

In the arsenal of new anti-inflammatory drugs, terpenoids as geroprotectors : the case of monoterpenes

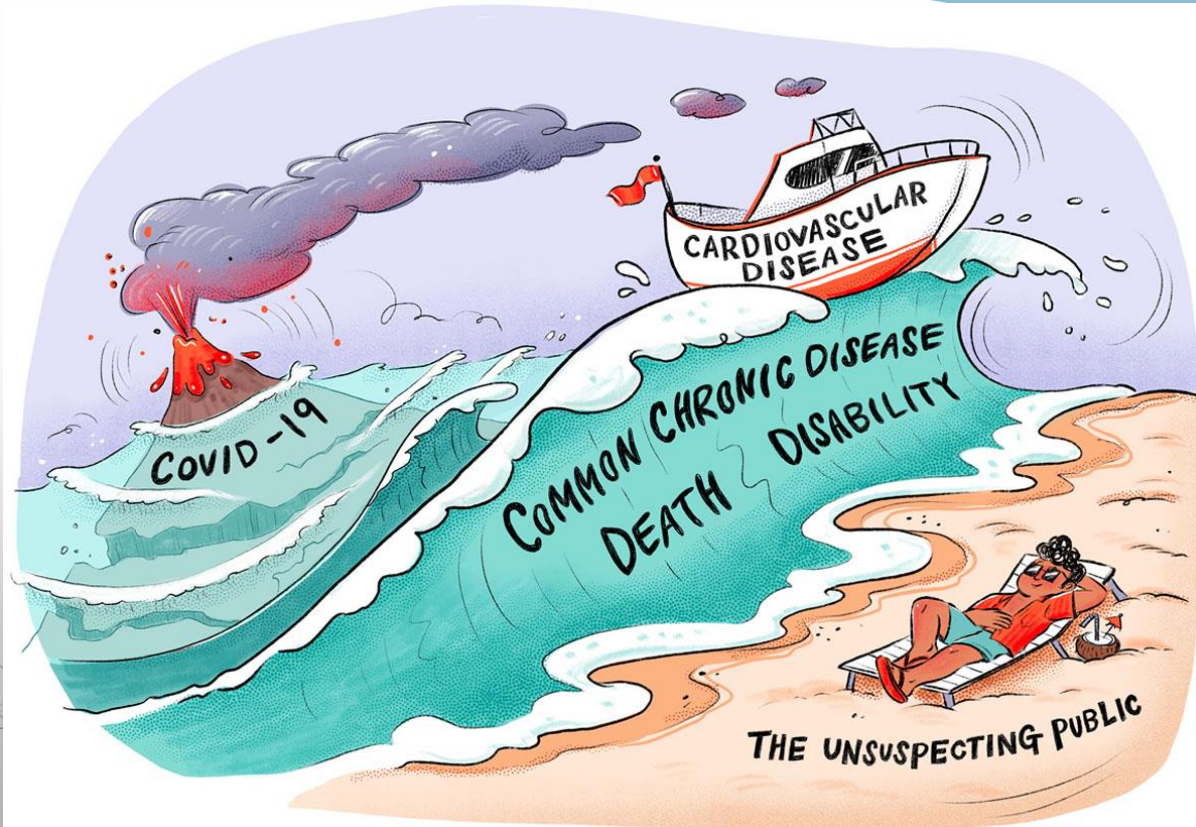
Pr Dr **Patrizia A d'Alessio**, MD PhD
Hematologist & Cell biologist



AISA
THERAPEUTICS



Covid-19 has allowed us to reassess chronic diseases



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

« 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

Fluvoxamine to cover for inflammatory and mood issues

to prevent Covid-19 hospitalisation

Articles

Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial



Gilmar Reis, Eduardo Augusto dos Santos Moreira-Silva, Daniela Carla Medeiros Silva, Lehana Thabane, Aline Cruz Milagres, Thiago Santiago Ferreira, Castilho Vitor Quirino dos Santos, Vitoria Helena de Souza Campos, Ana Maria Ribeiro Nogueira, Ana Paula Figueiredo Guimaraes de Almeida, Eduardo Diniz Callegari, Adhemar Dias de Figueiredo Neto, Leonardo Cançado Monteiro Savassi, Maria Izabel Campos Simplicio, Luciene Barra Ribeiro, Rosemary Oliveira, Ofir Harari, Jamie I Forrest, Hinda Ruton, Sheila Sprague, Paula McKay, Alla V Glushchenko, Craig R Rayner, Eric J Lenze, Angela M Reiersen, Gordon H Guyatt, Edward J Mills, for the TOGETHER investigators*



Summary

Background Recent evidence indicates a potential therapeutic role of fluvoxamine for COVID-19. In the TOGETHER trial for acutely symptomatic patients with COVID-19, we aimed to assess the efficacy of fluvoxamine versus placebo in preventing hospitalisation defined as either retention in a COVID-19 emergency setting or transfer to a tertiary hospital due to COVID-19.

Lancet Glob Health 2021

Published Online

October 27, 2021

[https://doi.org/10.1016/S2214-109X\(21\)00448-4](https://doi.org/10.1016/S2214-109X(21)00448-4)

S2214-109X(21)00448-4

Our anti-inflammatory arsenal is increasing

Gluco-corticoids and other steroids - NSAID drugs

Cox2 inhibitors - Biologics

Opaganib, an SK-2 (sphingosine-kinase-2) inhibitor

- ◆ anti-inflammatory activity in auto-immune / inflammatory diseases
- ◆ anti-viral effects

Fluvoxamine

anti-inflammatory
mood modulating effects

resulting in some immune resetting that allows to avoid hospitalisation.





Terpenoids as Potential Geroprotectors

Ekaterina Proshkina ¹^b, Sergey Plyusnin ^{1,2}^b, Tatyana Babak ¹, Ekaterina Lashir Faniya Maganova ³, Liubov Koval ^{1,2}, Elena Platonova ^{1,2}, Mikhail Shaposhnikov Alexey Moskaev ^{1,2,*}^b

Monoterpenes modulating cytokines - A review

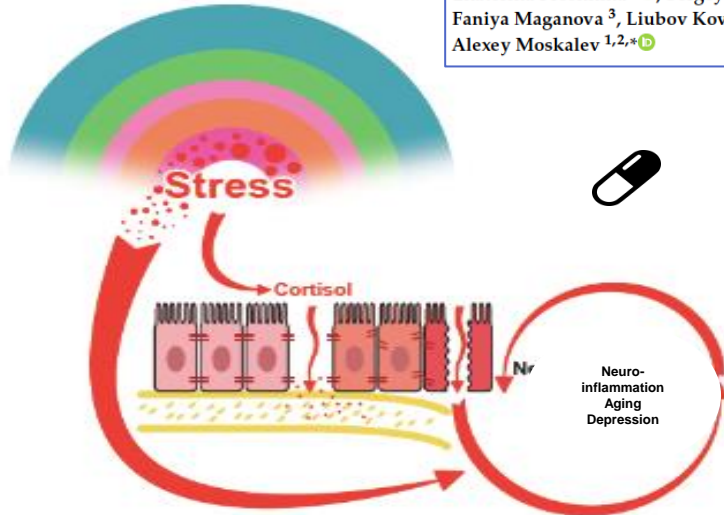
Jullyana S.S. Quintans^a, Saravanan Shanmugam^a, Luana Heimfarth^b, Adriano Antunes S. Araújo^b, Jackson R.G.da S. Almeida^c, Laurent Picot^d, Lucindo J. Quintans-Júnior^{a,*}

