



Stress, dysbiosis & « cytokine storm », Covid's deadly triad

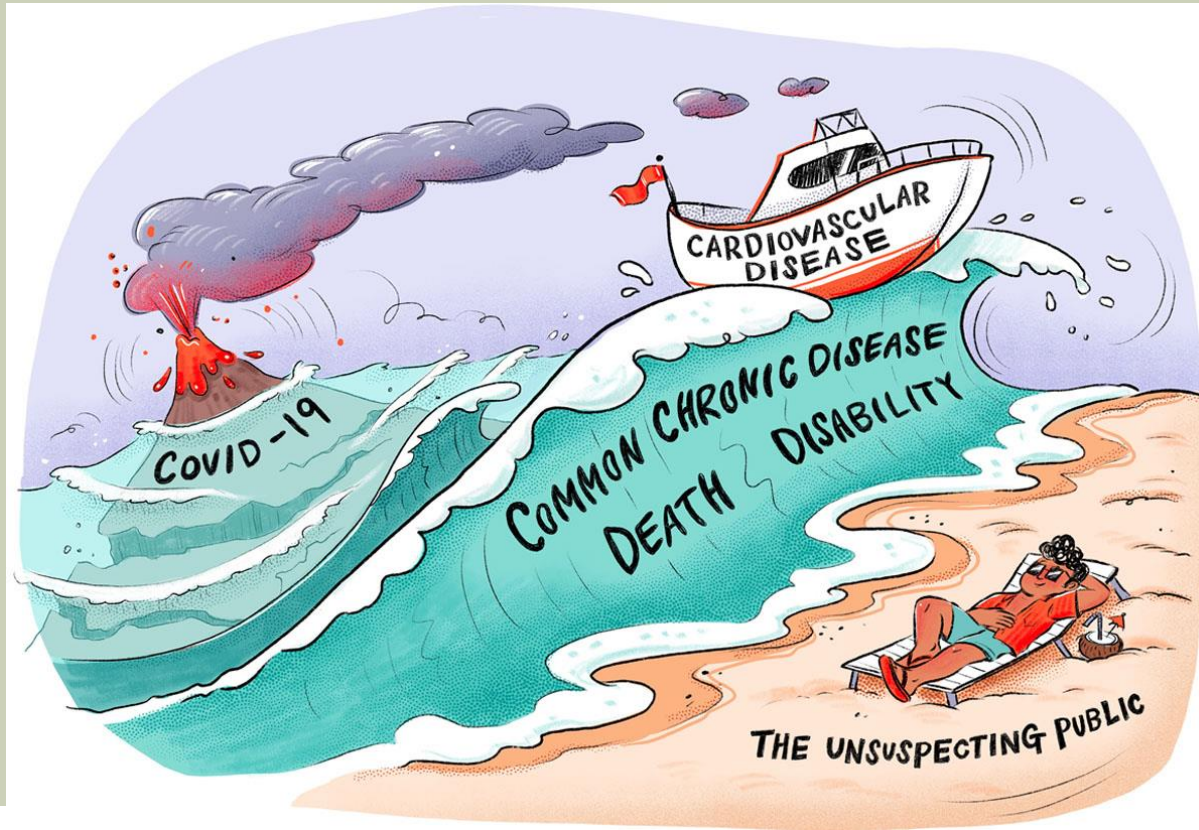
Pr Dr **Patrizia d'Alessio**, MD PhD
Hematologist & Cell biologist

CEO AISA Therapeutics



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

When routes of stress CROSS those of the immune response

◆ IS SARS-COV-2 INFECTION
TAKING ADVANTAGE OF OUR
STRESS ?

◆ In case of chronic **stress**, when symptoms start to appear, are we **already** experiencing a « chronic **disease** » ?



Because of the gut-brain axis...



