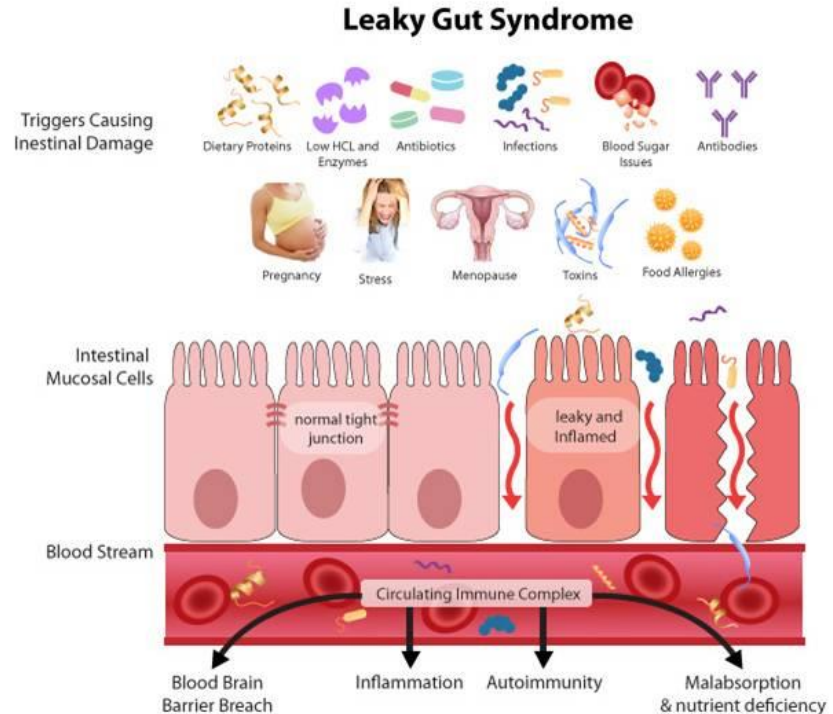
Significant modifications of inflammation markers (fibrinogen and IL-6) were observed in individuals with baseline moderate inflammation (**RISTOMED diet + AISA**) between D0 and D56.



“Leaky gut” also induces systemic inflammation

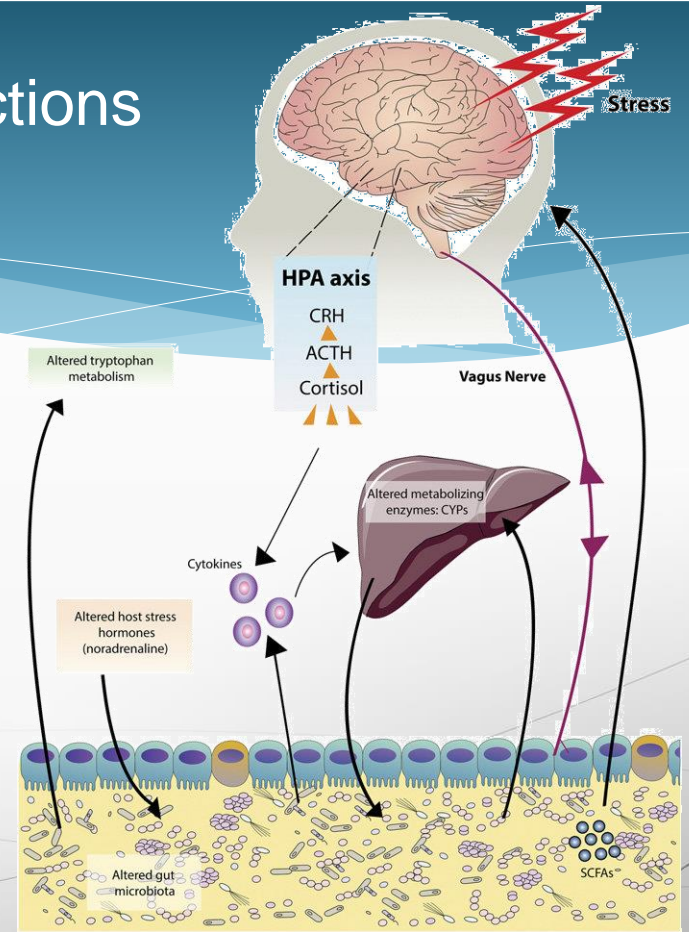
Cortisol

Aging



Stress changes immune reactions generating « sickness disease »

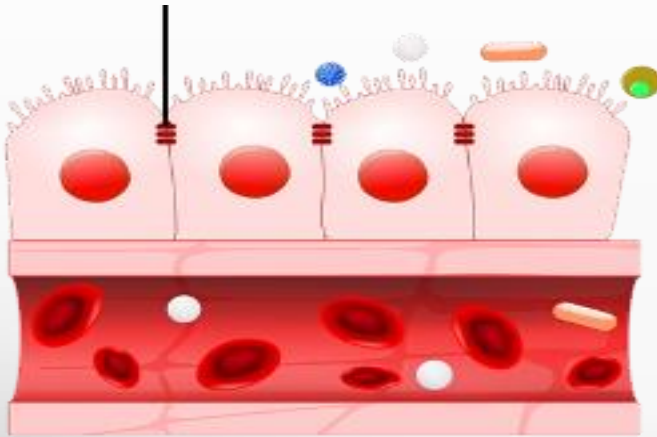
loss of memory,
anxiety,
refusal to meet social events,
obsessional thoughts,
difficulty to concentrate,
depression,
chronic fatigue syndrome,
sleeplessness,
loss of interest,
obsessional neurosis



