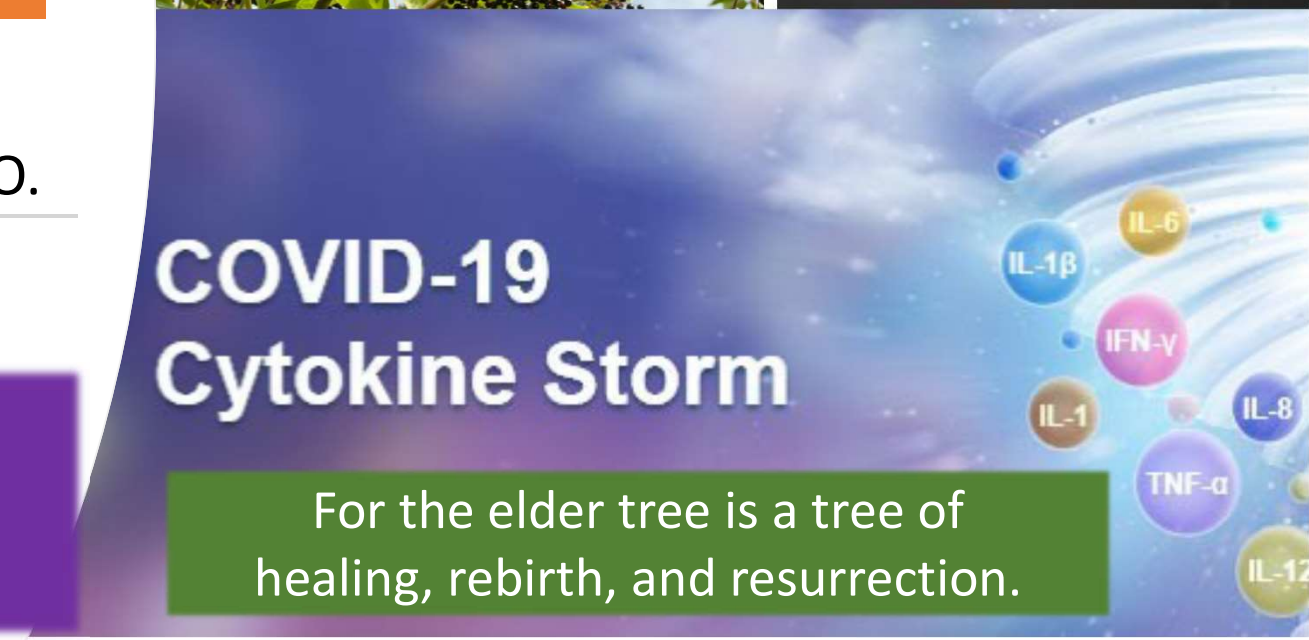
Targeting CoV -2019 Utilizing Unitive Medicine – Botanical, Nutritional, Dietary and Lifestyle

By Donald Yance RH (AHG),CN, SFO.

Donnieyance.com

If we could see the miracle of
a single flower clearly, our whole life
would change.
Gautama Buddha





For the elder tree is a tree of
healing, rebirth, and resurrection.

Overview of Presentation

- The dualistic role of the immune system and CoV
- The immune system, nervous system and Endocrine System connection
- Warning to those taking specific pharmaceuticals, namely NSAIDs, ACE inhibitors, and even PPIs
- Specific test relative to CoV
- Botanical Medicine and CoV - prevention, first line treatment, and adapting for specific presenting symptoms/complications, age, secondary chronic disease, and constitutional makeup
- The importance of a fever and how to use diaphoretic herbs in conjunction
- Specific Nutrients for prevention and treatment
- Specific diet recommendations for prevention and treatment
- Other modalities: Sinus flush, hydro (bath) therapy, Chest rubs and poultices, humming, chanting, laughter, etc.


There's no place like home


THANK YOU FOR WEARING A MASK...
©DAVEGRANLUND.COM

Never Shake Hands Again…



- Being hugged more frequently was associated with a 61% decreased risk of respiratory infection (OR = 0.39, 95% CI = 0.16, 0.96, p = 0.04)

Psychol Sci. Author manuscript; available in PMC 2016 Feb 1.
Published in final edited form as:
Psychol Sci. 2015 Feb; 26(2): 135–147.
Published online 2014 Dec 19. doi: 10.1177/0956797614559284

PMCID: PMC4323947
NIHMSID: NIHMS637169
PMID: 25526910

Does hugging provide stress-buffering social support? A study of susceptibility to upper respiratory infection and illness

Sheldon Cohen,[1] Denise Janicki-Deverts,[1] Ronald B. Turner,[2] and William J. Doyle[3]


NATURAL
IMMUKITY

Life Expectancy fell by 1.13 years in the United States, 2020 - Association of the COVID-19 Pandemic

- 2020 saw a decline in 2020 US life expectancy of 1.13 years for the total population, 0.68 years for the White population, 2.10 years for the Black population, and 3.05 years for the Latino population
- COVID-19 deaths through early April 2021 already indicate an almost 0.6-year reduction in overall 2021 US life expectancy with continued disproportionate changes for the Black and Latino populations.

Andrasfay T, Goldman N. Association of the COVID-19 Pandemic With Estimated Life Expectancy by Race/Ethnicity in the United States, 2020. *JAMA Netw Open.* 2021;4(6):e2114520. doi:10.1001/jamanetworkopen.2021.14520

JAMA Network™

From: **The Leading Causes of Death in the US for 2020**

JAMA. Published online March 31, 2021. doi:10.1001/jama.2021.5469

Table. Number of Deaths for Leading Causes of Death, US, 2015-2020[a]

	No. of deaths by year					
Cause of death	2015	2016	2017	2018	2019	2020
Total deaths	2 712 630	2 744 248	2 813 503	2 839 205	2 854 838	3 358 814
Heart disease	633 842	635 260	647 457	655 381	659 041	690 882
Cancer	595 930	598 038	599 108	599 274	599 601	598 932
COVID-19[b]						345 323
Unintentional injuries	146 571	161 374	169 936	167 127	173 040	192 176
Stroke	140 323	142 142	146 383	147 810	150 005	159 050
Chronic lower respiratory diseases	155 041	154 596	160 201	159 486	156 979	151 637
Alzheimer disease	110 561	116 103	121 404	122 019	121 499	133 382
Diabetes	79 535	80 058	83 564	84 946	87 647	101 106
Influenza and pneumonia	57 062	51 537	55 672	59 120	49 783	53 495
Kidney disease	49 959	50 046	50 633	51 386	51 565	52 260
Suicide	44 193	44 965	47 173	48 344	47 511	44 834

[a] Leading causes are classified according to underlying cause and presented according to the number of deaths among US residents. For more information, see the article by Heron.[4] Source: National Center for Health Statistics. National Vital Statistics System: mortality statistics (http://www.cdc.gov/nchs/deaths.htm). Data for 2015-2019 are final; data for 2020 are provisional.

[b] Deaths with confirmed or presumed COVID-19, coded to *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* code U07.1 as the underlying cause of death.

Table Title:

Number of Deaths for Leading Causes of Death, US, 2015-2020[aa] Leading causes are classified according to underlying cause and presented according to the number of deaths among US residents. For more information, see the article by Heron. Source: National Center for Health Statistics. National Vital Statistics System: mortality statistics (http://www.cdc.gov/nchs/deaths.htm). Data for 2015-2019 are final; data for 2020 are provisional.

[b] Deaths with confirmed or presumed COVID-19, coded to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision code U07.1 as the underlying cause of death.

European Journal of Clinical Nutrition (2020) 74:852–855
https://doi.org/10.1038/s41430-020-0646-z

PERSPECTIVE

COVID-19 pandemic: the effects of quarantine on cardiovascular risk

Anna Vittoria Mattioli[1] · Matteo Ballerini Puviani[2] · Milena Nasi[1] · Alberto Farinetti[1]

Received: 30 March 2020 / Revised: 16 April 2020 / Accepted: 22 April 2020 / Published online: 5 May 2020
© Springer Nature Limited 2020

- Quarantine carries some long-term effects on cardiovascular disease, mainly related to unhealthy lifestyle and anxiety
- The potential benefits of mandatory mass quarantine need to be weighed carefully against the possible long-term negative effects on cardiovascular risk burden

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

A-Z Index

Search

Advanced Search

Morbidity and Mortality Weekly Report (*MMWR*)

Mental Health, Substance Use, and Suicidal Ideation During the COVID-19 Pandemic — United States, June 24–30, 2020

Weekly / August 14, 2020 / 69(32);1049–1057

Mark É. Czeisler[1,2]; Rashon I. Lane, MA[3]; Emiko Petrosky, MD[3]; Joshua F. Wiley, PhD[1]; Aleta Christensen, MPH[3]; Rashid Njai, PhD[3]; Matthew D. Weaver, PhD[1,4,5]; Rebecca Robbins, PhD[4,5]; Elise R. Facer-Childs, PhD[1]; Laura K. Barger, PhD[4,5]; Charles A. Czeisler, MD, PhD[1,4,5]; Mark E. Howard, MBBS, PhD[1,2,6]; Shantha M.W. Rajaratnam, PhD[1,4,5] (View author affiliations)

Rapid Review

The psychological impact of quarantine and how to reduce it: rapid review of the evidence

Samantha K Brooks, Rebecca K Webster, Louise E Smith, Lisa Woodland, Simon Wessely, Neil Greenberg, Gideon James Rubin

- A recent study published in August 2021 that found U.S. adolescents, particularly girls, screened positive for depression and suicide risk during the COVID-19 pandemic.
- Researchers in several other studies have reported a high prevalence of mental health concerns among children and adolescents during the pandemic.

Stephanie L. Mayne, Chloe Hannan, Molly Davis, Jami F. Young, Mary Kate Kelly, Maura Powell, George Dalembert, Katie E. McPeak, Brian P. Jenssen and Alexander G. Fiks, COVID-19 and Adolescent Depression and Suicide Risk Screening Outcomes, Pediatrics August 2021, e2021051507; DOI: https://doi.org/10.1542/peds.2021-051507; Patrick SW, Henkhaus LE, Zickafoose JS, et al. Well-being of parents and children during the COVID-19 pandemic: a national survey. Pediatrics. 2020;146(4):e2020016824; Zhou SJ, Zhang LG, Wang LL, et al. Prevalence and socio-demographic correlates of psychological health problems in Chinese adolescents during the outbreak of COVID-19. Eur Child Adolesc Psychiatry. 2020;29(6):749–758

Loneliness and Social Isolation as Risk Factors for Mortality: a Meta-Analytic Review

Actual and perceived social isolation are both associated with increased risk for early mortality and influence of both objective and subjective social isolation on risk for mortality is comparable with well-established risk factors for mortality, such as smoking and obesity.



Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D., Perspect Psychol Sci. 2015 Mar;10(2):227-37. doi: 10.1177/1745691614568352.

Difficult Times Create Opportunities for Growth and to Experience a deepening of Love

"Everything that irritates us about others can lead us to an understanding of ourselves.
In the end, *the face we turn toward our self, is the face we will turn toward the outer world."*

Richard Rohr



C.S. Lewis, wrote: ***"Friendship is unnecessary, like philosophy, like art.... It has no survival value; rather it is one of those things which give value to survival."***

Environmental Chemistry Letters
https://doi.org/10.1007/s10311-021-01224-9

REVIEW

Smarter cures to combat COVID-19 and future pathogens: a review

Han Dai[1] · Jie Han[1] · Eric Lichtfouse[2,3]

Received: 4 December 2020 / Accepted: 12 March 2021
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2021



- Being close to nature by spending time in the natural outdoor environments can do wonders for one's health. There is a lot of hidden knowledge in these ecological medicines and treatments. For instance, Swinburn et al. told many stories about the health benefits of spending time in nature.

Swinburn BA, Walter LG, Arroll B, Tilyard MW, Russell DG., The green prescription study: a randomized controlled trial of written exercise advice provided by general practitioners, *Am J Public Health. 1998 Feb; 88(2):288-91.*)

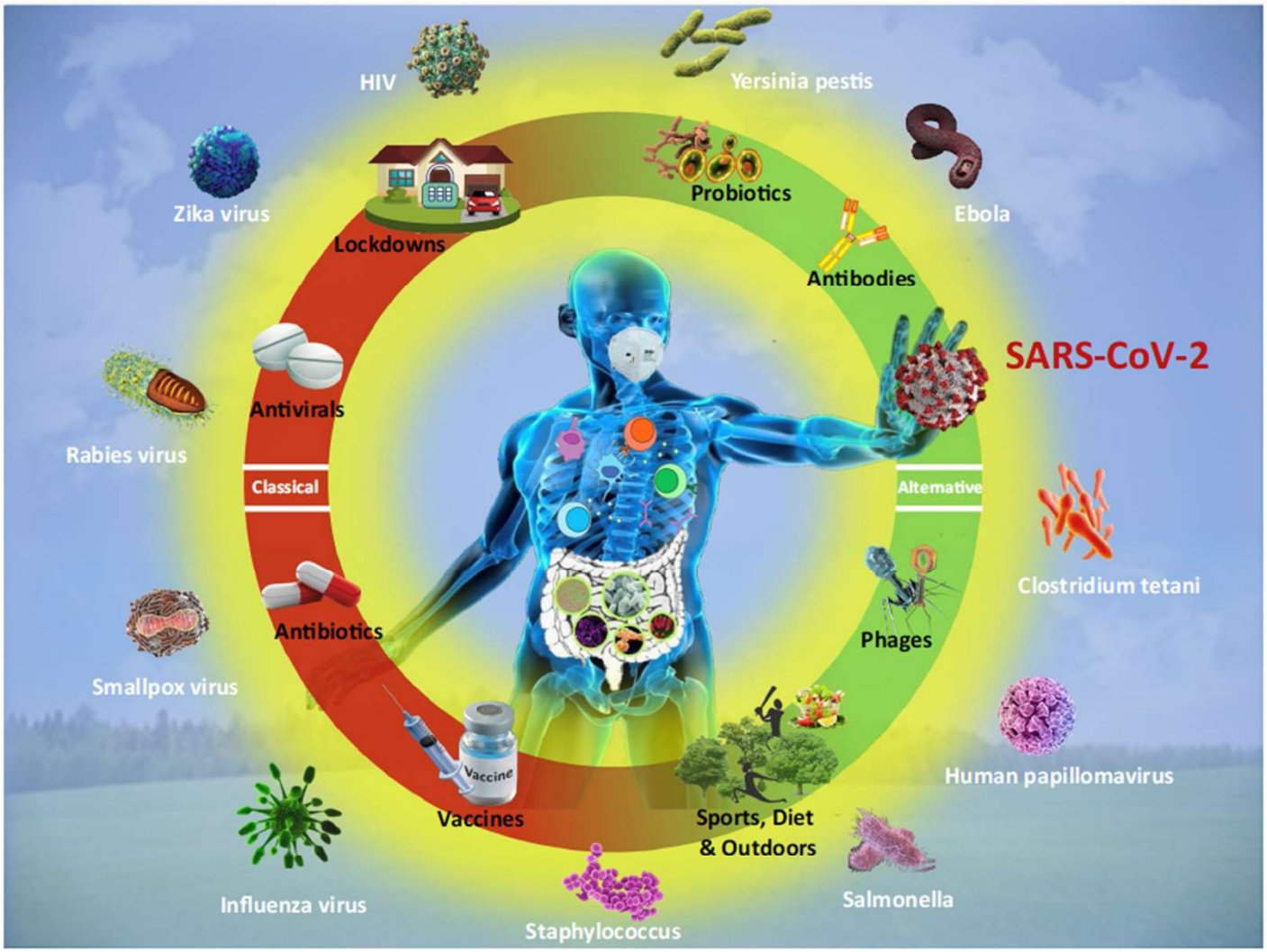


Fig. 1 Classical and alternative medicines. Classical medicine treats patients with chemical drugs and vaccines *after* disease appearance; this approach is limited by pathogen mutation and adaptation to drugs, e.g., antibiotic resistance. Alternative medicine treats patients *before* disease appearance with living organisms, e.g., phages, probiotics or by applying practices that reinforce human immunity, e.g., sports, yoga, music, dance, healthy diet and outdoor activities

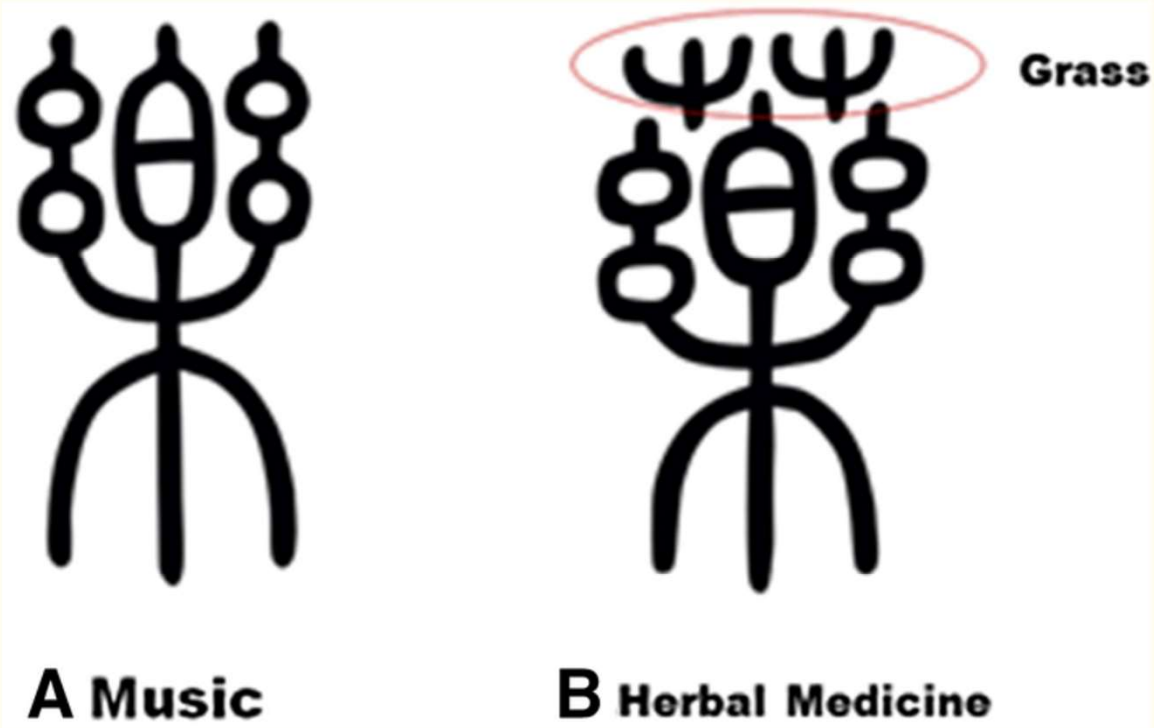
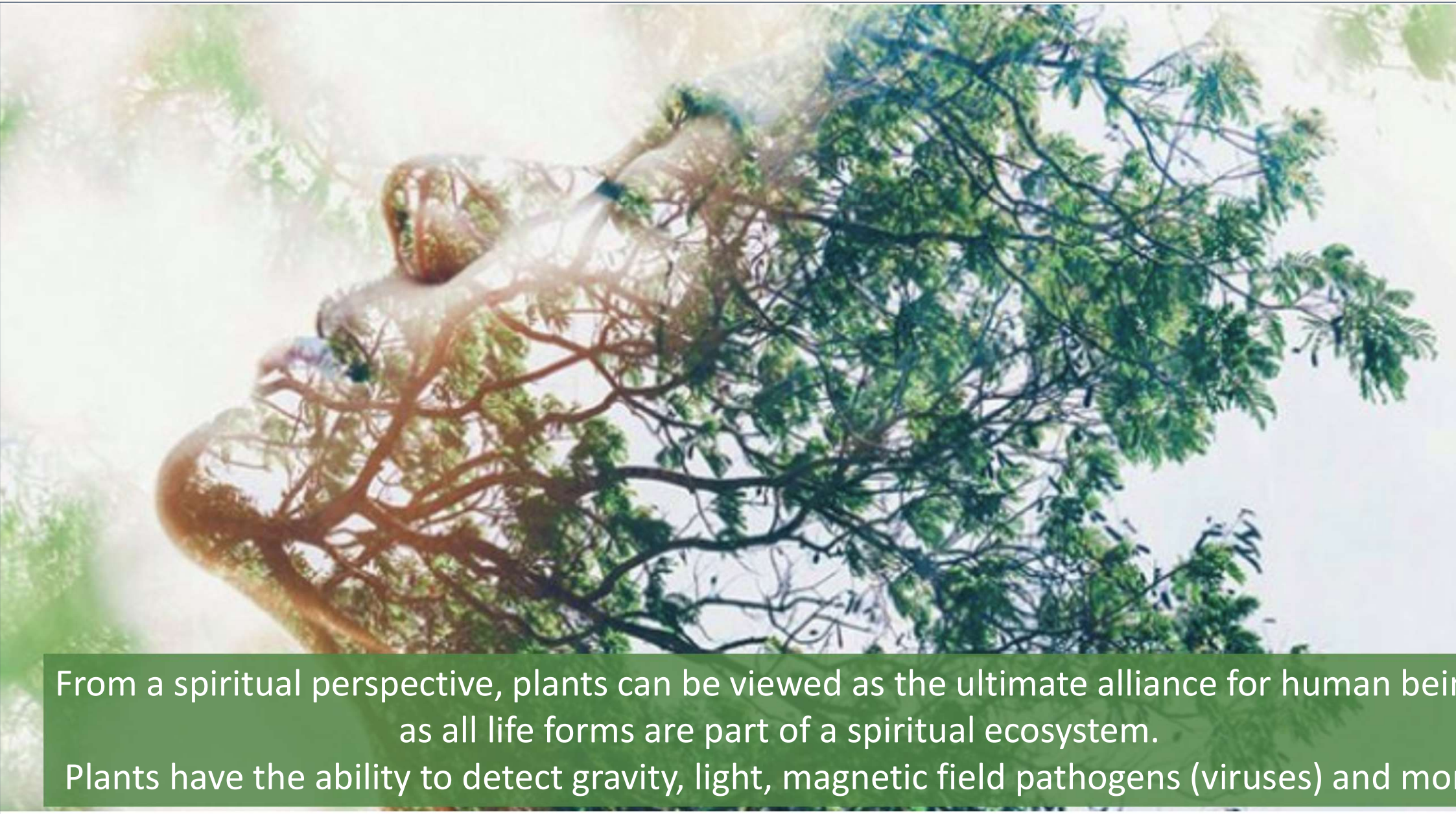


Fig. 2

Traditional Chinese characters of ‘music’ (**a**) and ‘herbal medicine’ (**b**). In ancient China, one of music’s earliest purposes was for healing. The two characters are similar on both strokes and pronunciations. Psychology and physiology are regarded as a unified whole in Chinese medicine, which means in the etiology, pathogenesis and treatment, changes in psychological and physiological interact together mostly (Karchmer 2013). Over 2000 years, music therapy is an important non-physiological approach for Chinese medicine in its therapeutic spectrum. Reprint from Zhang and Lai (2017)


From a spiritual perspective, plants can be viewed as the ultimate alliance for human bei
as all life forms are part of a spiritual ecosystem.
Plants have the ability to detect gravity, light, magnetic field pathogens (viruses) and mo

Journal of
Clinical Medicine

MDPI

Review

Herbal Medicine for the Treatment of Coronavirus Disease 2019 (COVID-19): A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Lin Ang [1,2], Eunhye Song [3,4], Hye Won Lee [5] and Myeong Soo Lee [1,2,*]

- Seven RCTs with a total of 855 patients were included.
- All included trials compared the combined therapy of herbal medicine with Western medicine to Western medicine alone.
- The combined therapy significantly improved the total effective rate

Received: 23 April 2020; Accepted: 20 May 2020; Published: 23 May 2020

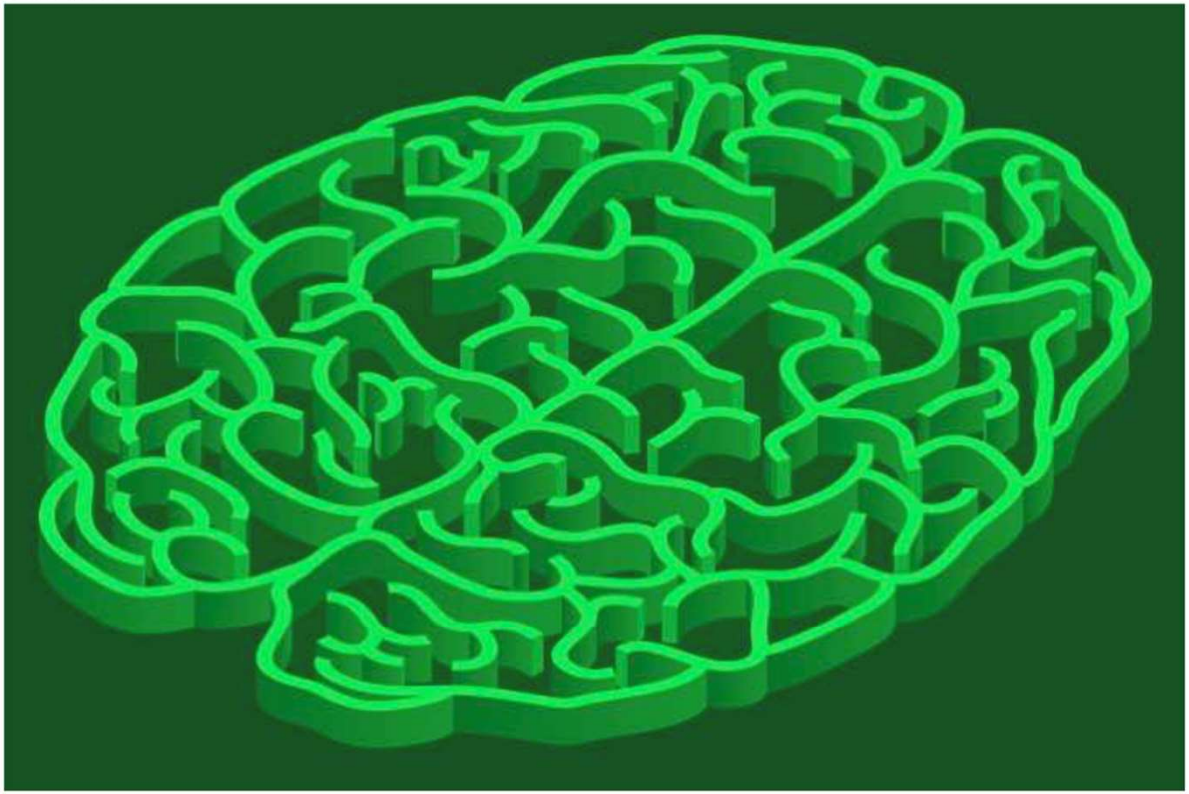
check for updates

MEDPAGE TODAY®

Zoloft Shortage; Google's Anxiety Self-Screening

— News and commentary from the psychiatry world

by Kristen Monaco, Staff Writer, MedPage Today
June 3, 2020

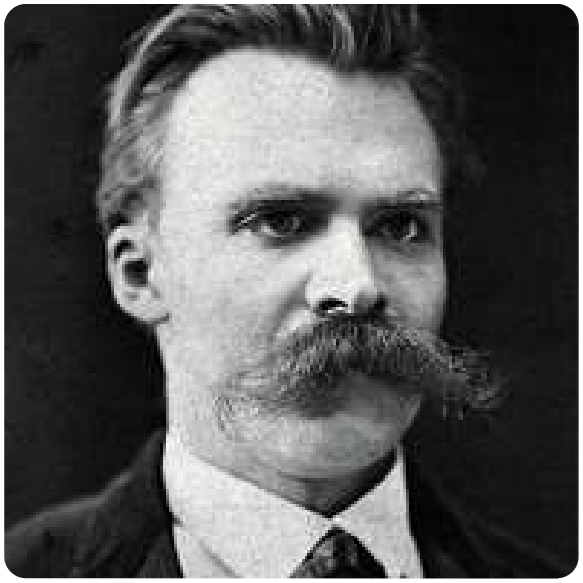


The antidepressant sertraline (Zoloft) was added to the FDA's shortage list due to increased demand amid the pandemic. (*Bloomberg Law*)

Biocides sprayed during COVID-19 in Italy and China









“What doesn’t kill us can makes us stronger”

- Since ancient times, people have proposed (and practiced) the idea that low doses of poison could be beneficial to health in the long run.
- The German philosopher Friedrich Nietzsche (1844–1900) made the famous statement that “What doesn’t kill us makes us stronger”

Int J Mol Sci. 2013 Jul; 14(7): 13109–13128.

Why Are Men at Higher Risk?

https://www.youtube.com/watch?v=A4UMyTnlaMY

- In an initial report of 41 patients infected in Wuhan, China, Huang et al reported a 78% male predominance, with 32% of all patients reporting underlying disease
- Men who get infected with Covid-19 in Ireland are 1.5 times more likely to be hospitalized, admitted to intensive care or die than women who catch the virus, new research revealed today.

https://www.msn.com/en-ie/news/other/men-with-symptomatic-covid-19-1-5-times-more-likely-to-face-severe-outcome-than-women/ar-AAODv33

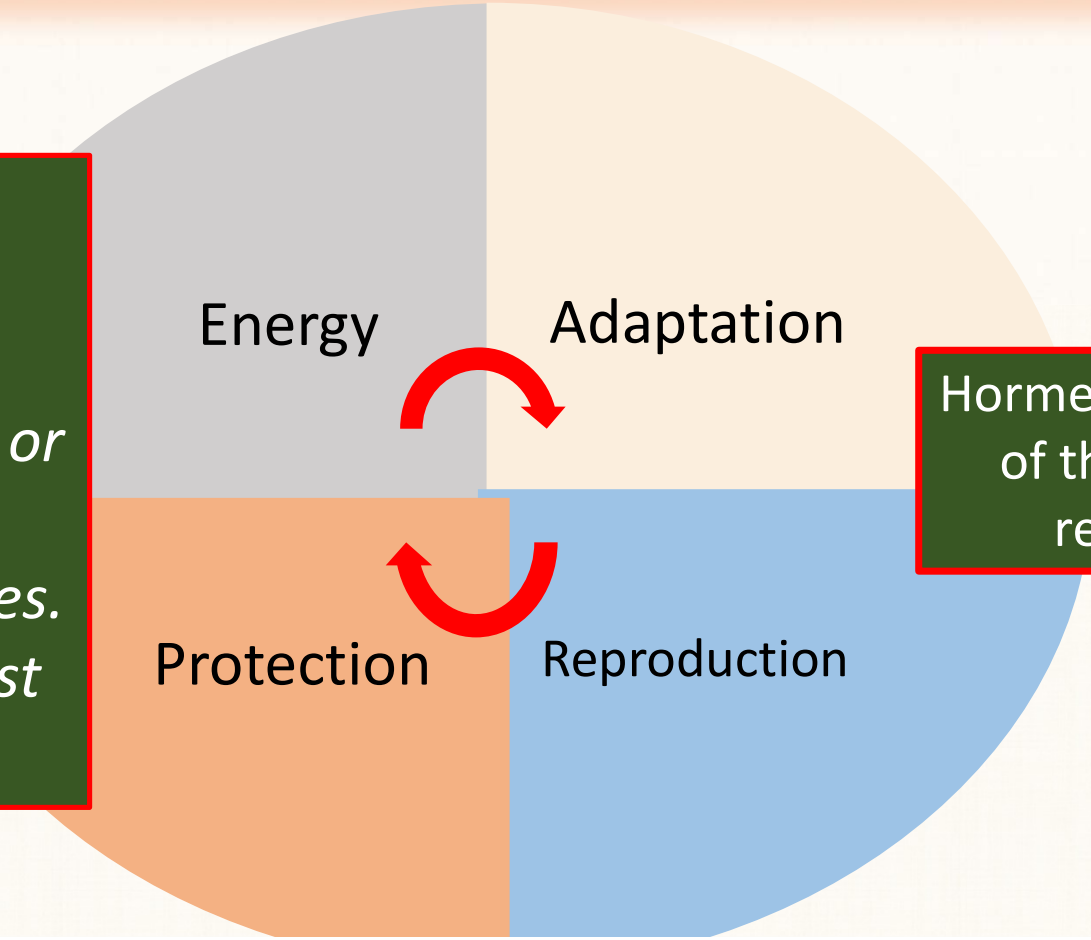
- **Resilience is** gaining strength from managing unwanted change.
- Vital to **recovery** and **longevity**

Curr Gerontol Geriatr Res. 2010: 525693.

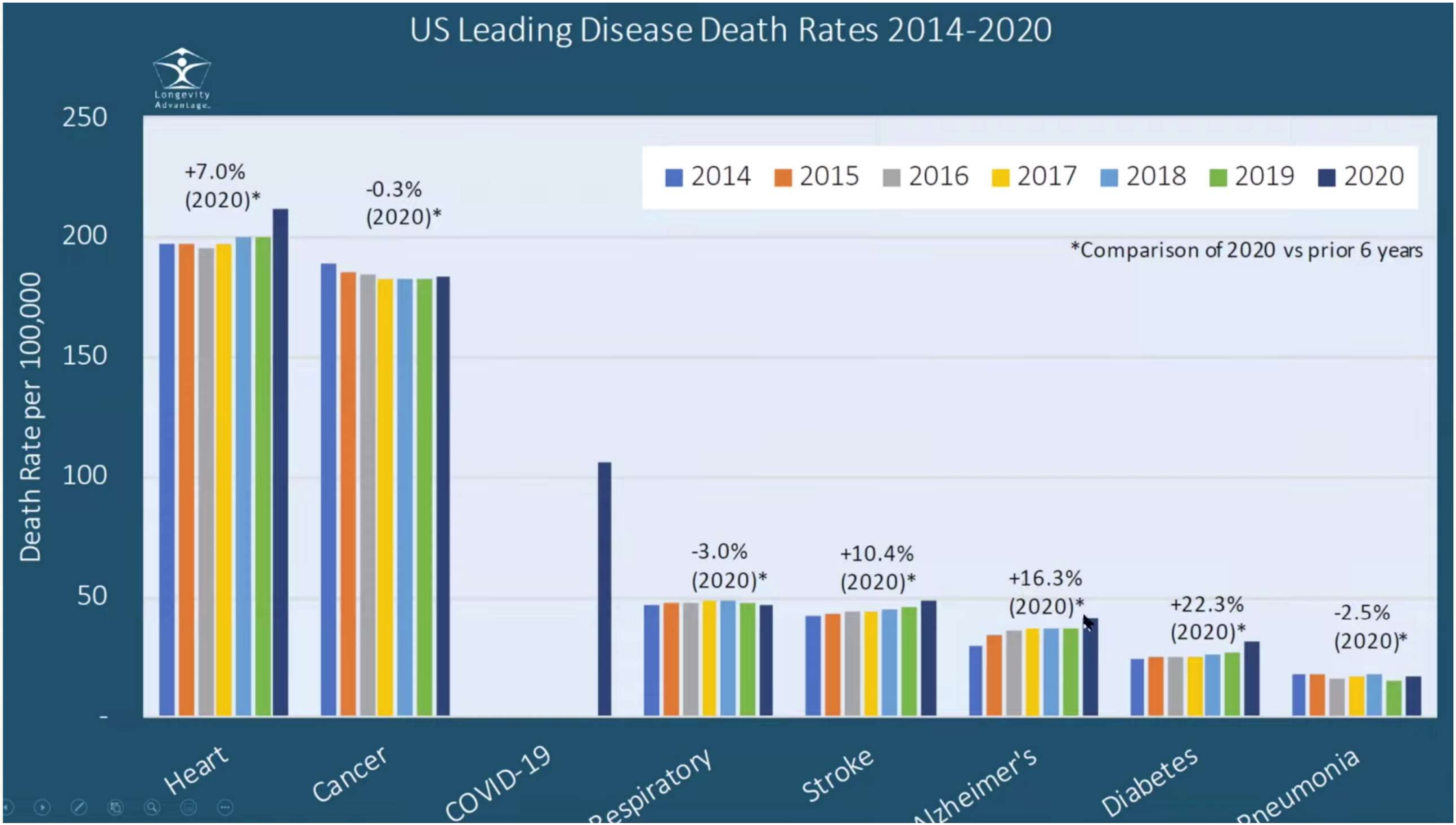


FOUR LIFE REQUIREMENTS

Charles Darwin said in *On the Origin of the Species:*
"It is not the strongest or the most intelligent of the species that survives. It is the one that is most adaptable to change."



Hormesis is a manifestation of the body's adaptive response to stress

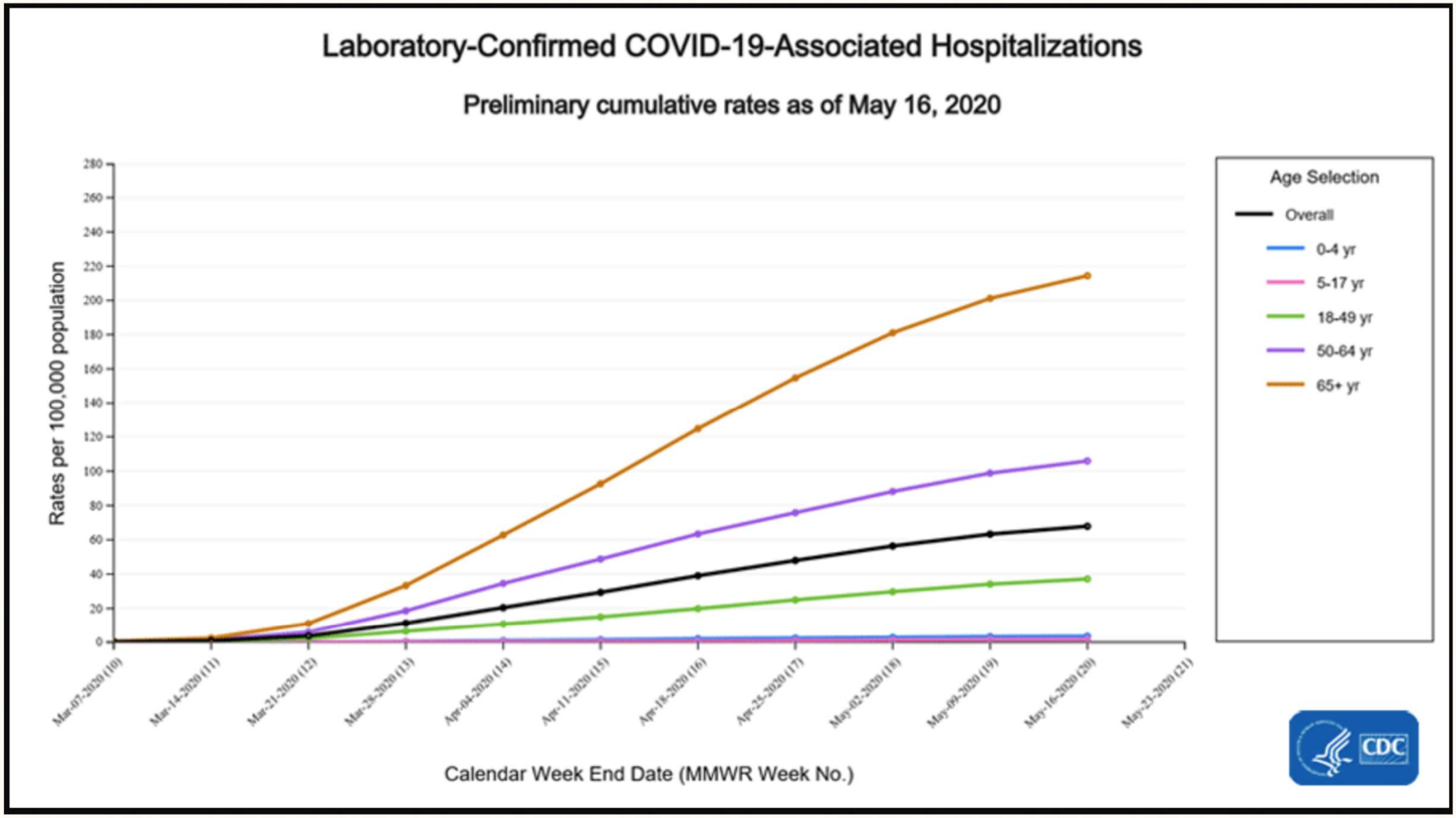

US Leading Disease Death Rates 2014-2020
Longevity Advantage
Death Rate per 100,000
250
200
150
100
50
-
2014
2015
2016
2017
2018
2019
2020
*Comparison of 2020 vs prior 6 years
+7.0% (2020)*
-0.3% (2020)*
-3.0% (2020)*
+10.4% (2020)*
+16.3% (2020)*
+22.3% (2020)*
-2.5% (2020)*
Heart
Cancer
COVID-19
Respiratory
Stroke
Alzheimer's
Diabetes
Pneumonia

MEDPAGE TODAY®

Over 85% of COVID-19 Infections in China Went Undetected Early On

— Number of mild or asymptomatic infections emphasizes need for mitigation measures

by Molly Walker, Associate Editor, MedPage Today
March 16, 2020


Laboratory-Confirmed COVID-19-Associated Hospitalizations
Preliminary cumulative rates as of May 16, 2020
Rates per 100,000 population
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
Mar-07-2020 (10)
Mar-14-2020 (11)
Mar-21-2020 (12)
Mar-28-2020 (13)
Apr-04-2020 (14)
Apr-11-2020 (15)
Apr-18-2020 (16)
Apr-25-2020 (17)
May-02-2020 (18)
May-09-2020 (19)
May-16-2020 (20)
May-23-2020 (21)
Calendar Week End Date (MMWR Week No.)
Age Selection
Overall
0-4 yr
5-17 yr
18-49 yr
50-64 yr
65+ yr
CDC

Why does the Covid-19 virus effect older adults more and why does the morbidity and mortality go up with age?