^a Laboratory of Neurosciences 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 UMS 0285 CNRS 7266 LEIRIS, University of La Rochelle, 17042, La Rochelle, France



Halt the cycle of chronic inflammation
Re-inforcement of gut and skin barriers
Improvement of metabolic parameters

Supplementary outcomes in QoL standards:
Intestinal compliance – Skin rejuvenation
Improved mood, sleep quality & concentration



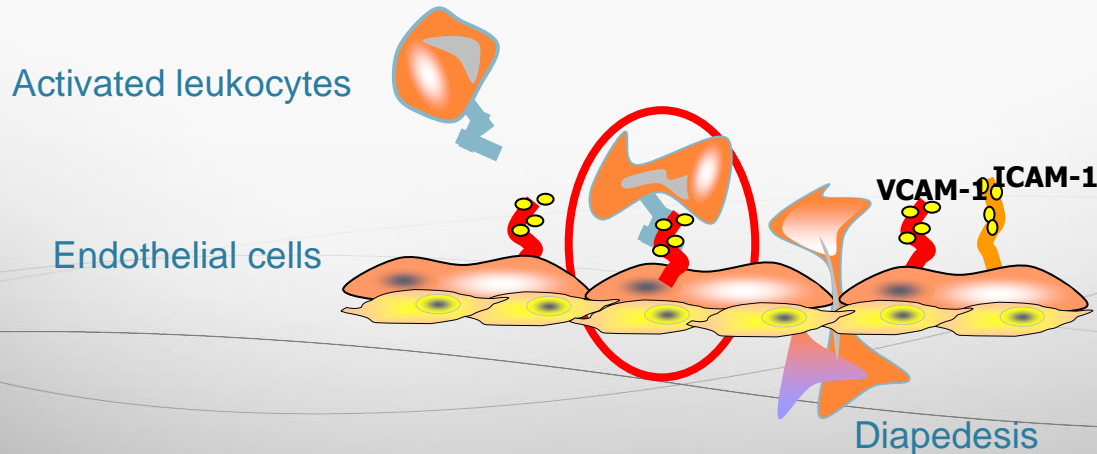
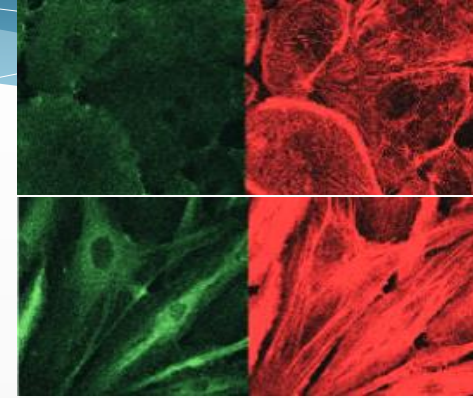
CONCEPTS - 1992 &
TECHNOLOGY - 2007 BY
A SA TECHNOLOGY



How did it all start ? Defining new markers for cell senescence

We defined senescence markers in endothelial cells :

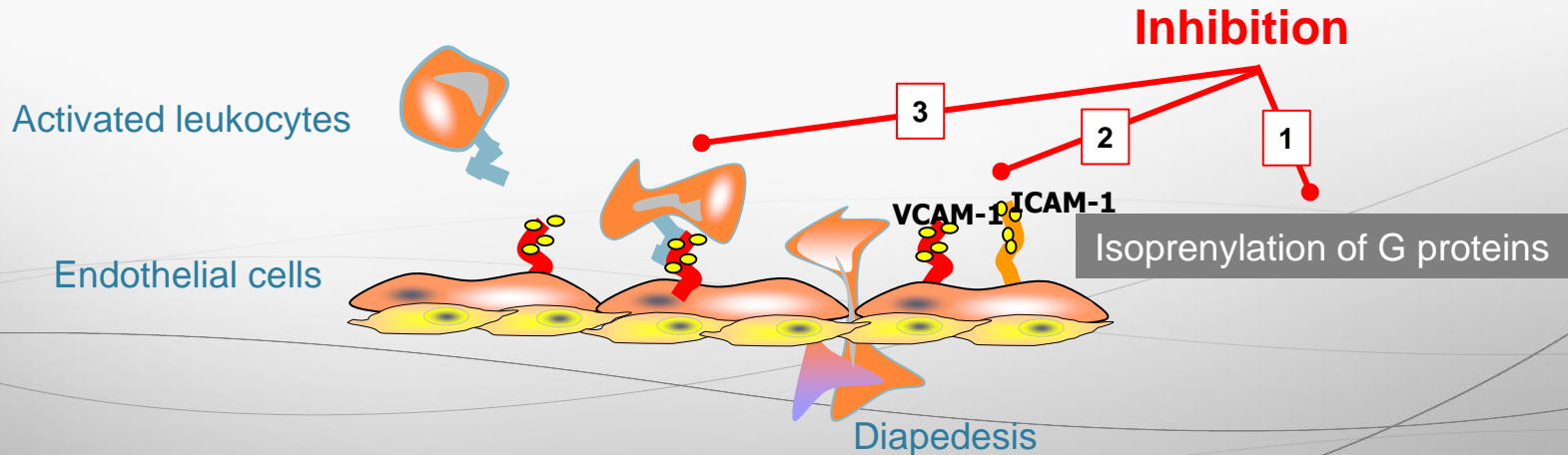
- 1/ **over-expression** of ICAM-1, VCAM-1, selectins
- 2/ **polymerization of actin cytoskeleton**, stress fibers
- 3/ induced by circulating **pro-inflammatory cytokines**