« Monoterpenes modulate cytokines »

Not only ! They repair the GUT BARRIER

Normal tight junctions



AISA: significant effect on strengthening the epithelial barrier function

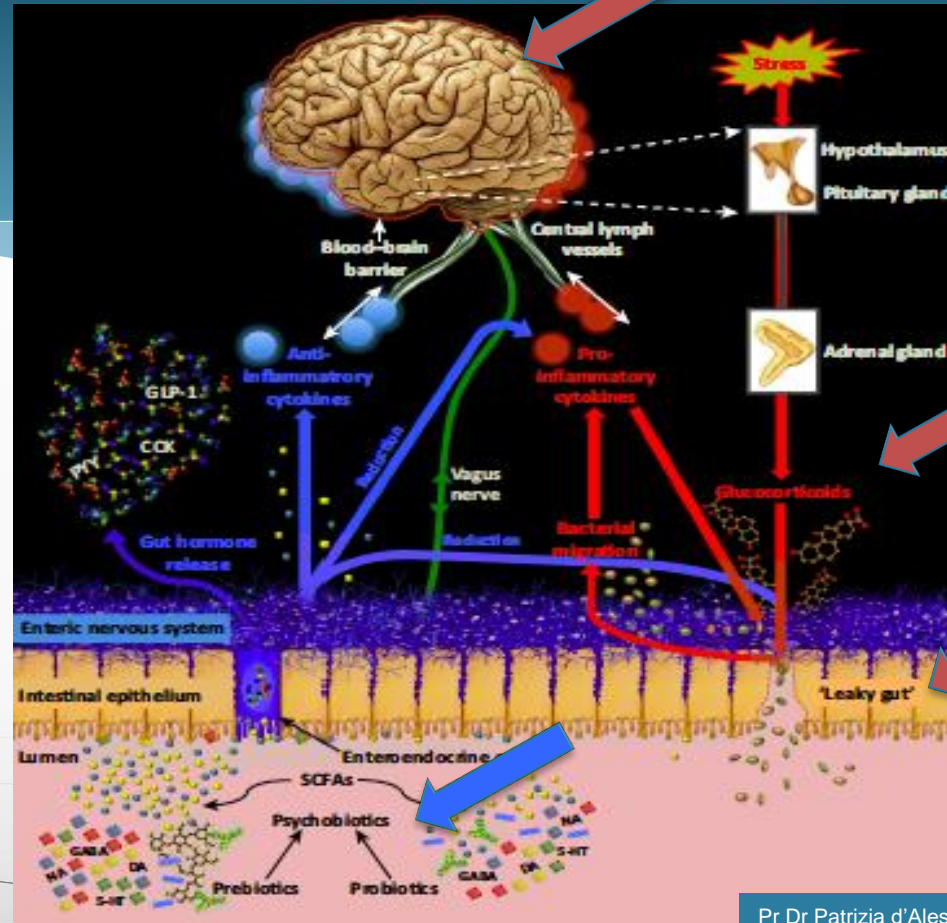
	Control	AISA			
		75 μ M	150 μ M	750 μ M	1500 μ M
R ^t	107 \pm 3%	106 \pm 4%	112 \pm 3%	132 \pm 3%	153 \pm 4%
n	9	6	6	6	6
p		n.s.	n.s.	<0.001	<0.001

Evaluation of electric resistance ($\Omega \cdot \text{cm}^2$)
as percentage of initial resistance R_t.



Gut barrier integrity for inflammation treatment

- ◆ Gut barrier dysfunction leads to systemic inflammation ...
- ◆ reversible by epigenetic – microbiome driven – modifications
- ◆ emphasizing the role of ***small molecules*** contained in nutrient components
- ◆ the ***new geroprotectors***



Pr Dr Patrizia d'Alessio, MD PhD

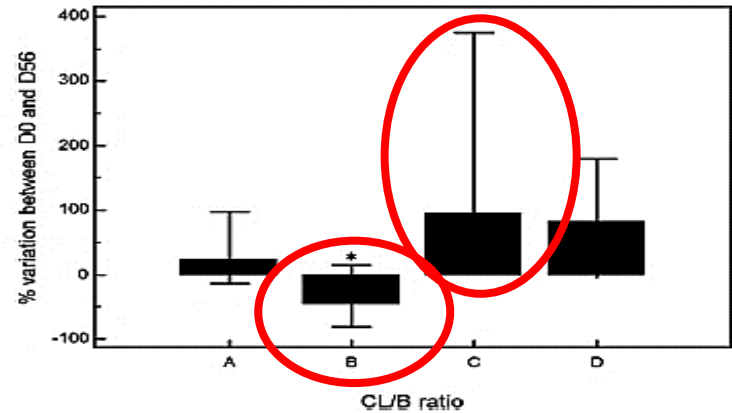
Monoterpenes as modulators of microbiota

Clostridium cluster IV / *Bifidobacteria* ratio

Probiotic supplementation with VSL#3 (B) tends to decrease the ratio of *Clostridium*/*Bifidobacteria* in patients with baseline mild or high inflammatory status.