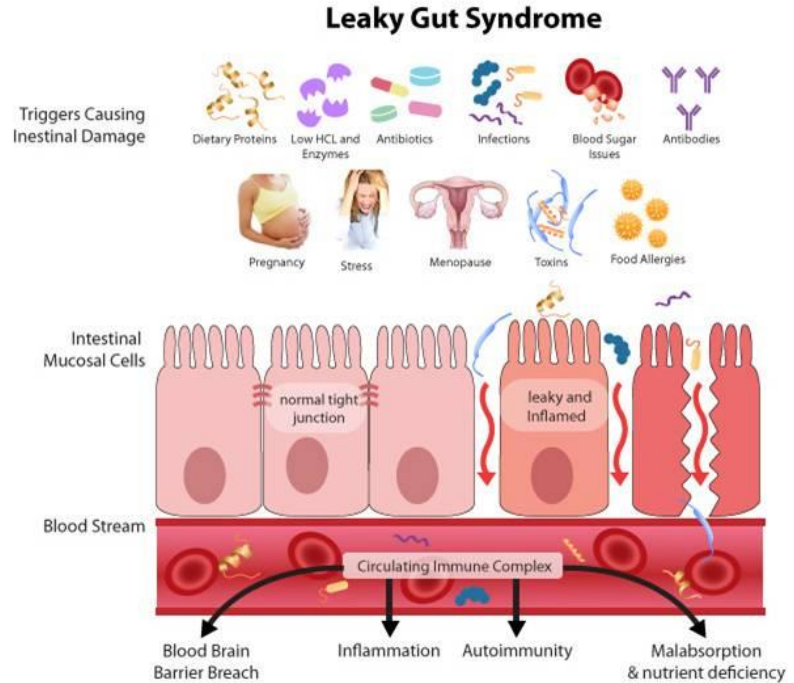
- ◆ each **on-going stress** translates into an increase of *inflammation*,
 - ◆ starting at the level of the gut barrier
 - ◆ and if not resolved, generalizes to the whole body.
-
- ◆ In Covid-19 an « **out-of-proportion inflammatory response** »
 - ◆ resulting in a « **cytokine storm** »