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





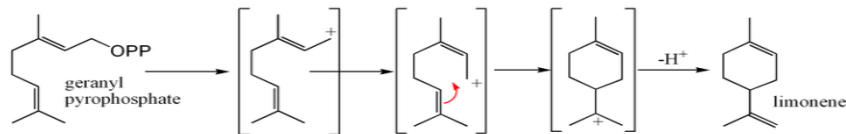
Bio-guided research

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

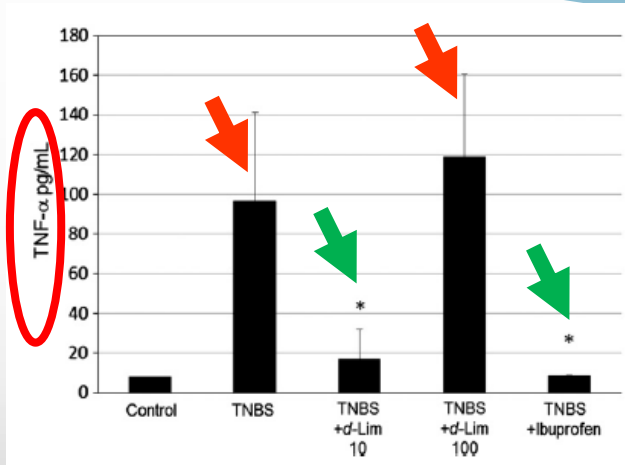




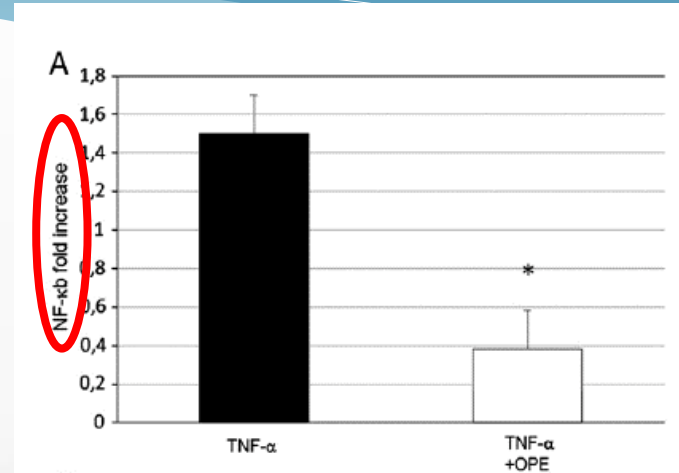
- ◆ From *in vitro* studies 2000-2004...
- ◆ ... to pre-clinical studies in rodents in gut, skin and stress FOB in 2007-2009...
- ◆ ...to first-in-human studies: RISTOMED EU project 2009-2013...
- ◆ ..all confirmed the anti-inflammatory effect and QoL



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



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

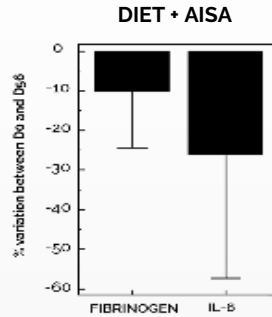


Anti TNF-α, IL-6, IL-1β, IFN-γ effect
& Inhibition of NF-κB

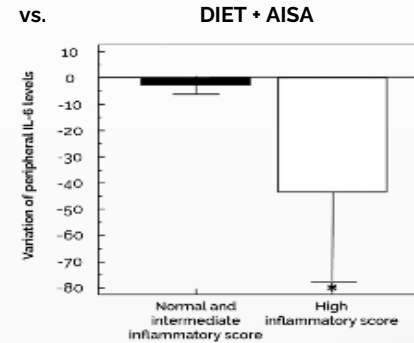
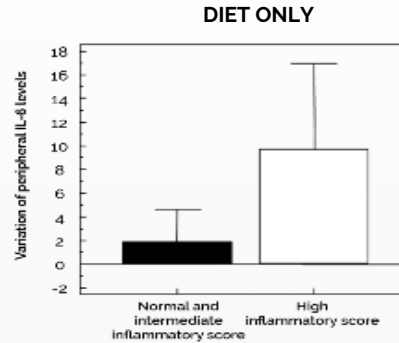
Life Sciences. 2013;92:1151-1156

First in human RISTOMED EU study 140 patients

Inflammation markers



Anti-IL-6 efficacy as food supplementation



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



Back to senescence, AISA can control SASP



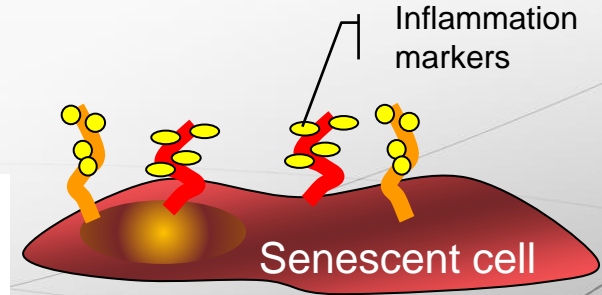
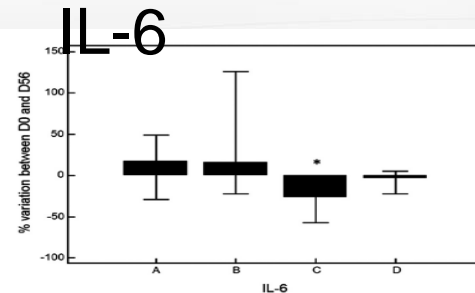
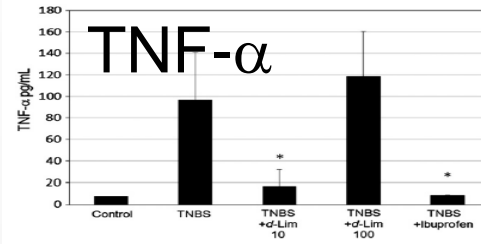
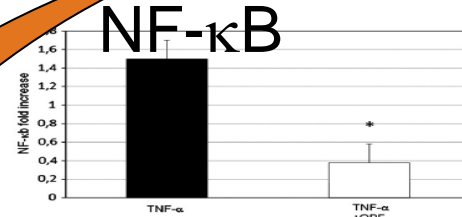
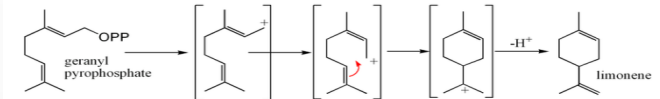
antioxidants



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,*}



Mechanisms of Ageing and Development 186 (2020) 111206

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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 Gémopole Biorégions, 4 rue Pierre Fontaine, 91058, Evry, France

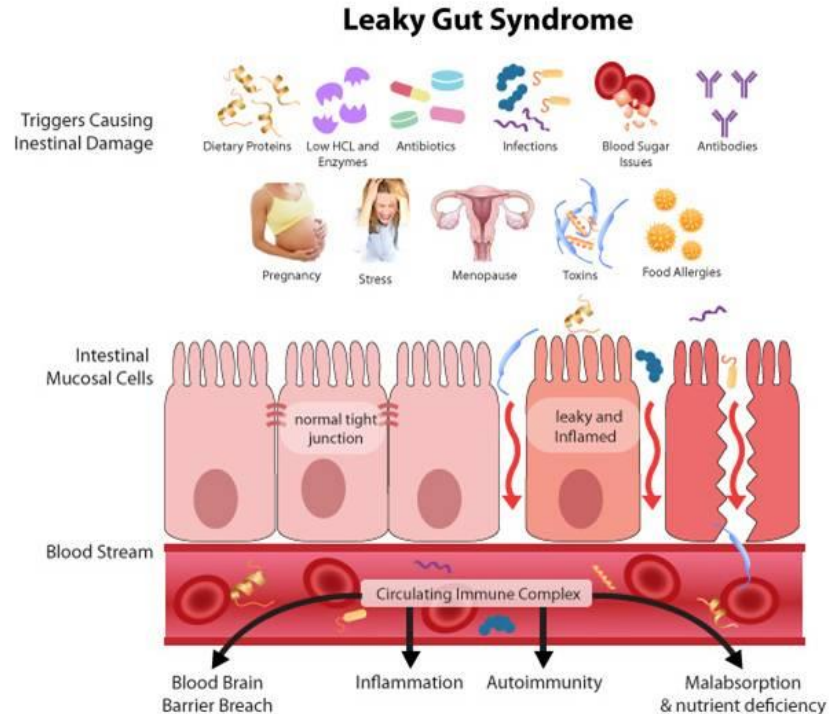
^b Pôle Laboratoire Service d'Hématologie Biologique CHU de Nantes, 9 Quai Moncousi, 44000, Nantes, France