Supplementation with *d*-Limonene (C) has the reverse effect.

This could be explained by different targets of these two nutraceuticals, acting either on the microbiote only or concomitantly on the barrier function of the gut epithelium.



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*

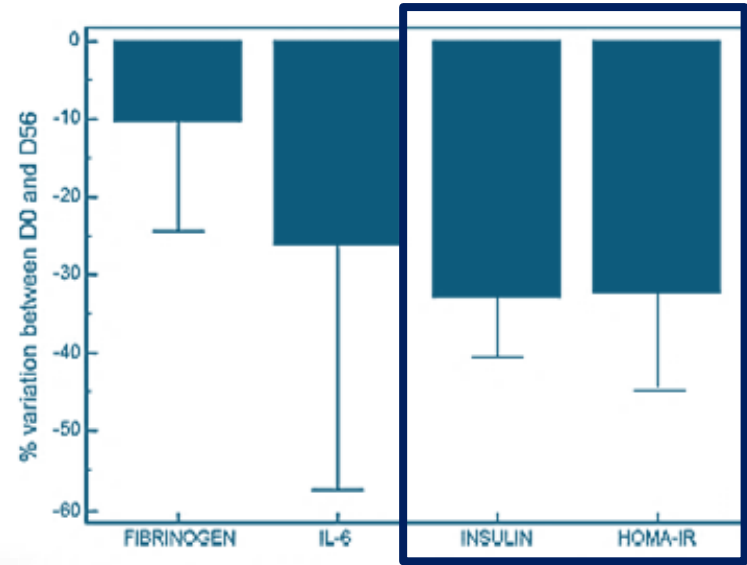
R. Ostan^a, M.C. Béné^b, L. Spazzafumo^c, A. Pinto^d, L.M. Donini^d, F. Pryen^e, Z. Charrouf^f, L. Valentini^g, H. Lochs^h, I. Bourdel-Marchasson^{i,j,k}, C. Blanc-Bisson^{l,j,k}, F. Buccoliniⁱ, P. Brigidì^m, C. Franceschi^{a,n,o}, P.A. d'Alessio^{a,*}

Markers of diabetes thrombosis and cardio-metabolic syndrome



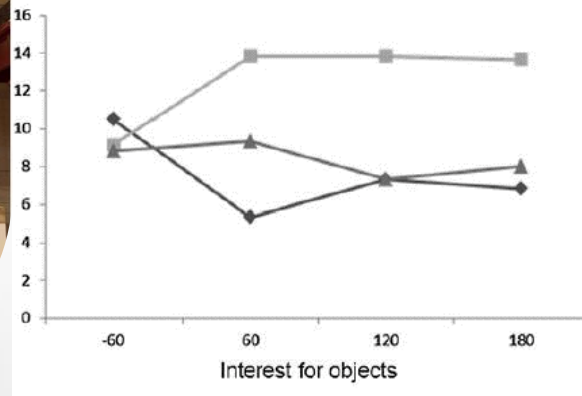
Monoterpenes target IL-6 and fibrinogen, but also insulin and **markers** of insulin resistance*

* Homeostatic model assessment of insulin resistance HOMA-IR



Anti-inflammation RESULTS in mood modulation

Motivational effect in rodents



Mood modulation effect in humans

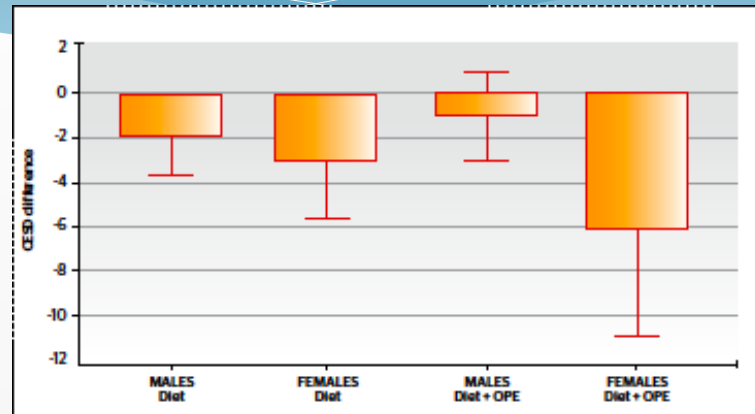


Figure 3 Gender partition and CES-D variation in diet versus diet plus OPE

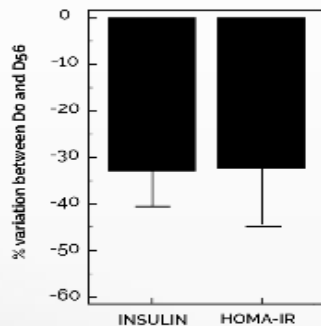
Rejuvenation Res.
2014;17:145-149

PRIME 2012; 30-37



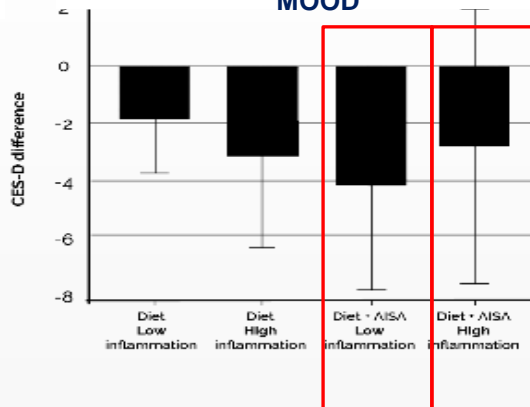
Mood is highly influenced by metabolic issues