- Older adults have weaker immune systems - the number and more importantly the health of immune fighting cells that find and help eliminate infections can decline and weaken
- The cells also become less adept at identifying new pathogens to fight and run out of energy. An immune response first requires a huge blast of energy to be directed at the present danger – the pathogen
- People with a weakened immune system are more susceptible to acute viruses including the flu and CoVs
- Our immune system has to recognize, respond, create specific antibodies, and then recover (go back to normal)
- All of this is easy in a generally healthy person, but not so in an unhealthy person

Public Health Fact Sheet - Flu http://www.state.ma.us/dph/cdc/factsheets/fsflu.htm
A Weakened Immune System, CDC, http://www.bt.cdc.gov/

Maria Branyas: 'Oldest woman in Spain' beats coronavirus at 113

12 May 2020

Coronavirus pandemic



GETTY IMAGES

A 113-year-old woman - believed to be the oldest woman in Spain - has recovered from the coronavirus, officials have said.

COVID-19 protection mechanism: hints from centenarians

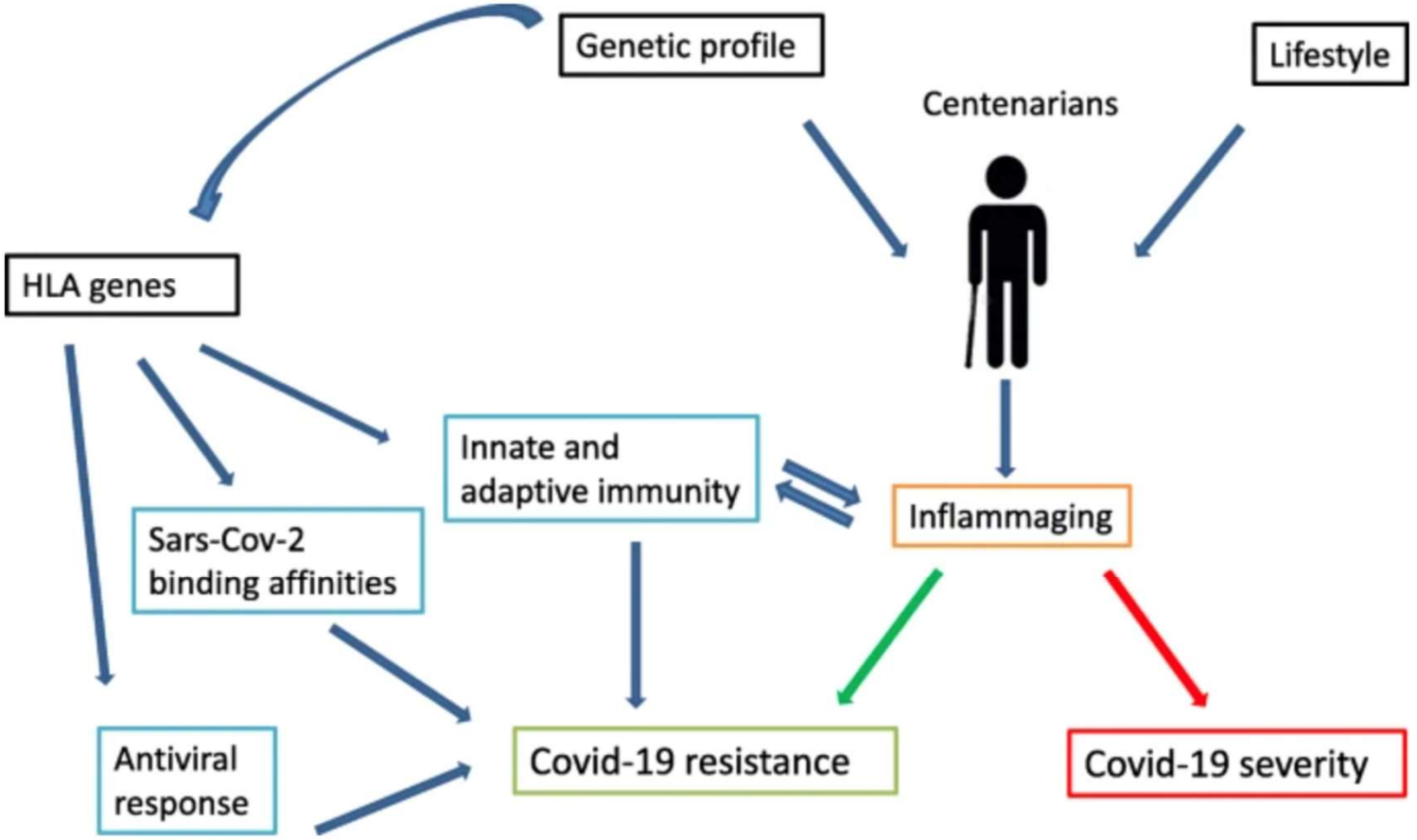
- Frailty could complicate the course of COVID-19, much more than the number of years lived.
- Centenarians showing remarkable capacity to recover after coronavirus infection.
- The human leukocyte antigen (HLA) is one of the major genetic regions associated with human longevity, due to its central role in the development of adaptive immune response and modulation of the individual's response to life threatening diseases.
- The HLA locus seems to be crucial in influencing susceptibility and severity of COVID-19.

Guerini FR, Cesari M, Arosio B. Hypothetical COVID-19 protection mechanism: hints from centenarians. Immun Ageing. 2021 Mar 30;18(1):15. doi: 10.1186/s12979-021-00226-z. PMID: 33785044.

COVID-19 protection mechanism: hints from centenarians

- In the era of COVID-19, it is interesting to underline that there are centenarians that showed a remarkable capacity to recover after coronavirus infection.
- In this regard, there are anecdotal observations that centenarians and sometime supercentenarians (people over 110 years old) survived and recovered after SARS-CoV-2 infection, as confirmed in a group of centenarians belonging to “Centenari a Trieste (CaT) study.”

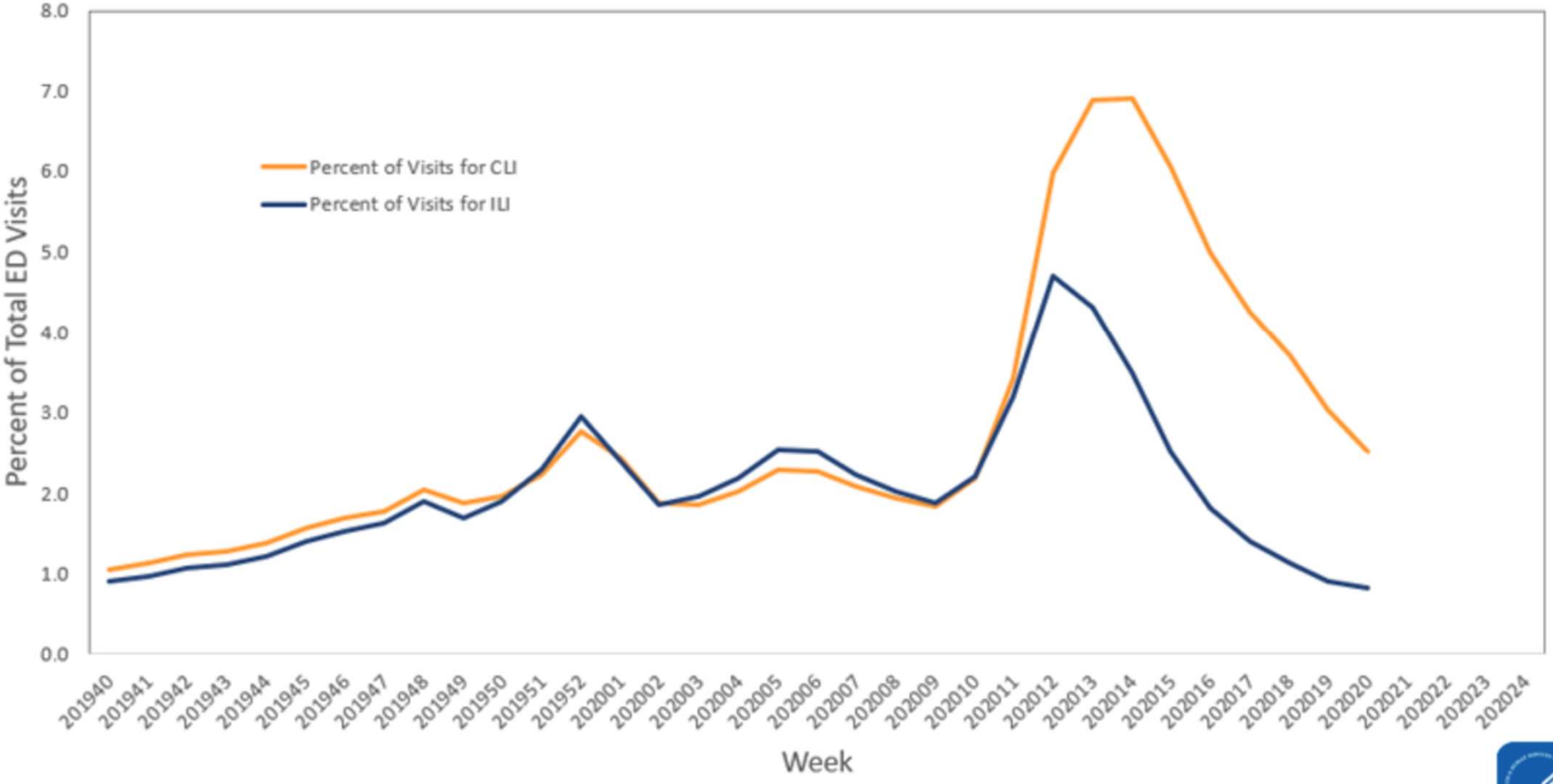
Abbatecola AM, Antonelli-Incalzi R. Editorial: COVID-19 spiraling of frailty in older Italian patients. J Nutr Health Aging. 2020;24(5):453–5. https://doi.org/10.1007/s12603-020-1357-9.
Marcon G, Tettamanti M, Capacci G, Fontanel G, Spanò M, Nobili A, Forloni G, Franceschi C. COVID-19 mortality in Lombardy: the vulnerability of the oldest old and the resilience of male centenarians. Aging. 2020;12(15):15186–95. https://doi.org/10.18632/aging.103872.



Centenarian's portfolio and biological mechanisms underlying the coronavirus infection. Centenarians are persons characterized by an exclusive signature resulting from the interaction between genes and environmental factors. Inflammaging identifies the low-grade inflammation status typical of the older persons that seems to drive the course of the infection. HLA genes play a crucial role in immune response and antiviral reactivity and the HLA alleles show a specific binding affinity with Sars-Cov-2 peptides

Immun Ageing. 2021 Mar 30;18(1):15.
doi: 10.1186/s12979-021-00226-z..

NSSP: Percentage of Visits for Influenza-Like Illness (ILI) and COVID-19-Like Illness (CLI)
to Emergency Departments
Weekly National Summary, September 29, 2019 - May 16, 2020



Infectious Disease > COVID-19

Hypertension, Obesity Common in U.S. COVID-19 Hospitalizations

— African Americans disproportionately affected

by Molly Walker, Associate Editor, MedPage Today April 8, 2020

COVID-19 deaths high in African Americans

- While everyone is susceptible to COVID-19 statistics show 70 percent of people who died of the disease in Louisiana are African American.
- 70 percent of deaths in Chicago are African American patients to a 30 percent population and only 26 percent of people in Milwaukee are black, but account for 81 percent of COVID-19 deaths in the area.

https://www.fox8live.com/2020/04/07/covid-deaths-high-african-americans/, retrieved 4/8/20

Why are patients with hypertension and diabetes mellitus at increased risk for CoV-19 related complications and more severe cases?

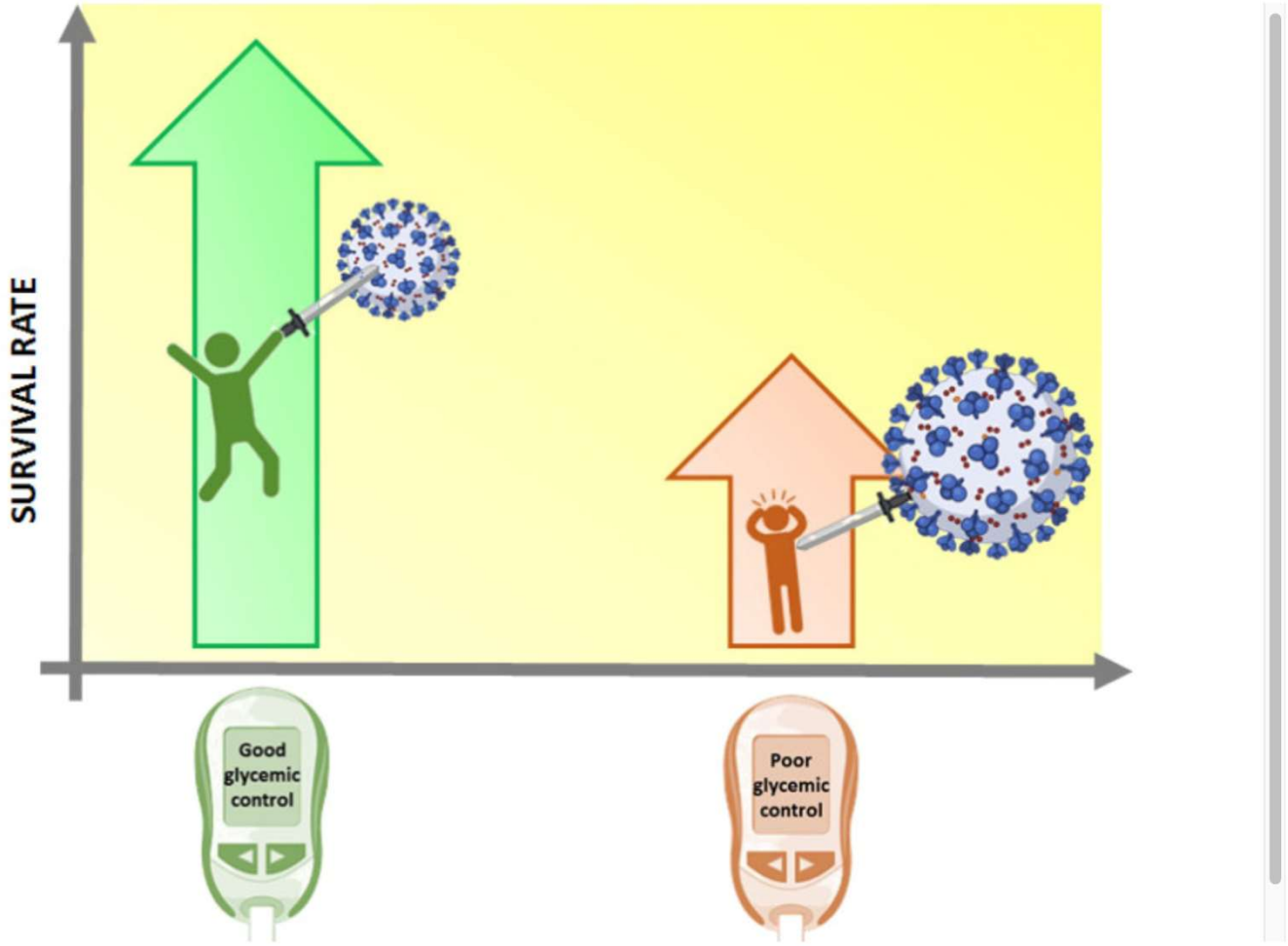
- The most frequent comorbidities reported in these three studies of patients with COVID-19 are often treated with angiotensin-converting enzyme (ACE) inhibitors; however, treatment was not assessed in either study
- According to a March 11th paper published in the Lancet, SARS-CoV and SARS CoV-2 bind to their target cells through ACE2, which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels
- ACE2 is essential for binding to the virus and surface – of course this leads to viral release and replicates and the spread of CoV-19.
- The CoV-19 actually increases encoding of the ACE2 protein which causes ACE2 receptor DOWNGRADE. That means the deaths may be due to a rapid increase of Angiotension II with no feedback to reduce back to Angiontension
- ACE2 can also be increased by thiazolidinediones and ibuprofen

Lancet Respir Med 2020; published online Feb 24. https://doi.org/10.1016/S2213- 2600(20)30079-5.

Diabetes increases mortality and severity of CoV-19, and ocular symptoms of SARS-CoV-2

- There is a strong association between diabetes and increased mortality and severity in COVID-19 pneumonia, and ocular symptoms of SARS-CoV-2.
- A systematic review and meta-analysis of 30 studies comprising 6,452 patients showed that diabetes was associated with mortality, severity, and acute respiratory distress syndrome (ARDS) in COVID-19, although the association was weaker in older patients and patients with hypertension.

Nan Hong et. al., Evaluation of ocular symptoms and tropism of SARS-CoV-2 in patients confirmed with COVID-19, First published:26 April 2020, https://doi.org/10.1111/aos.14445, Diabetes & Metabolic Syndrome: Clinical Research & Reviews, Acta Ophthalmologica https://www.sciencedirect.com/science/article/pii/S1871402120300837



Impact of COVID-19 on patients with diabetes. Survival rate is dramatically reduced in subjects with diabetes infected with SARS-CoV-2. Created with BioRender.com.

Ricordi C, Pacifici F, Lanzoni G, Palamara AT, Garaci E, Della-Morte D. Dietary and Protective Factors to Halt or Mitigate Progression of Autoimmunity, COVID-19 and Its Associated Metabolic Diseases. *Int J Mol Sci*. 2021;22(6):3134. Published 2021 Mar 19. doi:10.3390/ijms22063134

Smokers Face Greater Risk From COVID-19

— Health experts say now is the time to quit

by Salynn Boyles, Contributing Writer — April 8, 2020

MEDPAGE TODAY®

Could Proton Pump Inhibitors Increase COVID-19 Risk?

— Survey data suggest a link with biological plausibility

by Diana Swift, Contributing Writer
July 9, 2020



Taking proton pump inhibitors (PPIs) daily was associated with increased odds of testing positive for COVID-19, a population-based online survey found.

Almario CV, et al "Increased risk of COVID-19 among users of proton pump inhibitors" Am J Gastroenterol 2020.

MEDPAGE TODAY®

More Evidence Heartburn Drug May Help COVID-19 Patients

— Another observational study adds fuel to the fire, but more research is needed

by Molly Walker, Associate Editor, MedPage Today

August 17, 2020

- Famotidine (Pepcid AC), which is used to treat heartburn, was associated with improved clinical outcomes in COVID-19 patients.
- Use of famotidine in a small group of 83 patients was associated with a lower risk of in hospital mortality and a combined outcome of death and intubation, reported Jeffrey Mather, MS, of Hartford Hospital in Connecticut, and colleagues.
- Moreover, famotidine use was also associated with lower levels of serum markers indicating severe disease,

Mather JF, et al "Impact of famotidine use on clinical outcomes of hospitalized COVID-19 patients" Am J Gastroenterol; August 14, 2020.

DG News Oncology

March 16, 2021

Severe COVID-19 May Be Fuelled by Disrupted Gut Barrier Integrity

By Denise Baez

NEW YORK -- March 16, 2021 -- There appears to be a link between loss of gut barrier integrity and coronavirus disease 2019 (COVID-19) severity, according to a study presented at the 2021 Virtual Conference on Retroviruses and Opportunistic Infections

Table. Studies of the Effect of Mask Wearing on SARS-CoV-2 Infection Risk[a]

Source	Location	Population studied	Intervention	Outcome
Hendrix et al	Hair salon in Springfield, Missouri	139 Patrons at a salon with 2 infected and symptomatic stylists	Universal mask wearing in salon (by local ordinance and company policy)	No COVID-19 infections among 67 patrons who were available for follow-up
Payne et al	USS Theodore Roosevelt, Guam	382 US Navy service members	Self-reported mask wearing	Mask wearing reduced risk of infection by 70% (unadjusted odds ratio, 0.30 [95% CI, 0.17-0.52])
Wang Y et al	Households in Beijing, China	124 Households of diagnosed cases comprising 335 people	Self-reported mask wearing by index cases or ≥1 household member prior to index case's diagnosis	Mask wearing reduced risk of secondary infection by 79% (adjusted odds ratio, 0.21 [95% CI, 0.06-0.79])
Doung-ngern et al	Bangkok, Thailand	839 Close contacts of 211 index cases	Self-reported mask wearing by contact at time of high-risk exposure to case	Always having used a mask reduced infection risk by 77% (adjusted odds ratio, 0.23 [95% CI, 0.09-0.60])
Gallaway et al	Arizona	State population	Mandatory mask wearing in public	Temporal association between institution of mask wearing policy and subsequent decline in new diagnoses
Rader et al	US	374 021 Persons who completed web-based surveys	Self-reported mask wearing in grocery stores and in the homes of family or friends	A 10% increase in mask wearing tripled the likelihood of stopping community transmission (adjusted odds ratio, 3.53 [95% CI, 2.03-6.43])
Wang X et al	Boston, Massachusetts	9850 Health care workers (HCWs)	Universal masking of HCWs and patients in the Mass General Brigham health care system	Estimated weekly decline in new diagnoses among HCWs of 3.4% after full implementation of the mask wearing policy
Mitze et al	Jena (Thuringia), Germany	City population aged ≥15 y	Mandatory mask wearing in public spaces (eg, public transport, shops)	Estimated daily decline in new diagnoses of 1.32% after implementation of the mask mandate
Van Dyke et al	Kansas	State population	Mandatory mask wearing in public spaces	Estimated case rate per 100 000 persons decreased by 0.08 in counties with mask mandates but increased by 0.11 in those without
Lyu and Wehby	15 US states and Washington, DC	State populations	Mandatory mask wearing in public	Estimated overall initial daily decline in new diagnoses of 0.9% grew to 2.0% at 21 days following mandates
Karaivanov et al	Canada	Country population	Mandatory mask wearing indoors	Estimated weekly 25%-40% decline in new diagnoses following mask mandates

SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan, China

- The infection rate of SARS-CoV-2 in patients with cancer from a single institution was estimated at 0.79% (12 of 1524 patients; 95% CI, 0.3%-1.2%)
- This was higher than the cumulative incidence of all diagnosed COVID-19 cases that was reported in the city of Wuhan over the same time period (0.37%; 41 152 of 11 081 000 cases; data cutoff on February 17, 2020)
- Older patients (>60 years) and patients with NSCLC may be at the highest risk of COVID-19[1]

- Heart disease is significantly associated with fatal outcome (1/4 death rate) of CoV-19
- Inflammation may be a potential mechanism for myocardial injury[2]

JAMA Oncology Published online March 25, 2020; Downloaded From: https://jamanetwork.com/ on 03/25/2020;
JAMA Cardiol. doi:10.1001/jamacardio.2020.1017 Published online March 27, 2020.

Cancer Therapy Advisor

Home » News » Conference Coverage » American Association for Cancer Research (AACR) » AACR 2020

May 6, 2020

High Mortality Rates in Patients With Thoracic Cancer and COVID-19

- Patients with non-small cell lung cancer (NSCLC) and other thoracic cancers who also had COVID- 19 demonstrated an unexpectedly high mortality rate and were often not offered intensive care.

Garassino MC. TERAVOLT (Thoracic cancERs international coVid 19 cOLlaboraTion): First results of a global collaboration to address the impact of COVID-19 in patients with thoracic malignancies.
Presented at: American Association for Cancer Research (AACR) Virtual Annual Meeting I 2020; April 27-28, 2020.

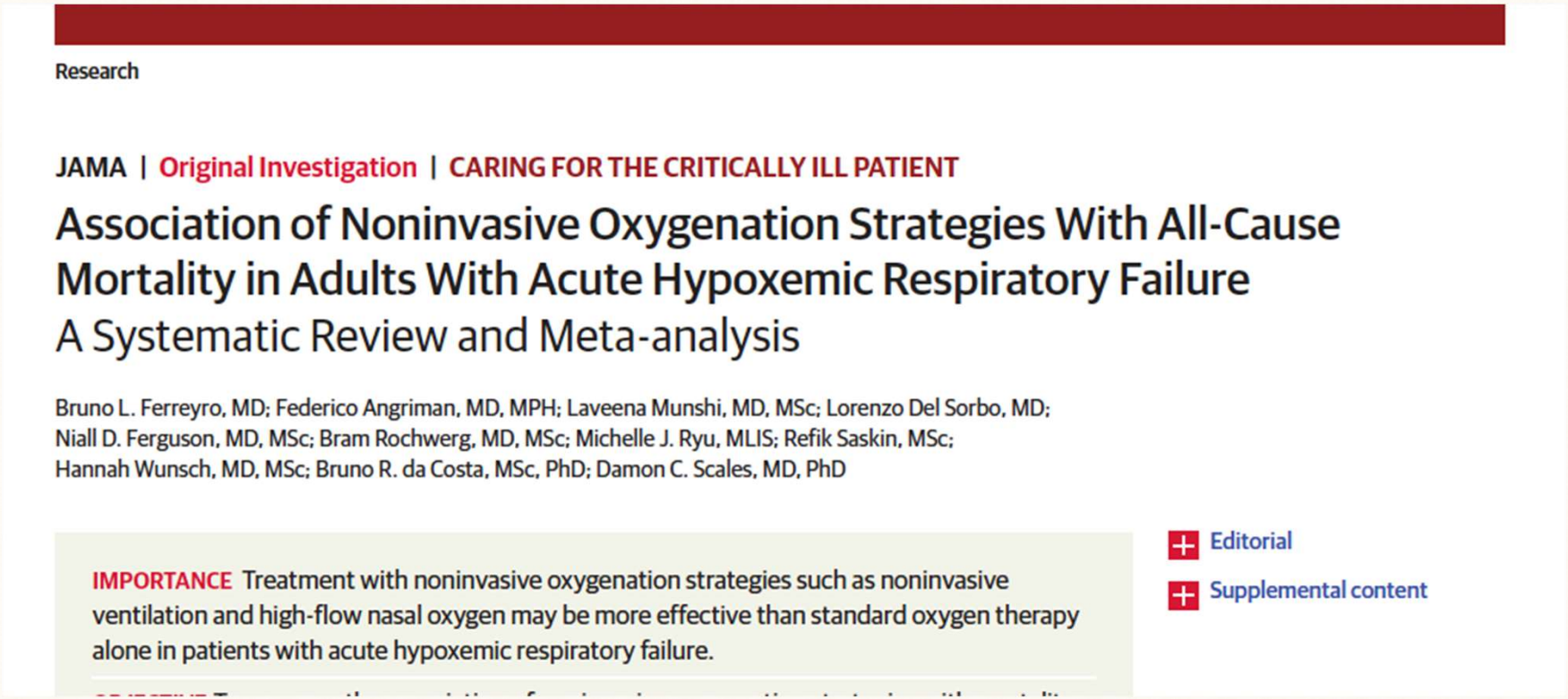
Secondary infections are reportedly common in hospitalized, severely ill COVID-19 patients, encompassing between ~10%-30% of cases with much greater frequency in the ICU setting.

- Patients with severe illness are much more likely (10x) to have bacterial/fungal secondary infections than viral (2x).
- ICU patients with prolonged illness/intubation have more frequent detection of multidrug-resistant Gram-negative pathogens, **likely reflecting hospital-acquired infection.**
- Coinfections in COVID-19, particularly with other seasonal respiratory viruses, are extremely common and are reflected in seropositivity rates of up to 80% and PCR positivity of ~20%; these do not appear to be above background levels of respiratory viral infections in non-COVID-19 patients presenting with respiratory symptoms.
- COVID-19 illness in children appears to be less severe, which may reflect underlying differences in immunology or biology; nevertheless, up to 6% of pediatric cases of COVID-19 may be severe/critical.

https://www.medpagetoday.com/infectiousdisease/covid19/86192?xid=nl_mpt_SRPrimaryCare_2020-04-29&eun=g1065123d0r&utm_source=Sailthru&utm_%E2%80%A6

Table. Excess, Coronavirus Disease 2019 (COVID-19)–Related, and Unintentional Opioid Overdose Deaths

HHS region	March-July 2020							March-July 2018	
	Expected deaths (95% CI), No.	Observed deaths, No.	Ratio of observed/ expected deaths (95% CI)	Excess deaths (95% CI), No.	COVID-19 deaths, No.	COVID-19 death rates per 100 000 person-months (95% CI)	Excess deaths attributed to COVID-19, %	Unintentional opioid overdose deaths, No.	Unintentional opioid overdose death rates per 100 000 person-months (95% CI)
US total	64 189 (61 822 to 66 556)	76 088	1.19 (1.14 to 1.23)	11 899 (9373 to 14 266)	4535	1.02 (0.99 to 1.06)	38	10 347	2.38 (2.33 to 2.43)
March	12 881 (11 952 to 13 855)	13 531	1.05 (0.98 to 1.13)	650 (−333 to 1579)	332	0.38 (0.34 to 0.42)	51	2119	2.44 (2.33 to 2.54)
April	12 602 (11 611 to 13 620)	15 106	1.20 (1.11 to 1.30)	2504 (1476 to 3495)	1539	1.74 (1.65 to 1.83)	61	1994	2.29 (2.19 to 2.40)
May	12 848 (11 786 to 13 895)	15 792	1.23 (1.14 to 1.34)	2944 (1883 to 4006)	848	0.96 (0.89 to 1.03)	29	2068	2.38 (2.28 to 2.48)
June	12 761 (11 671 to 13 851)	15 078	1.18 (1.09 to 1.29)	2317 (1190 to 3407)	604	0.68 (0.63 to 0.74)	26	2062	2.37 (2.27 to 2.48)
July	13 098 (11 897 to 14 234)	16 581	1.27 (1.16 to 1.39)	3483 (2258 to 4684)	1212	1.37 (1.29 to 1.45)	35	2104	2.42 (2.32 to 2.52)
Region 2	4128 (3879 to 4377)	6305	1.53 (1.44 to 1.63)	2177 (1928 to 2426)	1310	3.56 (3.37 to 3.76)	60	1229	3.23 (3.05 to 3.42)
March	825 (721 to 929)	1120	1.36 (1.21 to 1.55)	295 (191 to 399)	172	2.34 (2.00 to 2.71)	58	238	3.13 (2.74 to 3.55)
April	810 (702 to 918)	1867	2.30 (2.03 to 2.66)	1057 (949 to 1165)	842	11.44 (10.68 to 12.24)	80	218	2.87 (2.50 to 3.27)
May	826 (715 to 937)	1286	1.56 (1.37 to 1.80)	460 (349 to 571)	221	3.00 (2.62 to 3.42)	48	260	3.42 (3.02 to 3.86)
June	824 (709 to 938)	1033	1.25 (1.10 to 1.46)	209 (95 to 324)	56	0.76 (0.57 to 0.99)	27	250	3.29 (2.89 to 3.72)
July	843 (725 to 961)	999	1.18 (1.04 to 1.38)	156 (38 to 274)	19	0.26 (0.16 to 0.40)	12	263	3.46 (3.05 to 3.90)
Region 6	8504 (8127 to 8882)	10 408	1.22 (1.17 to 1.28)	1904 (1526 to 2281)	725	1.21 (1.12 to 1.30)	38	539	0.92 (0.85 to 1.00)
March	1711 (1546 to 1875)	1774	1.04 (0.95 to 1.15)	63 (−101 to 228)	31	0.26 (0.18 to 0.37)	49	101	0.86 (0.70 to 1.05)
April	1688 (1521 to 1854)	1932	1.14 (1.04 to 1.27)	244 (78 to 411)	118	0.98 (0.81 to 1.18)	48	105	0.90 (0.73 to 1.09)
May	1712 (1543 to 1880)	2072	1.21 (1.10 to 1.34)	360 (192 to 529)	74	0.62 (0.48 to 0.77)	21	124	1.06 (0.88 to 1.26)
June	1689 (1517 to 1860)	2132	1.26 (1.15 to 1.41)	443 (272 to 615)	122	1.01 (0.84 to 1.21)	28	107	0.91 (0.75 to 1.10)
July	1706 (1533 to 1880)	2498	1.46 (1.33 to 1.63)	792 (618 to 965)	380	3.16 (2.85 to 3.50)	48	102	0.87 (0.71 to 1.06)
Region 9	8351 (8054 to 8648)	10 094	1.21 (1.17 to 1.25)	1743 (1446 to 2040)	668	0.91 (0.84 to 0.99)	38	677	0.94 (0.87 to 1.01)
March	1643 (1515 to 1772)	1698	1.03 (0.96 to 1.12)	55 (−74 to 183)	28	0.19 (0.13 to 0.28)	51	141	0.98 (0.82 to 1.15)
April	1656 (1525 to 1787)	1764	1.07 (0.99 to 1.16)	108 (−23 to 239)	90	0.62 (0.49 to 0.76)	83	117	0.81 (0.67 to 0.97)
May	1660 (1528 to 1793)	2015	1.21 (1.12 to 1.32)	355 (222 to 487)	99	0.68 (0.55 to 0.82)	28	122	0.85 (0.70 to 1.01)
June	1667 (1532 to 1802)	2086	1.25 (1.16 to 1.36)	419 (284 to 554)	129	0.88 (0.74 to 1.05)	31	155	1.08 (0.91 to 1.26)
July	1725 (1588 to 1861)	2531	1.47 (1.36 to 1.59)	806 (670 to 943)	322	2.20 (1.97 to 2.46)	40	142	0.99 (0.83 to 1.16)



Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Association of Noninvasive Oxygenation Strategies With All-Cause Mortality in Adults With Acute Hypoxemic Respiratory Failure

A Systematic Review and Meta-analysis

Bruno L. Ferreyro, MD; Federico Angriman, MD, MPH; Laveena Munshi, MD, MSc; Lorenzo Del Sorbo, MD; Niall D. Ferguson, MD, MSc; Bram Rochwerg, MD, MSc; Michelle J. Ryu, MLIS; Refik Saskin, MSc; Hannah Wunsch, MD, MSc; Bruno R. da Costa, MSc, PhD; Damon C. Scales, MD, PhD

IMPORTANCE Treatment with noninvasive oxygenation strategies such as noninvasive ventilation and high-flow nasal oxygen may be more effective than standard oxygen therapy alone in patients with acute hypoxemic respiratory failure.

Editorial

Supplemental content

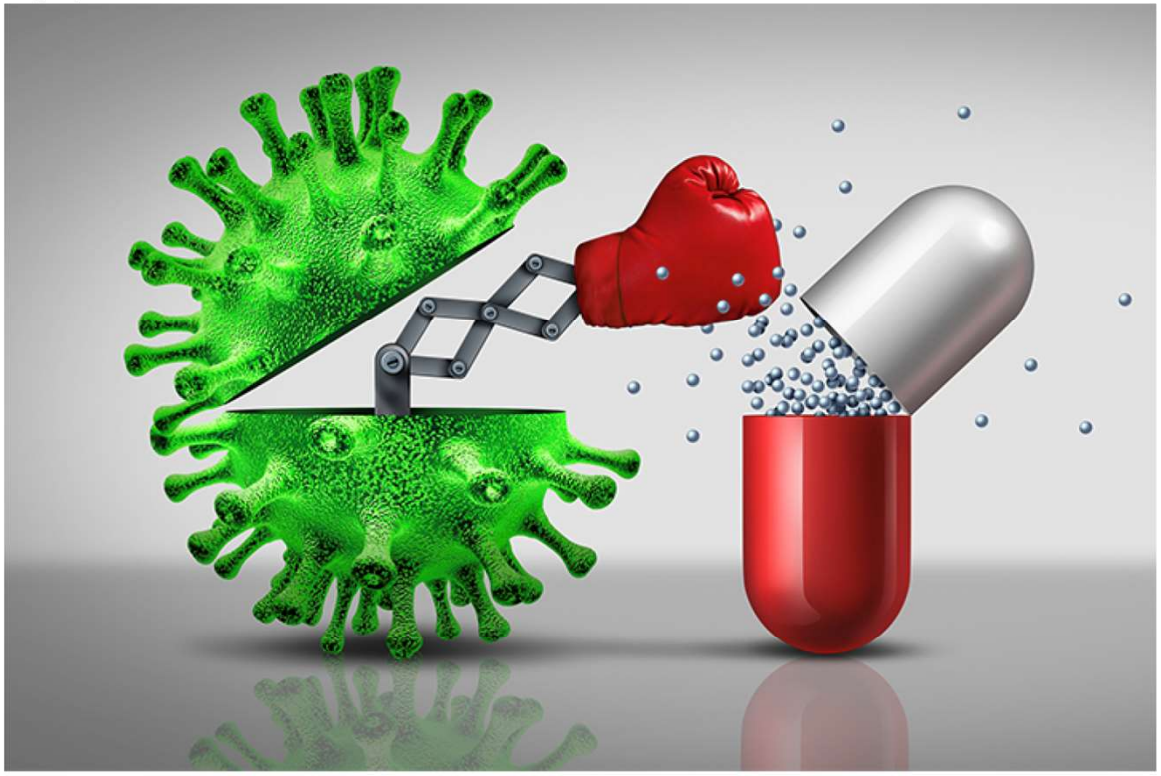
- In this network meta-analysis of trials of adult patients with acute hypoxemic respiratory failure, treatment with noninvasive oxygenation strategies compared with standard oxygen therapy was associated with lower risk of death.

MEDPAGE TODAY®

COVID-19 Antibiotic Overuse Puts Stewardship Efforts at Risk

— Researchers worry that copious prescriptions will worsen resistance problem

by Ryan Basen, Enterprise & Investigative Writer, MedPage Today
May 12, 2020



Many COVID-19 patients are getting antibiotics even when the drugs are unlikely to help, raising concerns about patient safety and antibiotic resistance, experts told *MedPage Today*.

MEDPAGE TODAY®

COVID-19 Risk 10-Fold Higher for Opioid Abusers

— Substance use disorders in general tied to higher coronavirus hospitalization rates

by Elizabeth Hlavinka, Staff Writer, MedPage Today
September 15, 2020

MEDPAGE TODAY®

CDC: Most Kids Dying From Coronavirus Had Underlying Conditions

— Enormous racial-ethnic disparities revealed as well

by Molly Walker, Associate Editor, MedPage Today
September 15, 2020

Journal of Thrombosis and Haemostasis / Accepted Articles

BRIEF REPORT

High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients

Jean-François Llitjos ✉, Maxime Leclerc, Camille Chochois, Jean-Michel Monsallier, Michel Ramakers, Malika Auvray, Karim Merouani

First published:22 April 2020
https://doi.org/10.1111/jth.14869

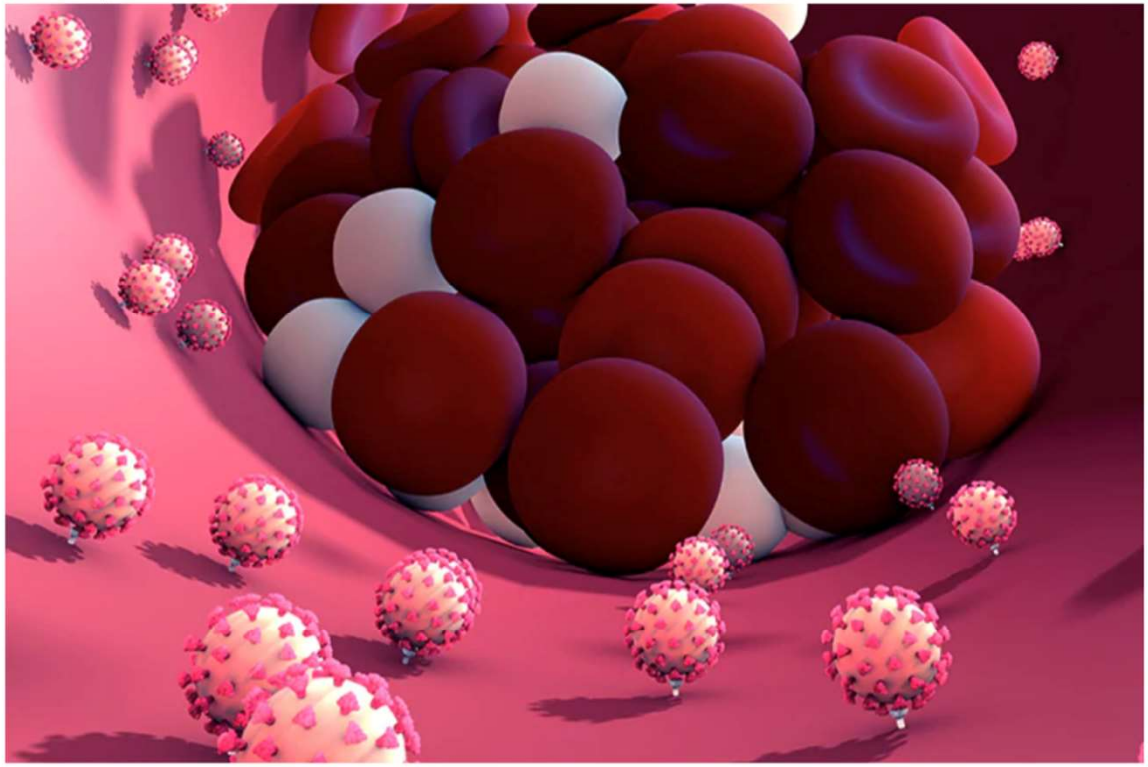
According to the clinical study the proportion of VTE was significantly higher in patients treated with prophylactic anticoagulation when compared to the other group (100% vs. 56%, respectively, p=0.03).
Surprisingly, found was a high rate of thromboembolic events in COVID-19 patients treated with therapeutic anticoagulation, with 56% of VTE and 6 pulmonary embolisms.