Stress changes immune reactions

Cortisol

Neuroinflammation
and sickness disease



“Leaky gut” + neuro-inflammation = aging

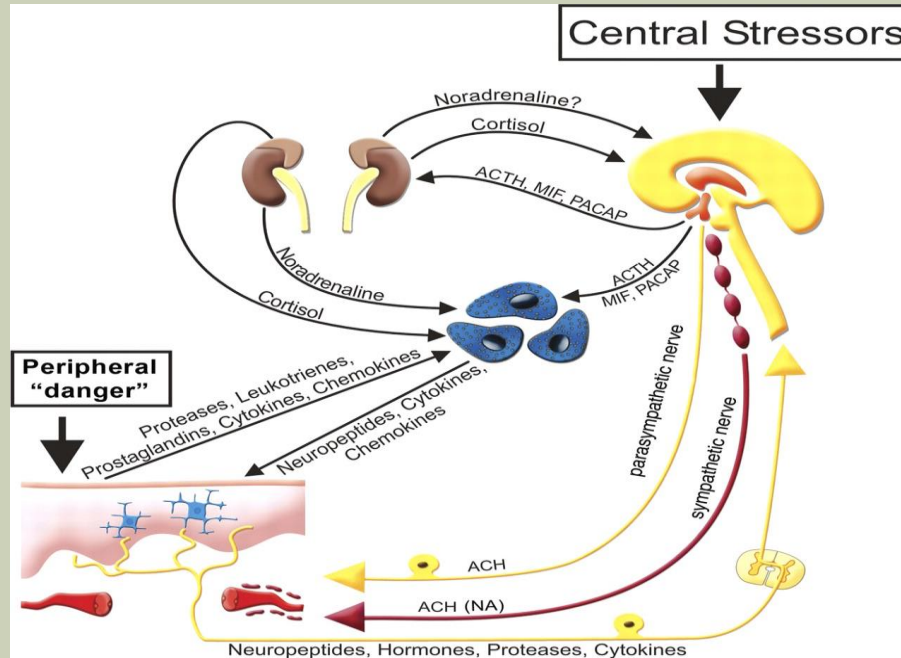


Aging

Cortisol-induced gut barrier leakage and consequent dysbiosis

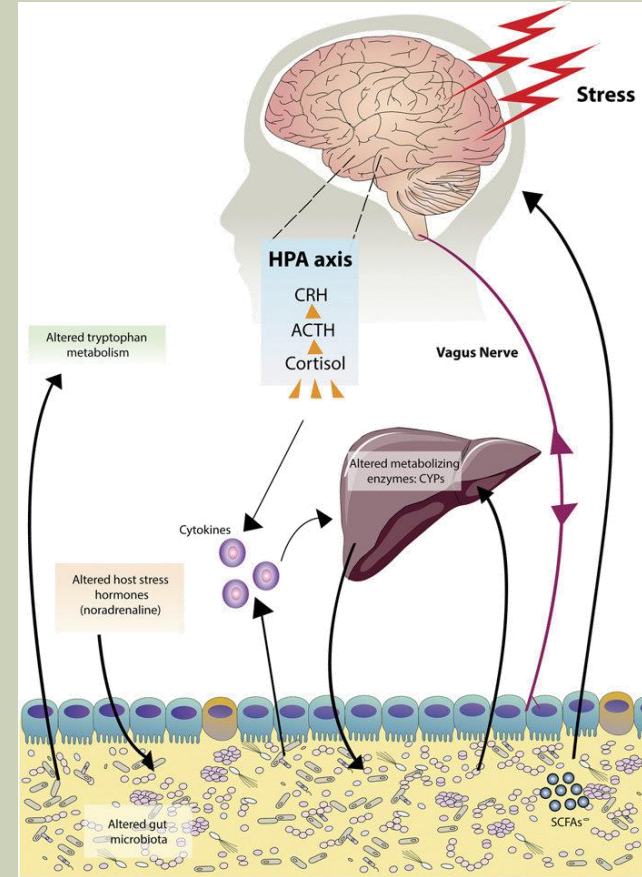
- ◆ malabsorption and auto-immune disease
- ◆ generalized inflammation and neuro-inflammation with « sickness disease »
 - ◆ Chronic fatigue syndrome
 - ◆ Depression
 - ◆ Insomnia
 - ◆ Obsessional thoughts
 - ◆ Lack of motivation
 - ◆ Lack of concentration
 - ◆ Loss of appetite for social interaction

Brain-gut connection CONCOMITANT to the brain-skin connection



Bioengineering in Wound Healing: A Systems Approach (book), 2017

Pharmacological Reviews 2019;71:198-224



Mood issues can precipitate suicide attempts

Aging is constantly challenging solitude & depression
Covid-19 has increased stress management issues

- ◆ Increased suicide attempts of **children 8-10 years** old, in Western countries
- ◆ In October 2020 - after six months of restrictions and lock-down - in Japan, the country of longevity, centenarians and blue zones :
 - A 70% increase in female suicides compared to October 2019 was identified.
- ◆ ***Do social restriction policies overimpose stress on an already stressed population ?***



« 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

COMMON BASES OF AGING AND COVID

« **Syndemics** are characterized by biological and social interactions

...that increase a person's susceptibility to harm or worsen their health outcomes. »

Two categories of diseases and specific populations

- ◆ 1. infection : severe acute respiratory SARS-CoV-2 syndrome
- ◆ 2. an array of non-communicable diseases (NCDs)
- ◆ **or common chronic diseases (CCD)**, considered as co-morbidities.

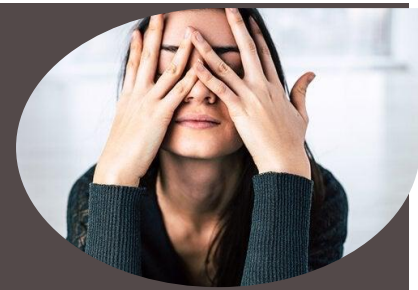


COVID, STRESS & READING EMOTIONS



Upon infection, immune overreaction could be linked to underlying stress due to health-preservation measures: lock-down, **mask-wearing**, remote work...

Limited social contact,
crucial for health,
adds on stress.



ORIGINAL RESEARCH ARTICLE
Front. Psychol., 25 September 2020 | <https://doi.org/10.3389/fpsyg.2020.566886>

Wearing Face Masks Strongly Confuses Counterparts in Reading Emotions

Claus-Christian Carbon^{1,2*}

Pr Dr Patrizia d'Alessio, MD PhD

WHAT CAN WE DO?