INSULIN RESISTANCE



Significant variation of metabolic markers (insulin and HOMA-IR) in subjects with moderate/high baseline inflammation between D0 and D56

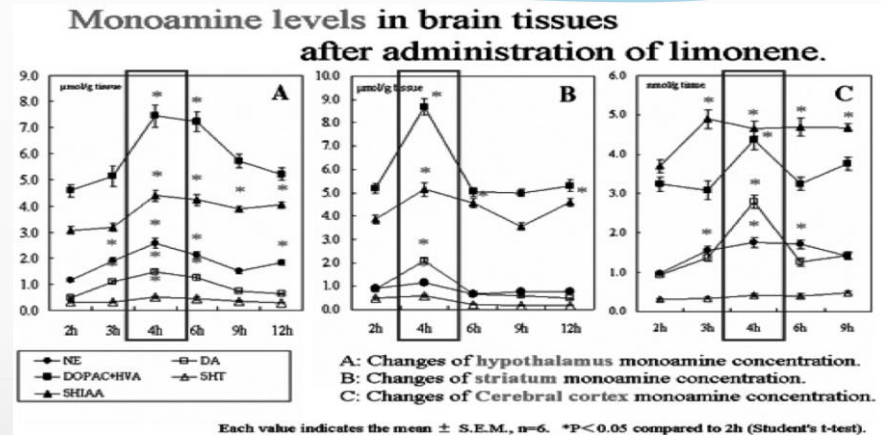
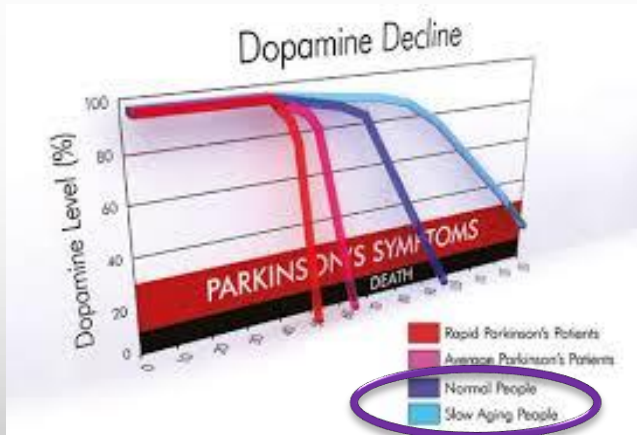
MOOD



Improvement of the **CES-D** score in subjects having received AISA supplementation.



A Japanese study and patent filed on demand of The Nestlé Foundation



Is it possible to reduce mental and physical stress with food components?

Hidehiko Yokogoshi

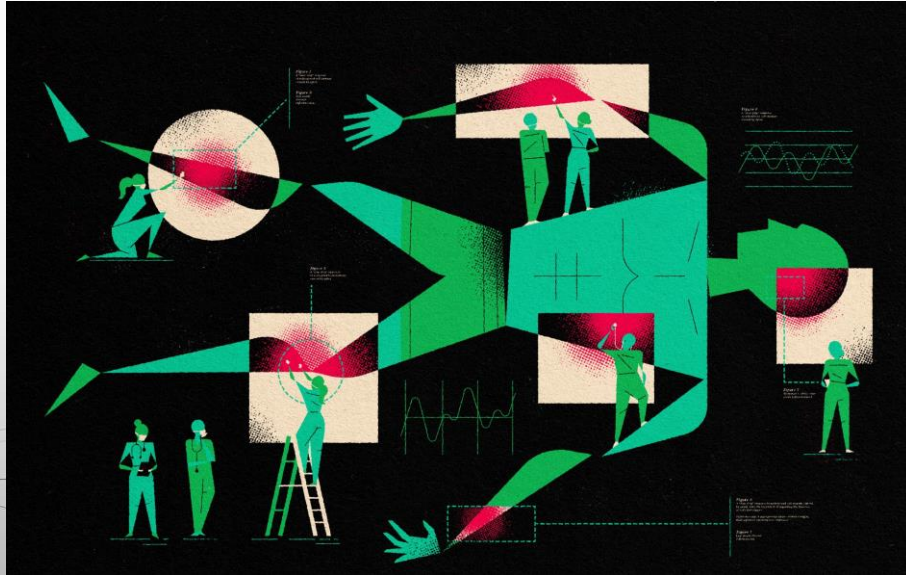
Monoterpenes seem thus to address the gut-brain axis...



- ◆ each on-going *stress* transduces into an increase of *inflammation*,
- ◆ starting at the level of the gut barrier
- ◆ and generalizing to the whole body,
- ◆ mimicking mood disorders.