MEDPAGE TODAY®

Anticoagulation for Sickest COVID-19 Patients: Tread Carefully

— ASH recommendations on preventing blood clots in COVID-19

by Nicole Lou, Staff Writer, MedPage Today
October 8, 2020



COVID-19 patients without overt venous thromboembolism (VTE) should receive anticoagulation in the hospital but only at relatively low doses, according to American Society of Hematology (ASH) draft guidance.

Code Blue for COVID-19 Patients: No Survivors

— One group reports 100% mortality from IHCA during the pandemic

- Survival chances were bleak among COVID-19 patients who sustained in-hospital cardiac arrest (IHCA), U.S. data showed.
- After a median 8 minutes of CPR on 54 such patients, 53.7% had return of spontaneous circulation, according to Corey Mayer, DO, MBA, of William Beaumont Hospital in Royal Oak, Michigan, and colleagues reporting online in JAMA Internal Medicine.
- Roughly half of those patients had their code status changed to "do not resuscitate"; the other half were re-coded but died nonetheless after additional CPR.
- Ultimately, none of the 54 COVID-19 patients survived to discharge after IHCA.

Modes ME, et al "Outcomes of cardiopulmonary resuscitation in patients with COVID-19 -- limited data, but further reason for action" JAMA Intern Med 2020; DOI: 10.1001/jamainternmed.2020.4779.

THE LANCET

Log in



CORRESPONDENCE | ONLINE FIRST

Hyperinflammatory shock in children during COVID-19 pandemic

Shelley Riphagen • Xabier Gomez • Carmen Gonzalez-Martinez • Nick Wilkinson • Paraskevi Theocharis

Published: May 07, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)31094-1

- During a period of 10 days in mid-April, 2020, we noted an unprecedented cluster of eight children with hyperinflammatory shock, showing features similar to atypical Kawasaki disease, Kawasaki disease shock syndrome,

CDC Details COVID-19's Massive Mental Health Impact

- Among 5,470 people surveyed in the last week of June, 30.9% reported symptoms of an anxiety or a depressive disorder, 25.3% reported a traumatic or stressor-related disorder (TSRD), and 13.3% said they were using substances to cope with the pandemic's stressors
- Specifically, the risk for suicidal ideation was elevated among respondents between ages 18 and 25 (25.5%), Hispanic respondents (18.6%), Black respondents (15.1%), unpaid adult caregivers (30.7%), and essential workers (21.7%).

NSAIDs and Aspirin (and I believe Tylenol as well) Associated with Worse Outcome

- By artificially lowering fever with NSAIDs, Tylenol or aspirin, infection can multiply and spread to internal organs
- From the 1950s to the 1980s, thousands of deaths among children following influenza and other infections (e.g., Reye syndrome) were unexplained until studies identified aspirin as the major contributor
- NSAID inhibit cyclo-oxygenase 1 and 2, which are essential for the production of the interferon response to viral infection, the primary defense against infection

Starko KM, Ray GC, Dominguez LB, Stromberg WL, Woodall DF., Reye's syndrome and salicylate use. Pediatrics 1980;66:859-64.
Waldman RJ, Hall WN, McGee H, Van Amburg G. Aspirin as a risk factor in Reye's syndrome. JAMA 1982;247:3089-94.
Halpin TJ, Holtzhauer FJ, Campbell RJ, et al. Reye's syndrome and medication use. JAMA 1982;248:687-91.
Pottathil R, Chandrabose KA, Cuatrecasas P, Lang DJ. Establishment of the interferon-mediated antiviral state: role of fatty acid cyclooxygenase. Proc Natl Acad Sci U S A. 1980 Sep;77(9):5437-40.

NIH Public Access
Author Manuscript
Cell Immunol. Author manuscript; available in PMC 2010 January 1.

Published in final edited form as:
Cell Immunol. 2009 ; 258(1): 18–28. doi:10.1016/j.cellimm.2009.03.007.

Ibuprofen and other widely used non-steroidal anti-inflammatory drugs inhibit antibody production in human cells

Simona Bancos[1], **Matthew P. Bernard**[1], **David J. Topham**[2], and **Richard P. Phipps**[1,*]

NIH-PA Author Manus

- Patients with MERS-CoV or influenza who were given corticosteroids were more likely to have prolonged viral replication, receive mechanical ventilation, and have higher mortality[1-5]

1.Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. *Lancet (London, England).* 2015;386(9997):995-1007.
2.Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. *American journal of respiratory and critical care medicine.* 2018;197(6):757-767.
3.Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet (London, England).* 2020;395(10223):473-475.
4.Corman VM, Albarrak AM, Omrani AS, et al. Viral Shedding and Antibody Response in 37 Patients With Middle East Respiratory Syndrome Coronavirus Infection. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2016;62(4):477-483.
5.Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam JS, Lim WS. Effect of corticosteroid therapy on influenza-related mortality: a systematic review and meta-analysis. *The Journal of infectious diseases.* 2015;212(2):183-194.

Dexamethasone Improves COVID-19 Survival in Trial

- Deaths in the dexamethasone arm were reduced by one-third (RR 0.65, 95% CI 0.48-0.88, P=0.0003) among patients receiving mechanical ventilation, and by one-fifth (RR 0.80, 95% CI 0.67-0.96, P=0.0021) among patients requiring oxygen versus patients receiving usual care.
- But dexamethasone showed no benefit among patients who did not require respiratory support (RR 1.22, 95% CI 0.86-1.75).
- In the trial thus far, 2,104 patients were randomized to receive 6 mg of dex via IV injection for 10 days compared to 4,321 patients receiving usual care.
- Among the usual care group, 28-day mortality was highest (41%) among patients
- requiring mechanical ventilation; mortality was 25% in those who required oxygen only and 13% among those not requiring any respiratory support.
- The investigators estimated that treating 8 ventilated patients or 25 requiring supplemental oxygen would prevent one death.

https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_v2final.pdf, retrieved June 16th, 2020



- 52 clinical trials of over 80,000 people assessed the safety and effectiveness of flu vaccines.
- Findings from 25 studies comparing inactivated parenteral influenza vaccine against placebo or do-nothing control groups as the most relevant to decision-making.
- Healthy adults who receive inactivated parenteral influenza vaccine rather than no vaccine probably experience less influenza, from just over 2% to just under 1%
- There was no difference in days missing from work between the two groups.

Demicheli V, Jeerson T, Ferroni E, Rivetti A, Di Pietrantonj C. Cochrane Database of Systematic Reviews 2018, Issue 2. Art. No.: CD001269. DOI: 10.1002/14651858.CD001269.pub6.

Vaccine 38 (2020) 350–354

Contents lists available at ScienceDirect

Vaccine

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

Influenza vaccination and respiratory virus interference among Department of Defense personnel during the 2017–2018 influenza season

Greg G. Wolff

Armed Forces Health Surveillance Branch Air Force Satellite, 2510 5th Street, Bldg 840, Wright-Patterson AFB, OH 45433, United States

"Receiving influenza vaccination may increase the risk of other respiratory viruses by 36%, a phenomenon known as virus interference."

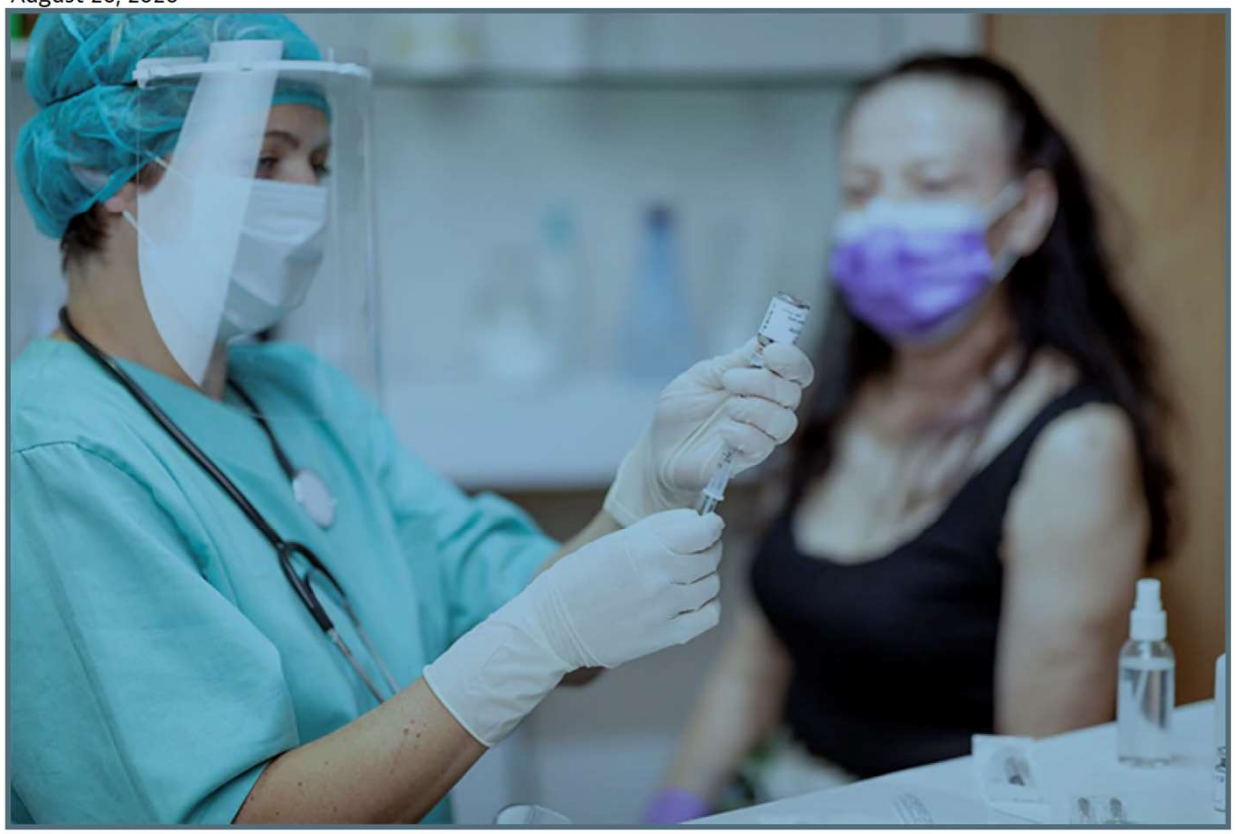
Why is this? You therefore didn't have the innate immune response against the flu that might protect you against other respiratory viruses for a few weeks.

MEDPAGE TODAY®

CDC: COVID-19 Patients Should Delay Flu Shot

— But vaccine especially important for high-risk patients this year, agency says

by Molly Walker, Associate Editor, MedPage Today
August 20, 2020



COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study

Lennard Y W Lee, Jean Baptiste Cazier*, T Starkey, C D Turnbull, UK Coronavirus Cancer Monitoring Project Team, Rachel Kerr†, Gary Middleton†*

Cancer patients with coronavirus disease 2019 (COVID-19) has concluded that recent chemotherapy use is not a significant contributor to more severe disease or a predictor of death from COVID-19.
Moreover, there were similar observations for immunotherapy, hormonal therapy, targeted therapy and radiotherapy.

Published Online May 28, 2020 https://doi.org/10.1016/S0140-6736(20)31173-9

JAMA Network Open

Original Investigation | Cardiology

Association of Azithromycin Use With Cardiovascular Mortality

Jonathan G. Zaroff, MD; T. Craig Cheetham, PharmD; Niki Palmetto, PhD; Lucy Almers, MPH; Charles Quesenberry, PhD; Jennifer Schneider, MPH; Nicolle Gatto, PhD; Douglas A. Corley, MD, PhD

Abstract

IMPORTANCE Azithromycin is one of the most commonly prescribed antibiotics in the US. It has been associated with an increased risk of cardiovascular death in some observational studies.

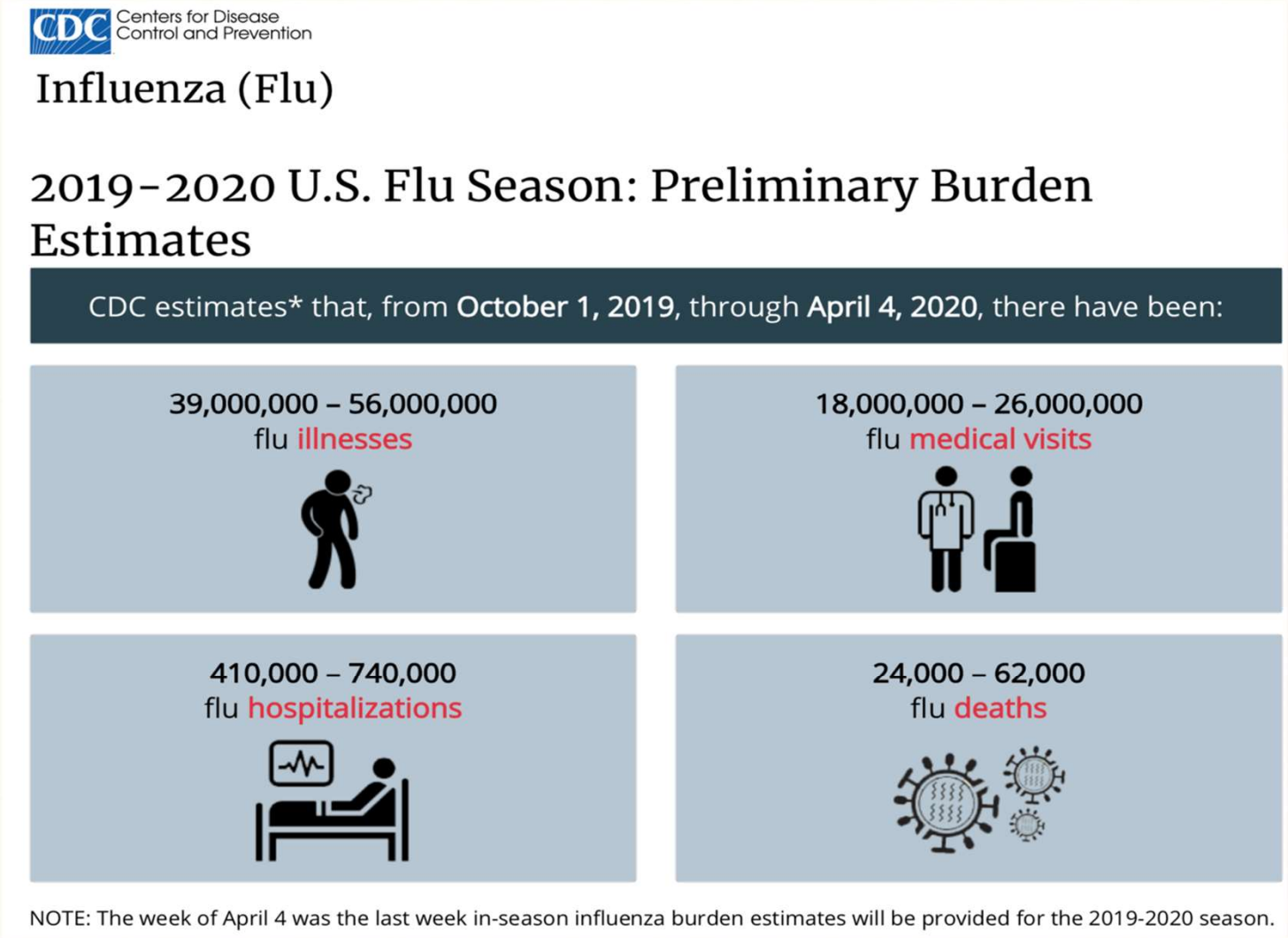
OBJECTIVE To estimate the relative and absolute risks of cardiovascular and sudden cardiac death after an outpatient azithromycin prescription compared with amoxicillin, an antibiotic not known to increase cardiovascular events.

Key Points

Question Is use of azithromycin in an outpaitent setting associated with an increased short-term risk of cardiovascular death and sudden cardiac death in a diverse, community-based population?

- These findings suggest that outpatient azithromycin use was associated with an increased risk of cardiovascular death and noncardiovascular death
- Causality cannot be established, particularly for noncardiovascular death, owing to the likelihood of residual confounding. JAMA Network Open. 2020;3(6):e208199. doi:10.1001/jamanetworkopen.2020.8199
- These findings suggest that prescribers should be aware of the potential association between azithromycin and cardiovascular death

Assessment of Deaths From COVID-19 and From Seasonal Influenza



Faust JS, del Rio C. Assessment of Deaths From COVID-19 and From Seasonal Influenza. *JAMA Intern Med.* Published online May 14, 2020.

ANNUAL REVIEWS

Annual Review of Virology

Seasonality of Respiratory Viral Infections

Miyu Moriyama,[1] Walter J. Hugentobler,[2] and Akiko Iwasaki[1,3,4]

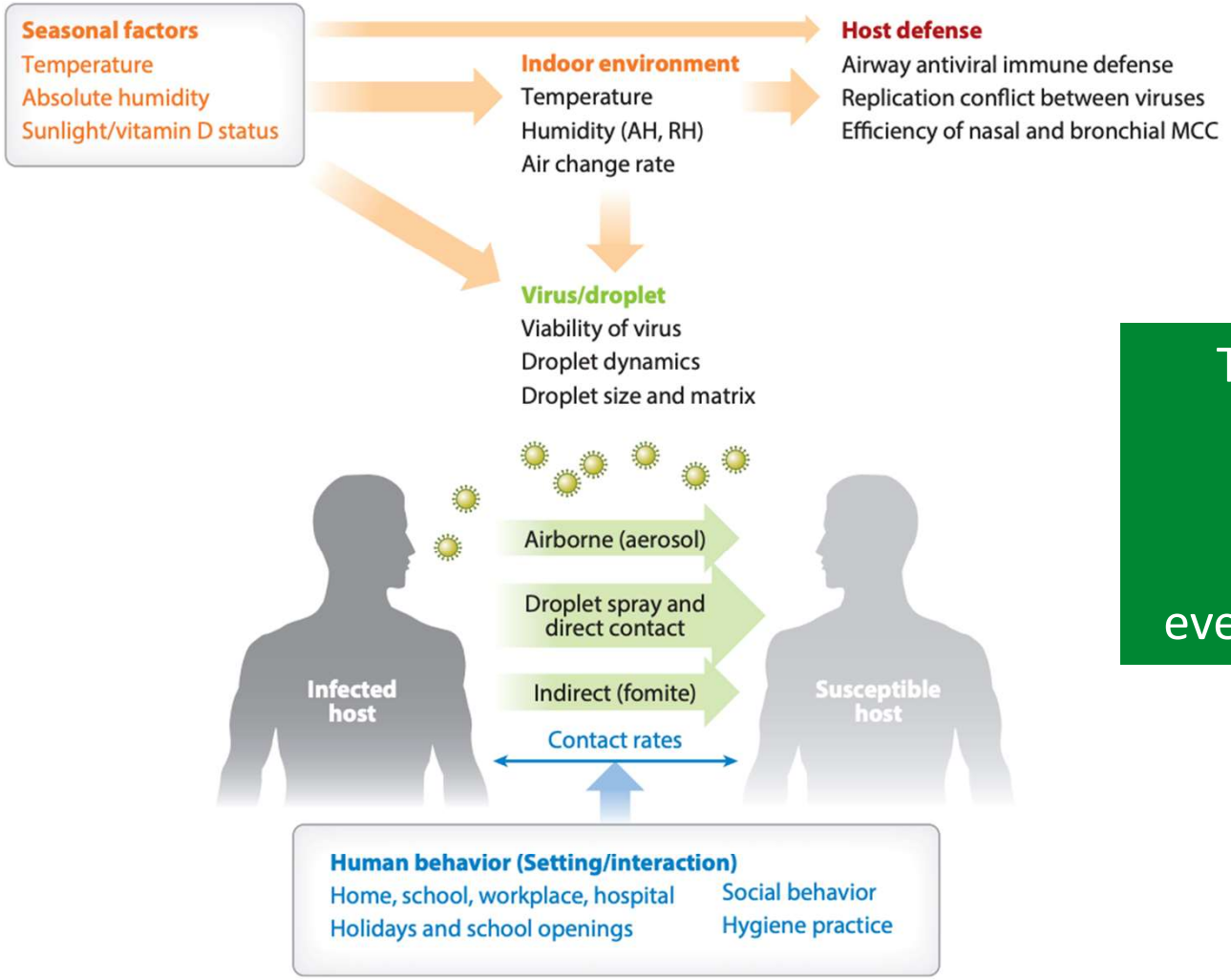
[1]Department of Immunobiology, Yale University School of Medicine, New Haven, Connecticut 06520, USA; email: akiko.iwasaki@yale.edu

[2]Institute of Primary Care, University of Zurich and University Hospital, Zurich, Switzerland CH-8091

[3]Department of Molecular, Cellular, and Developmental Biology, Yale University, New Haven, Connecticut 06512, USA

[4]Howard Hughes Medical Institute, Chevy Chase, Maryland 20815, USA

- Recent research highlights the importance of the environmental factors, especially temperature and humidity, in modulating host intrinsic, innate, and adaptive immune responses to viral infections in the respiratory tract.



The overwhelming majority of person-to-person transmission events happen indoors.

Figure 1

Factors that affect respiratory virus transmission. Seasonal environmental factors modulate host airway immune responses and affect viability and transmission ways of respiratory viruses. Human behavior affects the contact rates between infected and susceptible individuals. Abbreviations: AH, absolute humidity; MCC, mucociliary clearance; RH, relative humidity.

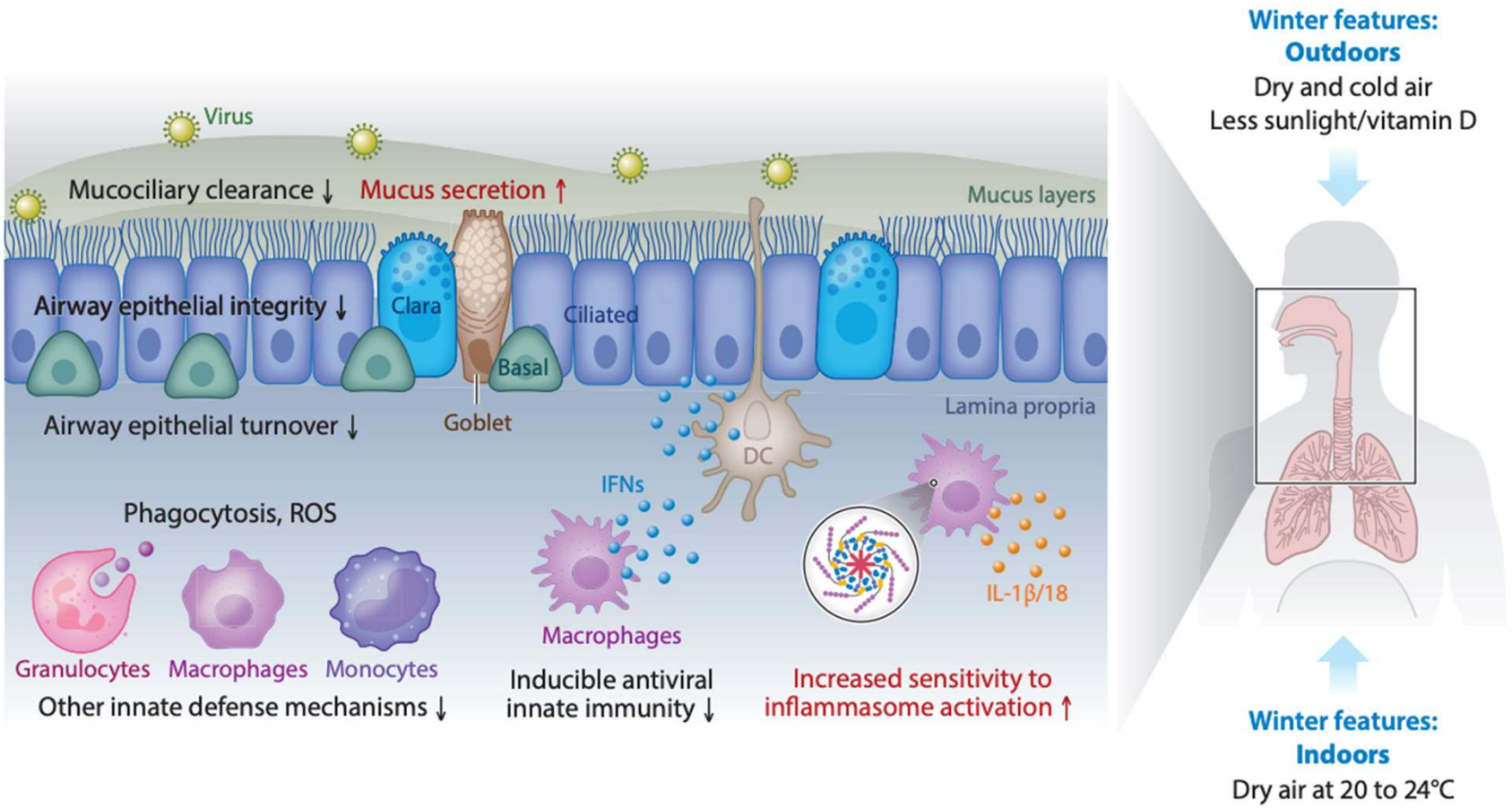


Figure 5

Possible mechanisms of increased host susceptibility to respiratory virus infections in winter. Inhalation of cold dry air directly affects the upper airway mucosa, impairs mucociliary clearance, and increases mucin production. In addition, inhalation of dry air per se causes epithelial damage. A short daylight period and consequent deficiency of vitamin D impair direct pathogen clearance. Cold and dry air impairs local antiviral innate immune responses after viral infection. Abbreviations: DC, dendritic cell; IFN, interferon; ROS, reactive oxygen species.

DOI: 10.1111/apt.15777

INVITED EDITORIAL

AP&T Alimentary Pharmacology & Therapeutics WILEY

Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees North supports vitamin D as a factor determining severity

- There are marked variations in mortality from COVID-19 between different countries. It is becoming clear that countries in the Southern Hemisphere are seeing a relatively low mortality.

Aliment Pharmacol Ther. 2020;00:1–4.

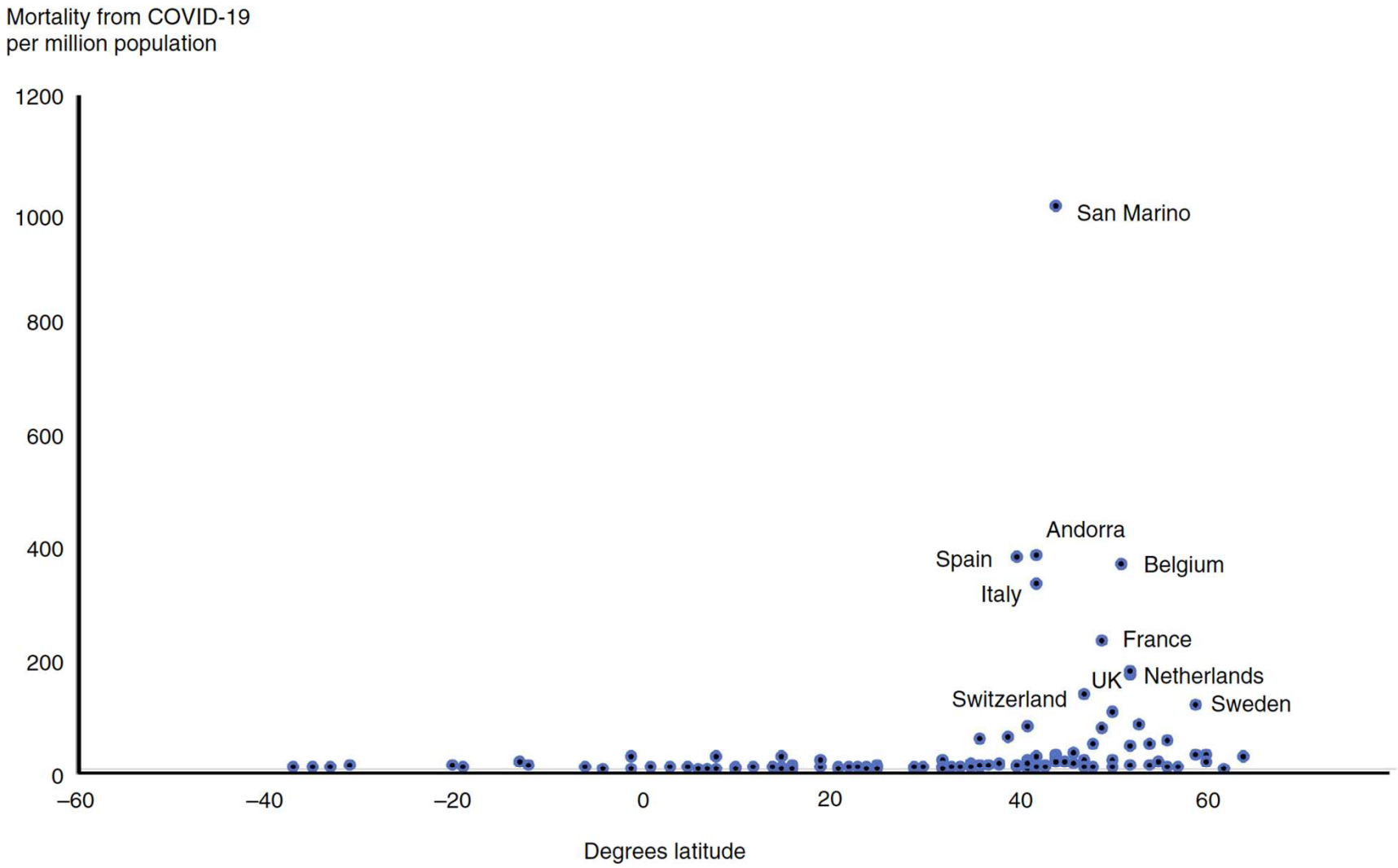
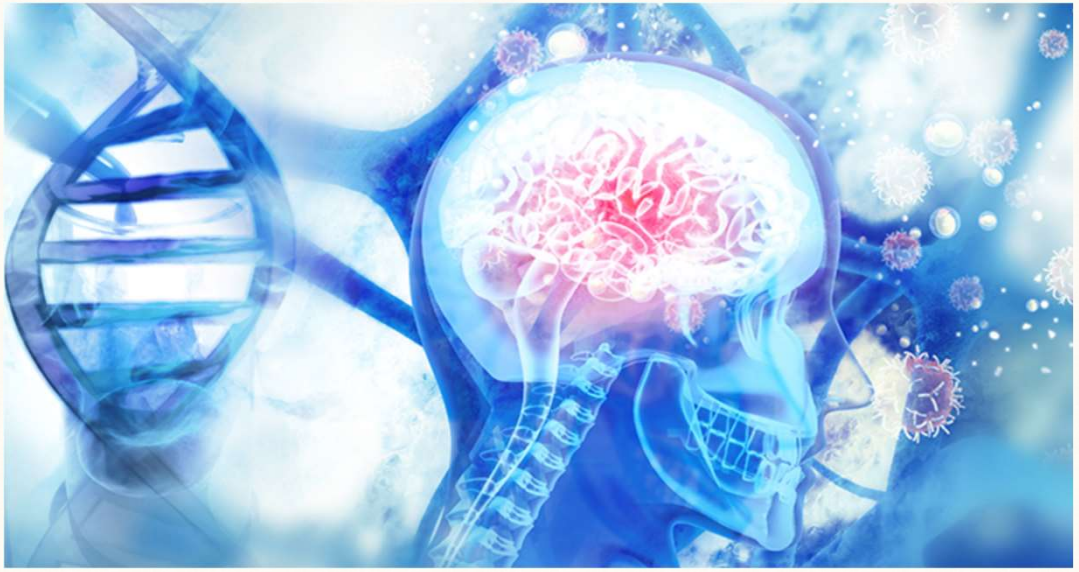


FIGURE 1 Correlation between mortality from COVID-19 per million by country and latitude. All countries with >150 cases included. Data are from https://www.worldometers.info/coronavirus/[3] accessed 15th April 2020. Latitude is for capital city. It can be seen that mortality is relatively low at latitudes less than 35 degrees North, the point below which adequate sunlight is likely to have been received to maintain vitamin D levels during the winter. Correlation between mortality and latitude $r = 0.53$, $P < 0.0001$ by Spearman's rank correlation

Aliment Pharmacol Ther. 2020;00:1–4.

Is Alzheimer's Gene Tied to Higher COVID Risk?



- Britons who had two copies of the APOE4 allele -- the most prevalent genetic risk factor for Alzheimer's disease -- were at markedly higher risk of testing positive for the COVID- 19 coronavirus

Kuo C-L, et al "APOE e4 genotype predicts severe COVID-19 in the U.K. Biobank community cohort" J Gerontol: Medical Sciences 2020; DOI: 10.1093/gerona/glaa131.

MEDPAGE TODAY®

Low Testosterone Could Be Bad News in COVID-19

— In small study, men with low levels were more likely to have severe illness

by Kristen Monaco, Staff Writer, MedPage Today
May 25, 2021

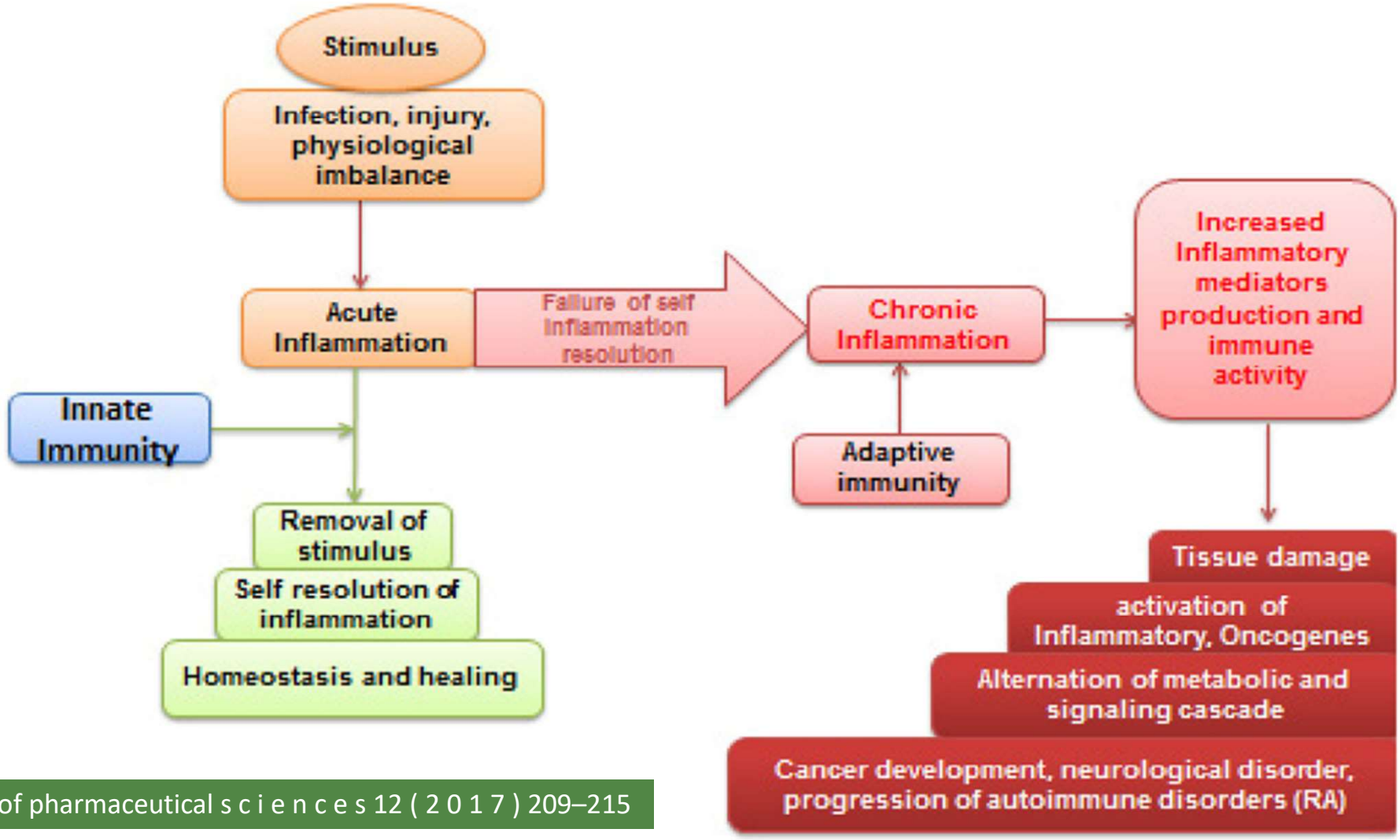
Testosterone levels may be indicative of COVID-19 severity, according to a new study.

In a small, single-center analysis, men with lower testosterone levels were more likely to have a severe case of COVID-19 compared with those with higher levels, Sandeep Dhindsa, MD, of St. Louis University School of Medicine in Missouri, and colleagues reported in *JAMA Network Open*.