What about the **mechanism** linking stress to inflammation

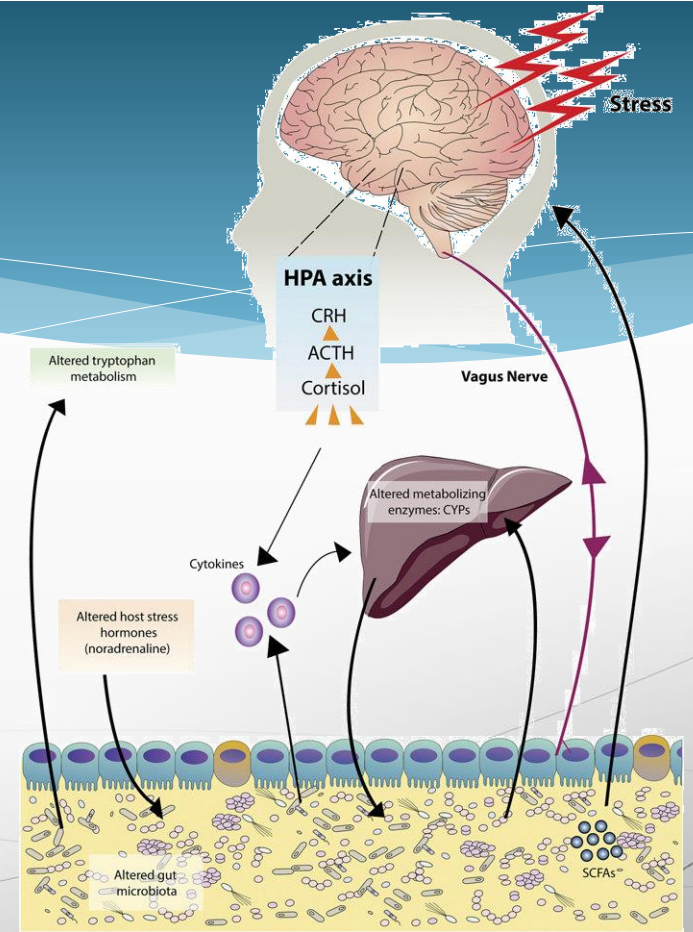
Cortisol

Aging



Stress changes immune reactions generating « sickness disease »

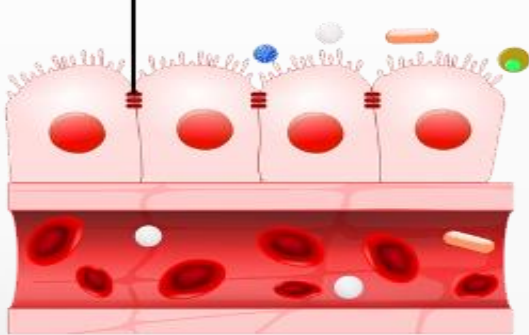
loss of memory,
anxiety,
refusal to meet social events,
obsessional thoughts,
difficulty to concentrate,
depression,
chronic fatigue syndrome,
sleeplessness,
loss of interest,
obsessional neurosis



« Monoterpenes modulate cytokines »

Not only ! They **repair** the GUT BARRIER

Normal tight junctions

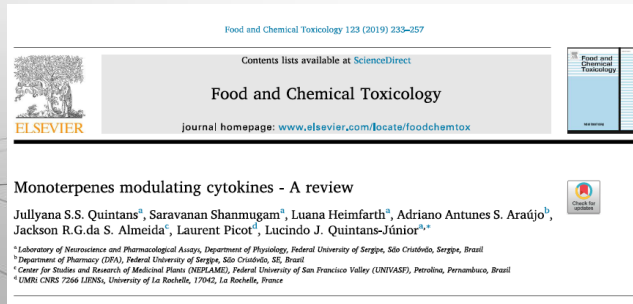


AISA: significant effect on strengthening the epithelial barrier function

	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

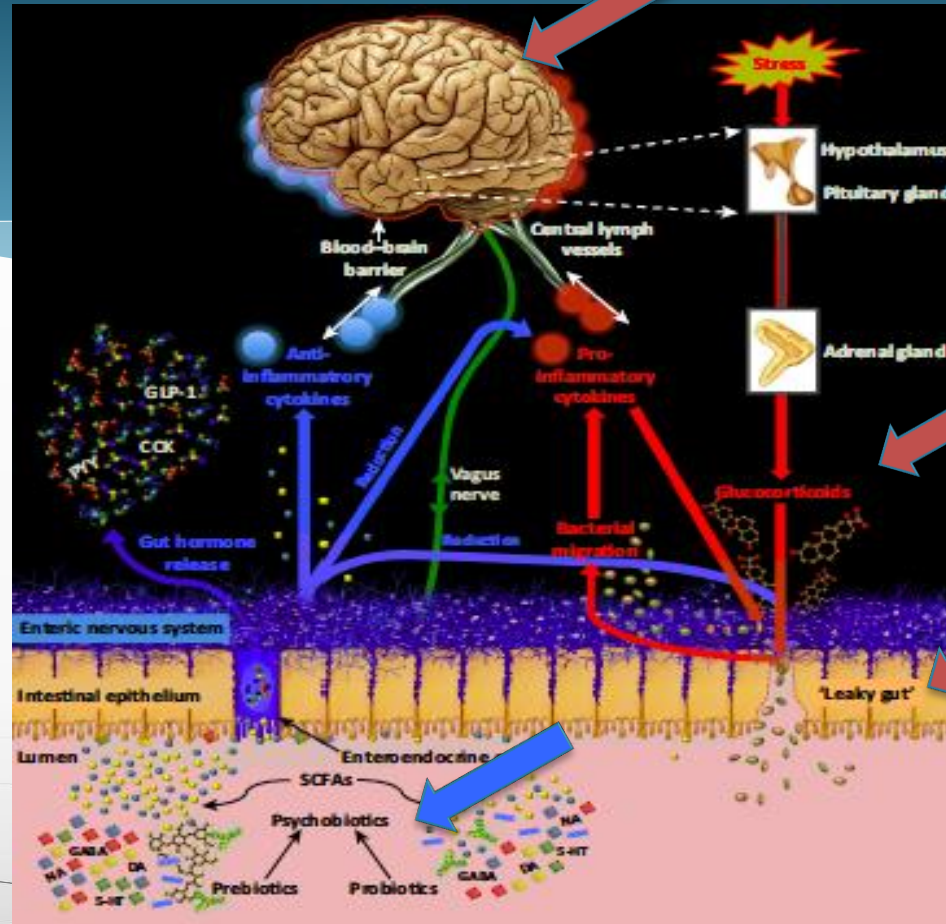
Evaluation of electric resistance ($\Omega \cdot \text{cm}^2$)
as percentage of initial resistance R_t.