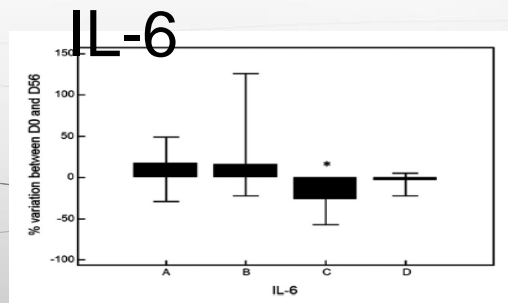
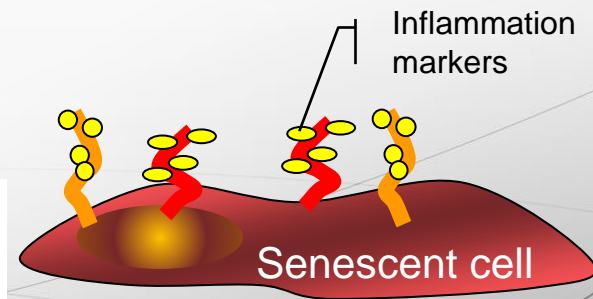
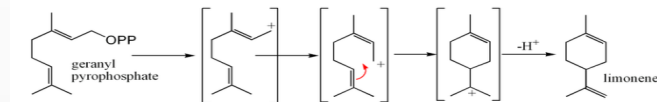
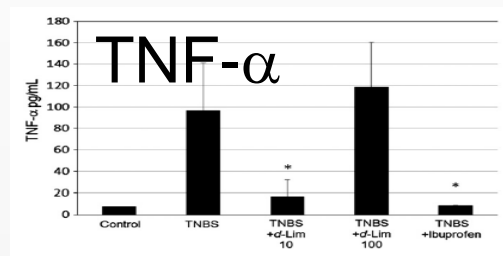
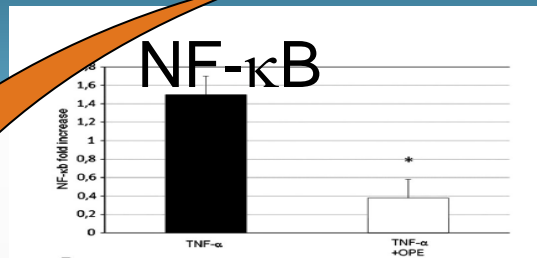
« Cytokine storm »

*“The fact is that the real morbidity and mortality of this disease is probably driven by **this out-of-proportion inflammatory response to the virus...**”*



Jamie Garfield,
Temple University Hospital

AISA can control SASP : relevant to aging ?

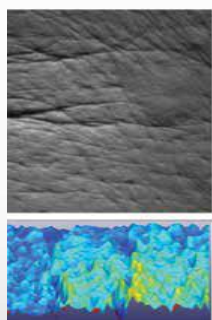


Mech Ageing Dev. 2020 Jan 2;186:111206. doi: 10.1016/j.mad.2019.111206. [Epub ahead of print]

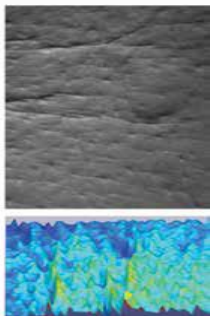
AISA can control the inflammatory facet of SASP.

d'Alessio PA¹, Béné MC².

The anti-aging effects of monoterpenes

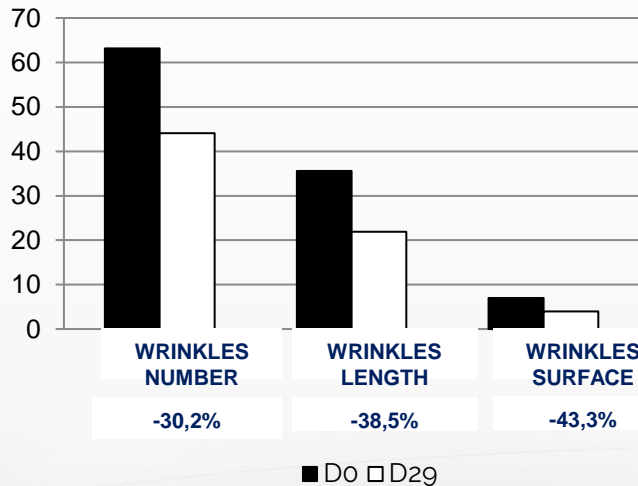


Day 0

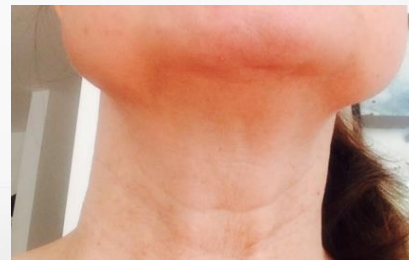


Day 29

WRINKLES DEPTH DECREASE



Day 0



Day 56

INSTRUMENTAL TEST on 21 subjects ; application twice a day during 29 days

d'Alessio PA, Menut C, Lejay J, Bisson JF, Béné MC. PRIME. November 2015; 19-25.