The New Coronavirus COVID-19 (Co-19)

- Causes pneumonia and multi-organ failure and has killed many people around the world, and most likely will continue for weeks upon months
- Good news is once you make the antibodies you are immune to it, unless it mutates, which could happen in the fall
- Therefore, our approach and motto is the same as the great Eclectic physicians and that is to "**Sustain the Life force!**" first and foremost and to "**do no harm**"
- Botanical Medicine is the medicine that first and foremost "nourishes the root system" of health, and enhances Robustness, Auto-regulation, and Auto-organization
- Which in turns provides our innate ability to "be aware," "recognize," "respond" and "recover"

When inflammation Is Important and Called upon



Asian journal of pharmaceutical s c i e n c e s 12 (2 0 1 7) 209–215

THE FASEB JOURNAL • RESEARCH • www.fasebj.org

Severe acute respiratory syndrome coronavirus ORF3a protein activates the NLRP3 inflammasome by promoting TRAF3-dependent ubiquitination of ASC

Kam-Leung Siu,* Kit-San Yuen,* Carlos Castaño-Rodriguez,† Zi-Wei Ye,‡ Man-Lung Yeung,‡ Sin-Yee Fung,* Shuofeng Yuan,‡ Chi-Ping Chan,* Kwok-Yung Yuen,‡ Luis Enjuanes,†,1 and Dong-Yan Jin*,2

*School of Biomedical Sciences and ‡Department of Microbiology, The University of Hong Kong, Pokfulam, Hong Kong; and †Department of Molecular and Cell Biology, Centro Nacional de Biotecnología-Consejo Superior de Investigaciones Científicas (CNB-CSIC), Madrid, Spain

Inflammasome activation exerts a weak suppressive effect on SARS-CoV replication

FASEB J. 33, 8865– 8877 (2019). www.fasebj.org

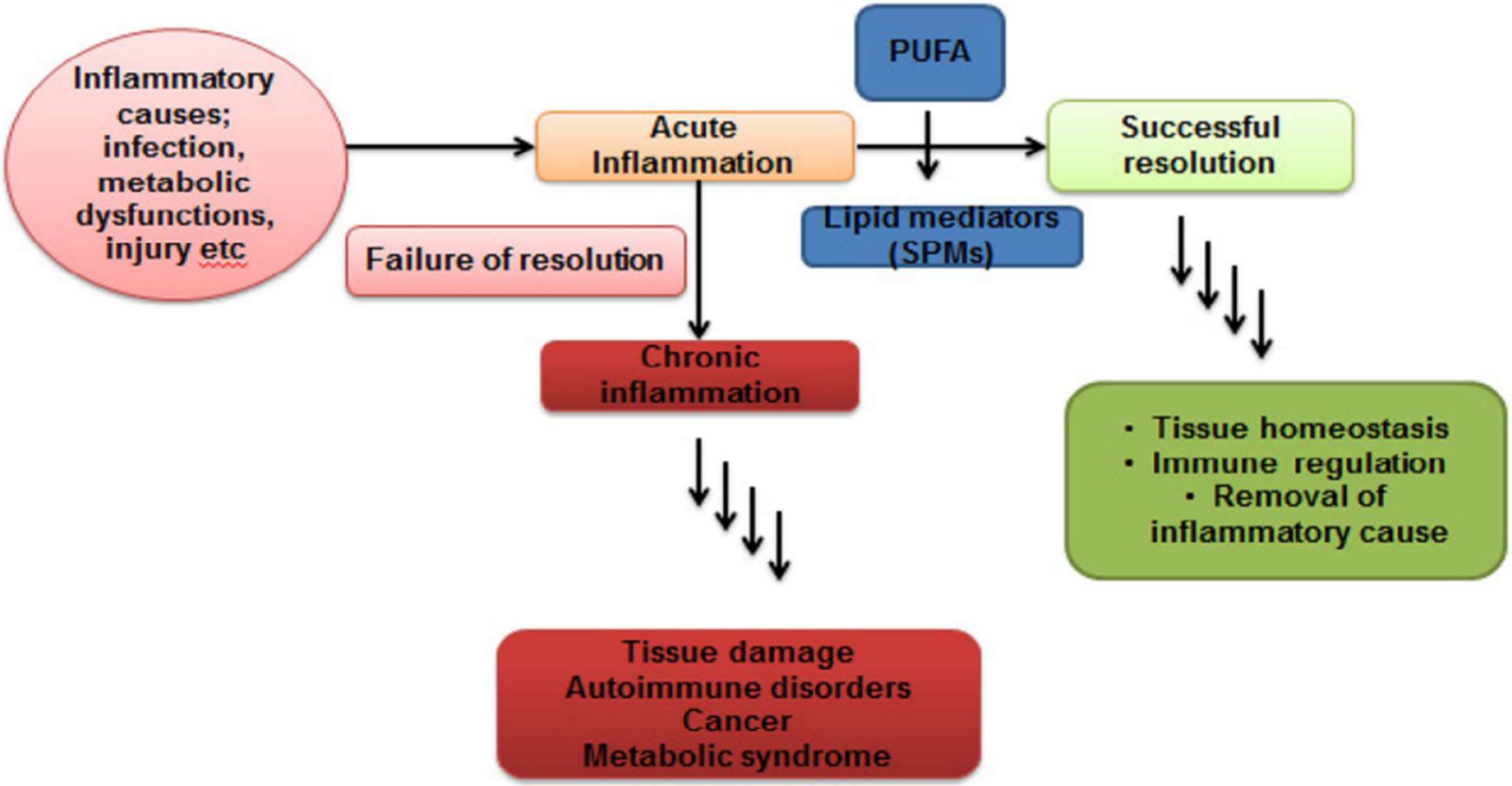
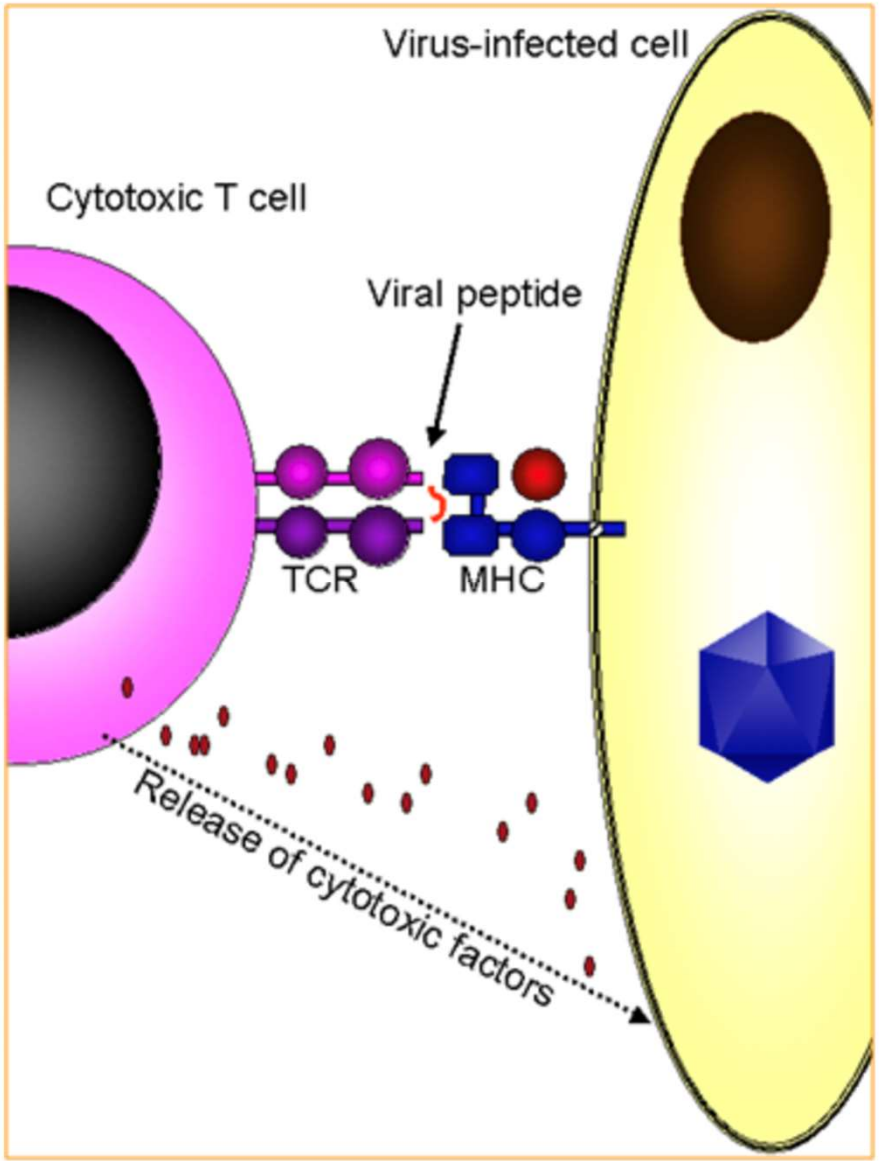


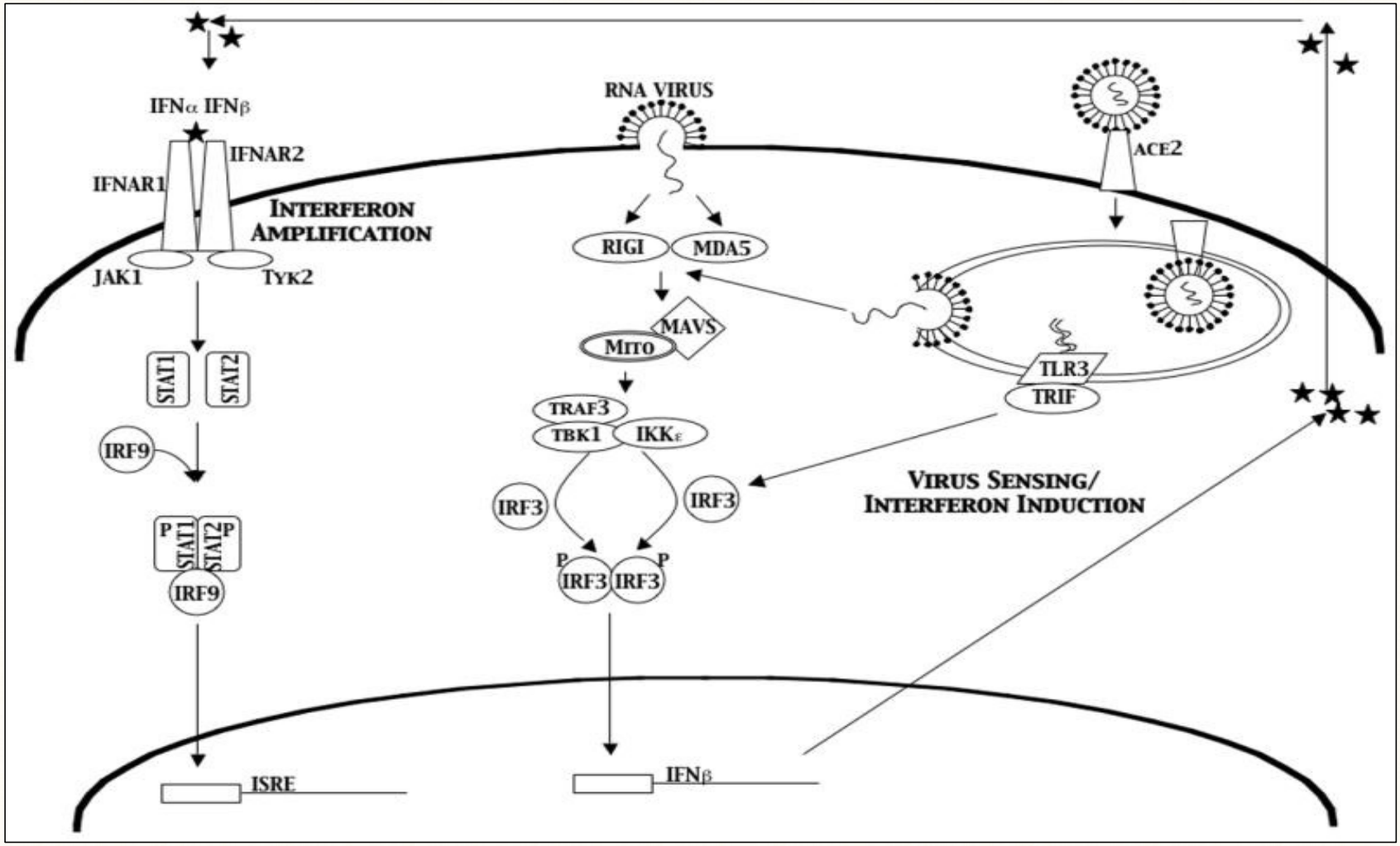
Fig. 3 – Scheme of resolution of inflammation: causes, acute and chronic inflammation.

- Viral interactions with the first line of defense "innate" immune system play a central role in determining the outcome of infection
- Early control of viral replication by **type I Interferons**, complement proteins, and other innate immune mediators limit viral spread within the host during the early phases of the disease
- Viruses are highly adaptable, and have developed ways to avoid detection by T cells
- Some viruses stop MHC molecules from getting to the cell surface to display viral peptides.
- If this happens, the T cell doesn't know

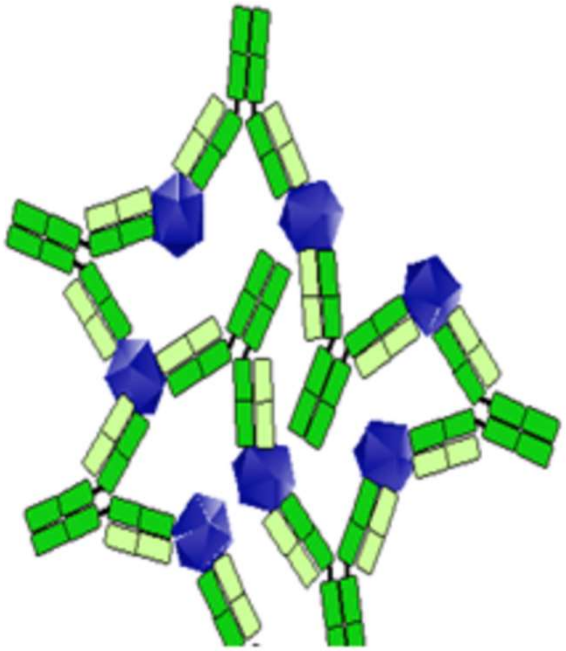


Matthew Frieman,1,* Mark Heise,2,3,4 and Ralph Baric. SARS CORONAVIRUS AND INNATE IMMUNITY, Virus Res. 2008 Apr; 133(1): 101–112. Published online 2007 Apr 23. doi: 10.1016/j.virusres.2007.03.015

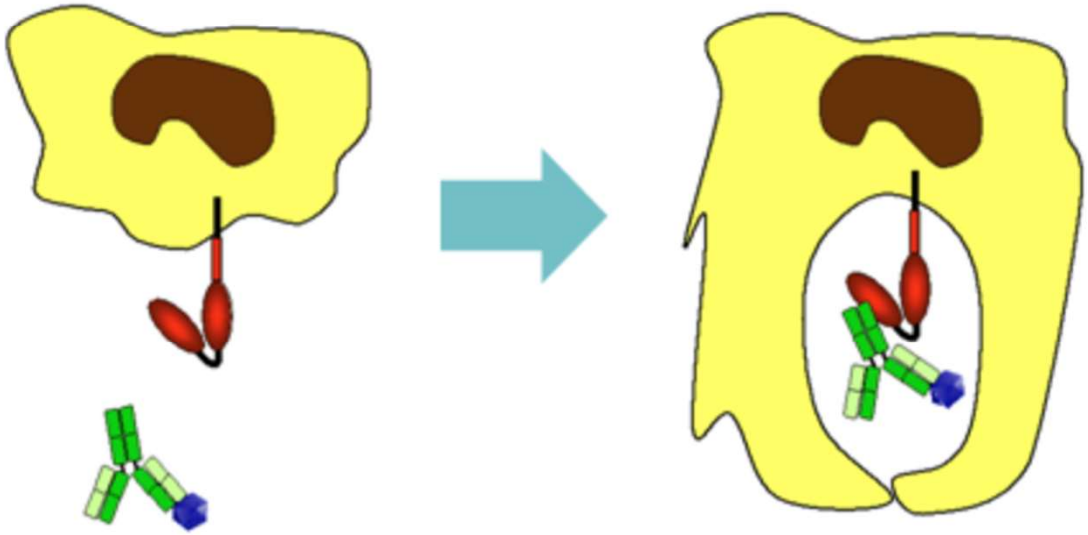
IFN Sensing and Signaling Pathway



Annu Rev Immunol. 2006; 24():705-38



Agglutination of virus particles by antibodies



Antibody mediated triggering of phagocytosis

Semin Immunopathol. 2016; 38(4): 471–482.

Acute tissue inflammation is characterized

- By specific cellular events, including increased endothelial and epithelial permeability, infiltration of polymorphonuclear leukocytes (PMNs) and inflammatory macrophages and lymphocytes.
- As the tissue resolves, barrier integrity is reestablished and further infiltration of PMNs is blocked.
- Cell clearance from the inflamed tissue is critical to resolution and is driven both by apoptosis of leukocytes.

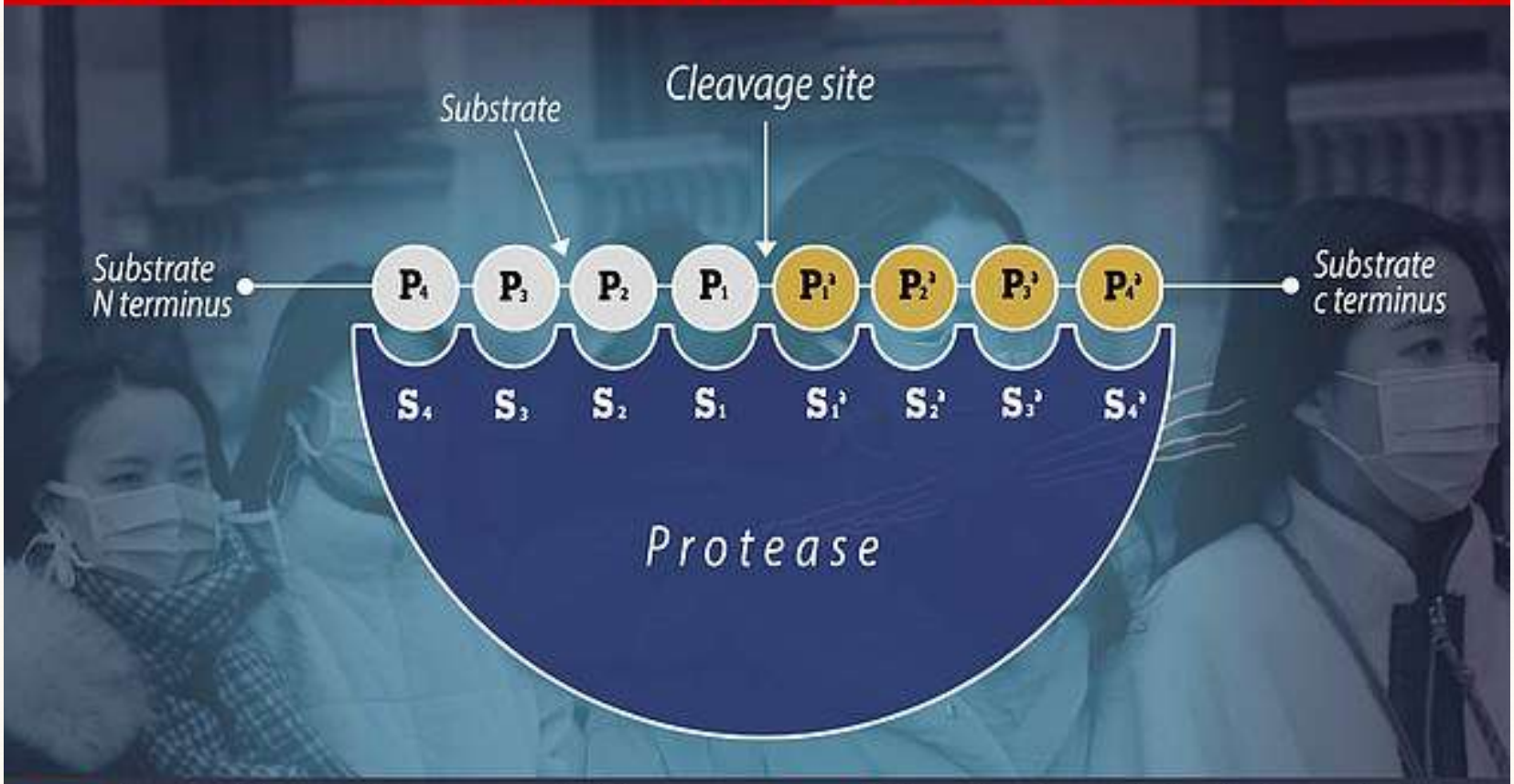
Haslett C. Resolution of acute inflammation and the role of apoptosis in the tissue fate of granulocytes. Clin Sci (Lond) 1992;83:639–48.
Rossi AG, Sawatzky DA, Walker A, et al. Cyclin-dependent kinase inhibitors enhance the Savill JS, Wyllie AH, Henson JE, Walport MJ, Henson PM, Haslett C. Macrophage phagocytosis of aging neutrophils in inflammation. Programmed cell death in the neutrophil leads to its recognition by macrophages. J Clin Invest. 1989;83:865–75. resolution of inflammation by promoting inflammatory cell apoptosis. Nat Med. 2006;12:1056–64.

Humoral and cellular immunity

- Antigen presentation subsequently stimulates the body's humoral and cellular immunity, which are mediated by virus-specific B and T cells.
- Similar to common acute viral infections, the antibody profile against SARS-CoV virus has a typical pattern of IgM and IgG production.
- The SARS-specific IgM antibodies disappear at the end of week 12, while the IgG antibody can last for a long time, which indicates IgG antibody may mainly play a protective role, and the SARS-specific IgG antibodies primarily are S-specific and N-specific antibodies.

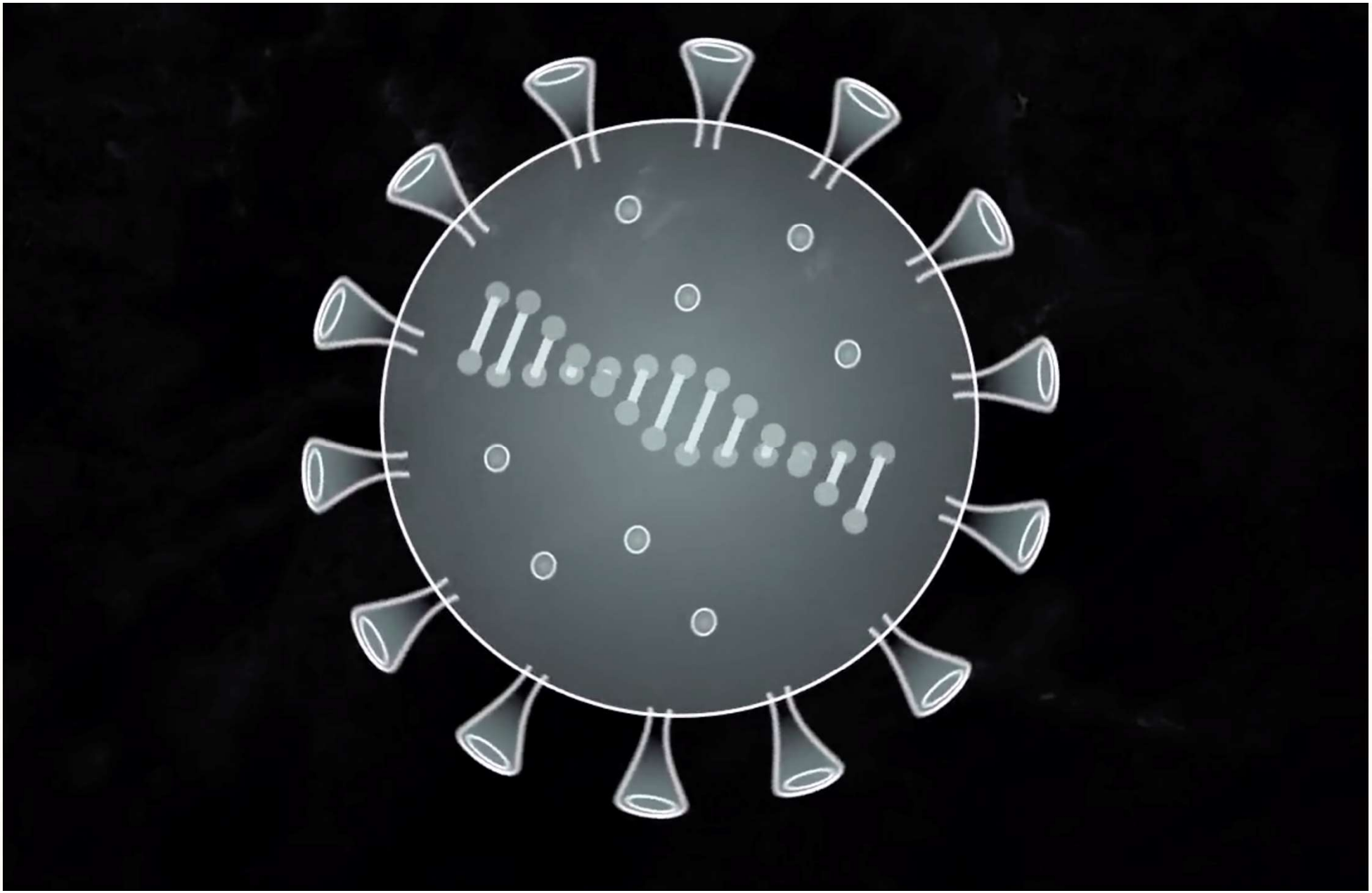
X. Li et al., Molecular immune pathogenesis and diagnosis of COVID-19, Journal of Pharmaceutical Analysis, https://doi.org/10.1016/j.jpha.2020.03.001

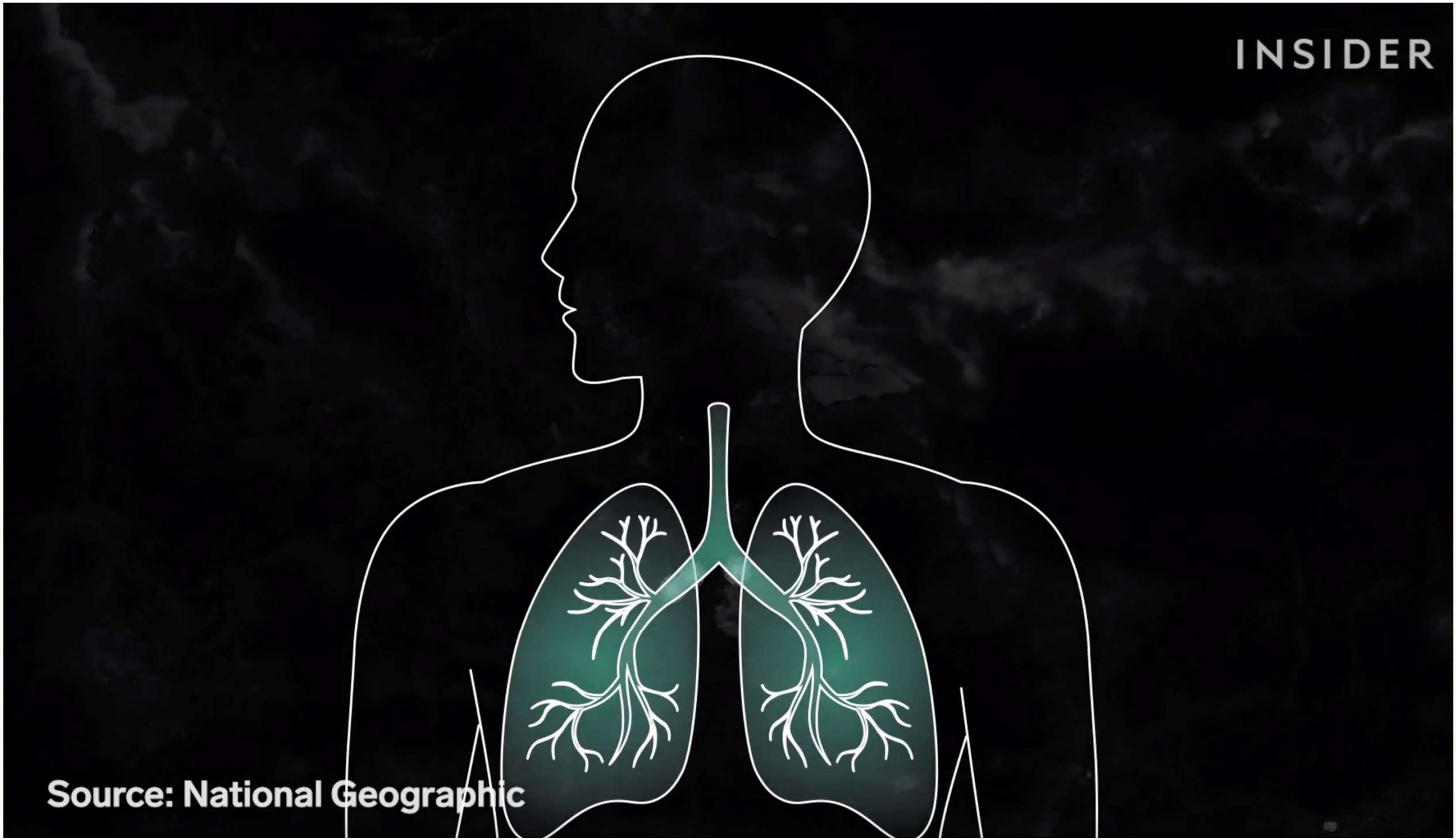
HOW DOES CORONAVIRUS LATCH ON TO HUMAN CELLS?

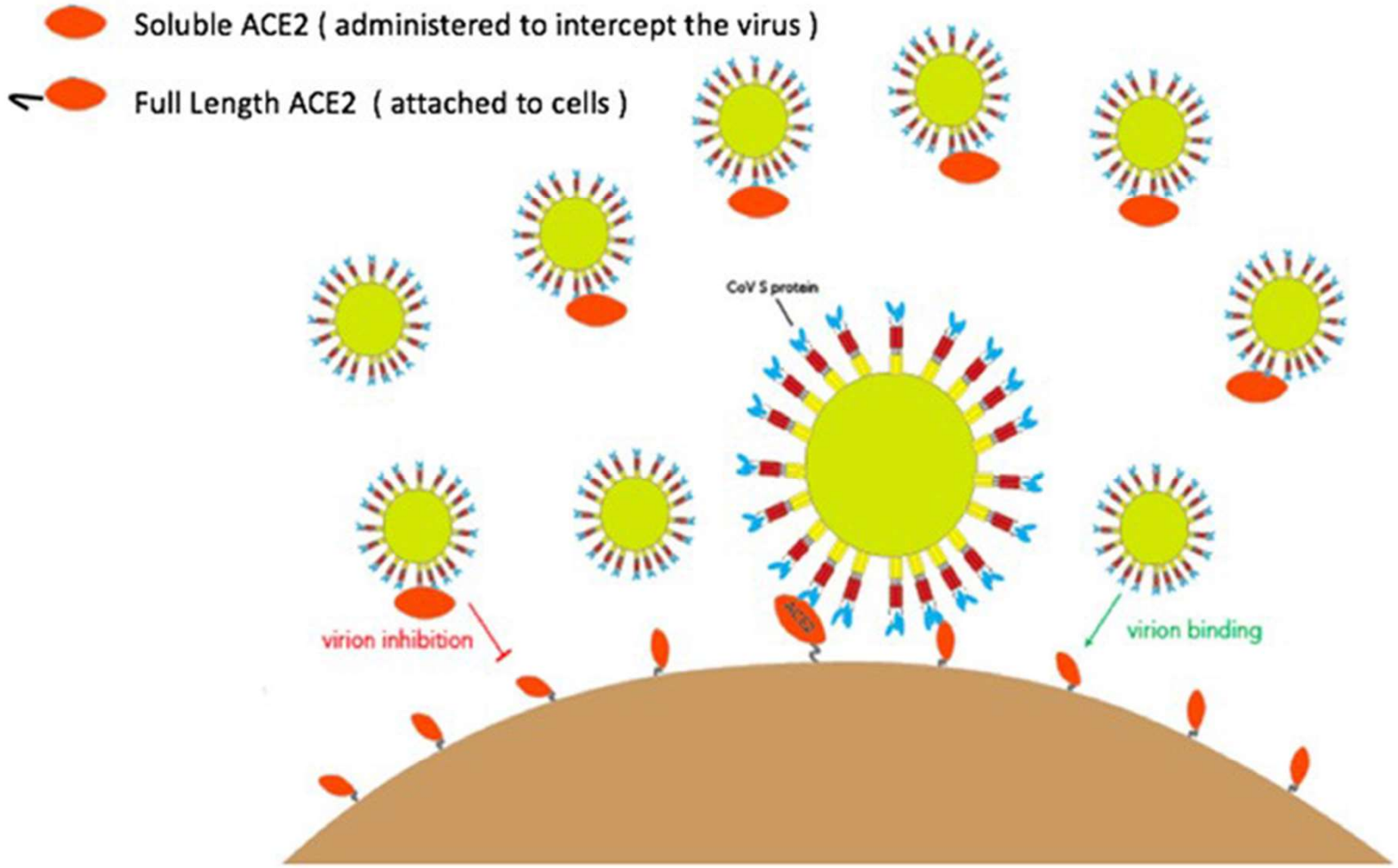


1. Coronavirus has 'cleavage sites' similar to those in HIV and Ebola
2. These sites carry viral proteins that are dormant and have to be 'cut' to be activated
3. When it enters the body through the nose, mouth or eyes, it targets an enzyme called furin
4. It tricks furin so it activates the protein and causes a 'direct fusion' between the virus and the human cells

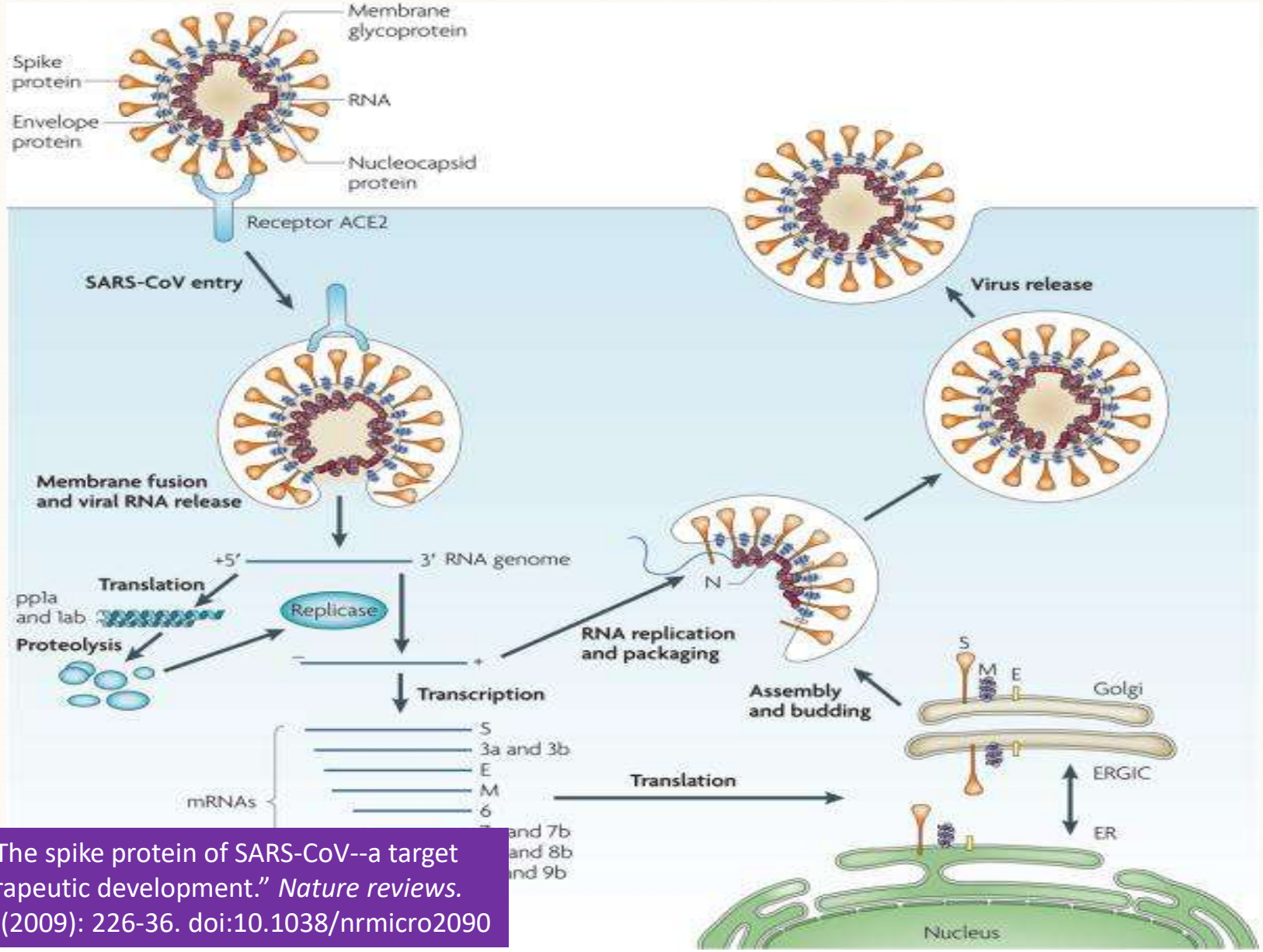
© MailOnline



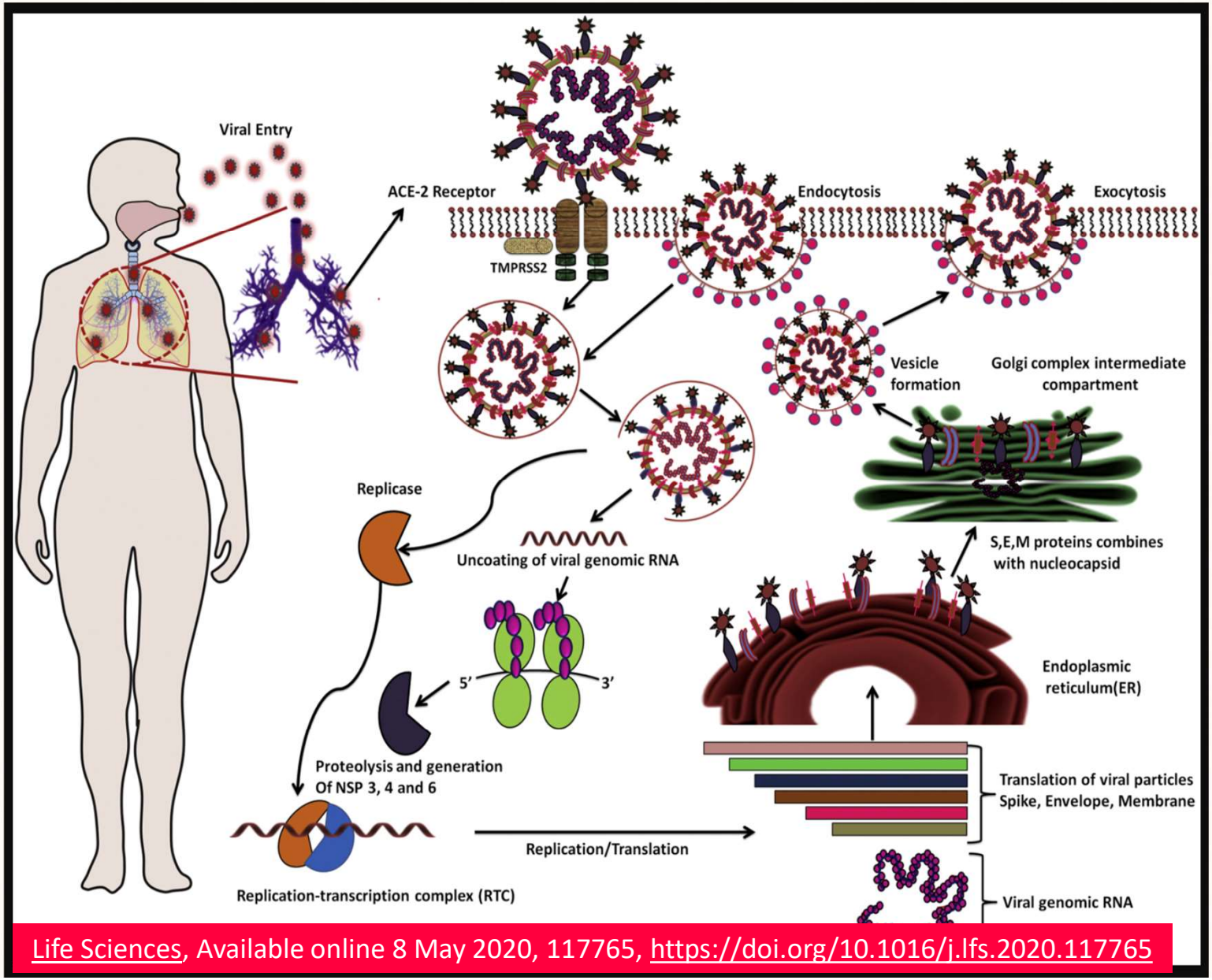

INSIDER
Source: National Geographic



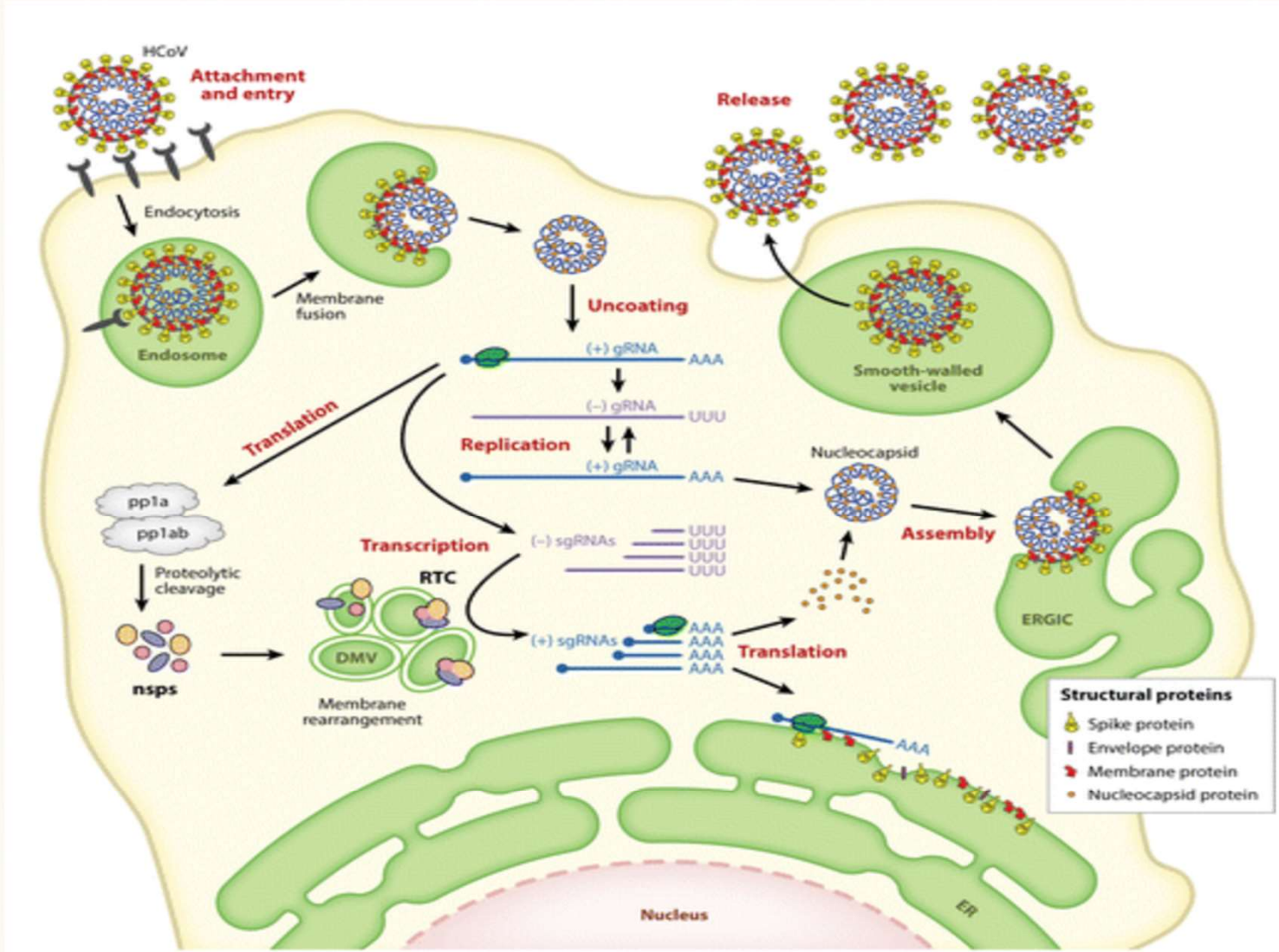
Schematic of CoV spike protein (S) binding to the surface receptor, which is the full-length ACE2 soluble ACE2 administration may intercept the coronavirus (Drawn by Nicole Inniss, Ph.D)