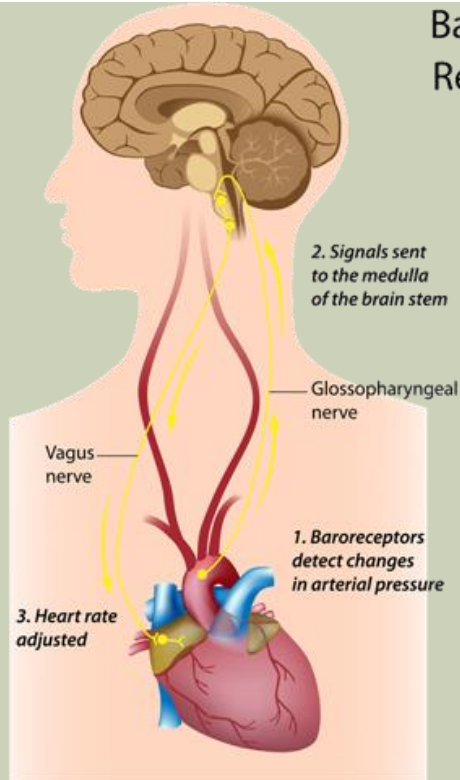
LIFESTYLE TO MANAGE INFLAMMATION ?



Cardio-Vascular Interoception



Tom Cruise playing Jack Reacher
Novelist, Lee Child

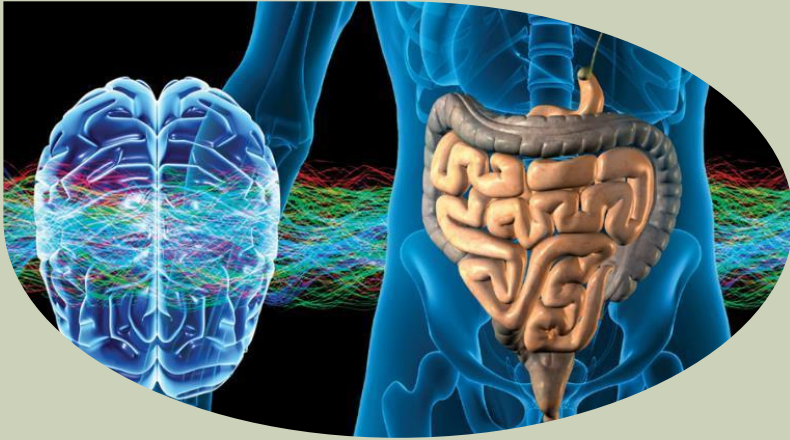


Baroreceptor Reflex

Cardiovascular interoception is measured by directing one own's attention towards the sensation of the heartbeat during various tasks :

for example **breathing**

Tensional states can alter body awareness



Signs from the “silent” gut, indicate to the brain the *tensional status*

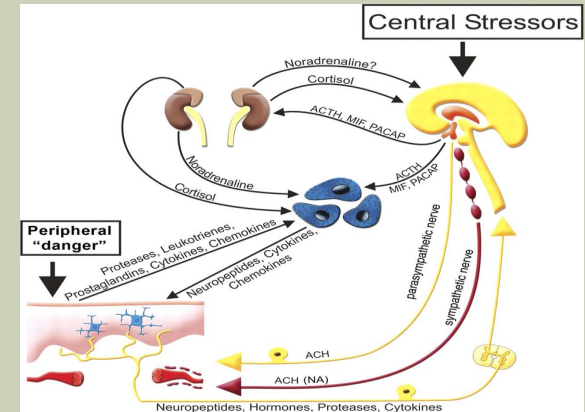
thus informing it about the **current state** of the body

Vagus activation : our main anti-inflammatory tool

...driving interoceptive signals, *via* somatosensory pathways from the skin...
touch sensory signals are integrated in the interoceptive processing.

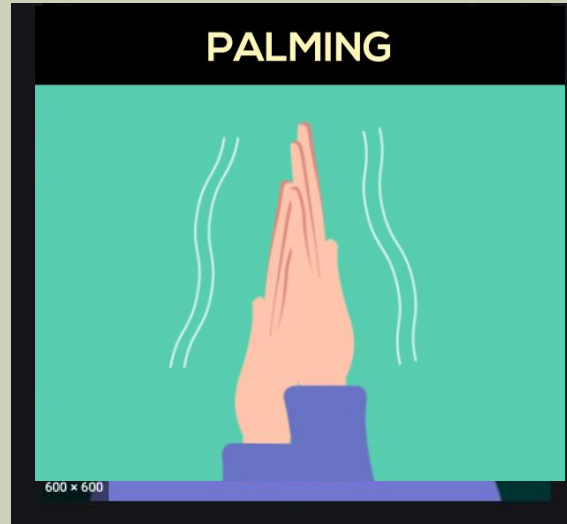


Last but not least, an affectionate touch...