CONFORME ISO 9001
CERTIFIÉ PAR
AFNOR



GUARANTEED
TO ALL
SKIN TYPES

Wound healing without angiogenesis

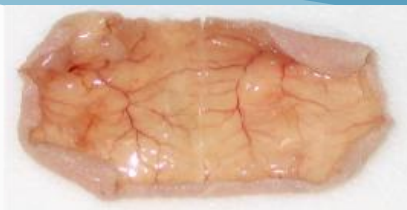


Inhibition of neo-angiogenesis

by *d*-Limonene and
perillyl alcohol
(POH)

Decrease of pro-
inflammatory
cytokines

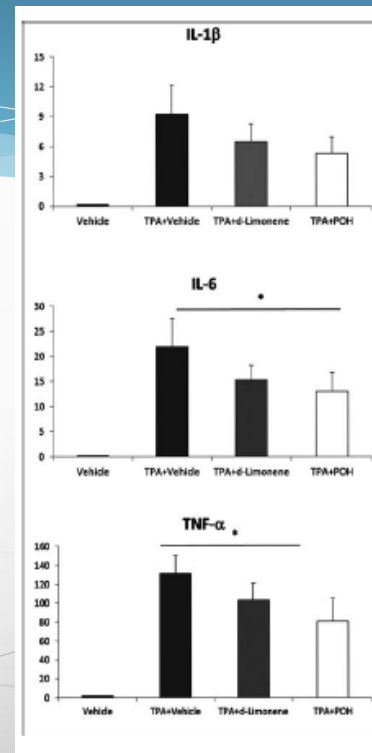
Vehicle



d Lim



POH



Tissue repair in a model of psoriasis / atopic dermatitis



Vehicle

TPA
lesion of
psoriasis and
atopic
dermatitis

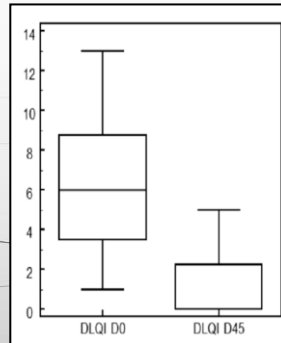
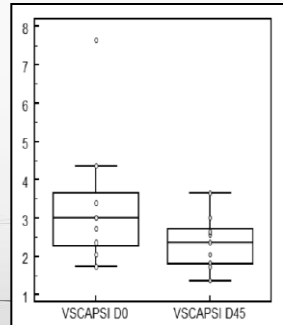
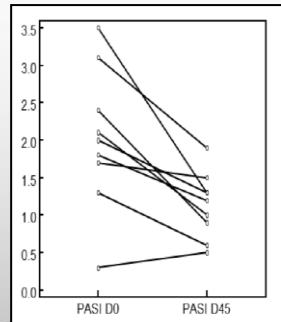
TPA + *d*-Lim

TPA + POH

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

Monoterpenes in human intermediate psoriasis

Topical application for 45 days
PASI *Psoriasis Area Severity Index*,
VSCAPSI *videodermoscopy Scalp*
Psoriasis Severity Index
DLQI *Daily Life Quality Index*



SAPIENZA
UNIVERSITÀ DI ROMA

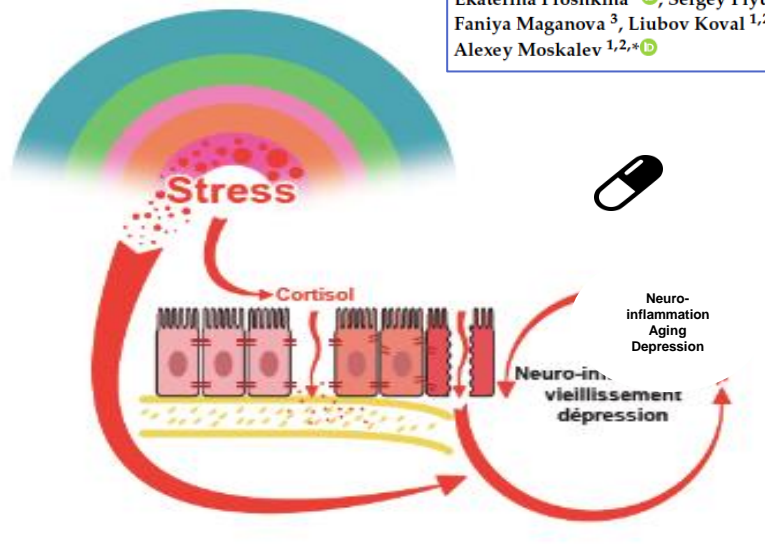


antioxidants

Review

Terpenoids as Potential Geroprotectors

Ekaterina Proshkina¹^b, Sergey Plyusnin^{1,2}^b, Tatyana Babak¹, Ekaterina Maganova³, Liubov Koval^{1,2}, Elena Platonova^{1,2}, Mikhail Shal'Alexey Moskaev^{1,2,*}^b



Monoterpenes modulating cytokines - A review

Jullyana S.S. Quintans^a, Saravanan Shanmugam^a, Luana Heimfarth^a, Adriano Antunes S. Araújo^a, Jackson R.G. da S. Almeida^a, Laurent Picot^c, 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 (NEPLAME), Federal University of San Francisco Valley (UNIVASF), Petrolina, Pernambuco, Brazil