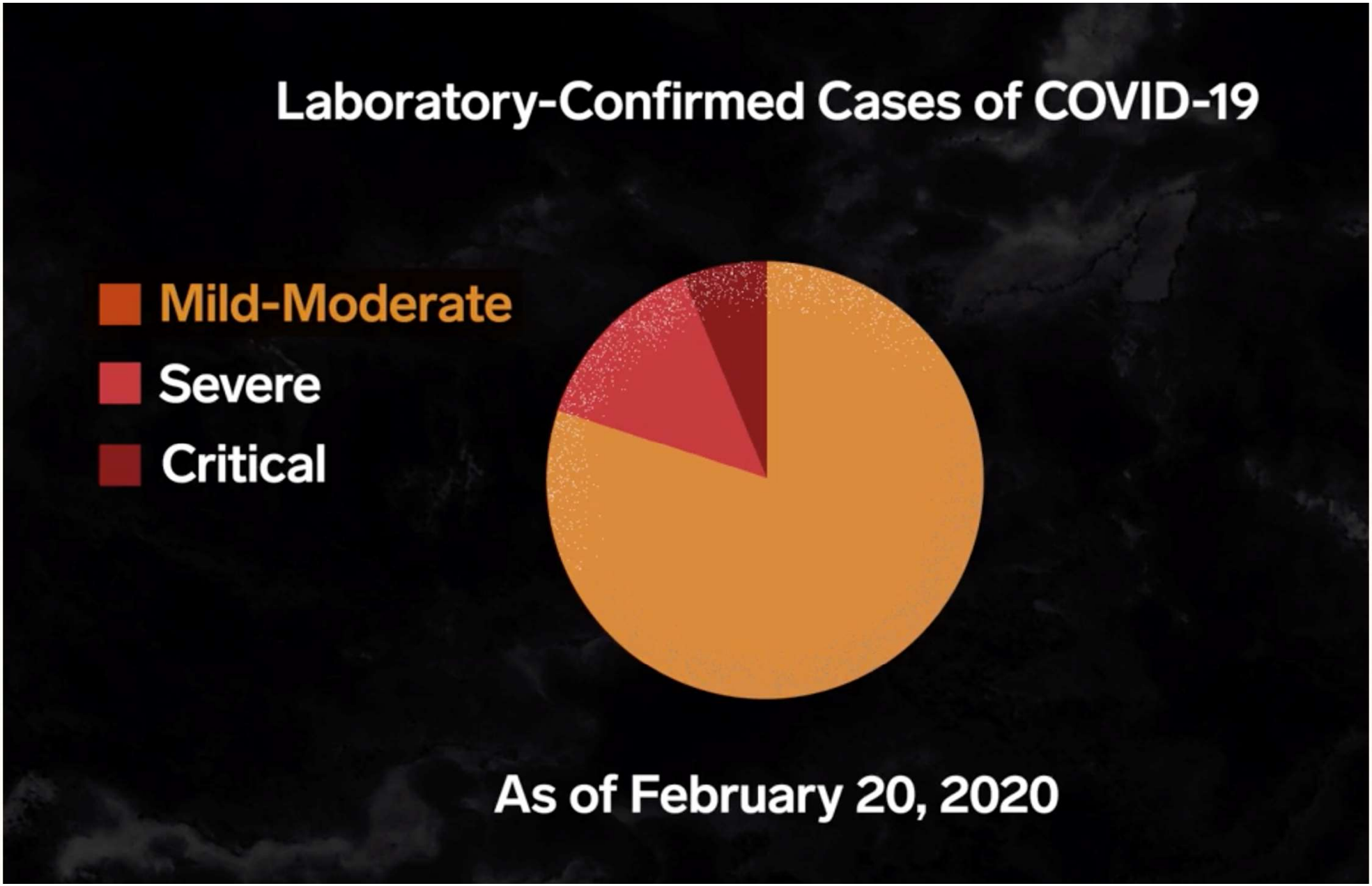
Du, Lanying et al. "The spike protein of SARS-CoV--a target for vaccine and therapeutic development." *Nature reviews. Microbiology* vol. 7,3 (2009): 226-36. doi:10.1038/nrmicro2090

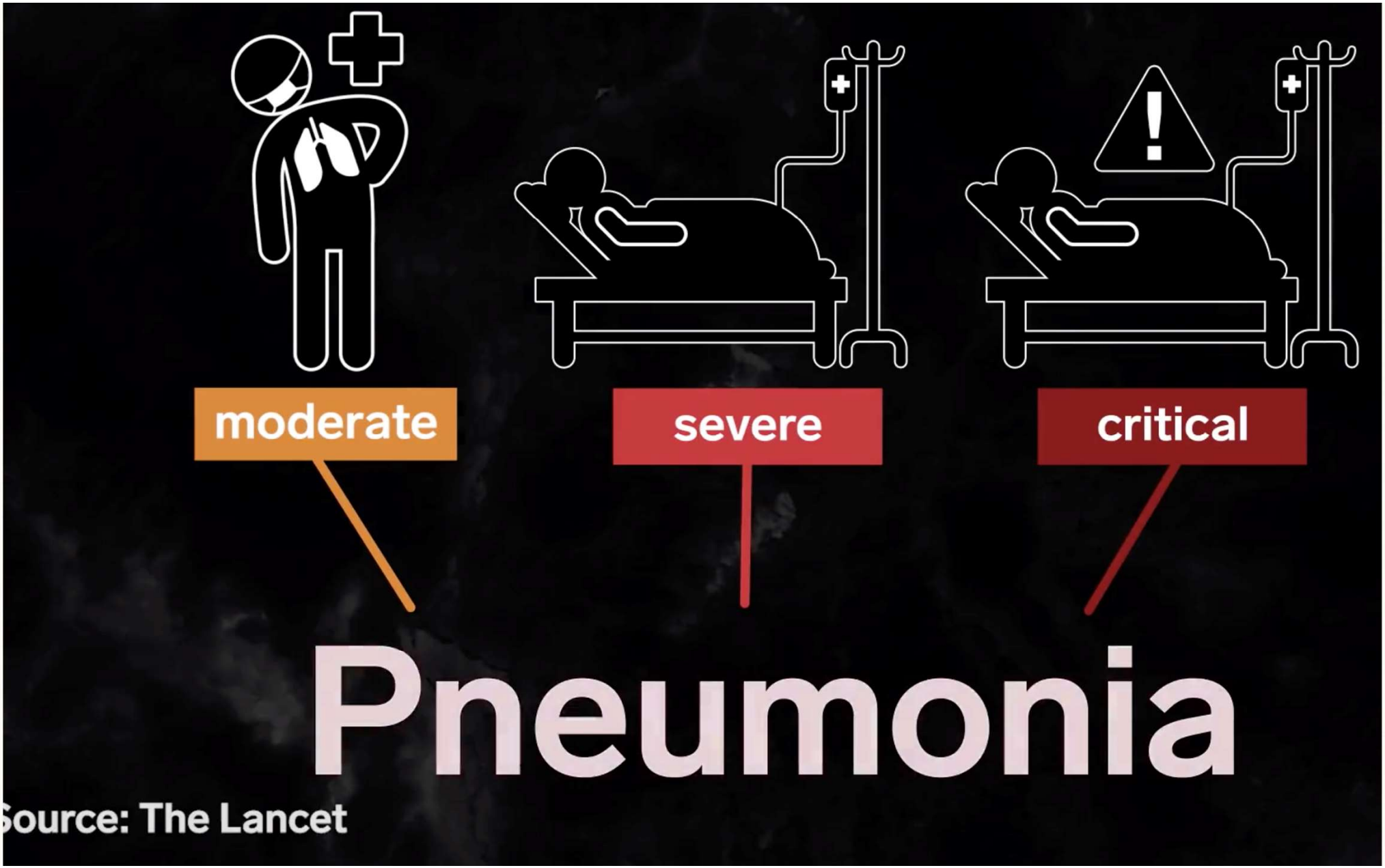


Life Sciences, Available online 8 May 2020, 117765, https://doi.org/10.1016/j.lfs.2020.117765

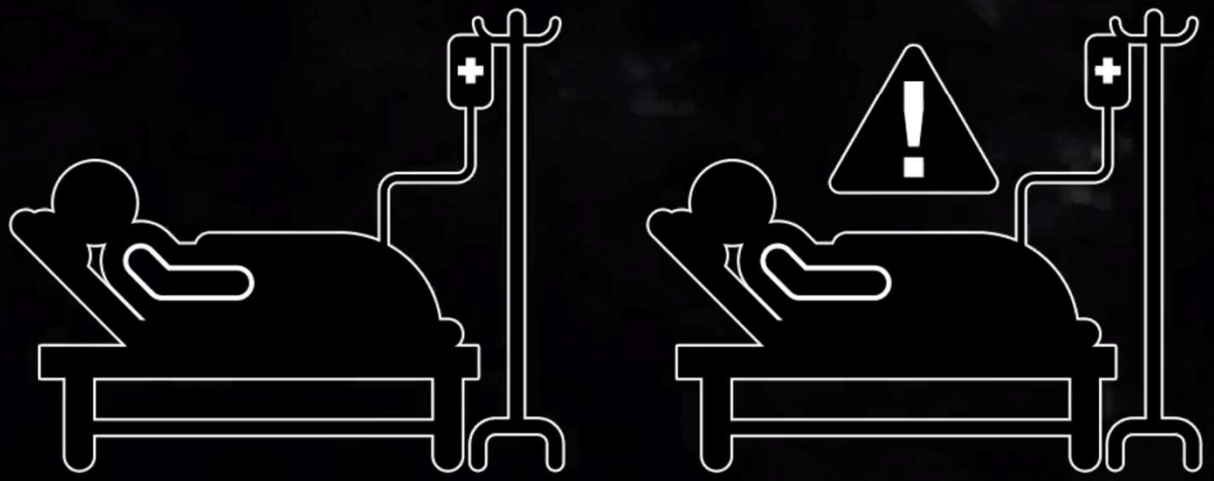


Fung TS, Liu DX. Human Coronavirus: Host-Pathogen Interaction, Annu Rev Microbiol. 2019 Sep 8; 73:529-557.


Laboratory-Confirmed Cases of COVID-19
Mild-Moderate
Severe
Critical
As of February 20, 2020


moderate
severe
critical
Pneumonia
Source: The Lancet

Acute Respiratory Distress Syndrome



Source: The Lancet


ARDS
30-40% of
cases are fatal
Source: Nature Reviews Disease Primers

MEDPAGE TODAY®

Near 90% Mortality Rate in Intubated COVID-19 Patients in NYC

— Comorbidities appeared to play a major role

by Molly Walker, Associate Editor, MedPage Today
April 22, 2020

- Among all patients who received mechanical ventilation, the mortality rate was 76.4% for adults ages 18 to 65, and nearly all patients over age 65 died (97.2%), reported Karina Davidson, PhD, of Northwell Health in New York City, and colleagues, writing in JAMA.
- By contrast, mortality rates among these age groups who did not receive mechanical ventilation were 19.8% and 26.6%, respectively.

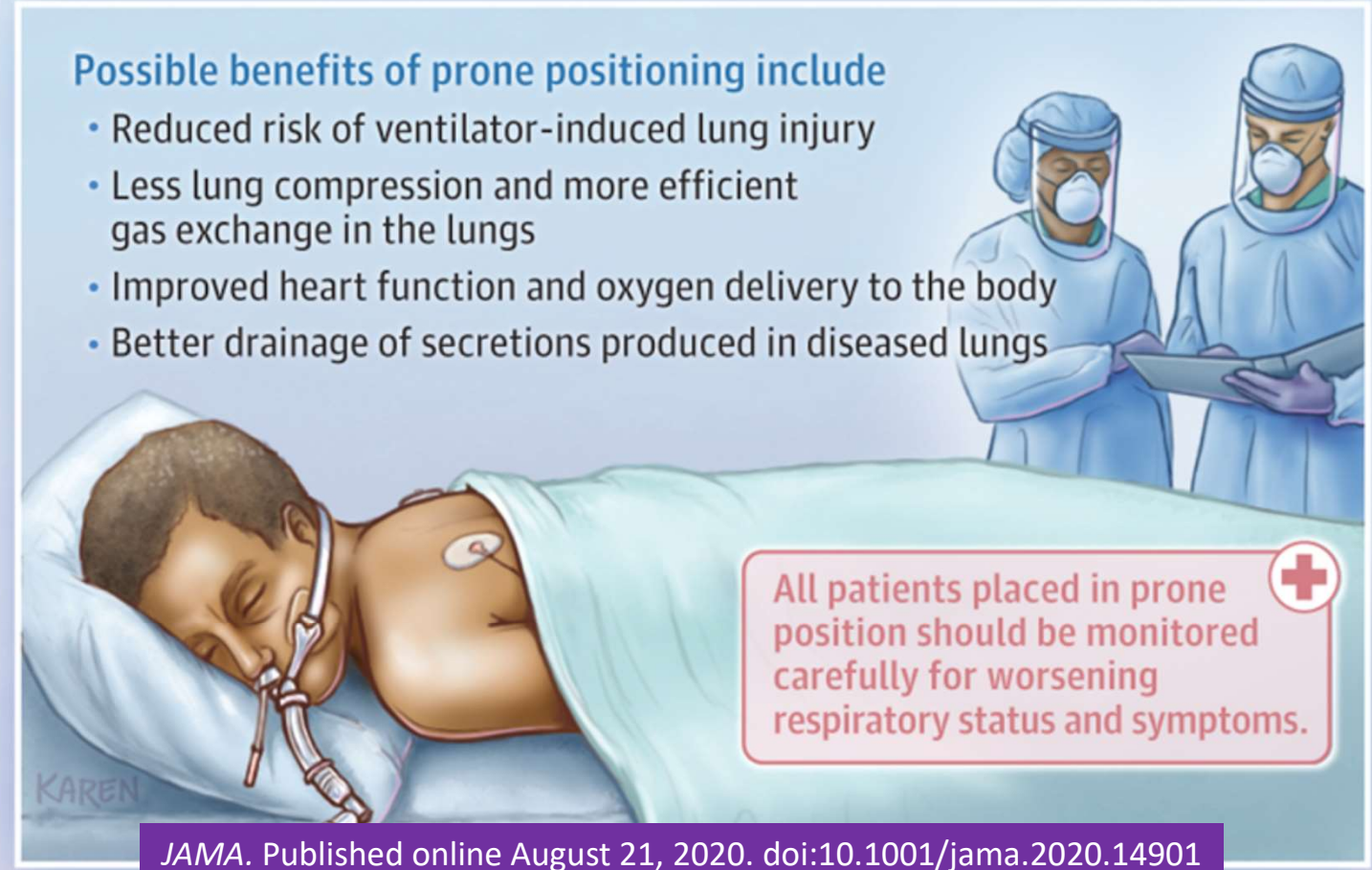
Richardson S, et al "Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area" JAMA 2020; DOI: 10.1001/jama.2020.6775.

Ventilators position matters

- Several studies reveal that the majority of patients with COVID-19 who require a ventilator -- as many as 84% -- will not survive, Jon Hamilton writes ~ Ventilators.[1]
- A total of 237 patients with ASRS were assigned to the **prone** group, and 229 patients were assigned to the **supine** group. The 28-day mortality was 16.0% in the prone group and 32.8% in the supine group ($P<0.001$).[2]

Are No Panacea for Critically Ill COVID-19 Patients (NPR), https://www.npr.org/sections/health-shots/2020/04/02/826105278/ventilators-are-no-panacea-for-critically-ill-covid-19-patients, retrieved April 7, 2010; n engl j med 368;23 nejm.org june 6, 2013.

Prone positioning is the technique of placing patients with breathing difficulties on their stomach to help them breathe better. Prone positioning is generally reserved for sedated patients who require a breathing machine, known as a ventilator, but it may be beneficial for awake patients with COVID-19.



JAMA. Published online August 21, 2020. doi:10.1001/jama.2020.14901

Some COVID-19 Patients Present With GI Symptoms Only

- A subgroup of patients may have digestive symptoms, such as diarrhea, as their only symptom of COVID-19, with or without ever developing respiratory symptoms or even a fever
- Compared with patients with only respiratory symptoms, those with digestive symptoms were more likely to test positive for COVID-19 in their stool and have a longer delay until viral clearance

Han C, et al "Digestive Symptoms in COVID-19 Patients with Mild Disease Severity: Clinical Presentation, Stool Viral RNA Testing, and Outcomes" Am J Gastroenterol 2020.

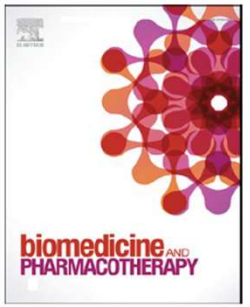
Biomedicine & Pharmacotherapy 132 (2020) 110859



Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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



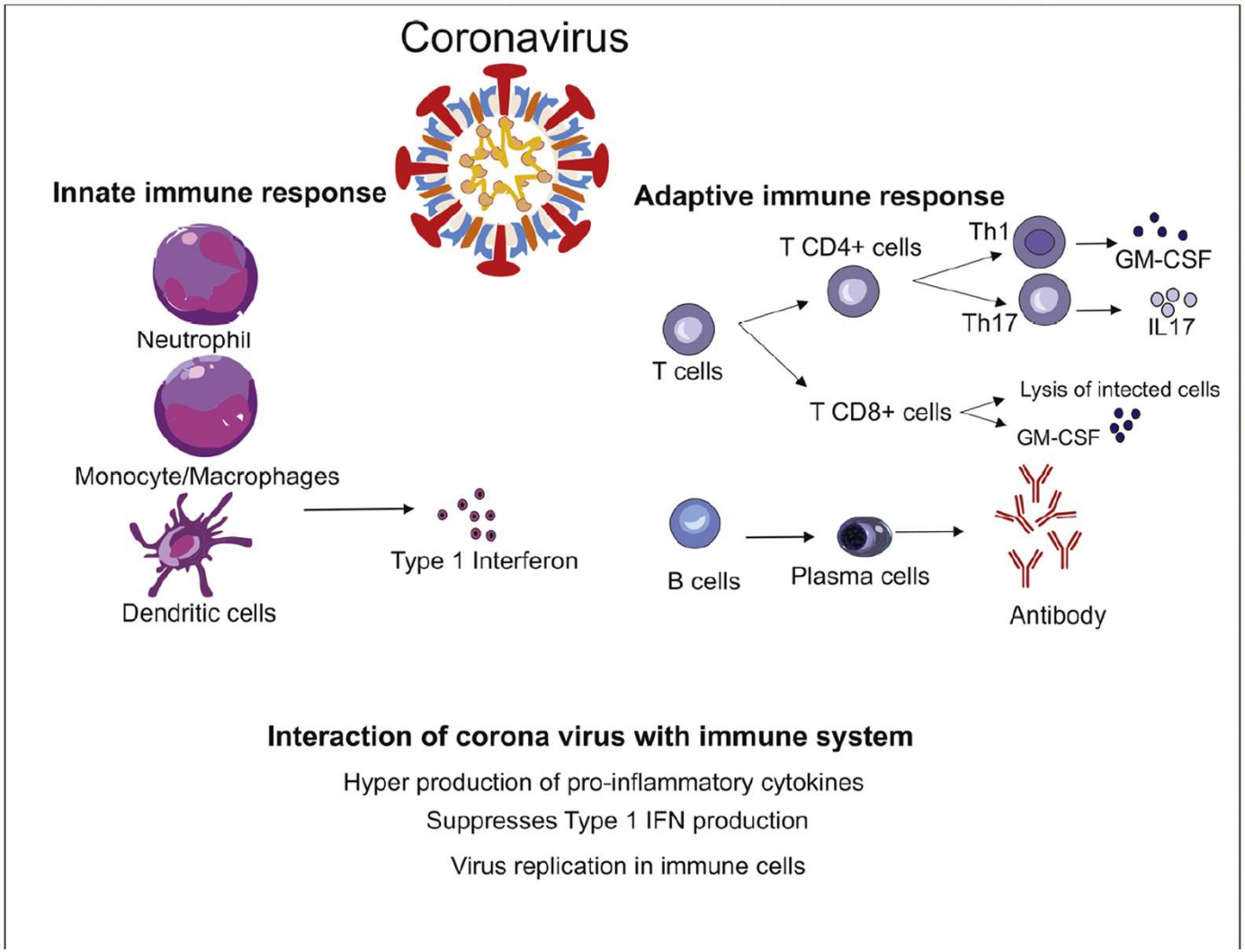
Review

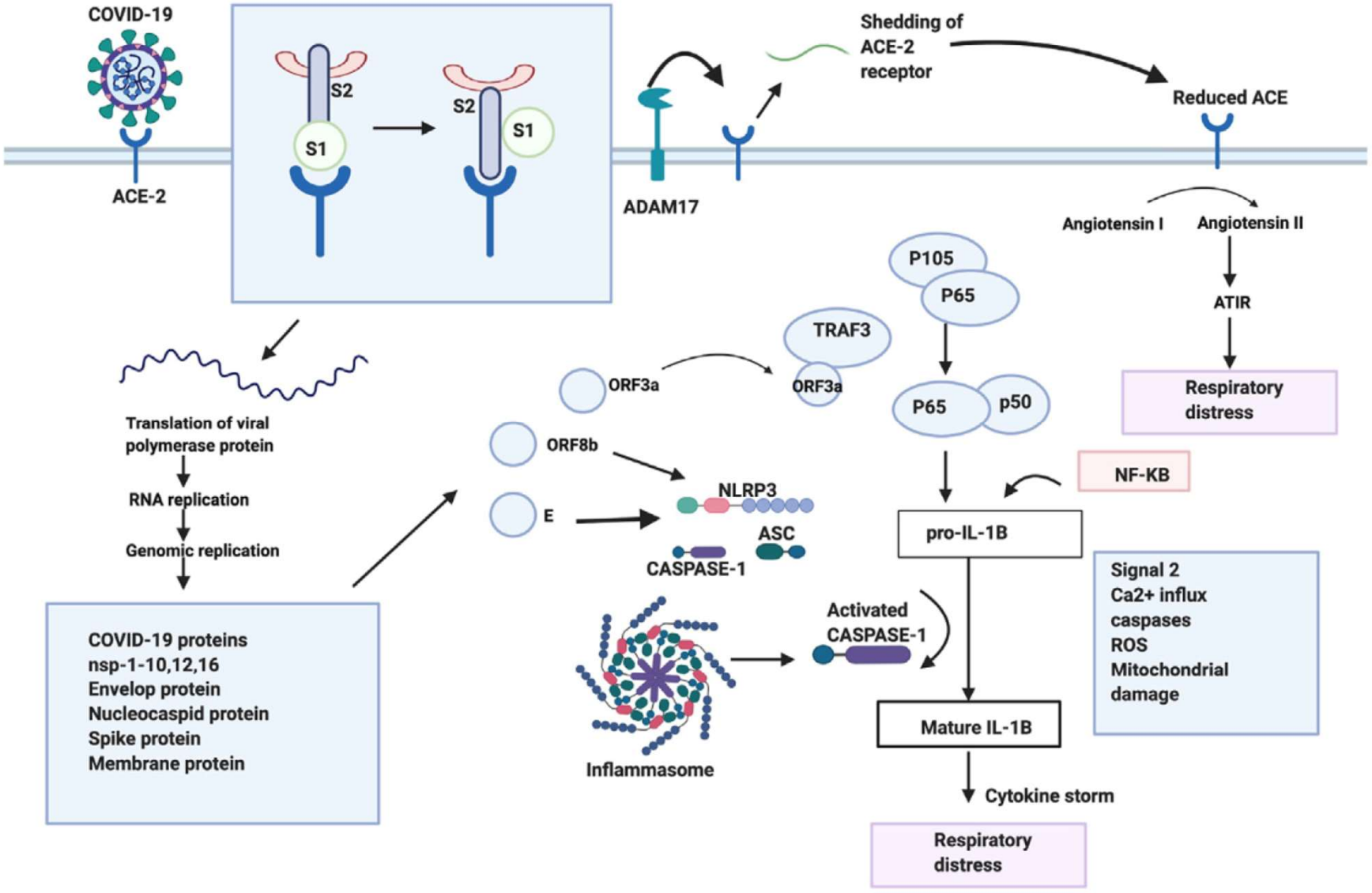


Innate and adaptive immune responses against coronavirus

Arezoo Hosseini [a,c], Vida Hashemi [b], Navid Shomali [a,c], Faezeh Asghari [d], Tohid Gharibi [a,c], Morteza Akbari [a], Saber Gholizadeh [e], Abbas Jafari [f,*]

The innate and adaptive immune responses against CoV infection.




COVID-19
ACE-2
S2
S1
S2
S1
ADAM17
Shedding of
ACE-2
receptor
Reduced ACE
Angiotensin I
Angiotensin II
ATIR
Respiratory
distress
P105
P65
TRAF3
ORF3a
ORF3a
P65
p50
NF-KB
Translation of viral
polymerase protein
RNA replication
Genomic replication
ORF8b
E
NLRP3
ASC
CASPASE-1
pro-IL-1B
Signal 2
Ca2+ influx
caspases
ROS
Mitochondrial
damage
COVID-19 proteins
nsp-1-10,12,16
Envelop protein
Nucleocaspid protein
Spike protein
Membrane protein
Activated
CASPASE-1
Inflammasome
Mature IL-1B
Cytokine storm
Respiratory
distress

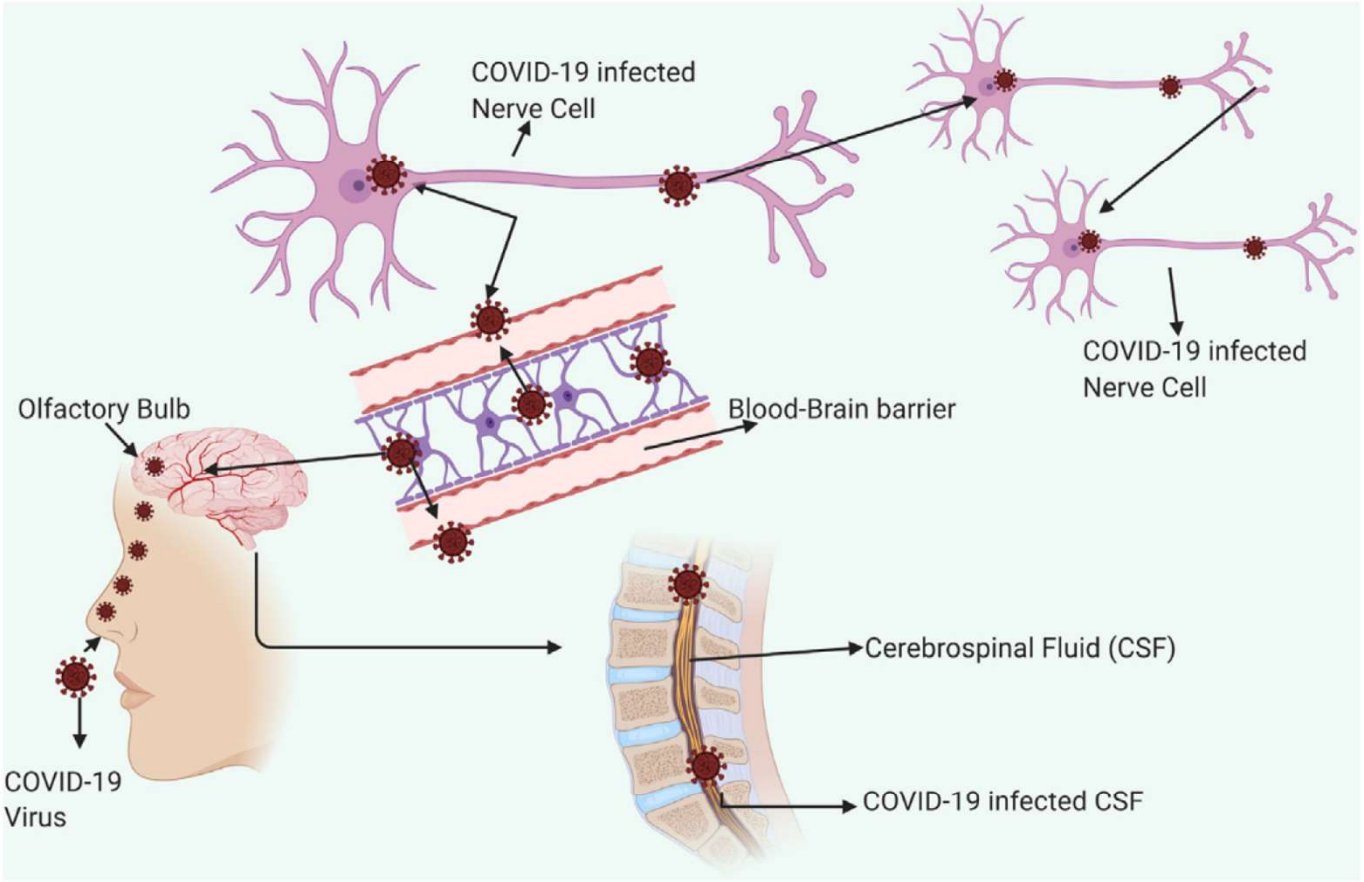


Fig. 3. COVID-19 entry into CNS. Entry of human Coronavirus in CNS through olfactory bulb upon nasal infection which causes inflammation and demyelination. Further it reaches the whole brain via Blood Brain Barrier and CSF via Blood- CSF barrier in <7 days. The possible entry of SARS-CoV-2 into the Brain and CNS is important to design effective antiviral drugs. Effective drugs that may cross Blood Brain Barrier and Blood CSF barrier may be taken in to consideration while designing and this could be a promising in treatment strategies.

nature medicine

LETTERS

https://doi.org/10.1038/s41591-020-0995-0

Check for updates

Humoral and circulating follicular helper T cell responses in recovered patients with COVID-19

Jennifer A. Juno[1,9], Hyon-Xhi Tan[1,9], Wen Shi Lee[1], Arnold Reynaldi[2], Hannah G. Kelly[1,3], Kathleen Wragg[1], Robyn Esterbauer[1,3], Helen E. Kent[1,4], C. Jane Batten[1], Francesca L. Mordant[1], Nicholas A. Gherardin[1,5], Phillip Pymm[6,7], Melanie H. Dietrich[6,7], Nichollas E. Scott[1], Wai-Hong Tham[6], Dale I. Godfrey[1,5], Kanta Subbarao[1,8], Miles P. Davenport[2], Stephen J. Kent[1,3,4,9] ✉ and Adam K. Wheatley[1,3,9] ✉

- Overall, although patients who recovered from COVID-19 displayed multiple hallmarks of effective immune recognition of S, the wide spectrum of neutralizing activity observed suggests that vaccines might require strategies to selectively target the most potent neutralizing epitopes.

Open access Commentary

Journal for ImmunoTherapy of Cancer

BCG vaccine and COVID-19: implications for infection prophylaxis and cancer immunotherapy

Madhuri Koti,[1,2] Alvaro Morales,[2] Charles H Graham,[1,2] David Robert Siemens[1,2]

Koti M, et al. J Immunother Cancer 2020;8:e001119. doi:10.1136/jitc-2020-001119

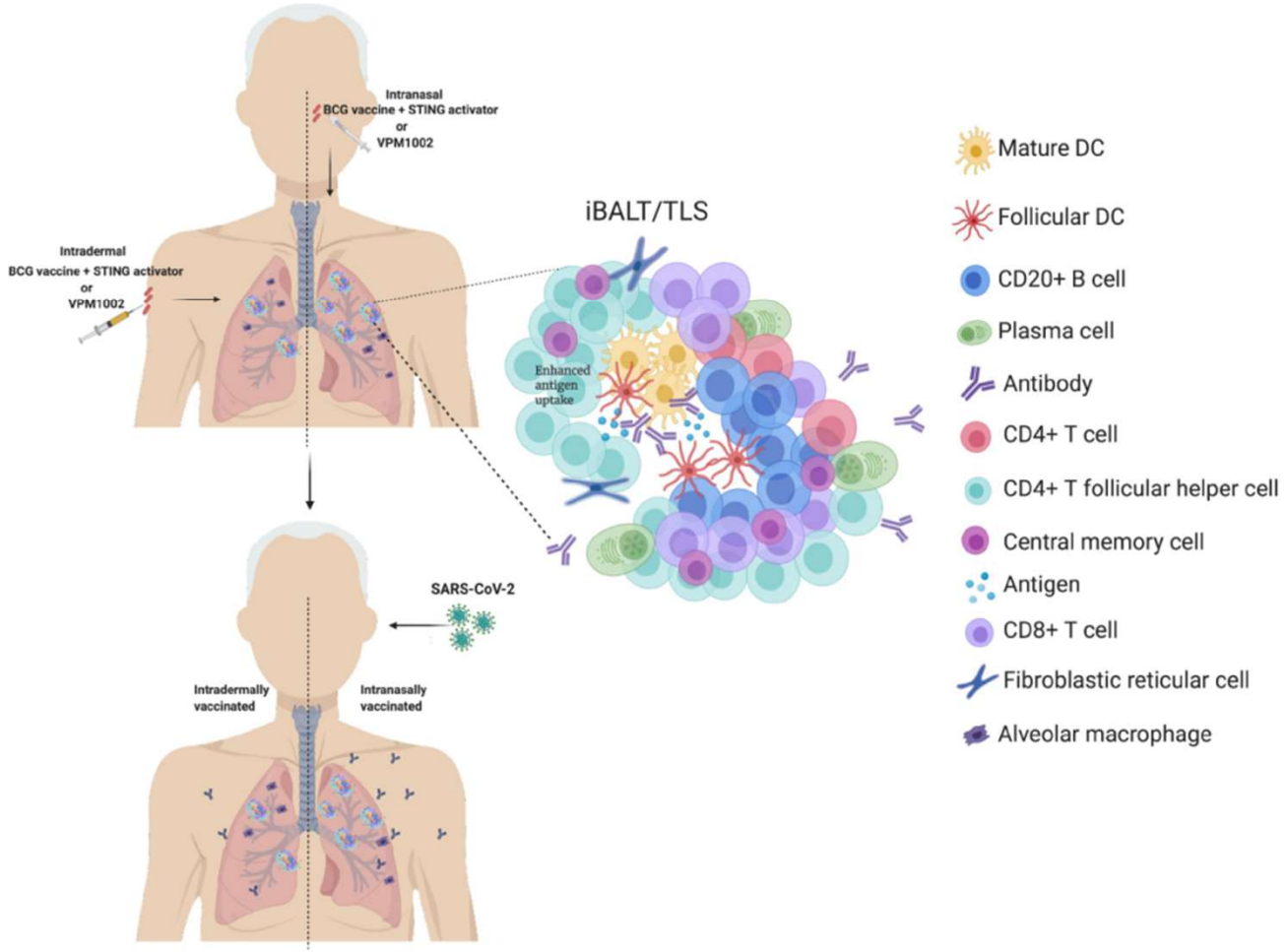


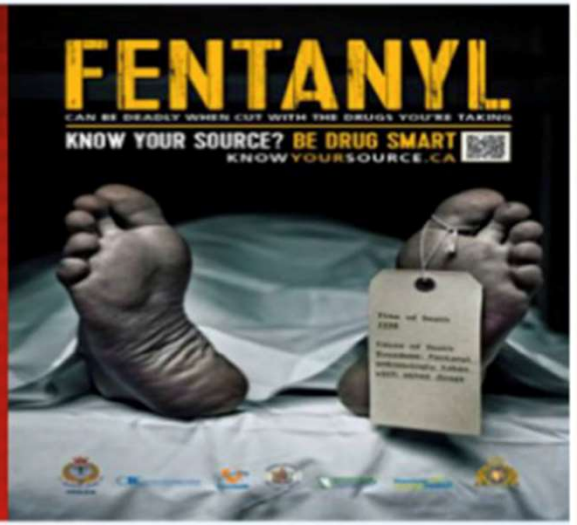
Figure 1 Hypothetical diagram showing enhanced protection by intranasally delivered BCG (in combination with a sting pathway activator) or with recombinant BCG (VPM1002), against SARS-CoV2 viral infection. iBALT, induced bronchus associated lymphoid tissue; STING, STimulator of INterferon Genes; TLS, tertiary lymphoid structure; DC, Dendritic cell; SARS-CoV2, Severe acute respiratory syndrome-coronavirus 2.