BODY AWARENESS, A MATTER OF QUALITY OF LIFE

Mindfulness induces
vagal activation
allowing to **escape**
the immune
« cytokine storm »



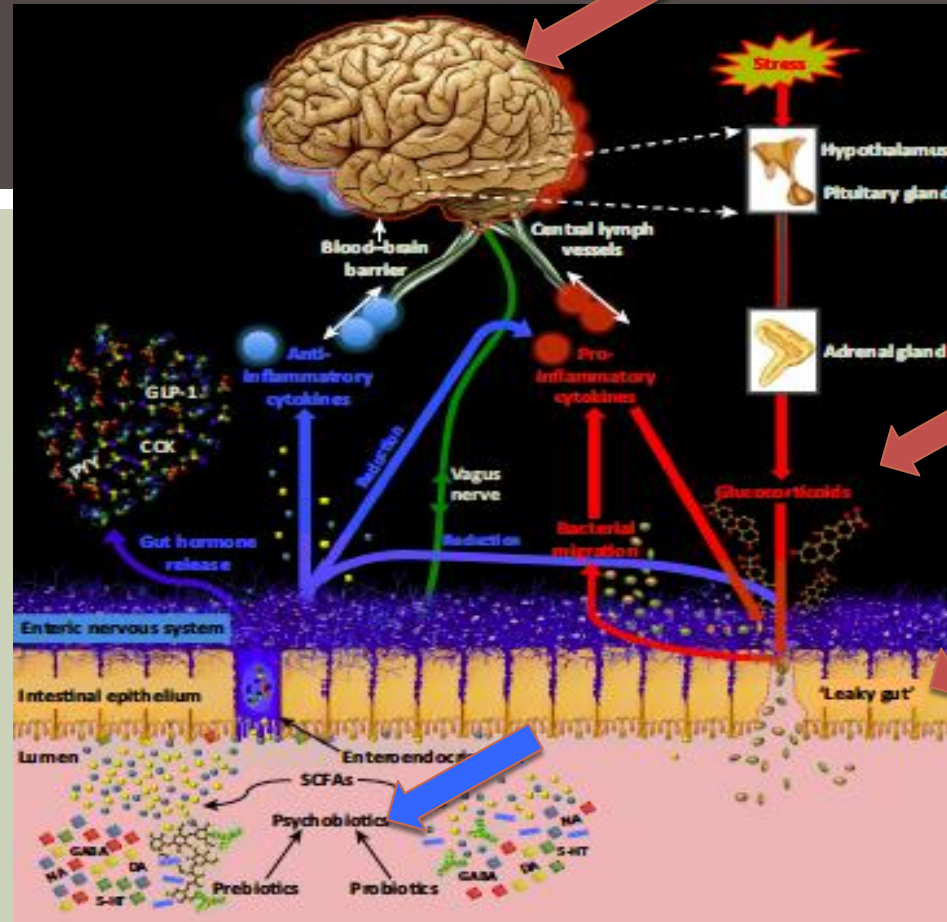
Eye yoga exercises will
reconnect you with the
whole body and lower the
tension in the neck. Gentle
breathing, footing, rooting



Self-esteem strategies by
concentration provide
shielding against different
sources of stress

Summary & perspectives

- ◆ 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.