Life Sciences. 2013;92:1151-1156



Gut barrier integrity for successful 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***



A. Sarkar et al Trends in Neurosciences Cell Press 11 : 763-781, 2016.

Monoterpenes are modulators of microbiota

Clostridium cluster IV / *Bifidobacteria* ratio



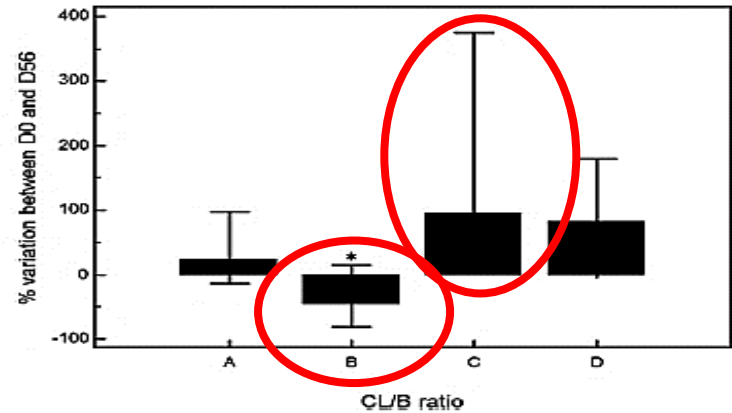
Future research collaboration

Prof. Peter C. Konturek
Head of Department of Internal
Medicine, University of Jena

Butyrate-producing *Faecalibacterium* /
Coprococcus bacteria associated QoL

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

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



Contents lists available at ScienceDirect
Clinical Nutrition
Journal homepage: <http://www.elsevier.com/locate/cinu>

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*

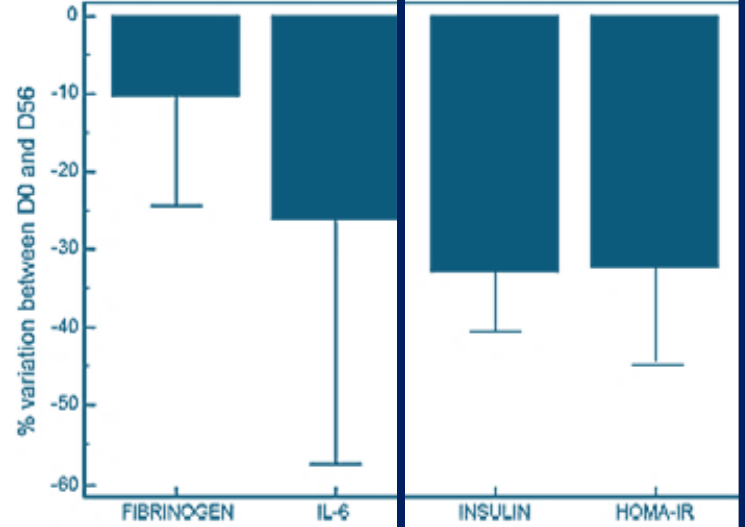
R. Ostan^a, M.C. Béné^b, L. Spazzafumo^c, A. Pinto^d, L.M. Donini^d, F. Pryen^e, Z. Charrouf^f, L. Valentini^g, H. Lochs^h, I. Bourdel-Marchasson^{i,j,k}, C. Blanc-Bisson^{i,j,k}, F. Buccolini^l, P. Brigidini^m, C. Franceschi^{n,o}, P.A. d'Alessio^p

Markers of cardio-metabolic syndrome, diabetes, thrombosis



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

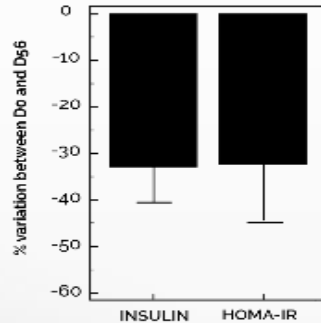
* Homeostatic model assessment of insulin resistance HOMA-IR



Clin Nutr. 2016;35:812-818.

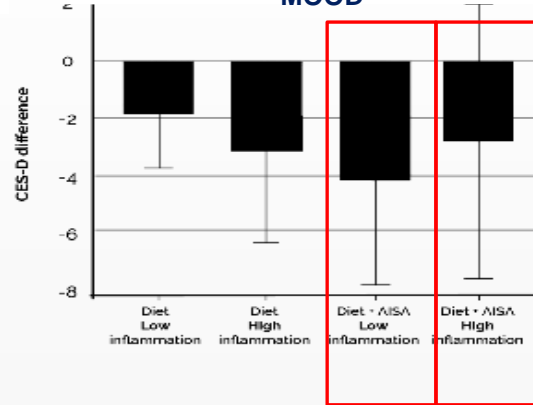
Mood is highly influenced by metabolic issues

INSULIN RESISTANCE



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

MOOD



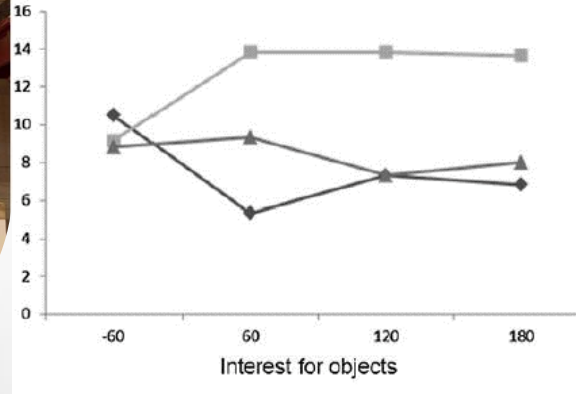
Improvement of the **CES-D** score in subjects having received AISA supplementation.