Koti M, et al. J Immunother Cancer 2020;8:e001119. doi:10.1136/jitc-2020-001119

Costs of Pathogenic Thinking







CHRONIC PAIN BY THE NUMBERS

Chronic pain affects
100 MILLION AMERICANS —
more than heart disease, cancer and diabetes combined.[3]

Chronic pain costs the U.S. health system up to **$300 BILLION ANNUALLY.**[6]



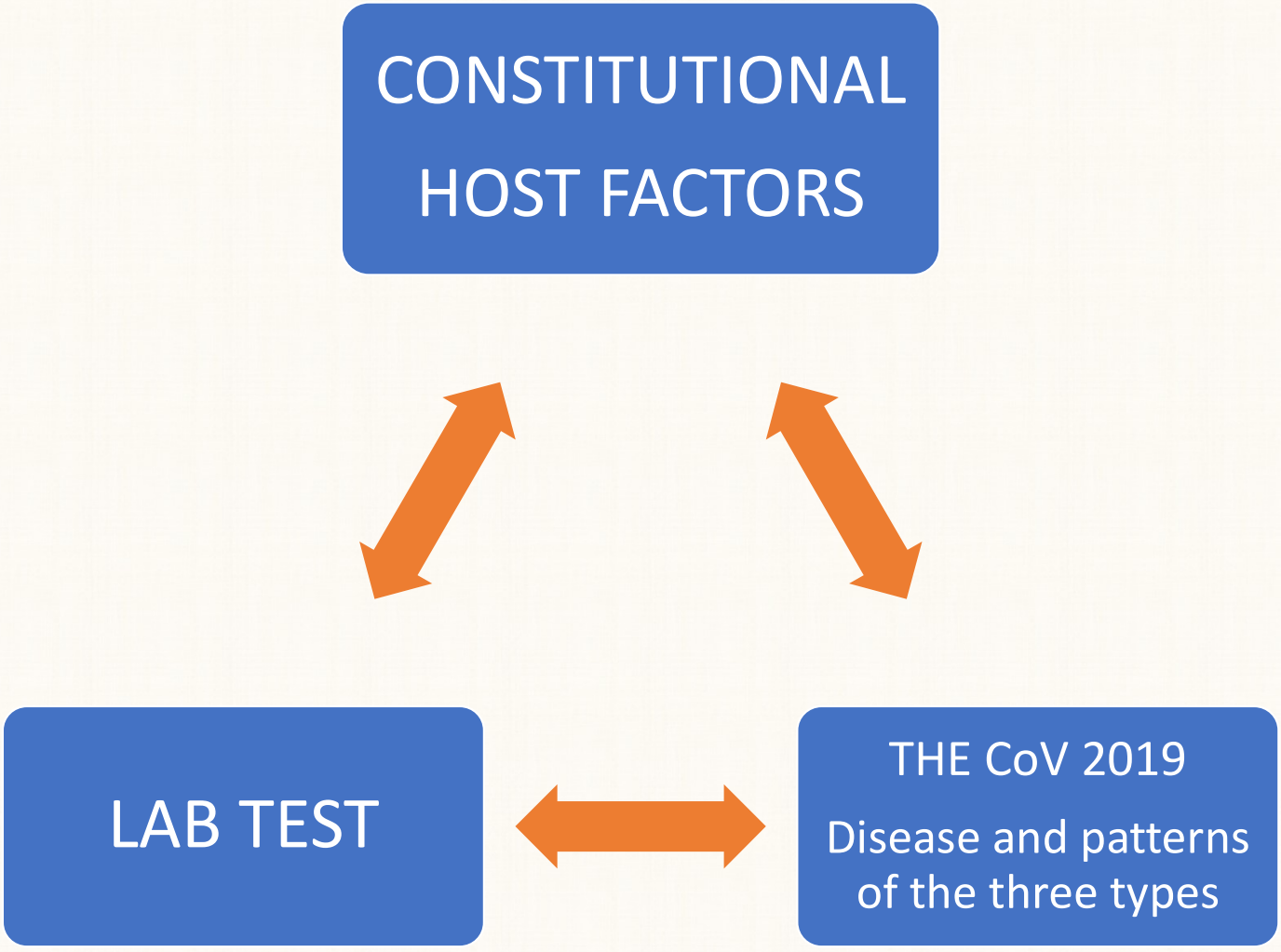


Costs include
515 MILLION WORKDAYS LOST
and **40 MILLION DOCTOR VISITS** annually.[4]



Chronic pain affects
1 IN 5 PEOPLE GLOBALLY.[5]

Target the Following, Both for Prevention and Treatment



COVID19: Identifying the symptoms

Symptoms	Covid-19 Symptoms range from mild to severe	Cold Gradual onset of symptoms	Flu Abrupt onset of symptoms
 Fever	Common	Rare	Common
 Fatigue	Sometimes	Sometimes	Common
 Cough	Common (usually dry)	Mild	Common (usually dry)
 Sneezing	No	Common	No
 Aches and pains	Sometimes	Common	Common
 Runny or stuffy nose	Rare	Common	Sometimes
 Sore throat	Sometimes	Common	Sometimes
 Diarrhoea	Rare	No	Sometimes for children
 Headaches	Sometimes	Rare	Common
 Shortness of breath	Sometimes	No	No

CoV 2019 APPEARS TO HAVE THREE VARIENTS

S1 Key symptom prediction:	S2 Key symptom prediction:	S3 Key symptom prediction:
• Chill and fever • Rash/bleeding underneath skin (e.g. rosy spots) • Lung edema • Kidney damage • Surge of steroid hormone may cause miscarriage • Spleen and/or pancreatic failure • Decrease in CNS & brain functions • Flaccid paralysis (may be temporary) • Muscle and joint pain • Increase in RBC • Unstable WBC • Shortness of breath • Headache • Less or no diarrhea • Myocarditis • SHOCK in children	• Symptoms are to SARS • Fever, may have rash • Lung edema • Shortness of breath • Muscle weakness may lead to paralysis • Decrease in WBC • Kidney damage • Unstable of steroid hormone can cause miscarriage • Decrease in CNS & brain functions • Liver failure • Spleen/Pancreatic damage • Unstable blood pressure • Diarrhea • Cough with phlegm	• Low or no fever, more likely to have chill and shivering • Inner lining necrosis (dehydration) of lung, respiratory & digestive tracts • Flaccid paralysis (may be temporary) • May have liver damage • Endocarditis • Loss of hair • Shortness of breath • Sweating • Cough with or without phlegm • Inflammation, dehydration & lesion of inner linings of respiratory and digestive tracts • Pus could be found later in Lung • SHOCK • Unstable blood pressure • Diarrhea • Headache

Table 2. Symptoms Associated with S1, S2 and S3 Predicted based on HUE Charts in Table 1

People with COVID-19



Source: WHO-China Joint Mission on COVID-19

BMJ Open Diabetes Research & Care

Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study

Jianfeng Wu,[1] Jianqiang Huang,[2] Guochao Zhu,[3] Qiongya Wang,[4] Qingquan Lv,[5] Ying Huang,[6] Yang Yu,[7] Xiang Si,[1] Hui Yi,[2] Cuiping Wang,[1] Yihao Liu ,[8,9] Han Xiao,[10] Qian Zhou,[8] Xin Liu,[11] Daya Yang,[12] Xiangdong Guan,[1] Yanbing Li ,[9] Sui Peng,[8] Joseph Sung,[13] Haipeng Xiao [9,14]

- Elevation of blood glucose level predicted worse outcomes in hospitalized patients with COVID-19.
- Our findings may provide a simple and practical way to risk stratify COVID-19 inpatients for hierarchical management, particularly where medical resources are in severe shortage during the pandemic.

BMJ Open Diab Res Care 2020;**8**:e001476. doi:10.1136/ bmjdrc-2020-001476

frontiers in Endocrinology

ORIGINAL RESEARCH
published: 10 July 2020
doi: 10.3389/fendo.2020.00525

Check for updates

Impaired Fasting Glucose and Diabetes Are Related to Higher Risks of Complications and Mortality Among Patients With Coronavirus Disease 2019

OPEN ACCESS

Edited by:
Hans Ulrich Häring,
Tübingen University Hospital, Germany

Jiaoyue Zhang[1,2†], Wen Kong[1,2†], Pengfei Xia[3†], Ying Xu[4], Li Li[5], Qin Li[6], Li Yang[7], Qi Wei[8], Hanyu Wang[1,2], Huiqing Li[1,2], Juan Zheng[1,2], Hui Sun[1,2], Wenfang Xia[1,2], Geng Liu[1,2], Xueyu Zhong[1,2], Kangli Qiu[1,2], Yan Li[5], Han Wang[1,2], Yuxiu Wang[1,2], Xiaoli Song[1,2], Hua Liu[1,2], Si Xiong[4], Yumei Liu[7], Zhenhai Cui[1,2], Yu Hu[9,10], Lulu Chen[1,2], An Pan[3*] and Tianshu Zeng[1,2*]*

Alternative and Complementary Therapies, Vol. 27, No. 2 |

Roundtable Discussion: COVID-19 and Obesity—Implications and Integrative Management

Moderator: Jane Hart, Participants: David L. Katz, Robert F. Kushner, Beth Frates, and Donald D. Hensrud

Published Online: 12 Apr 2021 | https://doi.org/10.1089/act.2021.29318.dlk

Research suggests significantly increased risks of both hospitalization and death if a person who is obese develops COVID-19.

- 79.1% of COVID patients hospitalized between March-December 2020 were overweight or obese.
- Just as levels of vitamin D and Zinc matter incrementally, the same is true when it comes to obesity - so people with 3 obesity (i.e., BMI >40) are at much higher risk than those with stage 1 or 2 obesity.
- Obesity's Role in COVID-19 Deaths: 'Profound' and Independent of CVD

CDC, https://www.cdc.gov/obesity/data/obesity-and-covid-19.html,12 Apr 2021 https://doi.org/10.1089/act.2021.29318.dlk, Tartof SY, Qian L, Hong V, et al. Obesity and mortality among patients diagnosed with COVID-19: results from an integrated health care organization. Ann Intern Med. 2020;

Changes in Body Mass Index Among Children and Adolescents During the COVID-19 Pandemic

- The COVID-19 pandemic has been associated with weight gain among adults,1 but little is known about the weight of US children and adolescents. To evaluate pandemic-related changes in weight in school-aged youths, we compared the body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of youths aged 5 to 17 years during the pandemic in 2020 to the same period before the pandemic in 2019
- Significant weight gain (9%) occurredduringtheCOVID-19 pandemic among youths in KPSC, especially among the youngest children.

Lin AL, Vittinghoff E, Olgin JE, Pletcher MJ, Marcus GM. Body weight changes during pandemic-related shelter-in-place in a longitudinal cohort study. JAMA Netw Open. 2021;4(3):e212536. doi:10.1001/jamanetworkopen.2021.2536

Lab Test Relative to Covid-19

- N to L ratio, CRP is elevated and patients with advanced CoV disease present with elevated LDH.
- Low platelets and platelet-to-lymphocyte (PLR) count is relative - Univariate analysis showed that age, platelet peaks, and PLR at peak platelet were the influencing factors in severe patients, and the PLR value at peak platelet during treatment was an independent influencing factor in severe patients
- LDH is present in numerous cell types, including platelets, which have high LDH activity - In some patients, levels of LDH (Lactate dehydrogenase) and AST are elevated and/or levels of lymphocytes are low
- Elevated D-dimer
- Loss of taste (Zinc deficiency, zinc pools being drained),
- Vitamin D (25 OH and 125 diOH) status
- Selenium levels
- Very low Testosterone in men

British Journal of Haematology, September 2019, **https://doi.org/10.1111/bjh.16183**, Wang D,Hu B,Hu C,et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China[J].JAMA,2020,Feb 7.doi:10.1001/jama.2020.1585; The Lancet VOLUME 395, ISSUE 10229, P1054-1062, MARCH 28, 2020;
Dhindsa S, Zhang N, McPhaul MJ, et al. Association of Circulating Sex Hormones With Inflammation and Disease Severity in Patients With COVID-19. *JAMA Netw Open.* 2021;4(5):e2111398. doi:10.1001/jamanetworkopen.2021.11398

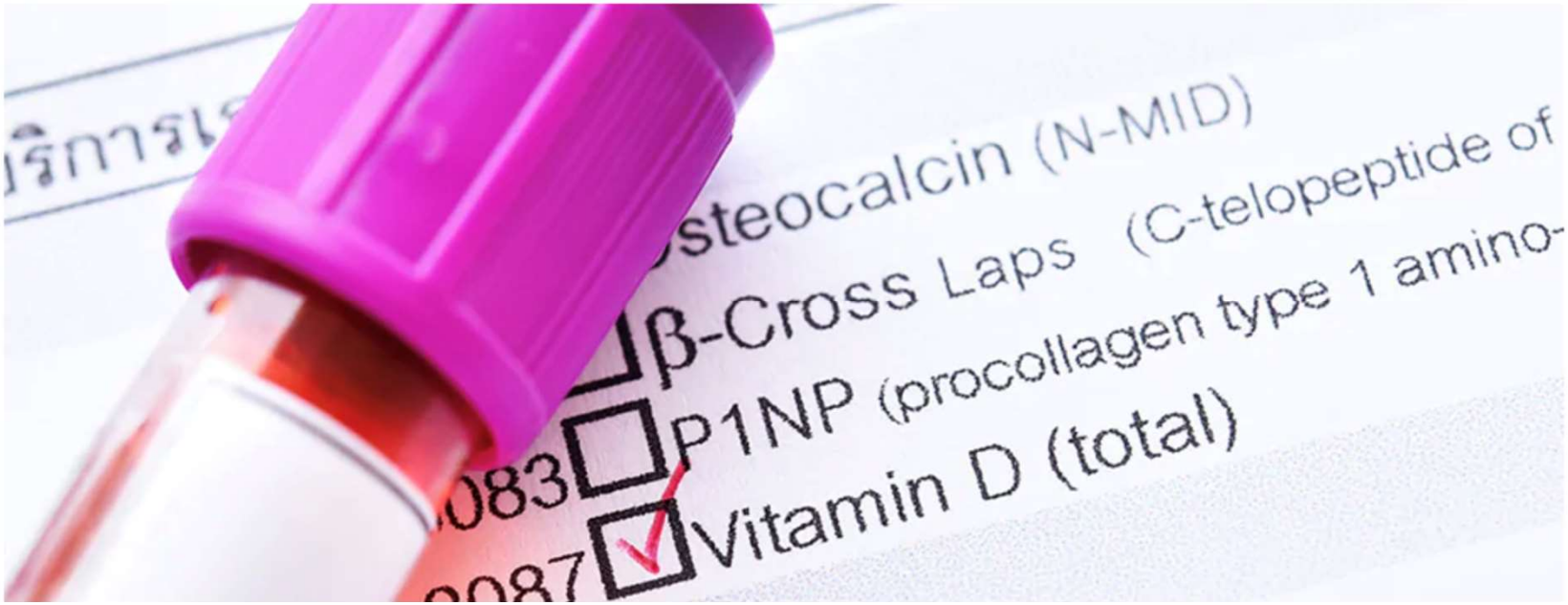
MEDPAGE TODAY®

Op-Ed: Don't Let COVID-19 Patients Die With Vitamin D Deficiency

— We can't wait for perfect evidence

by Richard H. Carmona, MD, MPH, Vatsal G. Thakkar, MD, and John C. Umhau, MD, MPH

January 5, 2021



Serum 25(OH)D Deficiency and High D-Dimer Levels are Associated with COVID-19 Pneumonia

- 124 patients (79 males) with a mean age of 38 ± 16.6 years.
- Fever was observed in 67 patients (54.0%), fatigue, cough, and dyspnea being observed in 94 (75.8%), 86 (69.3%), and 37 (29.8%), respectively.
- Of the 124 patients, 77 (62.1%) developed pneumonia. Common comorbidities in the patients with pneumonia were hypertension, diabetes, and cardiovascular disease.
- **D-dimer > 0.5 µg/mL; 25(OH)D < 20 µg/dL; and age > 60 years were variables showing significant correlation with COVID-19 pneumonia**.

Sunnetcioglu A, Sunnetcioglu M, Gurbuz E, Bedirhanoglu S, Erginoguz A, Celik S. Serum 25(OH)D Deficiency and High D-Dimer Levels are Associated with COVID-19 Pneumonia. Clin Lab. 2021 Jul 1;67(7). doi: 10.7754/Clin.Lab.2020.201050. PMID: 34258973.

International Journal of Antimicrobial Agents
Volume 56, Issue 2, August 2020, 106017



Letter to the Editor

Neutrophil-to-lymphocyte ratio and clinical outcome in COVID-19: a report from the Italian front line

Arturo Ciccullo [a, b], Alberto Borghetti [a], Lorenzo Zileri Dal Verme [a], Alberto Tosoni [a], Francesca Lombardi [b], Matteo Garcovich [a], Federico Biscetti [a], Massimo Montalto [a, c], Roberto Cauda [a, b], Simona Di Giambenedetto [a, b], GEMELLI AGAINST COVID Group [1]

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https://doi.org/10.1016/j.ijantimicag.2020.106017

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HIGHLIGHTS

- Clinicians are looking for a reliable prognostic marker for patients with COVID-19.
- In our cohort, clinical improvement was predicted by younger age and a NLR below 3.
- Transfer to ICU was instead predicted by a NLR over 4 (p=0.046).
- NLR is a fast, widely available and relatively inexpensive assessment.

Elevated IL-6 concentration is associated with poor prognosis

- “The extremely high level of IL-6 is a hallmark and important driving force of cytokine storm, which may cause multiple organ dysfunction in critically ill patients.”
- “Because the elevated IL-6 may be part of a larger cytokine storm which could worsen outcome, IL-6 could be a potential therapeutic target for critically ill patients with an excessive inflammatory response.”

Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality [published online ahead of print, 2020 Mar 29]. *Int J Antimicrob Agents*. 2020;105954. doi:10.1016/j.ijantimicag.2020.105954

Editorial J Biol Regul Homeost Agents, 34 (2) 2020 Mar 14[Online ahead of print]

Induction of Pro-Inflammatory Cytokines (IL-1 and IL-6) and Lung Inflammation by COVID-19: Anti-Inflammatory Strategies

P Conti [1], G Ronconi [2], A Caraffa [3], C Gallenga [4], R Ross [5], I Frydas [6], S Kritas # [7]

Corticosteroids should not be recommended and appear to exacerbate COVID-19-associated lung injury.

Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020; 395: 473–75.

JEM Journal of Experimental Medicine

PERSPECTIVE

Targeting potential drivers of COVID-19: Neutrophil extracellular traps

Betsy J. Barnes[1], Jose M. Adrover[2], Amelia Baxter-Stoltzfus[3], Alain Borczuk[3], Jonathan Cools-Lartigue[4], James M. Crawford[5], Juliane Daßler-Plenker[2], Philippe Guerci[6], Caroline Huynh[4,7], Jason S. Knight[8], Massimo Loda[3], Mark R. Looney[9], Florencia McAllister[10], Roni Rayes[4,7], Stephane Renaud[6], Simon Rousseau[11], Steven Salvatore[3], Robert E. Schwartz[12], Jonathan D. Spicer[4,7], Christian C. Yost[13], Andrew Weber[14], Yu Zuo[8], and Mikala Egeblad[2]

Coronavirus disease 2019 (COVID-19) is a novel, viral-induced respiratory disease that in ∼10–15% of patients progresses to acute respiratory distress syndrome (ARDS) triggered by a cytokine storm. In this Perspective, autopsy results and literature are presented supporting the hypothesis that a little known yet powerful function of neutrophils—the ability to form neutrophil extracellular traps (NETs)—may contribute to organ damage and mortality in COVID-19. We show lung infiltration of neutrophils in an autopsy specimen from a patient who succumbed to COVID-19. We discuss prior reports linking aberrant NET formation to pulmonary diseases, thrombosis, mucous secretions in the airways, and cytokine production. If our hypothesis is correct, targeting NETs directly and/or indirectly with existing drugs may reduce the clinical severity of COVID-19.

Blood type may matter

- People with blood group A have a significantly higher risk for acquiring COVID-19 compared with non-A blood groups, whereas blood group O has a significantly lower risk for the infection compared with non-O blood groups
- In an initial study of 265 patients with COVID, the authors observed that blood group O individuals were significantly under-represented amongst patients who required hospitalization for severe COVID-19 infection. Conversely, blood group A was significantly more common in patients with severe COVID-19 compared to the local population.

Zhao, Jiao, ewt. Al., Relationship between the ABO Blood Group and the COVID-19 Susceptibility, DO - 10.1101/2020.03.11.20031096

O' Sullivan, Jamie, et. al., More on 'Association between ABO blood groups and risk of SARS-CoV-2 pneumonia', British Journal of Haematology · May 2020, DO - 10.1111/bjh.16845

Ellinghaus, D., et. al., The ABO blood group locus and a chromosome 3 gene cluster associate with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis, medRxiv 2020.05.31.20114991; doi: https://doi.org/10.1101/2020.05.31.20114991

Zietz M, Tatonetti NP. Testing the association between blood type and COVID-19 infection, intubation, and death. *medRxiv*. 2020;2020.04.08.20058073. Published 2020 Apr 11. doi:10.1101/2020.04.08.20058073

Tocilizumab Shows Benefit in a Patient With COVID-19 and Multiple Myeloma

- A new report has described a multiple myeloma patient with COVID-19 who recovered after being treated with the interleukin 6 (IL-6)-blocking agent tocilizumab.
- The case report published in *Blood Advances*[1] details the disease course of a man aged 60 years in China who was diagnosed with COVID-19 in early February 2020 after developing a fever, cough, and chest tightness.

Zhang X, Song K, Tong F, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. *Blood Adv*. 2020;4(7):1307-1310.

International Immunopharmacology 90 (2021) 107209

Contents lists available at ScienceDirect

International Immunopharmacology

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

Pentoxifylline decreases serum LDH levels and increases lymphocyte count in COVID-19 patients: Results from an external pilot study

Valente Maldonado [a,b,*], Claudia Hernandez-Ramírez [b], Eniel Alonso Oliva-Pérez [c], César Omar Sánchez-Martínez [c], Jorge Fabián Pimentel-González [c], José Raúl Molina-Sánchez [c], Yeimmy Zuyenn Jiménez-Villalba [c], Jaime Chávez-Alderete [d], Marco A. Loza-Mejía [a]

[a] *Faculty of Chemical Sciences, Universidad La Salle-México, Cuauhtémoc, Mexico City 06140, Mexico*

[b] *Department of Allergy and Clinical Immunology Internal Medicine, General Hospital of Zone 27 Mexican Institute of Social Security, Lerdo 311, Nonoalco Tlatelolco, Cuauhtémoc, Mexico City 6390, Mexico*

[c] *Department of Internal Medicine, General Hospital of Zone 27 Mexican Institute of Social Security, Nonoalco Tlatelolco, Cuauhtémoc, Mexico City 6390, Mexico*

[d] *Department of Bronchial Hyperreactivity, National Institute of Respiratory Diseases Ismael Cosío Villegas, Tlalpan, Mexico City 14080, Mexico*

Inflammation Resolution: A Dual-Pronged Approach to Averting Cytokine Storms in COVID-19?

- SARS-CoV-2 may trigger a cell death ("debris")-induced "eicosanoid storm", including prostaglandins and leukotrienes, which in turn initiates a robust inflammatory response.
- A paradigm shift is emerging in our understanding of the resolution of inflammation as an active biochemical process with the discovery of novel endogenous specialized pro-resolving lipid autacoid mediators (SPMs), such as resolvins.
- Resolvins and other SPMs stimulate macrophage-mediated clearance of debris and counter pro-inflammatory cytokine production, a process called inflammation resolution.
- SPMs and their lipid precursors exhibit anti-viral activity at nanogram doses in the setting of influenza without being immunosuppressive.

Panigrahy D, Gilligan MM, Huang S, et al. Inflammation resolution: a dual-pronged approach to averting cytokine storms in COVID-19? *Cancer Metastasis Rev*. 2020;10.1007/s10555-020-09889-4. , doi:10.1007/s10555-020-09889-4

- SPMs also promote anti-viral B cell antibodies and lymphocyte activity, highlighting their potential use in the treatment of COVID-19
- Resolvins stabilize arachidonic acid-derived epoxyeicosatrienoic acids (EETs), which also promotes the production of pro-resolution mediators, activating anti-inflammatory processes, and **preventing the cytokine storm.**
- **Both resolvins and EETs also attenuate pathological thrombosis and promote clot removal, which is emerging as a key pathology of COVID-19 infection.**
- Thus, both SPMs and sEH inhibitors may promote the resolution of inflammation in COVID-19, thereby reducing acute respiratory distress syndrome (ARDS) and other life-threatening complications associated with robust viral-induced inflammation.

Panigrahy D, Gilligan MM, Huang S, et al. Inflammation resolution: a dual-pronged approach to averting cytokine storms in COVID-19? *Cancer Metastasis Rev*. 2020;10.1007/s10555-020-09889-4. , doi:10.1007/s10555-020-09889-4

International Journal of
Molecular Sciences

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Review

Mast Cell Responses to Viruses and Pathogen Products

Jean S. Marshall [1,2,*], Liliana Portales-Cervantes [1,2] and Edwin Leong [2]

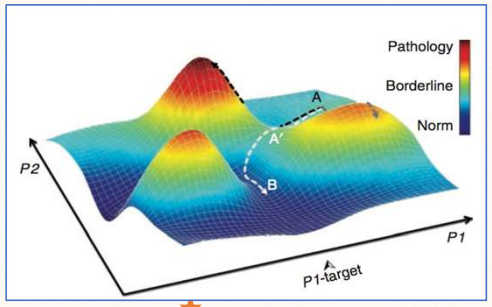
- There is substantial evidence for mast cell mobilization and activation of effector cells and mobilization of dendritic cells following viral challenge
- These cells are a major and under-appreciated local source of type I and III interferons following viral challenge
- However, mast cells have also been implicated in inappropriate inflammatory responses, long term fibrosis, and vascular leakage associated with viral infections

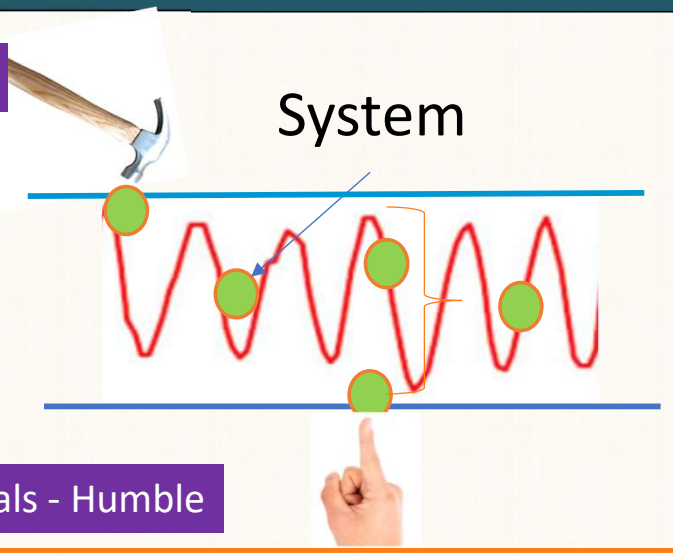
Int. J. Mol. Sci. 2019, 20, 4241; doi:10.3390/ijms20174241

General Hypothesis
MEDICINE SHOULD LEND A HELPING HAND

"True progress quietly and persistently moves along without notice."
St. Francis of Assisi

Pharmaceuticals - Glamorous



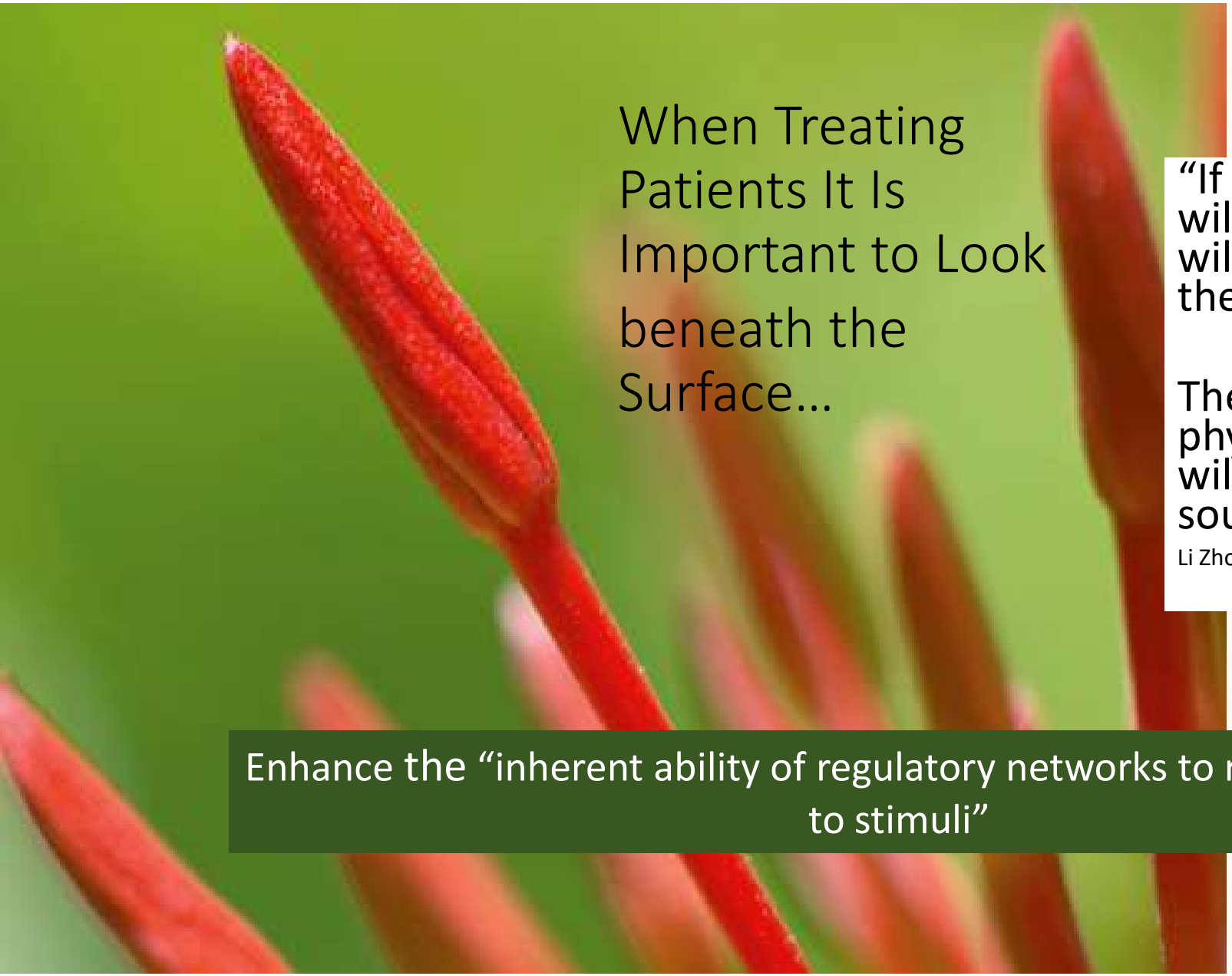


Range of Dynamic Stability

Botanicals - Humble

- A healthy system operates / behaves within a range of dynamic stability
- This behavior is driven in part by powerful intrinsic properties including self-organization & robustness
- Therefore, it may be sufficient to provide a 'gentle push', at the right time, to bring a dysregulated system back into this range of dynamic stability

Kohl P, Crampin EJ et al. Systems Biology: An approach. Clin Pharmacol Ther. 2010;88(1) 25-33



When Treating Patients It Is Important to Look beneath the Surface…

"If we water a root, it will grow and branches will sprout; these are the laws of nature.

The experienced physician, therefore, will always consider the source."

Li Zhongzi, (Yizong Bidu), 1637

Enhance the "inherent ability of regulatory networks to respond and adapt to stimuli"

VIS CONSERVATRIX

- This (Vis conservatrix) capacity was described as vitality, vital powers, **Life force** and conservative power
- They believed the most effective therapeutic change is one that accesses and supports the individual's innate capacity to heal. Their motto was "*Sustain the Life force.*"

''The (Life) Force is what gives a Jedi his power. It's an energy field created by all living things. It surrounds us and penetrates us.''
(Obi Wan Kenobi, Star Wars: Episode IV—A New Hope)

ETMS Builds with Adaptogens and Tonics which Enhances 'Autoregulation'

"A healthy system is one that *self-regulates* in the face of network perturbations"

Biological significance of autoregulation through steady state analysis of genetic networks

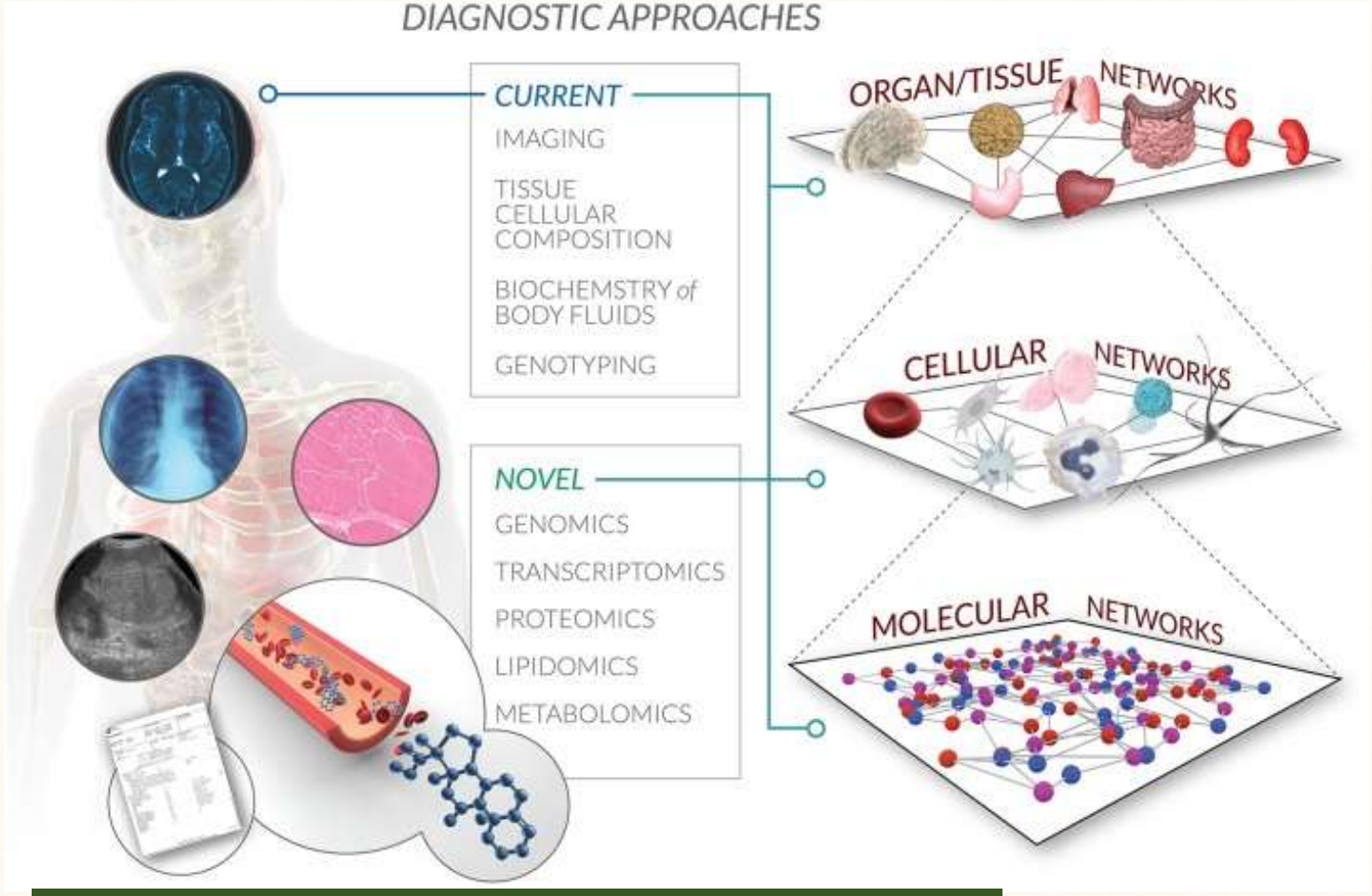
Malkhey Verma [a], Subodh Rawool [a], Paike Jayadeva Bhat [b], K.V. Venkatesh [a,b,*]

"Our steady state analysis clearly demonstrates that autoregulation is a fundamental mechanism in genetic networks and is highly context dependent."

Is this referring to the "Vis medicatrix Naturae"?

Multi-Scale Self-Regulatory Networks





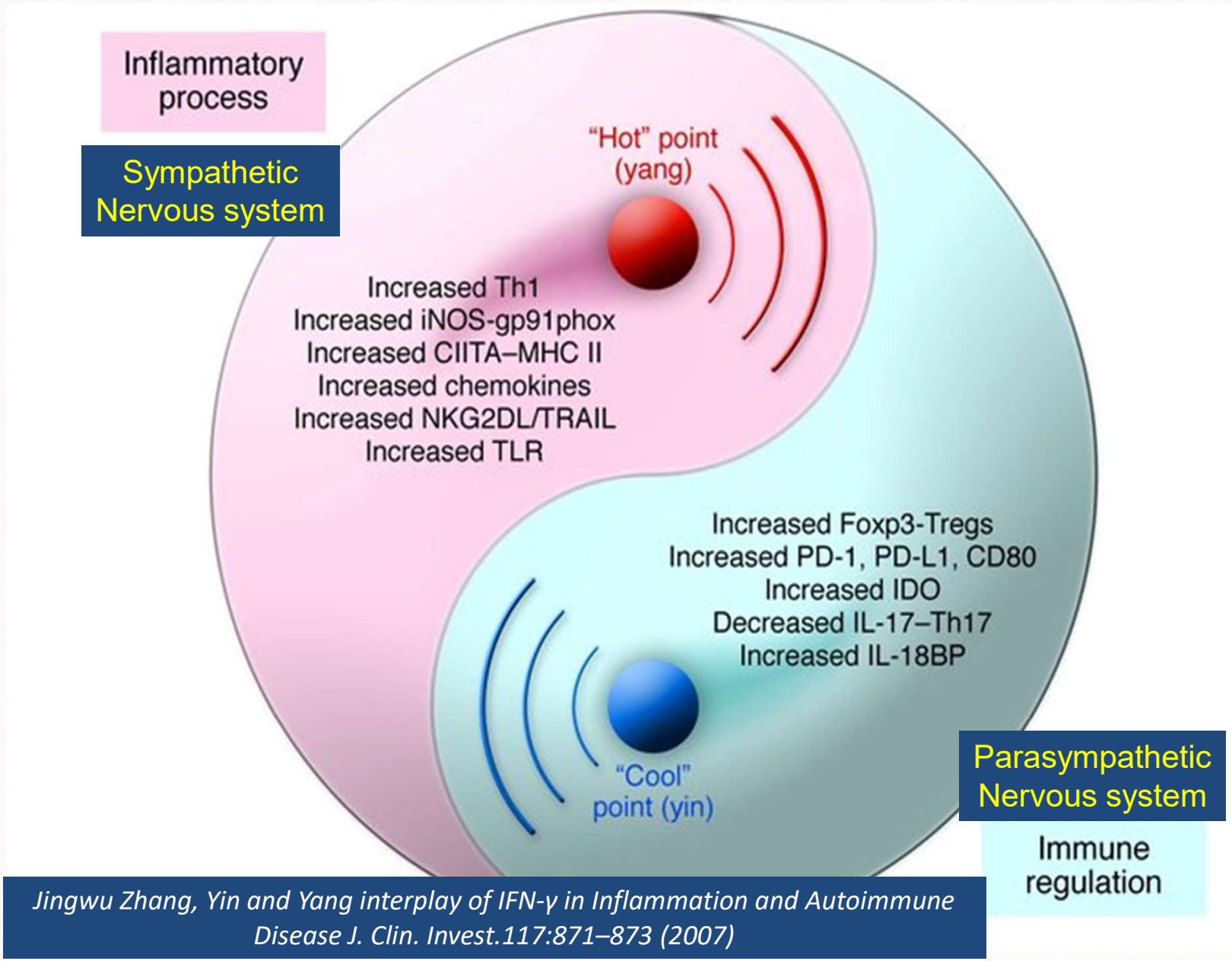
Front Physiol. 2015; 6: 225; 10.3389/fphys.2015.00225

Yin and Yang



- Zhuangzi (1020–1078 AD), a Chinese philosopher of Taoism said, “Material force moves and flows in all directions and in all manners
- Its two elements (yin and yang) interact and unite to establish harmony, so it gives rise to the concrete
- Thus the multiplicity of things is produced. In their ceaseless successions the two elements of yin and yang constitute the great principles of the universe”

Du, W.M. 1989. The Continuity of Being: Chinese Visions of Nature. In Nature in Asian Traditions of Thought



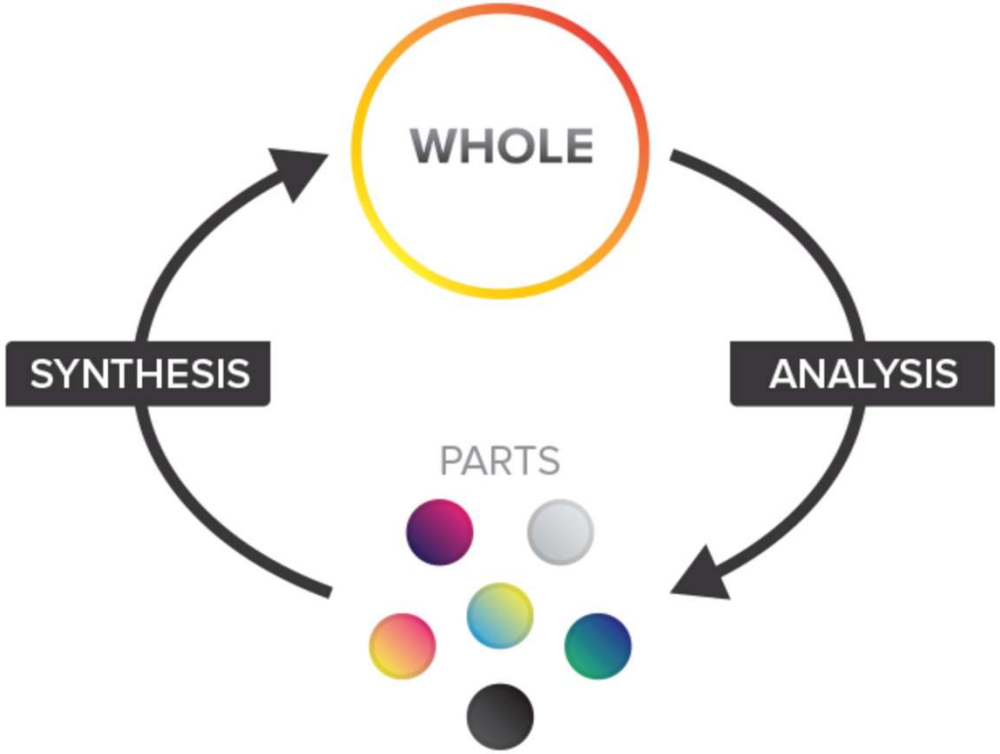
Jingwu Zhang, Yin and Yang interplay of IFN-γ in Inflammation and Autoimmune Disease J. Clin. Invest.117:871–873 (2007)