^d CNRS UMR 7266 LERINS, University of La Rochelle, 17045, La Rochelle, France

- Halt the cycle of chronic inflammation
- Re-inforcement of gut and skin barriers
- Improvement of metabolic parameters
- Skin repair/ rejuvenation
- Improved mood and concentration



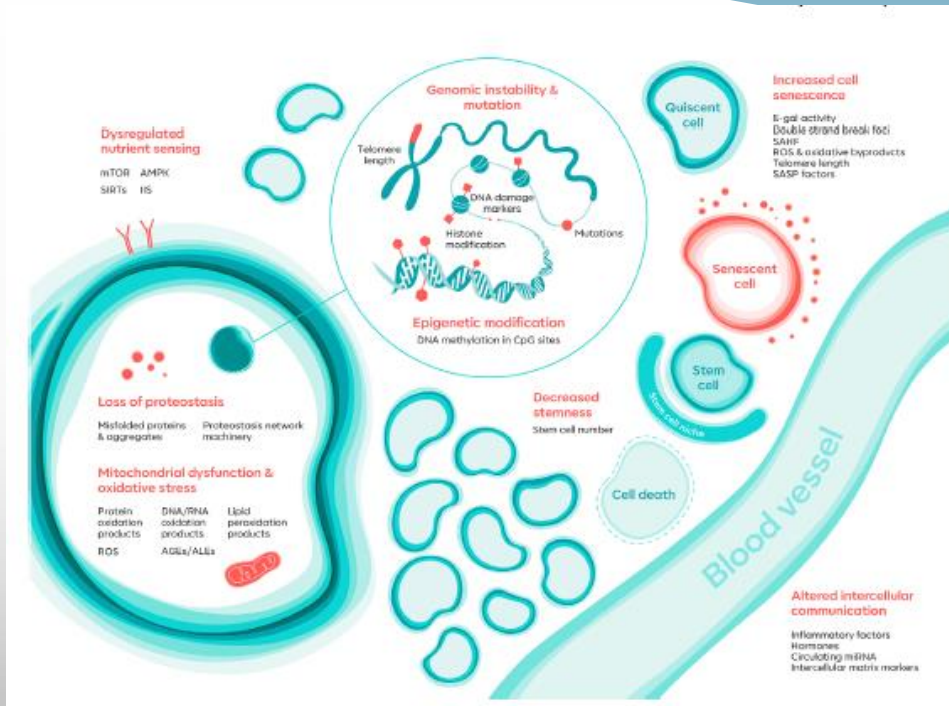
RESEARCH & INNOVATION
A SA TECHNOLOGY

Perspectives ?



Hangzhou library

Do monoterpenes modulate aging markers ?



Systemic Biomarkers

- ◆ Blood-based markers
- ◆ Inflammatory markers
- ◆ Metabolic markers

Non-molecular Biomarkers

- ◆ Physical sensors
- ◆ Wearable devices

Les marqueurs du vieillissement biologique « Markers of biological aging ». **d'Alessio PA.** Corresp. Onco-Hématol. 2018;13:18-20.

Review

Aging Biomarkers: From Functional Tests to Multi-Omics Approaches

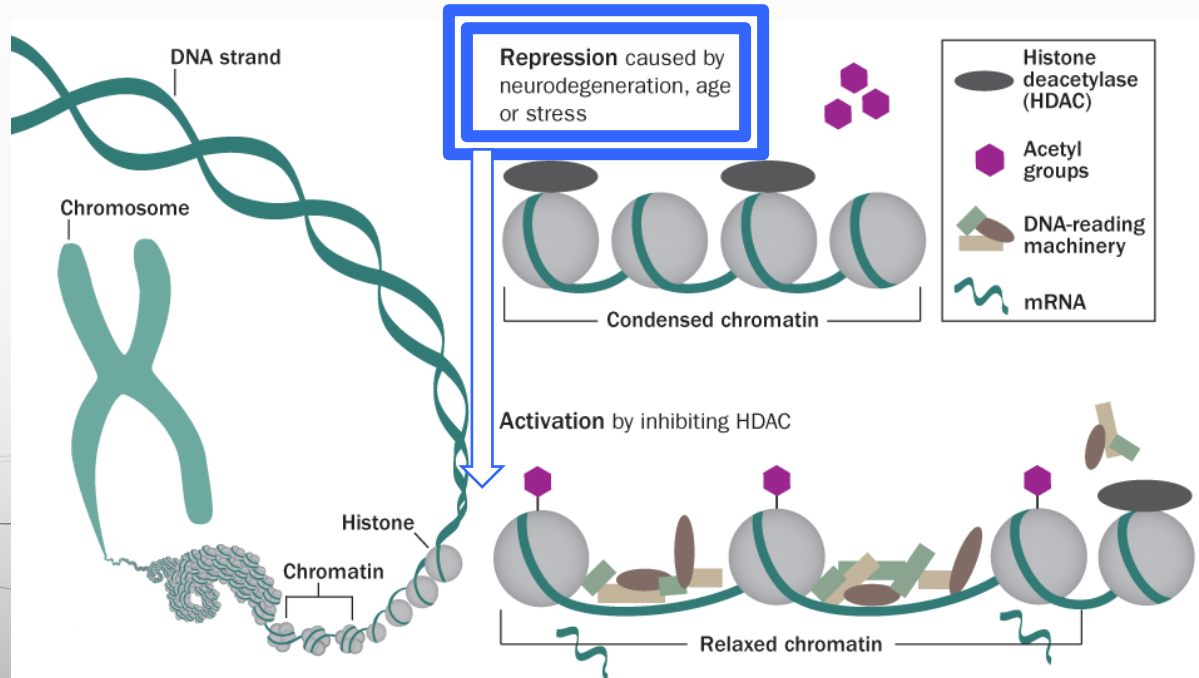
Ksenia S. Kudryashova, Ksenia Burka, Anton Y. Kulaga, [Nataliya S. Vorobyeva](#), Brian K. Kennedy ... See fewer authors