Terpenoids as geroprotectors



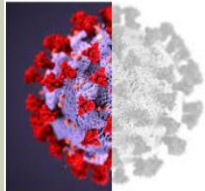
antioxidants



Review

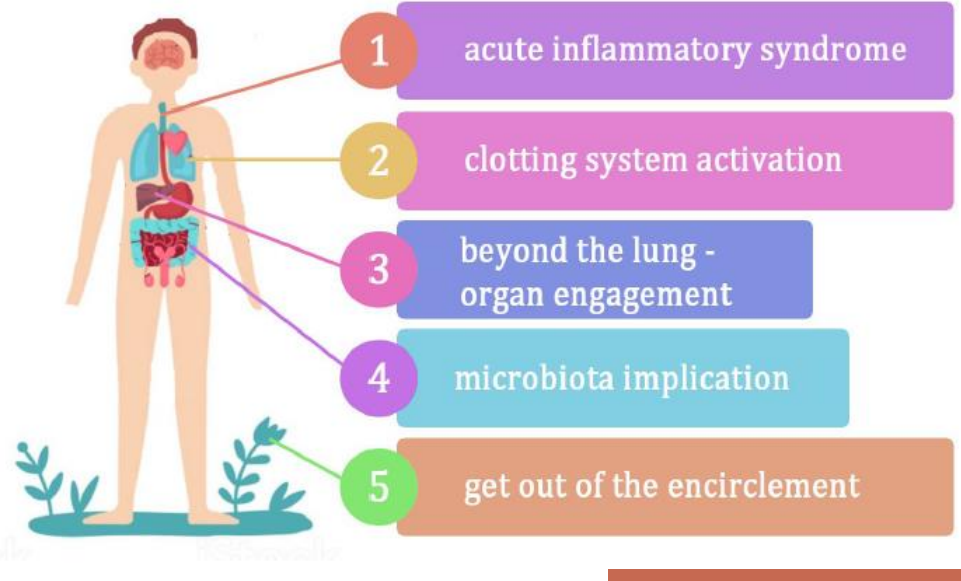
Terpenoids as Potential Geroprotectors

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



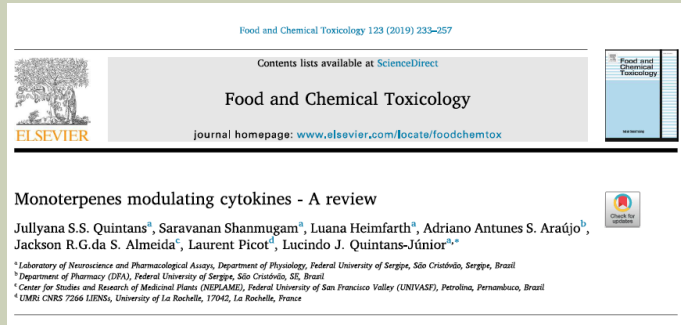
SARS-COV-2 INFECTION HALLMARKS AND POSSIBLE REMEDIES

Patrizia A d'ALESSIO MD PhD¹



« Monoterpenes modulate cytokines »

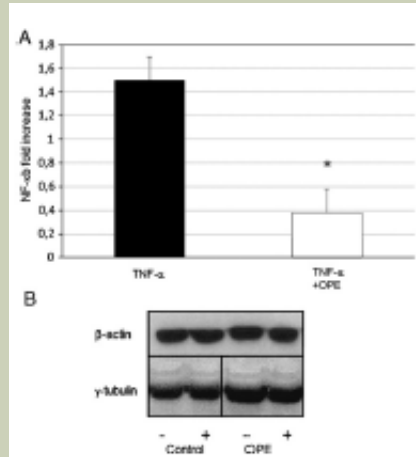
Inhibition of NF- κ B



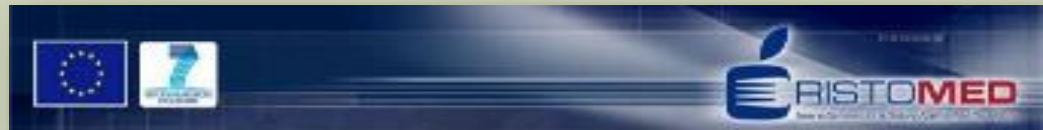
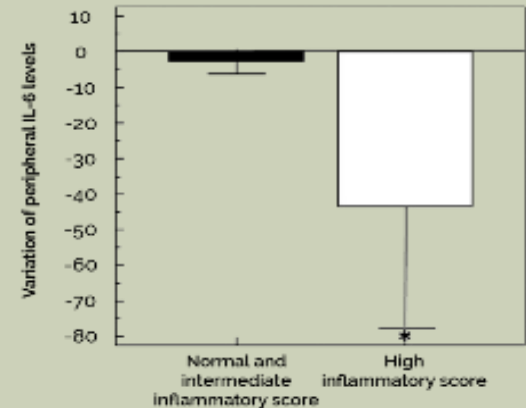
Life Sciences. 2013;92:1151-1156