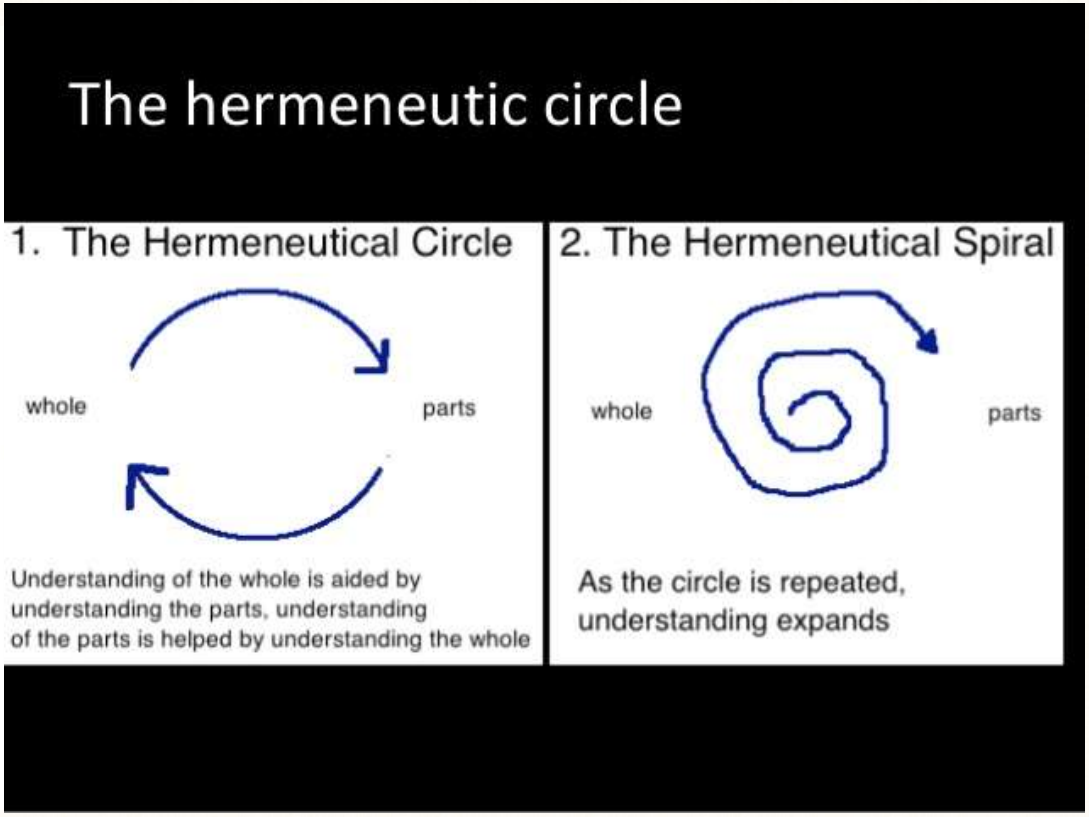
The Earth and all the Universe is Self-Balancing

- There is no greater law, because PERFECT BALANCE = STILLNESS = GOD. What some people call “rest,” is STILLNESS
- We come from STILLNESS and return to STILLNESS



Mederi Medicine Applies Wisdom and Critical Thinking Analyzing Multiple Parts in Serving the Whole, as ‘1’







3CL^{pro} predicted Structure



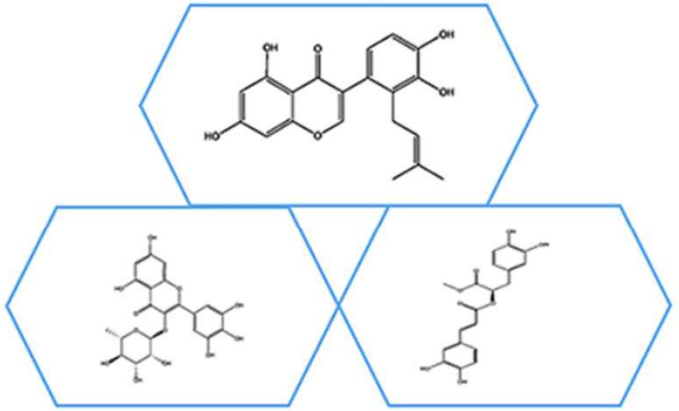
Molecular Docking



MD Simulations

MPD3 MAPS PubChem ZINC NPACT chEMBL

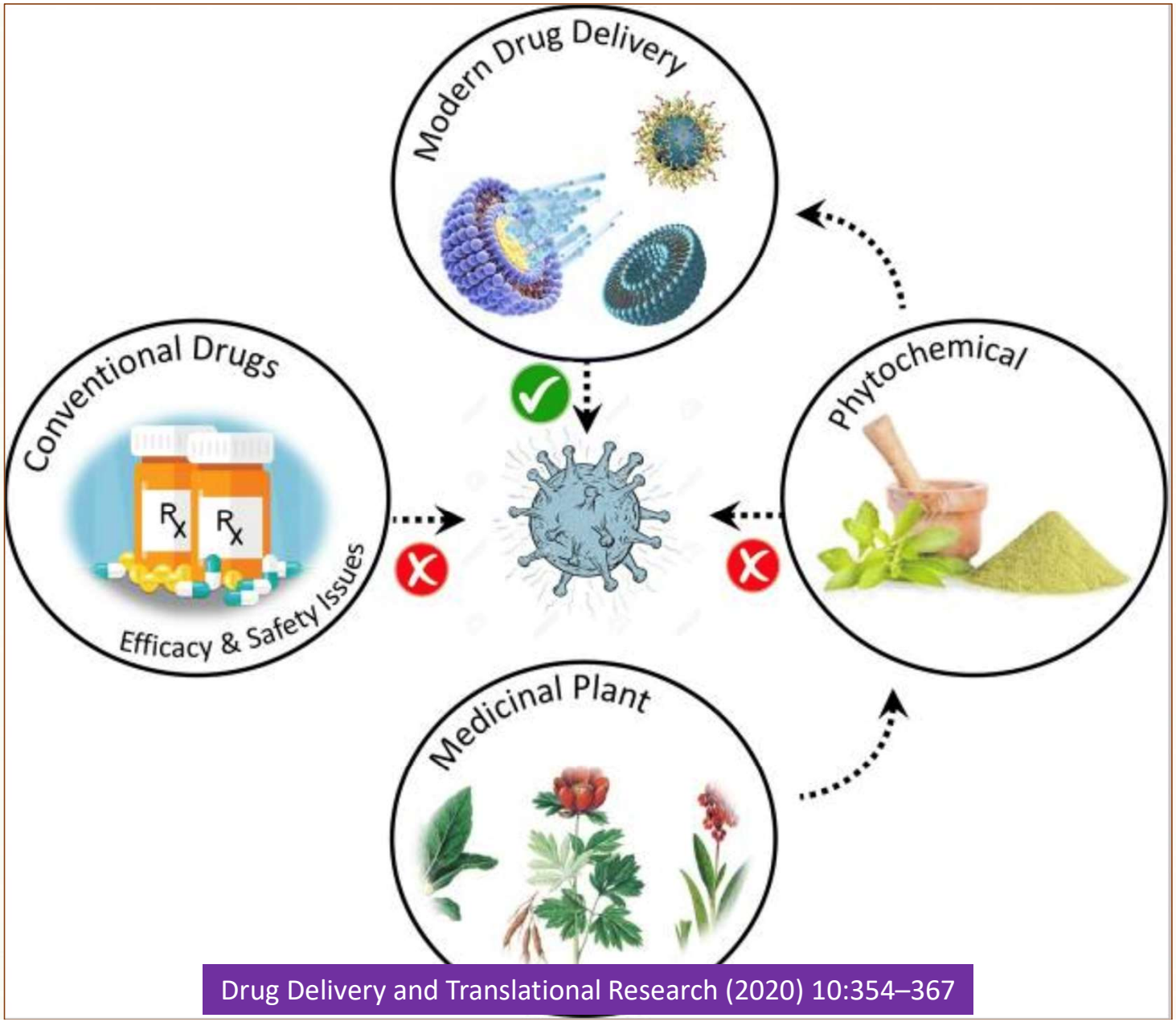
Natural Compounds Structures Sources



Screened Phytochemicals



Phytochemical's Drug Ability Analysis



Drug Delivery and Translational Research (2020) 10:354–367

COVID-19
Various treatment options

1. Preventive strategies

aintaining social distance,,wearing masks and using hand nitizers

Vaccines: mRNA-1273, BCG, ChAdOx1 nCoV-19 etc.

Immune boosters: Vitamin C, Ocimum, Curcumin etc.

Viral entry inhibitors: Chloroquine, Teicoplanin etc.

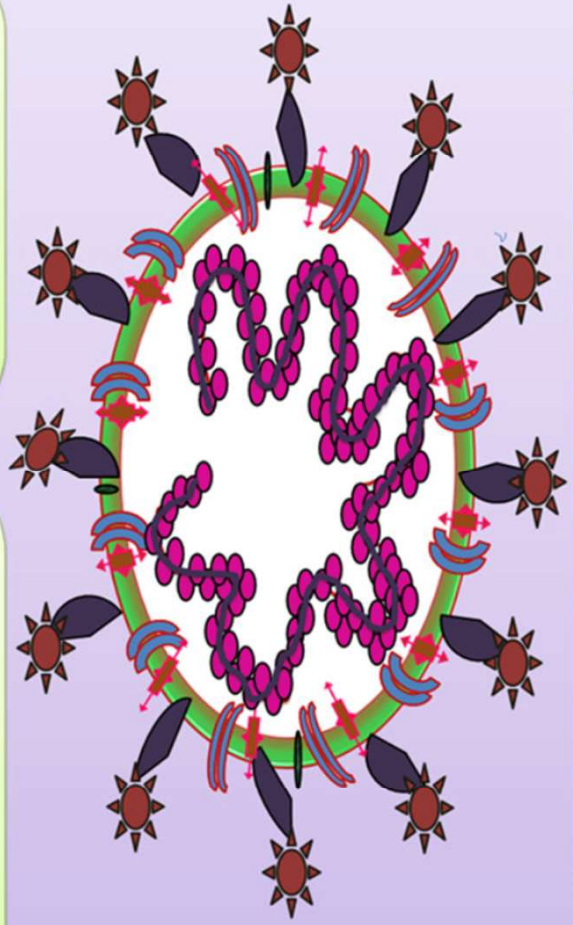
3. Management of ARDS and Cytokine storm

Monoclonal antibodies: Siltuximab, Tocilizumab, Sarilumab etc.

Chloroquine/hydroxychloroquine as immunomodulators

upportive therapies such as antibacterials, corticosteroids, nd NSAIDs: Azithromycin, Dexamethasone, Acetiminophen

Natural products: Curcumin, Resveratrol, Withaferin A, Quercetin etc.



2. Therapeutic options

Repurposing antiviral drugs: Remdesivir, Lopinavir/Ritonavir, Oseltamivir etc.

Novel antiviral drugs: ASC09F

Repurposing antimalarial, anthelmintic and antiparasitic drugs: Chloroquine, niclosamide, Ivermectin etc.

Convalescent plasma

Interferons: Interferon alfacon-1, INF-α and IFN-β

Natural killer cells and cytotoxic T cells

Vaccines: LV-SMENP-DC and Recombinant Novel CoV Vaccine

Mesenchymal stem cells: Wharton's Jelly, Umbilical Cord-Derived, Dental pulp MSCs

ACE inhibitors: Lisinopril and Losartan

Life Sciences, Available online 8 May 2020, 117765, https://doi.org/10.1016/j.lfs.2020.117765

Resolvins and protectins
newly discovered compounds involved in mitigating inflammation

- Acute tissue inflammation is characterized by specific cellular events, including increased endothelial and epithelial permeability, infiltration of polymorphonuclear leukocytes (PMNs) and inflammatory macrophages and lymphocytes
- As the tissue resolves, barrier integrity is reestablished and further infiltration of PMNs is blocked. Cell clearance from the inflamed tissue is critical to resolution and is driven both by apoptosis of leukocytes

Haslett C. Resolution of acute inflammation and the role of apoptosis in the tissue fate of granulocytes. Clin Sci (Lond) 1992;83:639–48.
Rossi AG, Sawatzky DA, Walker A, et al. Cyclin-dependent kinase inhibitors enhance theresolution of inflammation by promoting inflammatory cell apoptosis. Nat Med. 2006;12:1056–64.
Savill JS, Wyllie AH, Henson JE, Walport MJ, Henson PM, Haslett C. Macrophage phagocytosis of aging neutrophils in inflammation. Programmed cell death in the neutrophil leads to its recognition by macrophages. J Clin Invest. 1989;83:865–75.

molecules

MDPI

Review

COVID-19 Prophylaxis Efforts Based on Natural Antiviral Plant Extracts and Their Compounds

Oksana Sytar [1,2,*], Marian Brestic [1,3,*], Shokoofeh Hajihashemi [4], Milan Skalicky [3], Jan Kubeš [3], Laura Lamilla-Tamayo [3], Ulkar Ibrahimova [5], Sayyara Ibadullayeva [5] and Marco Landi [6,*]

- Plants represent a major source of chemical-diversity on the planet, and it is likely that some safe and effective plant compounds can be found that could help to protect human lives from the devastation of COVID-19.
- The most promising compounds to develop plant-based drugs can be recommended the kaempferol glycosides, the scutellarein, baicalin and quercetin flavonoids; the saikosaponins triterpenoids; the lycorine, tetrandrine, fangchinoline, and cepharanthine alkaloids; the triterpene oleanane; and the terpene cycloart-25-ene-3b,24-diol.

Molecules 2021, 26, 727

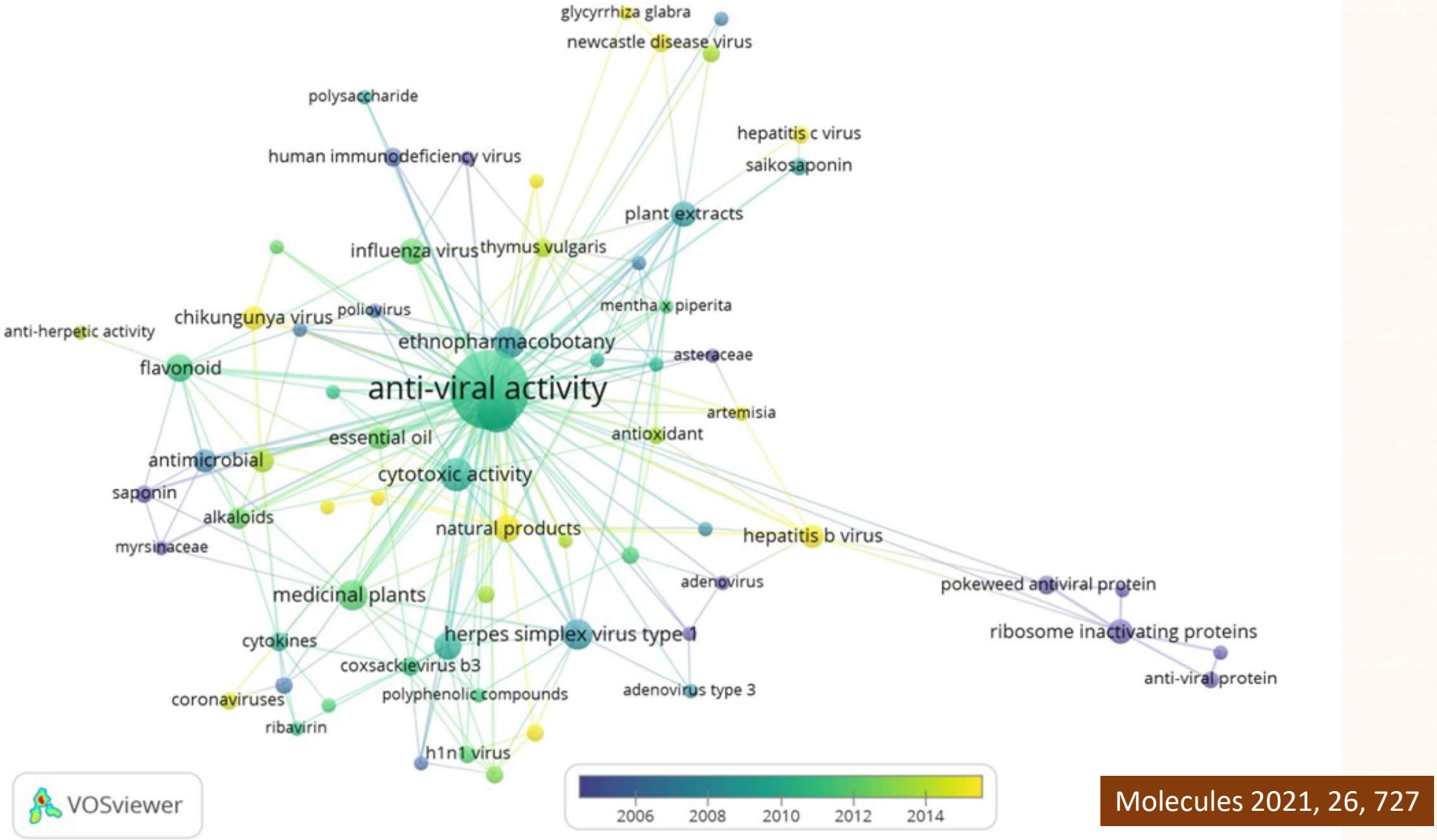
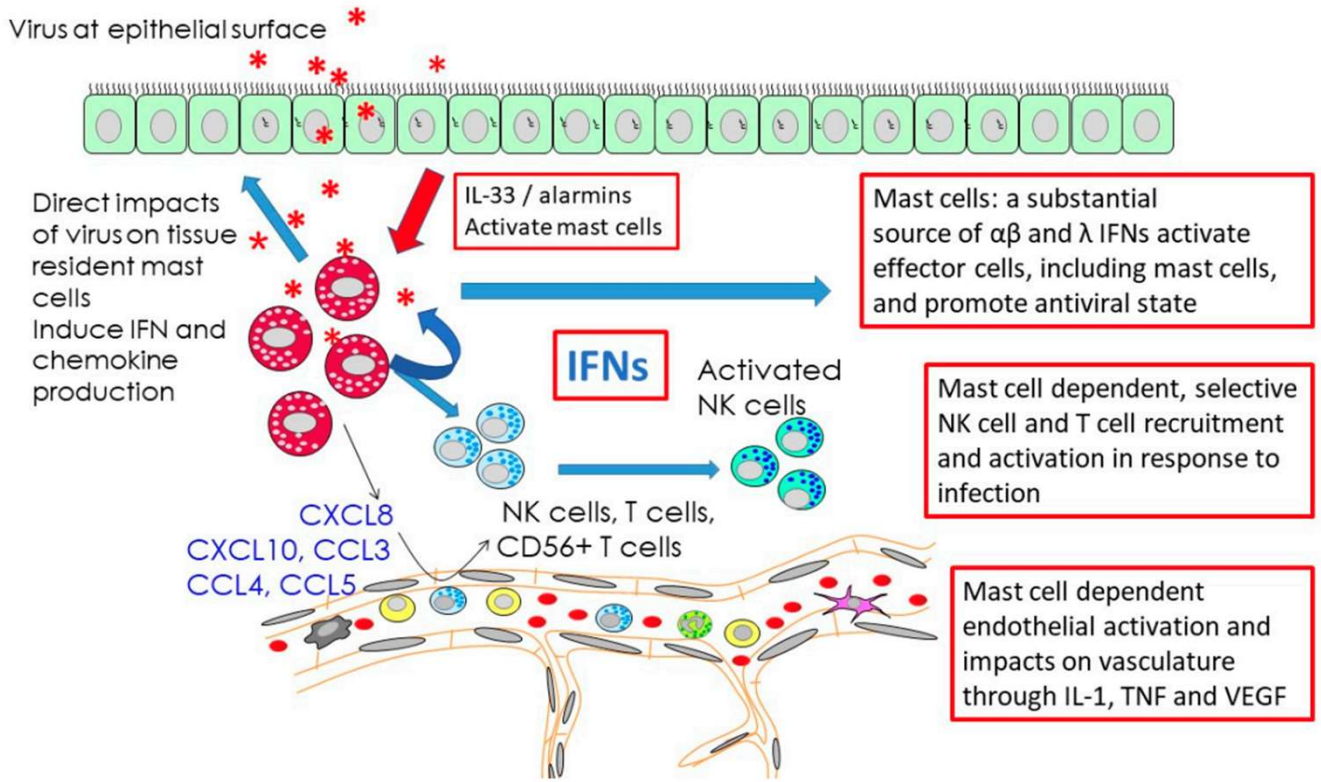


Figure 1. Schematic visualization of analyzed scientific data regarding the antiviral potential of natural plant resources.



Quercetin Is More Effective than Cromolyn in Blocking Human Mast Cell Cytokine Release
Quercetin inhibits histamine, IL-6, leukotrienes and PGD2

PLoS ONE | www.plosone.org
March 2012 | Volume 7 |
Issue 3 | e33805

- Selected, critical and early mast cell responses to viral infections can be activated directly by active viral infection or by contact with viral particles.
- They can also be activated by alarmins released as a result of infection of neighboring or epithelial cells

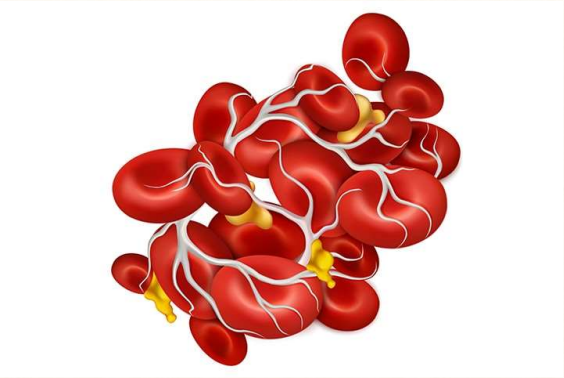
Reduced Vitamin K Status as A Potentially Modifiable Prognostic Risk Factor in COVID-19

- Vitamin K status was assessed by measuring desphospho-uncarboxylated matrix Gla protein (dp-ucMGP; inversely related to vitamin K status)
- We included 123 patients who were admitted with COVID-19 and 184 controls
- *Results:* Dp-ucMGP levels were significantly elevated in COVID-19 patients (1,673Å}1,584 pmol/L) compared to controls (536±291 pmol/L; p<0.0005)
- Dp-ucMGP levels were significantly higher in COVID-19 patients with unfavorable outcome compared to those with less severe disease

Dofferhoff, A.S.; Piscaer, I.; Schurgers, L.J.; Walk, J.; van den Ouweland, J.M.; Hackeng, T.M.; Lux, P.; Maassen, C.; Karssemeijer, E.G.; Wouters, E.F.; Janssen, R. Reduced Vitamin K Status as A Potentially Modifiable Prognostic Risk Factor in COVID-19. *Preprints* **2020**, 2020040457 (doi: 10.20944/preprints202004.0457.v1).

Severe COVID-19 and Hypercoagulation

- Systemic clotting problems emerging in severe and critically-ill COVID-19 patients
- Elevated D-dimer, a fibrin degradation product indicating thrombosis, at admission has also been linked to substantially higher odds of death in hospital among COVID-19 patients in Wuhan, China.
- Endothelial damage leading to subsequent clotting has been promoted as the mechanism



Zhang Y, et al "Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19" N Engl J Med 2020; DOI: 10.1056/NEJMc2007575.

Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study

Fei Zhou, Ting Yu*, Ronghui Du*, Guohui Fan*, Ying Liu*, Zhibo Liu*, Jie Xiang*, Yeming Wang, Bin Song, Xiaoying Gu, Lulu Guan, Yuan Wei, Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao*

Lancet 2020; 395: 1054–62

Published Online March 9, 2020 https://doi.org/10.1016/S0140-6736(20)30566-3

Summary

Background Since December, 2019, Wuhan, China, has experienced an outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Epidemiological and clinical characteristics of patients with COVID-19 have been reported but risk factors for mortality and a detailed clinical course of illness, including viral shedding, have not been well described.

- **d-dimer greater than 1 μg/mL could help clinicians to identify patients with poor prognosis at an early stage.**

The Nervous System, Endocrine and Immune System Relationship, Medicine Must Reflect This

- Central autonomic neural networks are informed of peripheral immune status via numerous communicating pathways
- Cytokines and other immune factors affect the level of activity and responsivity of discharges in sympathetic and parasympathetic nerves innervating diverse targets
- Interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interferon-α (IFN-α), lipopolysaccharide (LPS), and other inflammatory mediators, such as those from the cyclooxygenase pathway are regulated through cross-talk between systems
- The cytokine IL-1β mediates many of the diverse physiological responses of the acute-phase reaction

Compr Physiol. 2014 July ; 4(3): 1177–1200. doi:10.1002/cphy.c130051.

Biochemical and Biophysical Research Communications xxx (xxxx) xxx

Contents lists available at ScienceDirect

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

The broad spectrum host-directed agent ivermectin as an antiviral for SARS-CoV-2 ?

David A. Jans [a, *], Kylie M. Wagstaff [b]

[a] Nuclear Signaling Lab., Department of Biochemistry and Molecular Biology, Biomedicine Discovery Institute, Monash University, Melbourne, Australia

Ivermectin highly effective against COVID-19 both as a prophylactic

- Given the significant upsurge in cases of SARS-CoV-2 infection that has occurred in recent months, the use of ivermectin could reduce transmission-rates, as well as decrease short term morbidity and mortality in mild, moderate and even severe phases of the disease.
- In this regard, it has been shown that treatment with ivermectin could produce IgG titers for SARS-CoV-2 around 5 to 10 times higher as compared to the titrations of untreated patients in 85% of people who had come into contact with the virus asymptomatically (Ref. 1-7)

Ivermectin highly effective against COVID-19 both as a treatment

- Recently, a meta-analysis has been published analyzing mortality in 28 clinical trials. The odds of death was lower in the Ivermectin arm compared to the non-Ivermectin arm (OR 0.39, 95% CI 0.22-0.70; I2=81%). (9)
- Evidence regarding the effectiveness of ivermectin for the treatment of persistent COVID-19 symptoms is provided by two prospective observational studies conducted in 33 and 21 adult patients with post-acute symptoms of COVID-19, respectively. (10)
- In a trial of sixty-nine COVID-19 patients a single dose of ivermectin was well-tolerated in symptomatic patients with COVID-19, and important clinical features of COVID-19 were improved with ivermectin use, including dyspnea, cough, and lymphopenia (12)

Ivermectin highly effective against COVID-19 both as a treatment

- An earlier published meta-analysis study in Diabetes Metabolic Syndrome Journal that reviewed 9 randomized controlled trials comprised of 1788 patients found that Ivermectin was associated with decreased mortality in COVID-19
- The benefit of Ivermectin and mortality was reduced by hypertension, but was not influenced by age, sex, or diabetes
- A 56% reduction in mortality offered by Ivermectin means about 350,000 lives could have been saved from COVID-related deaths, and perhaps many more (11)

Ivermectin highly effective against COVID-19 both as a treatment

- A study reported and assessed 24 randomized trials totaling 3,328 patients that involved some type of control, whether it was standard of care or another therapy.
- Eight of the studies have been published, nine were preprints, six were unpublished results shared for the analysis, and one was reported on a trial registry website. In the 11 trials (totaling 2,127 patients) that focused on moderate or severe infection, there was a 56% reduction in mortality with Ivermectin usage. (13)
- Aguirre et al., carried out another study in 33 patients with subacute symptoms of COVID-19 between weeks 4 and 12 from the onset of symptoms. They received two consecutive daily doses of ivermectin 200 - 400 mg/kg depending on the severity of the symptoms. An improvement of symptoms (total or partial) was observed in 94% of patients, and a total improvement in 87.9% of them. (14)

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6. Chamie, Juan. Real-world evidence: the case of Peru. Causality between ivermectin and COVID-19 infection fatality rate. Availble in: https://www.researchgate. net/publication/344469305_Real-World_Evidence_The_Case_of_Peru_Causality_between_Ivermectin_and_COVID-19_Infection_Fatality_RateTaggedEnd accessed on December, 2020.

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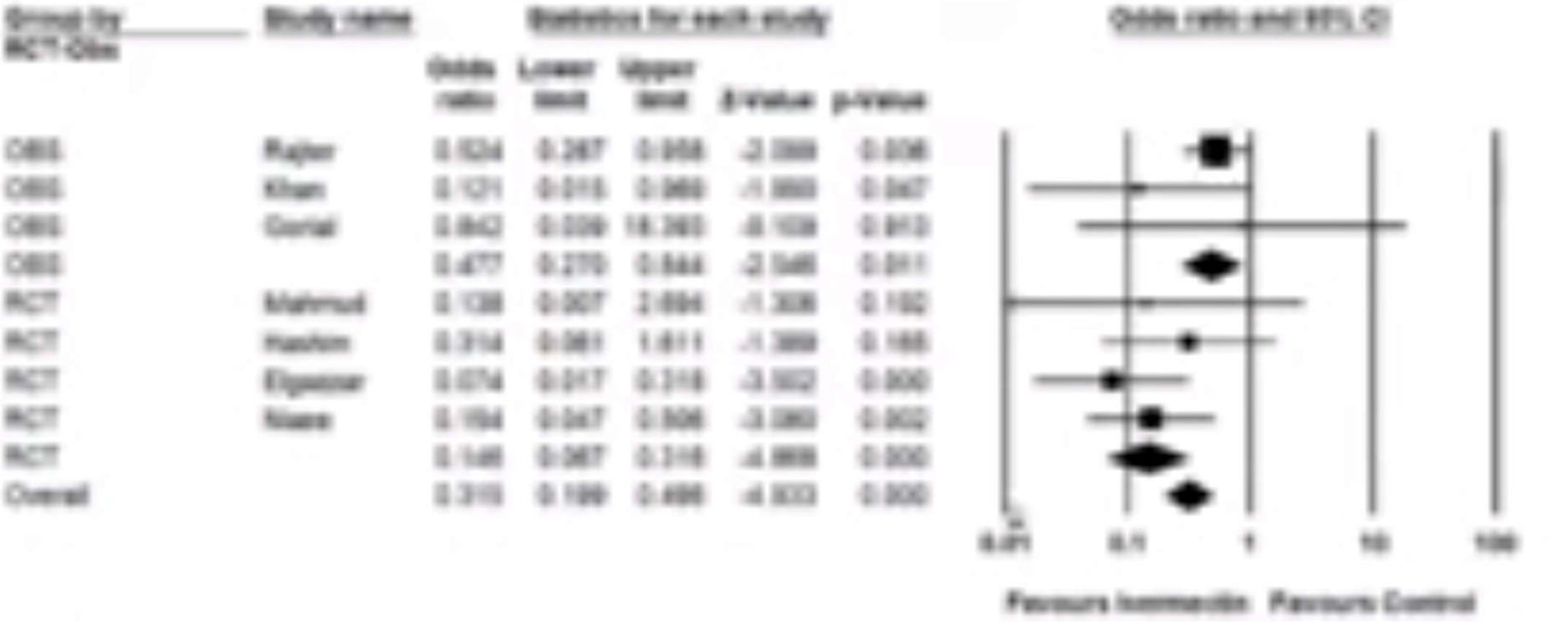
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12. Shahbaznejad L, Davoudi A, Eslami G, Markowitz JS, Navaeifar MR, Hosseinzadeh F, Movahedi FS, Rezai MS. Effects of Ivermectin in Patients With COVID-19: A Multicenter, Double-Blind, Randomized, Controlled Clinical Trial. Clin Ther. 2021 May 6:S0149-2918(21)00201-0. doi: 10.1016/j.clinthera.2021.04.007. Epub ahead of print. PMID: 34052007; PMCID: PMC8101859.
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14. Aguirre-Chang G, Saavedra G, Manuel Y, Trujillo-Figueredo Aurora, Cordova- Masías JA. Post-acute or prolonged covid-19: ivermectin treatment for patients with persistent symptoms or post-acute. https://www.researchgate.net/publication/344318845_POST-ACUTE_OR_PROLONGED_COVID-19_IVERMECTIN_TREATMENT_FOR_PATIENTS_WITH_PERSISTENT_SYMPTOMS_OR_POST-ACUTE (preprint) 2020
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16. Duthaler U, Suenderhauf C, Karlsson MO, Hussner J, Meyer Zu Schwabedissen H, et al. Population pharmacokinetics of oral ivermectin in venous plasma and dried blood spots in healthy volunteers. Br J Clin Pharmacol 2019;85(3):626–33. doi:10.1111/bcp.13840.
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Ivermectin: In-Hospital Studies

Mortality



Meta Analysis

Failed and Successful Rx for COVID-19 by Phase of Illness

	Pre-exposure/ Post-Exposure/ Incubation	Symptomatic Phase	Pulmonary/ inflammatory phase
Hydroxychloroquine	Unclear benefit	No benefit	↑Trend to harm
Remdesivir	n/a	↑ Reduced time to recovery No mortality benefit	No benefit
Lopinvar-Ritonavir	n/a	No benefit	No benefit
Interferon α/β	Inhaled ↑ Benefit	No benefit	↑Trend harm
Tocilizumab	n/a	n/a	No Benefit
Convalescent Serum	n/a	Unlikely	No Benefit
Corticosteroids	n/a	Trend to harm	BENEFIT
Ivermectin	BENEFIT	BENEFIT	BENEFIT

Mederi is Network Medicine

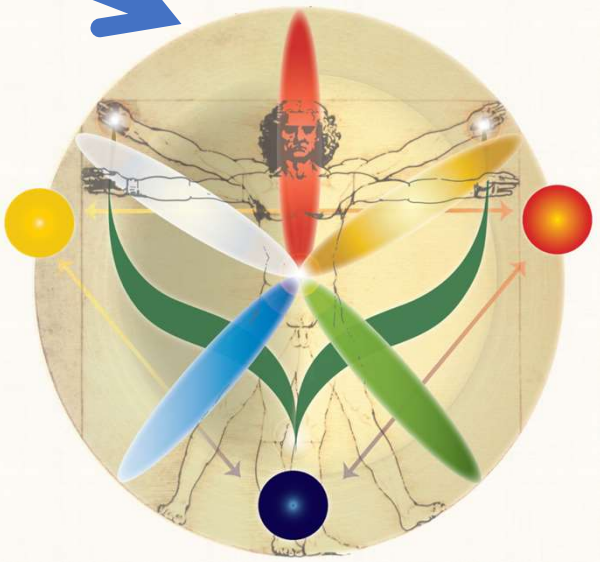
Essence Endocrine System

Heart Nervous System





Immune System



At the heart of us, there is a physiologic connection and rhythm between our divinity and our physical existence.

Stress Response System (Allostatic Overload)

Continued stress

↓

Body attempts to adapt

↓

Continues to release cortisol

↓

Down or up-regulates immune system

↓

Suppresses vital force

- fatigue, depression
- anxiety, insomnia
- gut health disturbances
- weight imbalance
- decreased sexual behavior
- altered cognition (neurodegeneration)
- Immune dysfunction
- autoimmune disease

→ Shortened Lifespan

Journal Pre-proof



Herbal medicine and pattern identification for treating COVID-19: a rapid review of guidelines

Lin Ang Hye Won Lee Jun Yong Choi Junhua Zhang Myeong Soo Lee

PII: S2213-4220(20)30039-1

DOI: https://doi.org/doi:10.1016/j.imr.2020.100407

Reference: IMR 100407

To appear in: *Integrative Medicine Research*

Received Date: 19 March 2020



Pharmacological Research

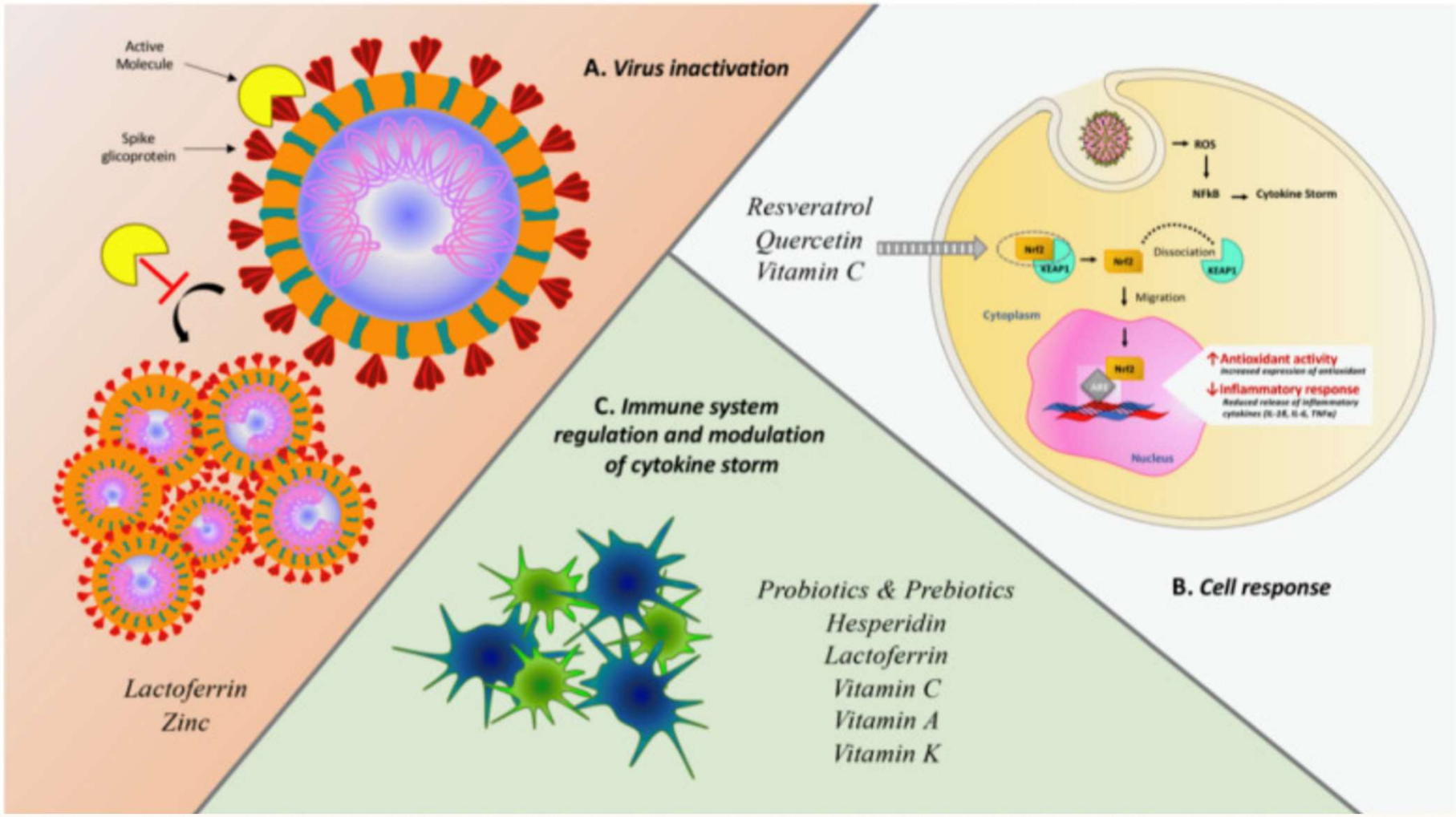
journal homepage: www.elsevier.com/locate/yphrs



Letter to the Editor

Traditional Chinese medicine for COVID-19 treatment





Parisi GF, Carota G, Castruccio Castracani C, Spampinato M, Manti S, Papale M, Di Rosa M, Barbagallo I, Leonardi S. Nutraceuticals in the Prevention of Viral Infections, including COVID-19, among the Pediatric Population: A Review of the Literature. Int J Mol Sci. 2021 Feb 28;22(5):2465. doi: 10.3390/ijms22052465. PMID: 33671104; PMCID: PMC7957644

Herbal Medicine
What makes it so special?

- The ultimate reality is that botanical medicine goes far beyond the grasp of mere intellect
- Herbal medicine is a kinship between the intellect (mind), and the mystical (spirit), and this needs to be acknowledged before the true healing potential of botanical medicine can be fully embraced by the modern medical world
- Within our body's herbs and herbal compounds play different roles in signaling pathways depending on the type of cell, disease and even stage of the disease.

Plants are good at combating viruses
Let take advantage - Xenohormesis!

- Healing with medicinal plants is as old as humankind itself.
- Plants respond to viruses using elaborate networks of genetic interactions.
- Viruses employ an array of elaborate strategies to overcome plant defense mechanisms and must adapt to the requirements of the host translational systems.
- Plants also induce hypersensitive and systemic acquired resistance responses, which together, limit the virus to infected cells and impart resistance to the noninfected tissues



Kranthi K. Mandadi and Karen-Beth G. Scholthof, Plant Immune Responses Against Viruses: How Does a Virus Cause Disease?The Plant Cell May 2013, 25 (5) 1489-1505; DOI: https://doi.org/10.1105/tpc.113.111658.