Monoterpenes modulating DNA methylation ? Acting as HDAC inhibitors ?

What would be the mechanism ?

HAT add acetyl groups and displace HDAC

HDAC inhibitors have the same effect





ICAD 2018

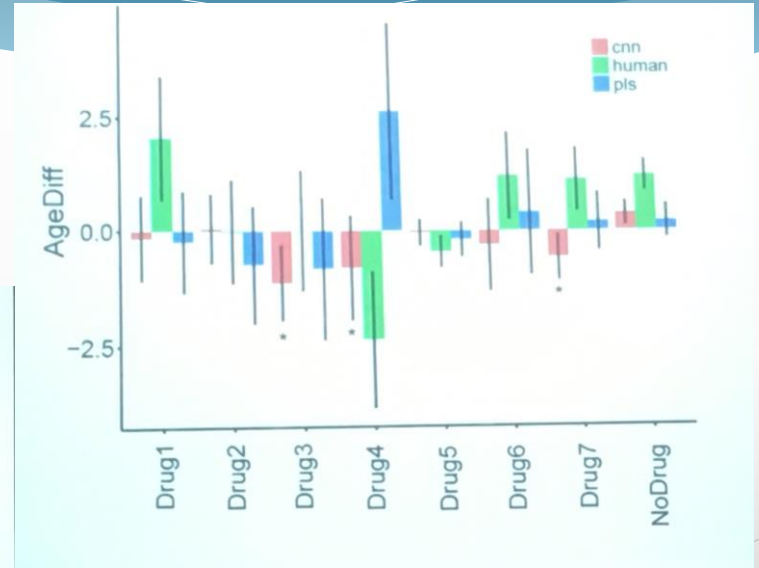
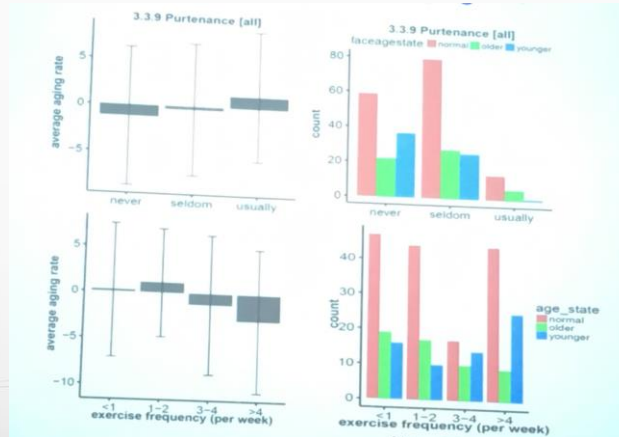
Nice, France | October 5-8, 2018

The 3rd International Conference on Aging and Disease

Life styles associated with aging rate



Pr Jing Dong Jackie HAN



Drugs that delay aging

Salutogenesis and beyond. d'Alessio PA, Dermatol Ther 2019; 32:e1278.

Metchnikoff's legacy, studying the cause of human longevity

ESSAIS OPTIMISTES

PAR

ÉLIE METCHNIKOFF

MEMBRE-ORDREUR DE L'ACADÉMIE FRANÇAISE

AVEC 27 FIGURES DANS LE TEXTE

PARIS

A. MALOINE, ÉDITEUR

22-27, Rue de l'Épicerie-Médicament

1907

Dans l'état actuel de nos connaissances, il est impossible de préciser la cause principale de la longévité humaine, mais il sera tout naturel de la chercher dans la même voie que la cause de la longévité des animaux. Puisque la longévité humaine accuse souvent un caractère local et se manifeste chez des époux qui n'ont de commun que le genre de vie, il sera permis de chercher dans la flore intestinale et dans les moyens que possède l'organisme de combattre son effet nuisible, des facteurs qui influencent cette longévité. Il est tout naturel de supposer que dans la même localité et chez des personnes vivant sous le même toit, la flore intestinale doit présenter une grande analogie. Ce n'est que par des recherches

CREDITS AND QUESTIONS



SAPIENZA
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Valeria M Ursini, Joerg D Schulzke, Marie C Béné, Olivier Herault



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



ISOAD International Society on Aging and Disease



THANK YOU FOR
YOUR ATTENTION

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