Clin Nutr. 2016;35:812-818
PRIME 2012

Anti-inflammation RESULTS in mood modulation

Motivational effect in rodents



Mood modulation effect in humans

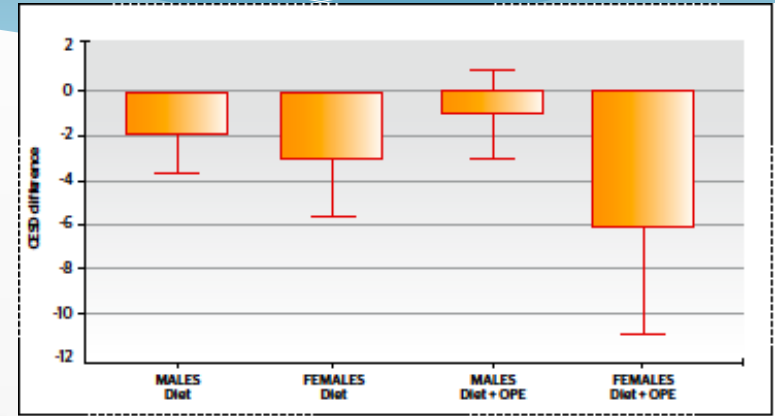


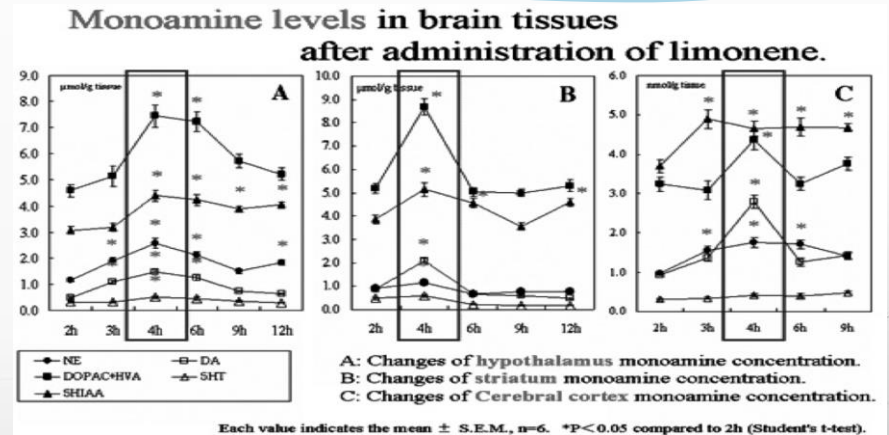
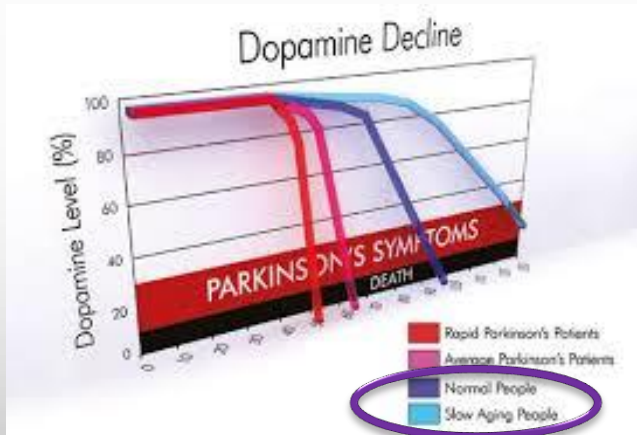
Figure 3 Gender partition and CES-D variation in diet versus diet plus OPE

Rejuvenation Res.
2014;17:145-149

PRIME 2012; 30-37



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... and thus skin !



- ◆ 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 :
- ◆ skin is connected to the gut-brain axis
 - ◆ via its HPA-axis receptors.

The Gut-brain axis is relevant to skin aging.
d'Alessio PA PRIME July 2020, Vol 10 Issue 4, 36-42

Beyond gut barrier : repair activity in skin models /1

Wound healing without neo-angiogenesis

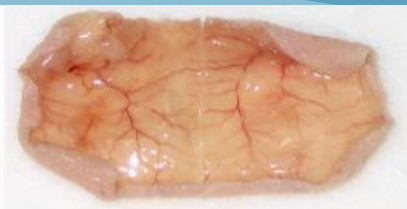


Inhibition of neo-angiogenesis

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

Decrease of pro-
inflammatory
cytokines

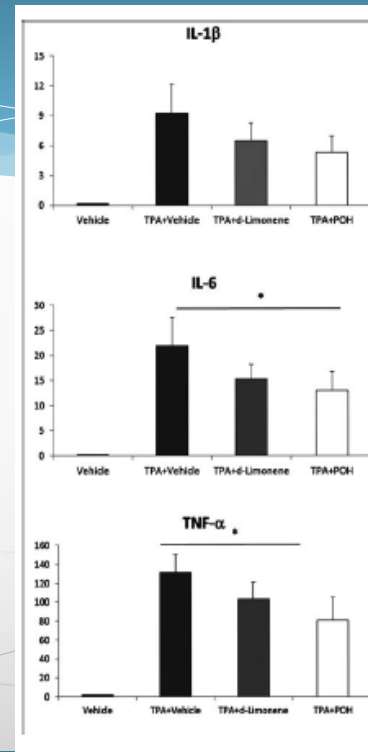
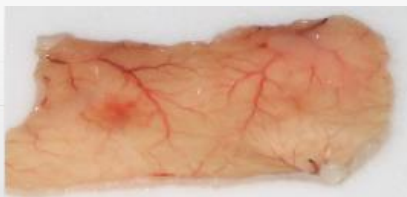
Vehicle



d Lim



POH



Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry 2014;13:29-35.

Repair activity in skin models /2 psoriasis / atopic dermatitis



Vehicle

TPA
lesion of
psoriasis and
atopic
dermatitis

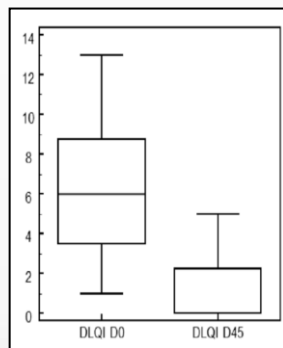
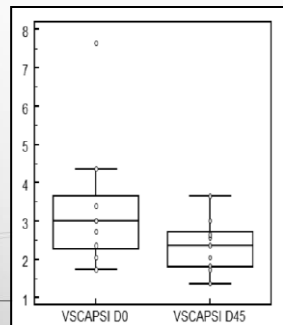
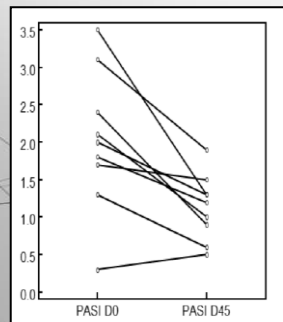
TPA + *d*-Lim

TPA + POH

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

Monoterpenes in human intermediate psoriasis, a disease related to metabolic and stress issues

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

Global J Dermatol Venerol. 2015;3:1-4

Atopic dermatitis (eczema)
worsened by repeated topic
cortisol treatment

A recent striking case

High levels of zonulin / IgG

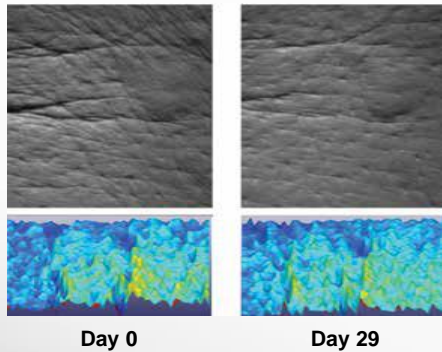
Partial restoration after 10 days
cure with **anti-inflammatory**
terpenoids