Anti-Inflammatory & Anti-Allergy Agents 2014;13:29-35

Clin Nutr. 2016;35:812-818



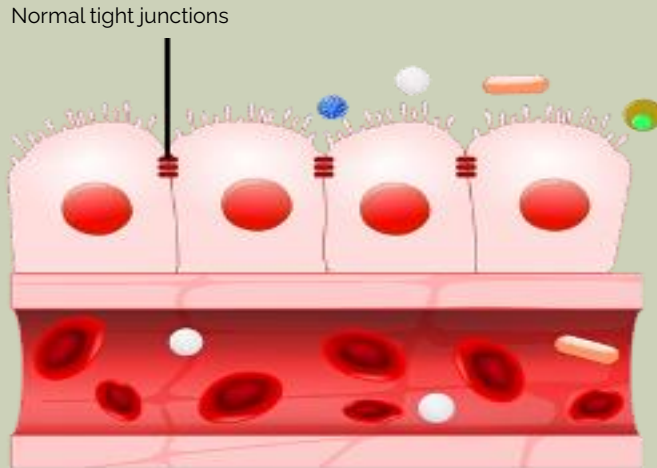
Anti-inflammatory effect



Pr Dr Patrizia d'Alessio, MD PhD

« Monoterpenes modulate cytokines »

Not only ! They repair the GUT BARRIER



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

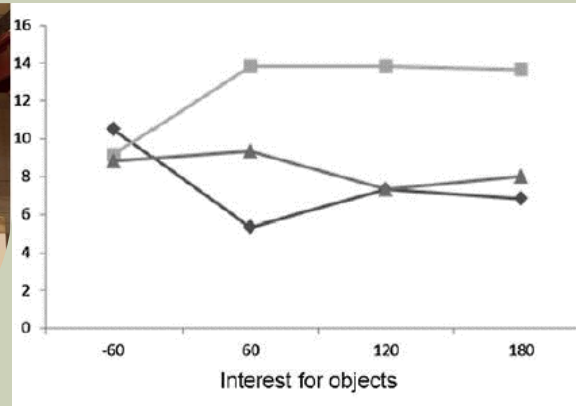
Evaluation of electric resistance ($\Omega \cdot \text{cm}^2$)
as percentage of initial resistance R_t.

Life Sciences. 2013;92:1151-1156



Anti-inflammation RESULTS also in mood modulation

Motivational effect in rodents



Rejuvenation Res.
2014;17:145-149

PRIME 2012; 30-37

Mood modulation effect in humans

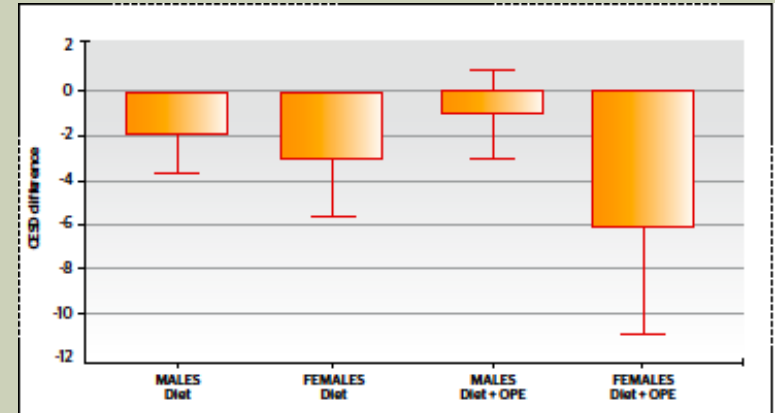
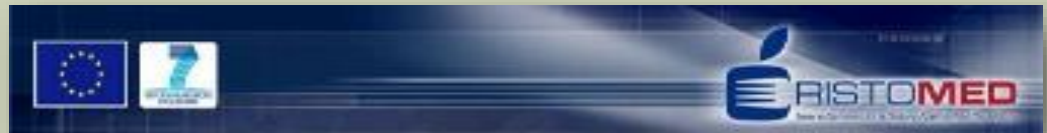


Figure 3 Gender partition and CES-D variation in diet versus diet plus OPE



MANAGING THE BALANCE IS THE KEY



TWO TYPES OF CONSEQUENCES OF THE UNANTICIPATED SOCIETAL CHANGES OF THE “SYNDEMIC” :

- ◆ **AN INCREASE IN LONELINESS AND DEPRESSIVE STATES , BUT ALSO :**
- ◆ **POSITIVE THINKING ABOUT GETTING ON WITH LIFE IN A PEACEFUL WAY.**

This could allow us some **unforeseen free time** for thinking, reading, reflecting, that we often so cruelly have missed.

Stay in closer contact with our more fundamental **values** that we might have **forgotten** about,

Caught by the rush of a non-stop flow of information, events, challenges...

CREDITS AND QUESTIONS



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**