Gut **barrier repair**, with
restitution of skin quality

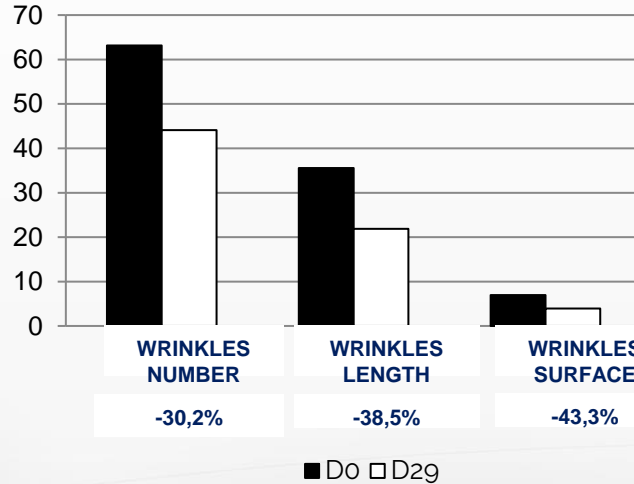
Visible **mood** amelioration



What about aging skin ? Monoterpenes as game changers ?



WRINKLES DEPTH DECREASE



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.

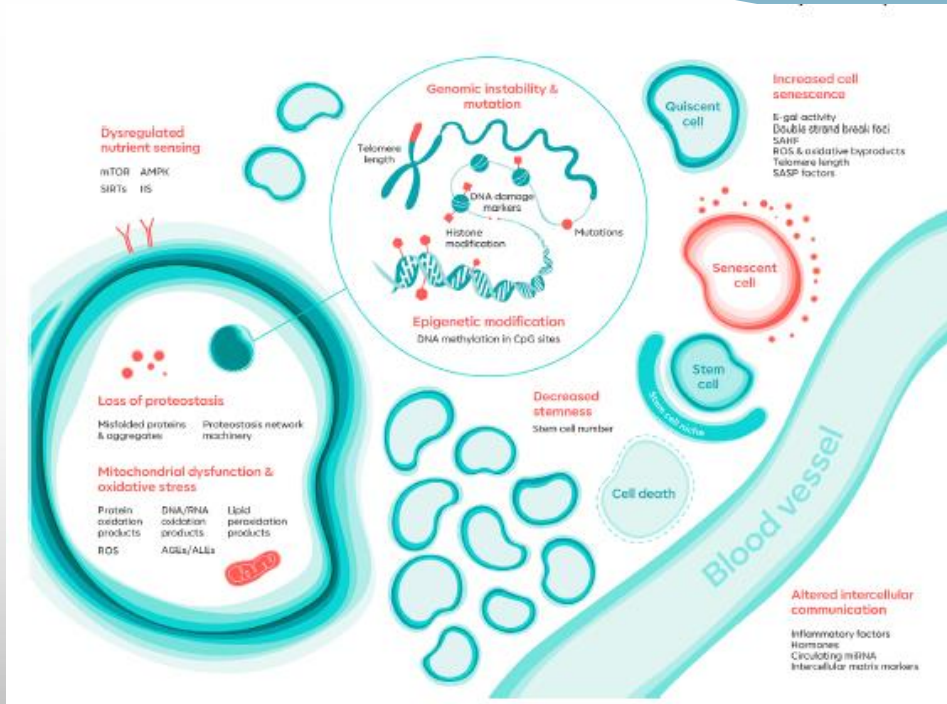


Perspectives ?



Hangzhou library

Can Monoterpenes modulate aging markers ?



Systemic Biomarkers

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

Non-molecular Biomarkers

- ◆ Physical sensors
- ◆ Wearable devices

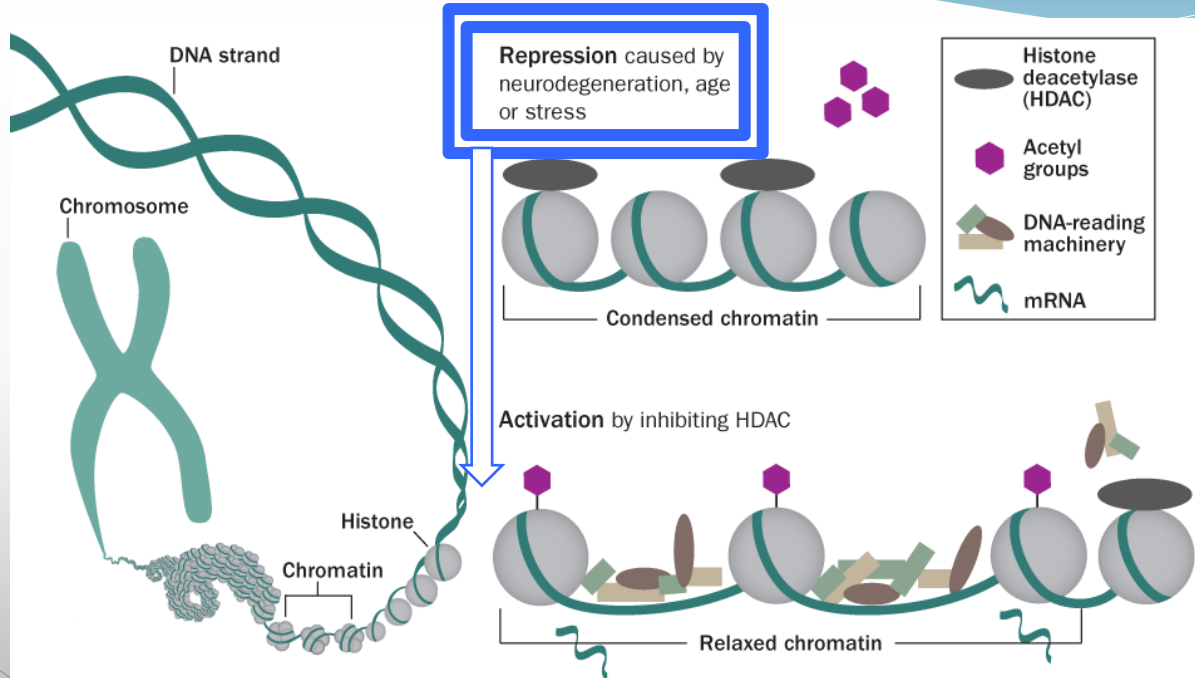
Les marqueurs du vieillissement biologique « Markers of biological aging ». **d'Alessio PA.** Corresp. Onco-Hématol. 2018;13:18-20.

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 ?



Healthy Longevity
Thursday, 10 Dec 2020
7pm to 8pm SGT
[Register Now](#)

Topic
What drives ageing and can we slow down the clock?

The process of ageing has always been a topic of fascination for the public. The search for eternal youth is a mix of hope and despair, as the scientific community has made considerable progress in understanding the mechanisms underlying ageing. For example, the discovery that ageing is controlled by several genes, including the insulin-like growth factor (IGF) pathway, has led to the development of anti-ageing therapies. The development and application of anti-ageing therapies such as dietary restriction, exercise and medical interventions to promote healthy ageing have also generated interest among scientists, medical professionals and the public.

As the scientific community continues to explore the mechanisms of ageing, it is becoming increasingly clear that the process of ageing is not just a matter of time, but also a matter of health. The discovery that ageing is controlled by several genes, including the insulin-like growth factor (IGF) pathway, has led to the development of anti-ageing therapies. The development and application of anti-ageing therapies such as dietary restriction, exercise and medical interventions to promote healthy ageing have also generated interest among scientists, medical professionals and the public.

Join us now! Professor Brian Kennedy and Professor Moskalev, as they share with us the genetics of ageing and how we can slow down the clock. They will also discuss the latest research on the role of HDACs in ageing and how we can use HDAC inhibitors to slow down the clock.

About The Webinar

The webinar series aims to inform us on how we can keep free of disease by leading the common-sense steps of disease prevention, ageing, and brain health. The series will focus on the role of HDACs in ageing and how we can use HDAC inhibitors to slow down the clock.

Host
Professor Brian Kennedy

Prof Brian Kennedy is the Director for the Healthy Longevity Translational Research Programme at the Yong Loo Lin School of Medicine, National University of Singapore. He is also the Director of the Centre for Healthy Ageing, National University of Singapore. He is a leading expert in the field of ageing research and has made significant contributions to our understanding of the mechanisms of ageing. He is also a leading expert in the field of ageing research and has made significant contributions to our understanding of the mechanisms of ageing.

[NUS Medicine](#) [NUS Medicine](#) [NUS Medicine](#) [NUS Medicine](#)

NUS
National University of Singapore

Mechanism ? HAT add acetyl groups and displace HDAC, inhibitors have the same effect, using monoterpenes as lead candidates.



ICAD 2018

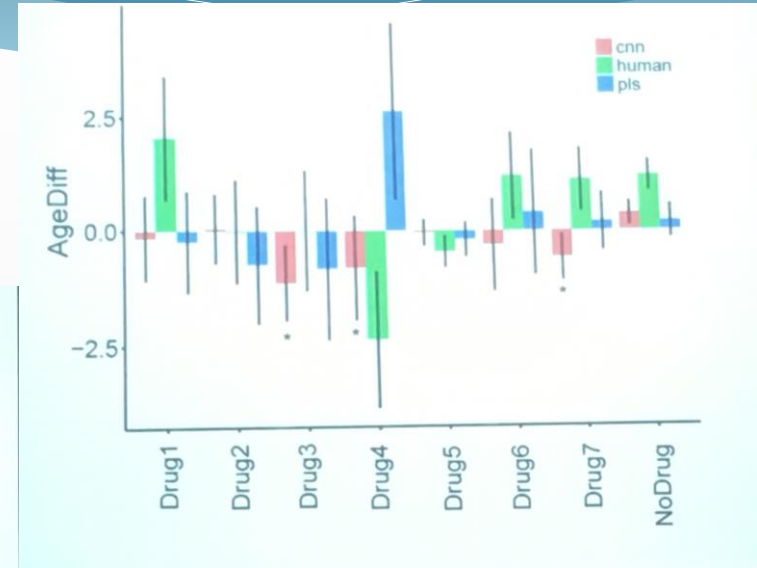
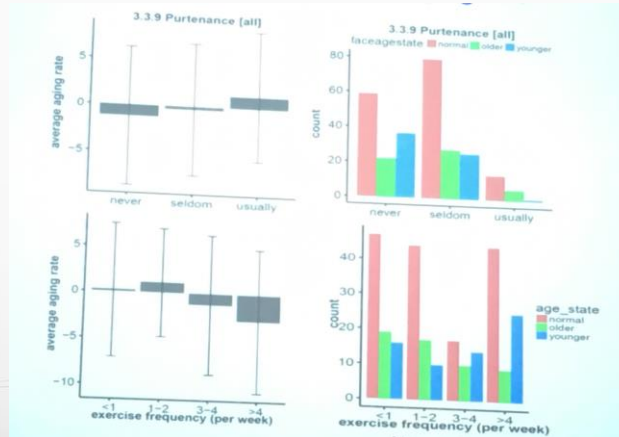
Nice, France | October 5-8, 2018

The 3rd International Conference on Aging and Disease

Life styles associated with aging rate



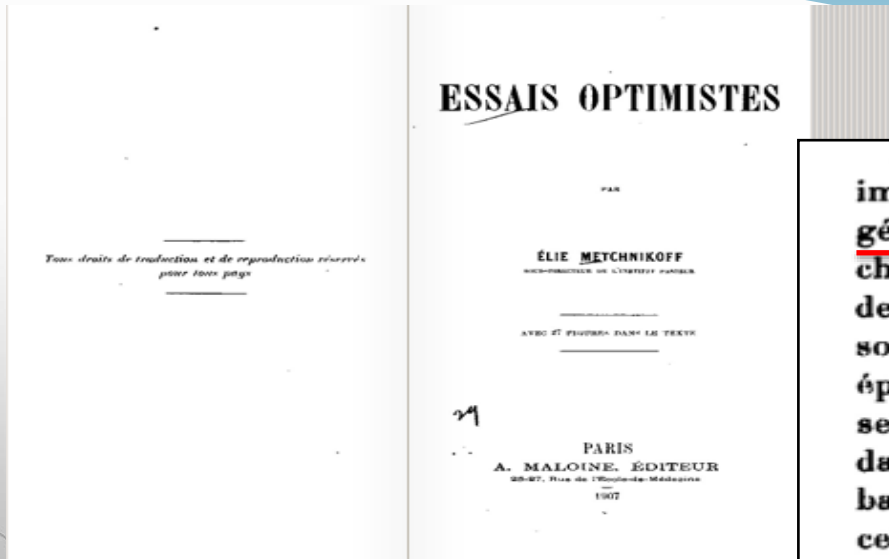
Pr Jing Dong Jackie HAN



Drugs that delay aging

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

Metchnikoff's legacy, studying the cause of human longevity



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
UNIVERSITÀ DI ROMA



Pierre Potier, Chantal Menut, Jean-François Bisson, Claudio Franceschi,
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

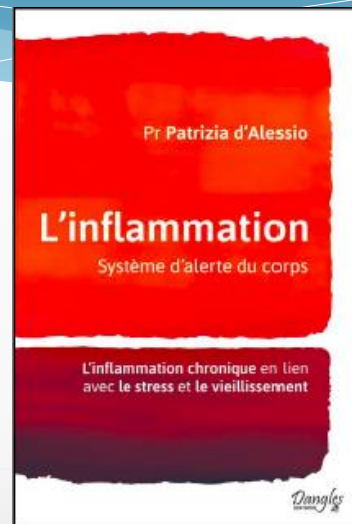


THANK YOU FOR YOUR ATTENTION

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