Xenohormesis: Understanding Biological Effects of Traditional Chinese Medicine From an Evolutionary and Ecological Perspective



- Emerging evidence suggests that hormetic phytochemicals produced by environmentally stressed plants can activate and moderate cellular stress-response mechanisms at a subtoxic level in humans, which may enhance tolerance against severe dysfunction or disease
- **Ginsenosides** regulate diverse evolutionarily conserved cellular stress response pathways by the subsequent stress tolerance against various dysfunctions or diseases
- **Ginseng (red) and Vitamin C increased immune cell activity and decreased lung inflammation induced by Influenza H1N1 Infection.**

HY Qi et al. Med Res Rev 38 (2), 625-654. Mar 2018. PMID 28586505. Zhongguo Zhong Yao Za Zhi, 38 (19), 3388-94 Oct 2013, *J Pharm Pharmacol*. 2016;68(3):406–420. doi:10.1111/jphp.12529

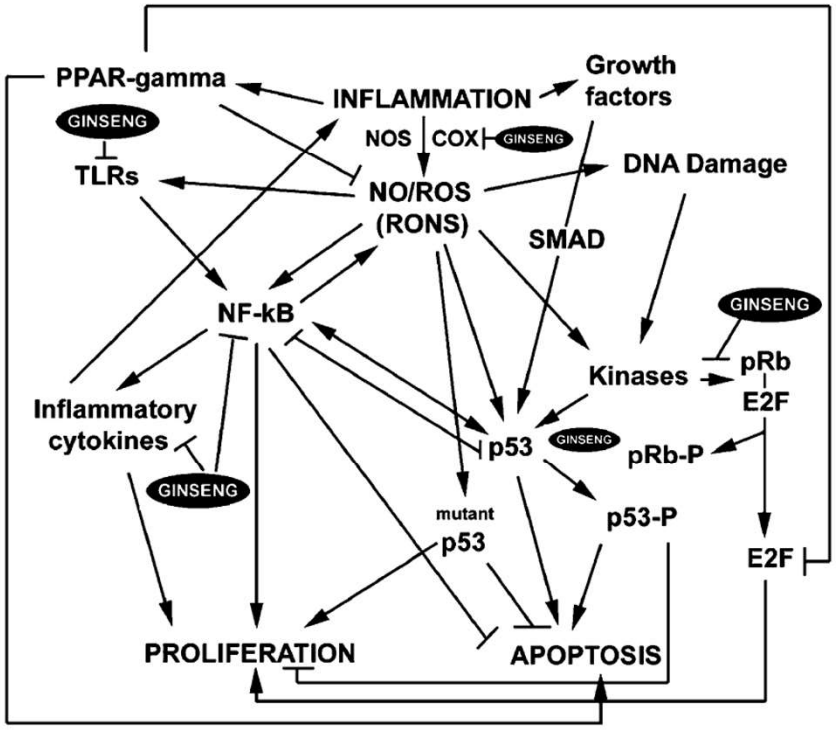
The Journal of Nutrition
International Research Conference on Food, Nutrition, and Cancer

Inflammation, Cancer, and Targets of Ginseng[1–3]

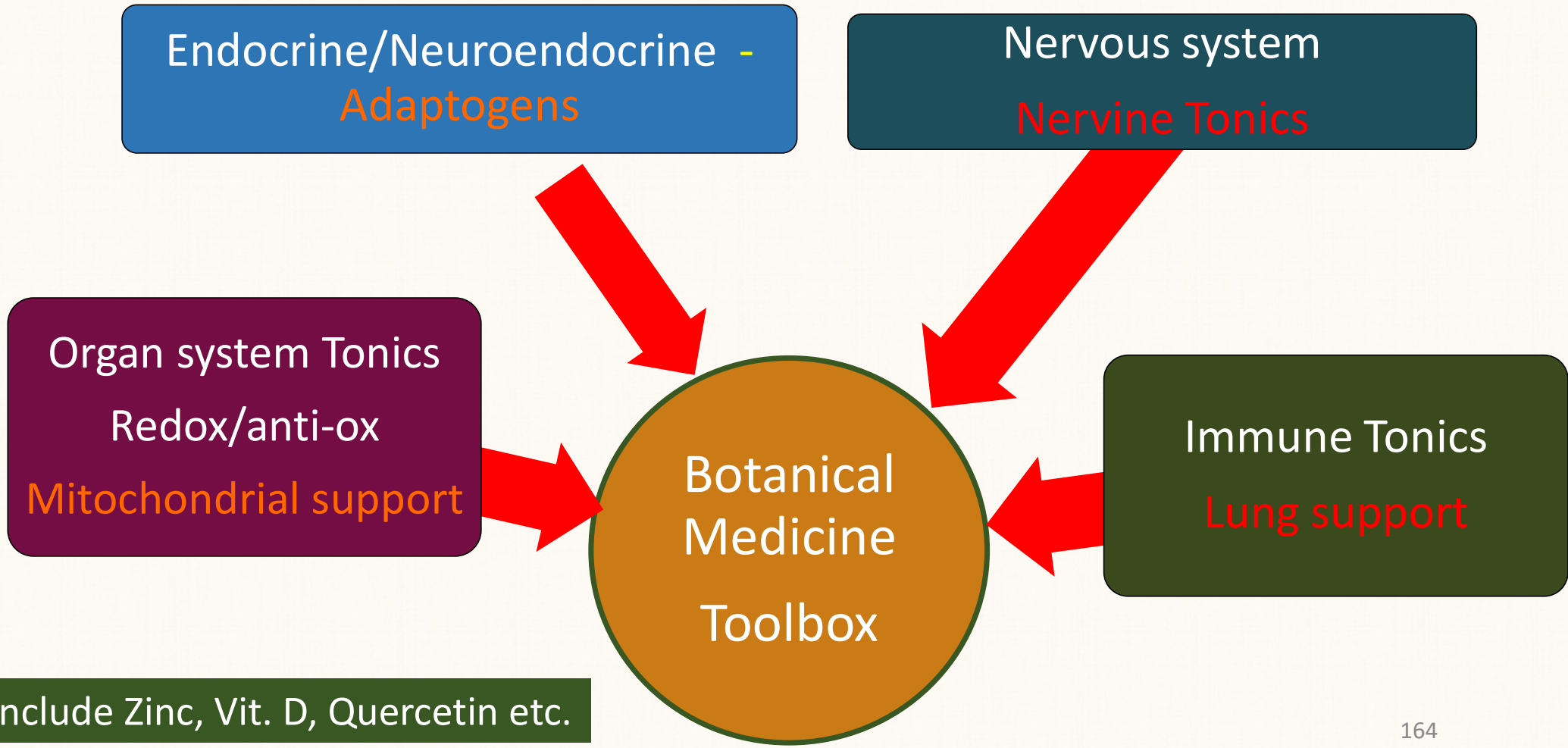
Lorne J. Hofseth[4]* and Michael J. Wargovich[5]

The ubiquitous effects of ginseng on key players involved in the inflammation-to-cancer sequence.

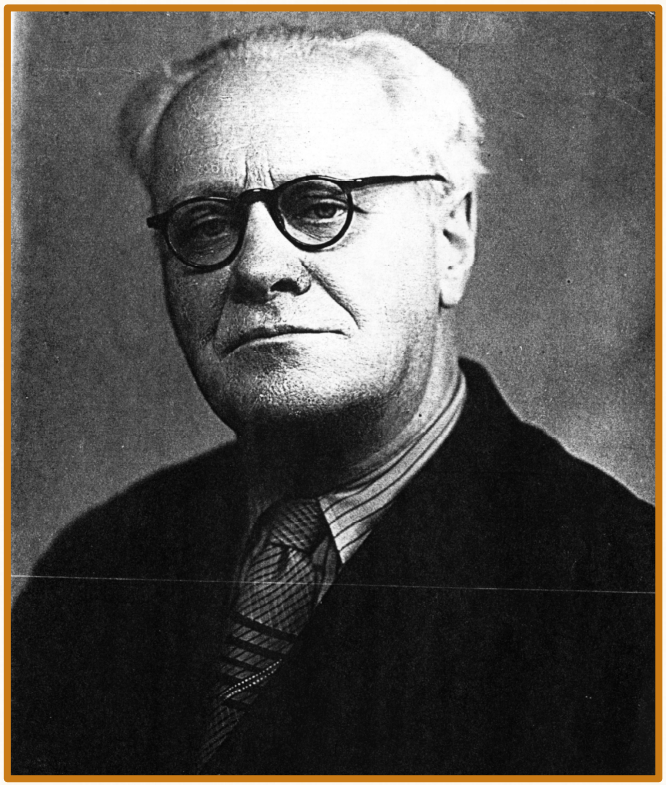
J. Nutr. 137: 183S–185S, 2007.



Prophylactic Deep Tonic Medicine for Immune Enhancement



Adaptogens Pave the Way for Naturally Restoring Health and Vitality



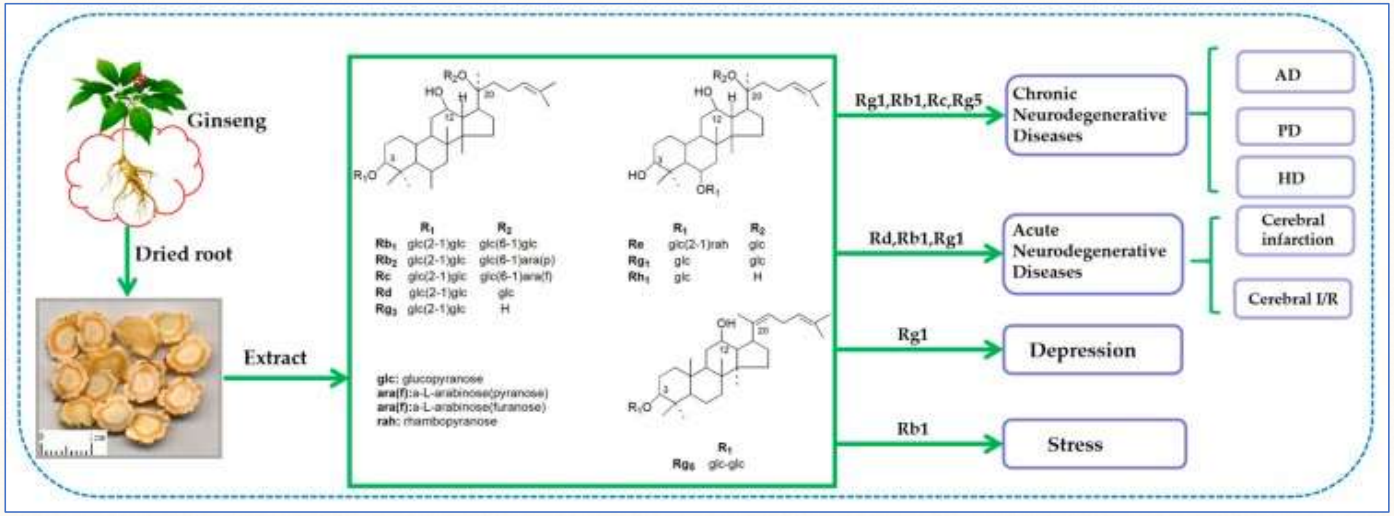
"Any substance that exerts effects on both sick and healthy individuals by 'correcting' any dysfunction(s) without producing unwanted side effects."

-- *Dr. Nickolai Lazarev*

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Adaptogens

- Adaptogens are “metabolic regulators, which increase the ability of an organism to adapt to environmental factors and to avoid damage from such factors”
- Adaptogens enhance immune surveillance
- Adaptogenic compounds affect key mediators of the adaptive stress response at intracellular and extracellular levels of communication



Ann. N.Y. Acad. Sci. 1401 (2017) 49–64 C 2017 Panossian, A., G. Wikman & H. Wagner. 1999. Plant adaptogens. III. Earlier and more recent aspects and concepts on their mode of action. Phytomedicine 6: 287–300.

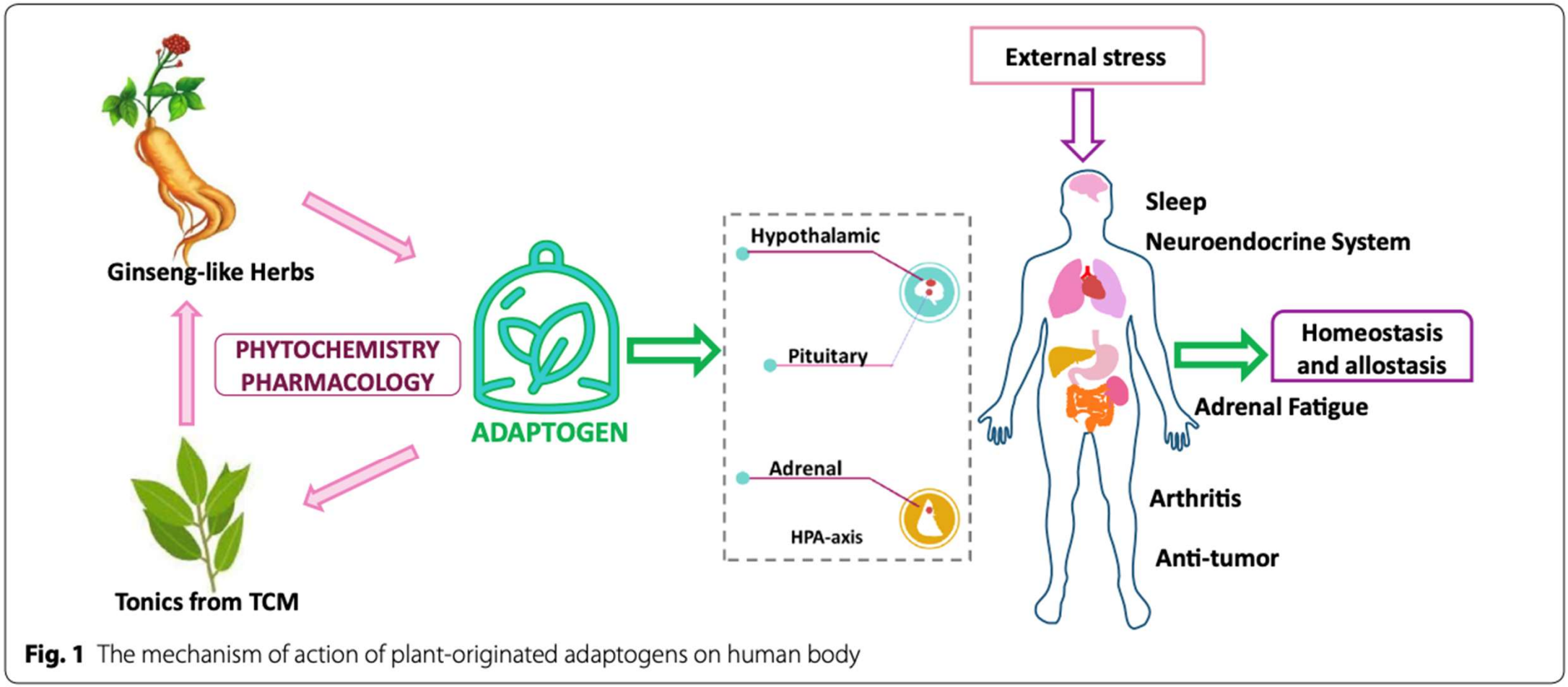


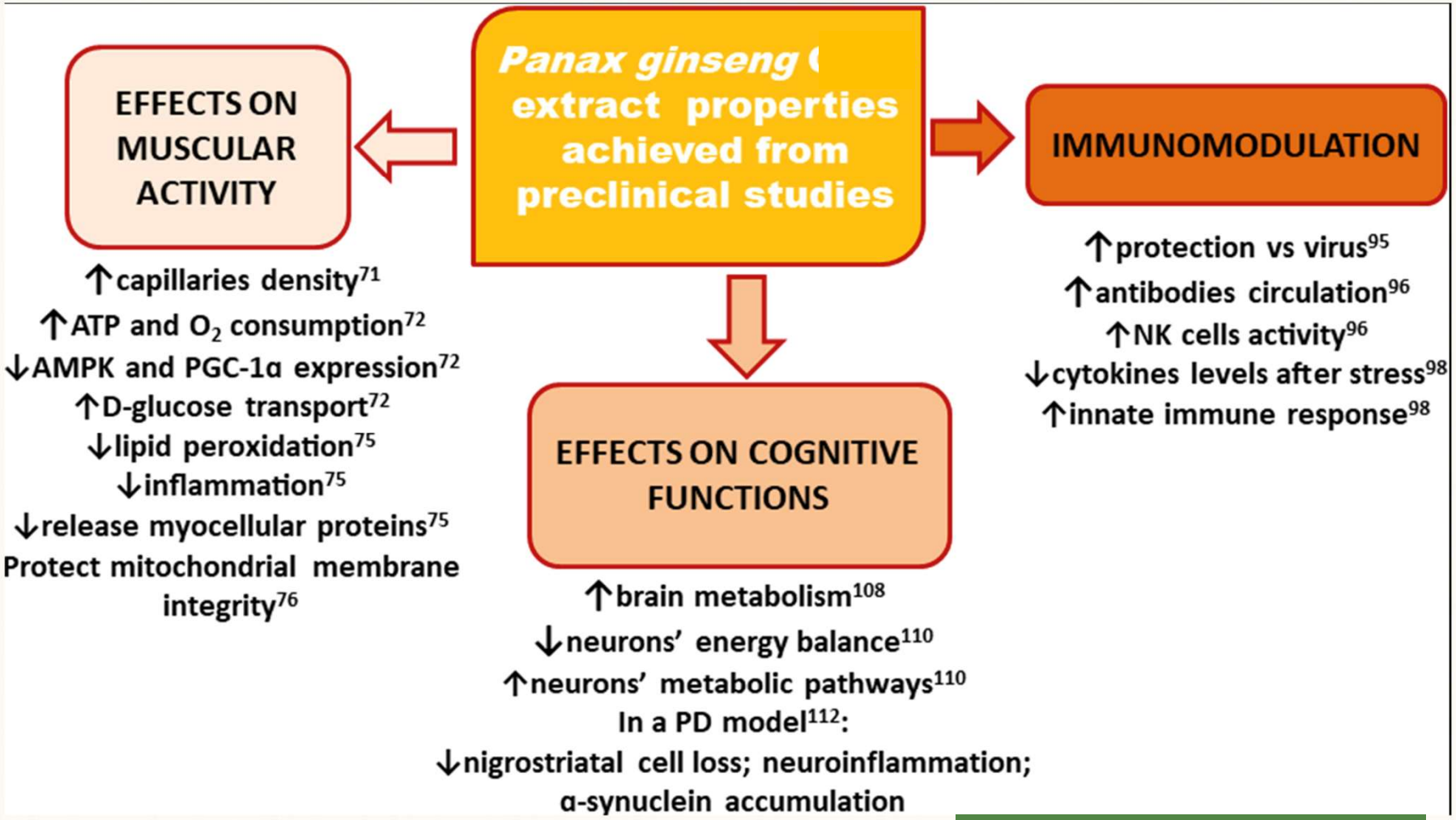
Fig. 1 The mechanism of action of plant-originated adaptogens on human body

Liao LY, He YF, Li L, et al. A preliminary review of studies on adaptogens: comparison of their bioactivity in TCM with that of ginseng-like herbs used worldwide. *Chin Med*. 2018;13:57. Published 2018 Nov 16. doi:10.1186/s13020-018-0214-9

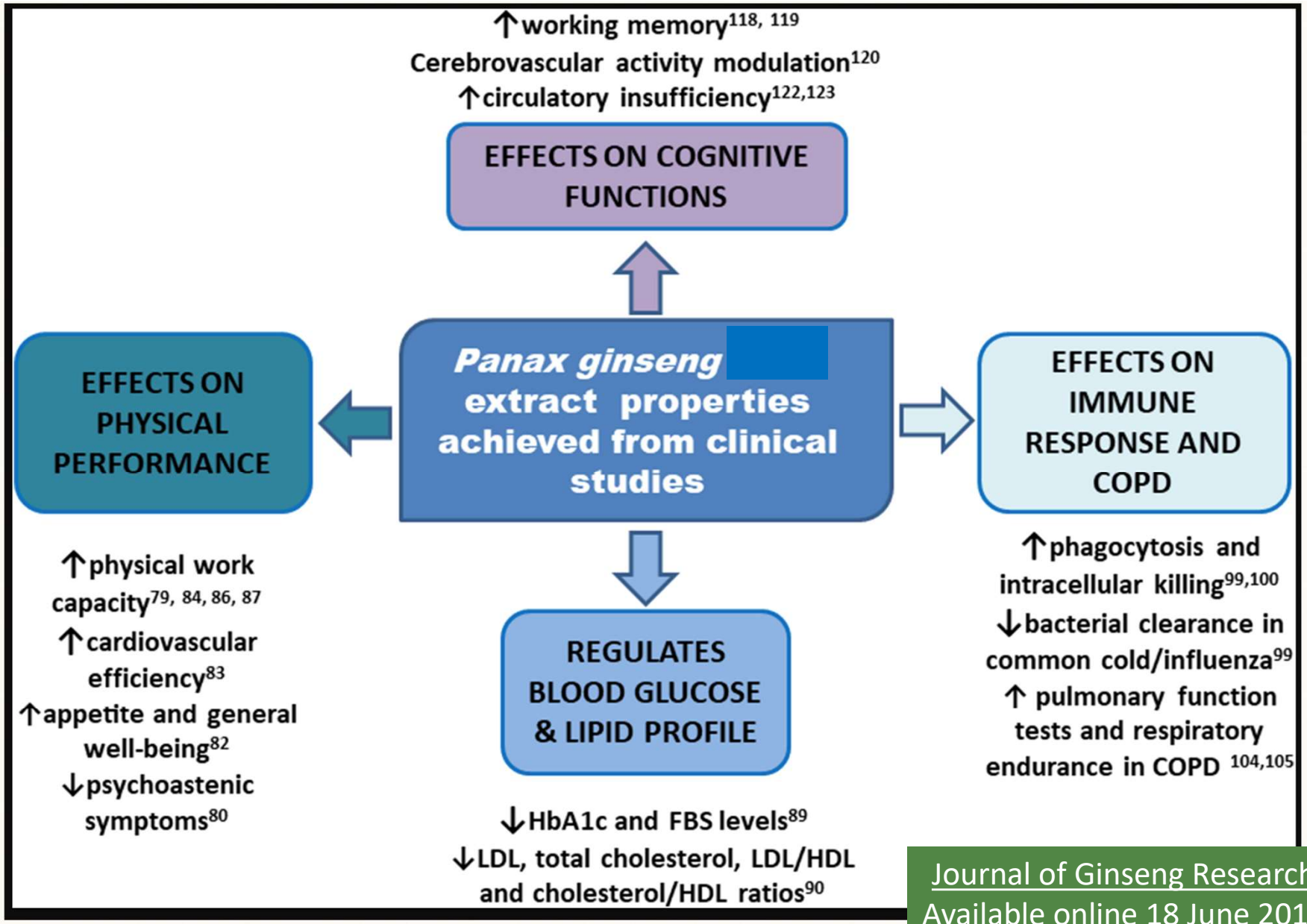
Adaptogenic Formula Immune Potentiating

- The well-known adaptogens and immunomodulators such as Rhodiola rosea, Withania somnifera, Bacopa monnieri, Emblica officinalis, Glycyrrhiza glabra, Asparagus racemosus, Ocimum sanctum and Panax notoginseng have significant antioxidant & anticarcinogenic properties due to the presence of various biologically active chemical compounds
- Their immunopotentiating activity is mediated through the modulation of T-cell immunity, transcription factors, some genes and factors associated with tumor development and progression
- The combinatory formulation of active immunostimulating constituents from these plants provides better homeostasis/allostasis

Kaur P, Robin, Makanjuola VO, Arora R, Singh B, Arora S. Immunopotentiating significance of conventionally used plant adaptogens as modulators in biochemical and molecular signalling pathways in cell mediated processes. Biomed Pharmacother. 2017 Sep 26;95:1815-1829. doi: 10.1016/j.biopha.2017.09.081. Review.



Journal of Ginseng Research
Available online 18 June 2019



Journal of Ginseng Research
Available online 18 June 2019

Effects of Adaptogens on the Central Nervous System

A.Panossian and G.Wikman

Arquivos Brasileiros de Fitomedicina Científica • Vol. 3 • número • april 2005

Effects of *Eleutherococcus senticosus, Rhodiola rosea,* and *Schisandra chinensis*

Adaptogens:

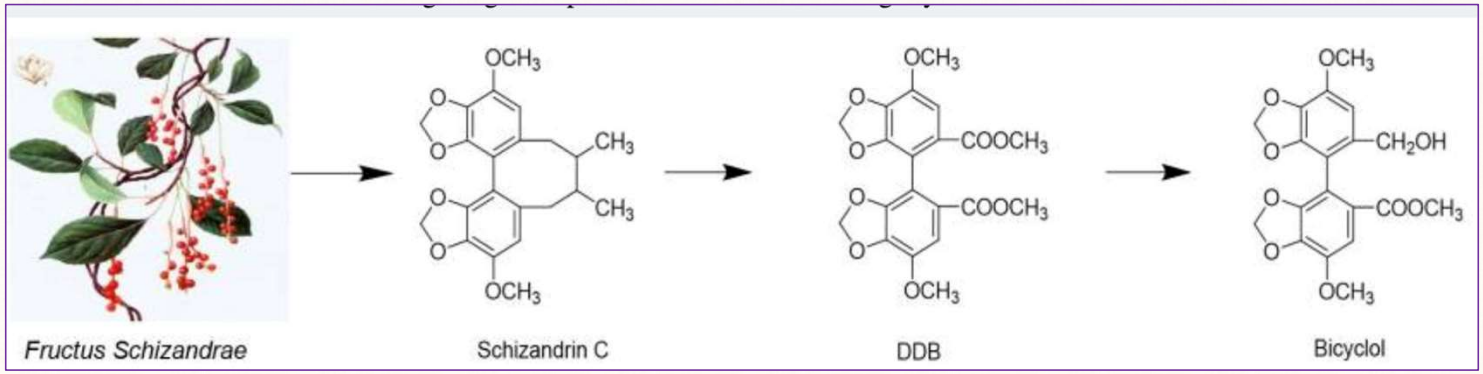
- are metabolic regulators that reduce the damaging effects of various stressors by virtue of a buffering of the reactivity of the host defense system
- They increase the ability of the organism to cope with stress, implying a curative effect on stress induced disorders
- The **mechanisms** of action relate to the

  1) regulation of the stress nervous system

  2) neuroendocrine

  3) immune complex, and are associated with the biochemical adaptation of cells and organisms to stress.

Schizandrin C



- Schizandrin C is the most active compound in protection against liver injury in mice.
- Bicyclol has been found to be highly effective in protection against liver injury and was also showed to inhibit hepatitis virus replication in vitro and in vivo.

Molecules. 2020 Jan; 25(1): 183.

Cornelius *et al. Immunity & Ageing* 2013, **10**:15
http://www.immunityageing.com/content/10/1/15



IMMUNITY & AGEING

REVIEW Open Access

Stress responses, vitagenes and hormesis as critical determinants in aging and longevity: Mitochondria as a "chi"

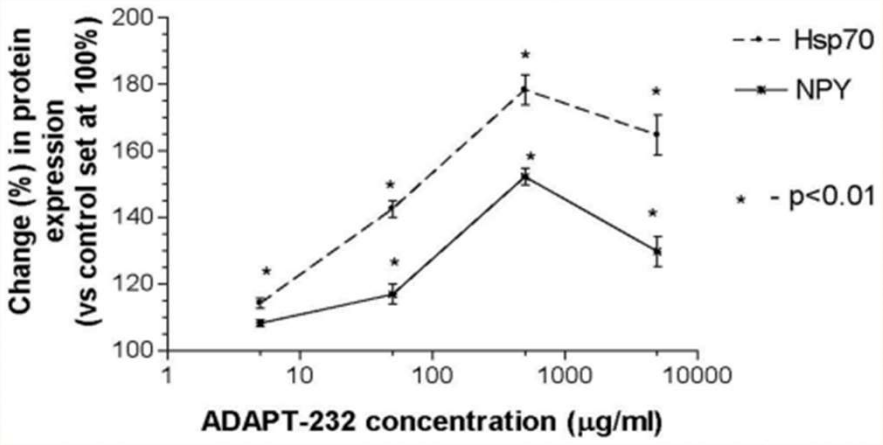
Carolin Cornelius[1], Rosario Perrotta[2], Antonio Graziano[2], Edward J Calabrese[3] and Vittorio Calabrese[1*]

Molecular Biomarkers for Adaptogens Acting on Vita-genes Stress Protectors

Adaptogens such as

- Eleutherococcus senticosus root
- Schisandra chinensis
- Rhodiola rosea root extracts

stimulated the expression and release of neuropeptide Y and molecular chaperone Hsp72 from isolated human neurolgia cells



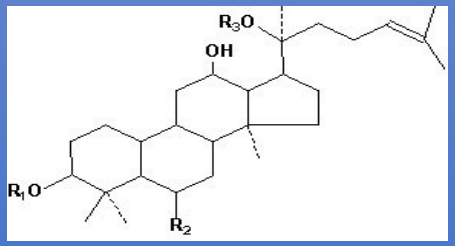
Adaptogen Formula

Asea A, Kaur P, Panossian A, Wikman KG. Evaluation of molecular chaperons Hsp72 and neuropeptide Y as characteristic markers of adaptogenic activity of plant extracts, Phytomedicine. 2013 Aug 3. pii: S0944-7113(13)00245-6. doi: 10.1016/j.phymed.2013.07.001; A, Wikman G, Kaur P, Asea A., Adaptogens stimulate neuropeptide y and hsp72 expression and release in neuroglia cells.Panossian Front Neurosci. 2012;6:6. doi: 10.3389/fnins.2012.00006.

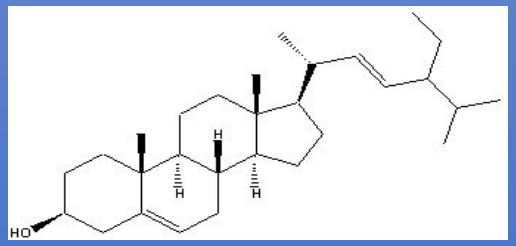
Some Adaptogenic Plants
Build Robustness • Autoregulation/Organization • Adaptation

Adaptogenic Plant	Main Compound
Panax ginseng (ginseng) & ***Panax q.***	Ginsenosides
Withania somniferum (ashwagandha)	Withanolides
Eleutherococcus senticosus	Eleutherosides
Astragalus membranaceus	Astragalosides
Ocimum sanctum (holy basil)	Triterpenic acids
Rhodiola rosea (rose crown)	Flavonoids
Schisandra chinensis (5 spice)	Lignans
Rhaponticum carthamoides (Leuzea)	Phytoecdysterones
Cordyceps sinensis	Cordycepic acid, cordycepin, vanadium

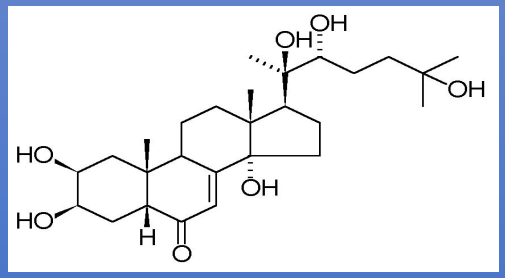
Active Compounds in Adaptogenic Plants



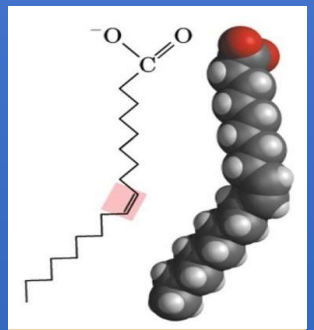
Triterpenes



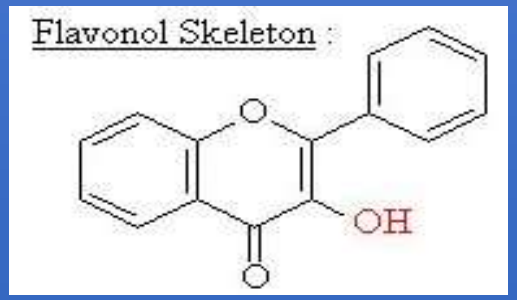
Phytosterols



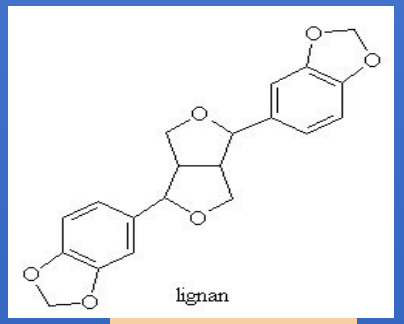
Phytoecdysterones



Fatty acids



Flavonoids



Lignans

176

Eleutherococcus Senticosus Antiviral Activity

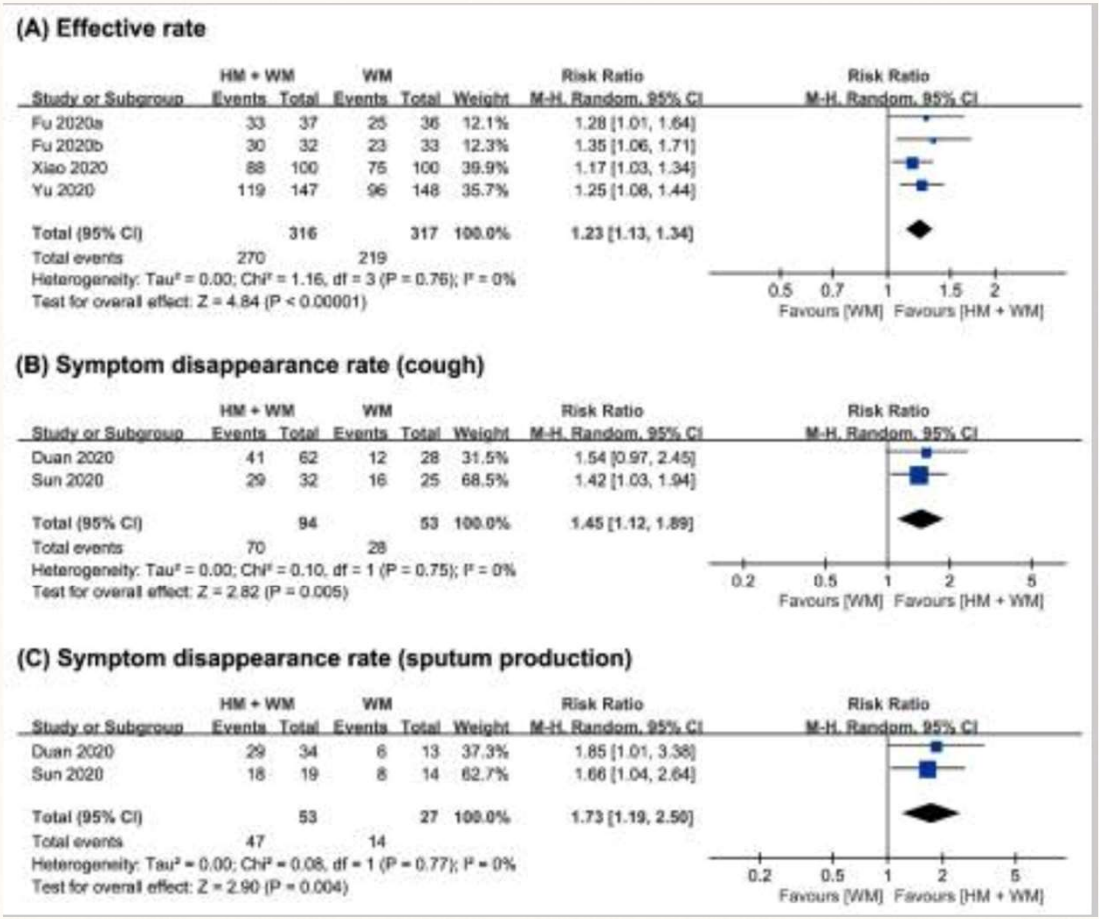
- A liquid extract from Eleutherococcus senticosus roots inhibited the productive replication of human rhinovirus (HRV), respiratory syncytial virus (RSV) and influenza A virus in cell cultures infected with these viruses, all of which belong to the RNA type viruses.
- The results of the study demonstrate that the Eleutherococcus extract inhibited the replication of all RNA viruses studied so far.
- Effect of eleutheroside B1 on non-coding RNAs and protein profiles of influenza A virus-infected A549 cells
- Eleutheroside B1 for use in the prevention and treatment of influenza A virus-mediated infections.

Antiviral Res. 2001;50(3):223–228. doi:10.1016/s0166-3542(01)00143-7; *International Journal of Molecular Medicine. 2020 Jan 17; 45(3): 753-768; Int J Mol Med*. 2018;42(5):2776–2792. doi:10.3892/ijmm.2018.3863

The Positive Effects of Herbal Medicine on COVID-19 A Cochrane Meta-analysis Review

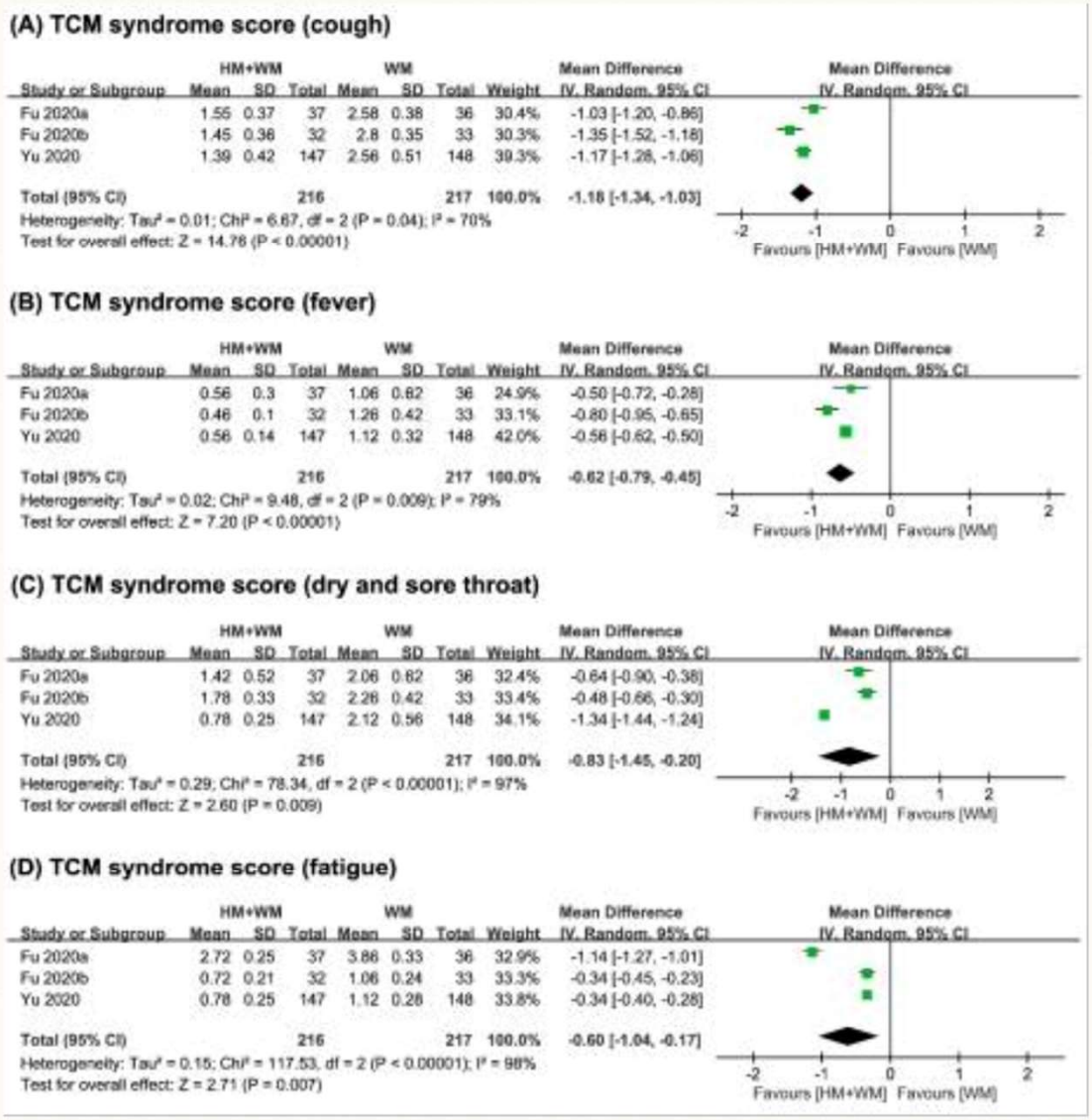
- This review aims to evaluate the effectiveness and adverse events of herbal medicines for the treatment of COVID-19. Methods: Twelve databases were searched through 12 May 2020. Randomized controlled trials (RCTs) and quasi-RCTs assessing the effects of herbal medicines for the treatment of COVID-19 were eligible. The study selection and data extraction were performed by two independent reviewers.
- Conclusion: Significant effects of the combined therapy of herbal medicine with Western medicine were found, and revealed the potential role of herbal medicine in treating COVID-19.

J Clin Med. 2020;9(5):1583. Published 2020 May 23. doi:10.3390/jcm9051583



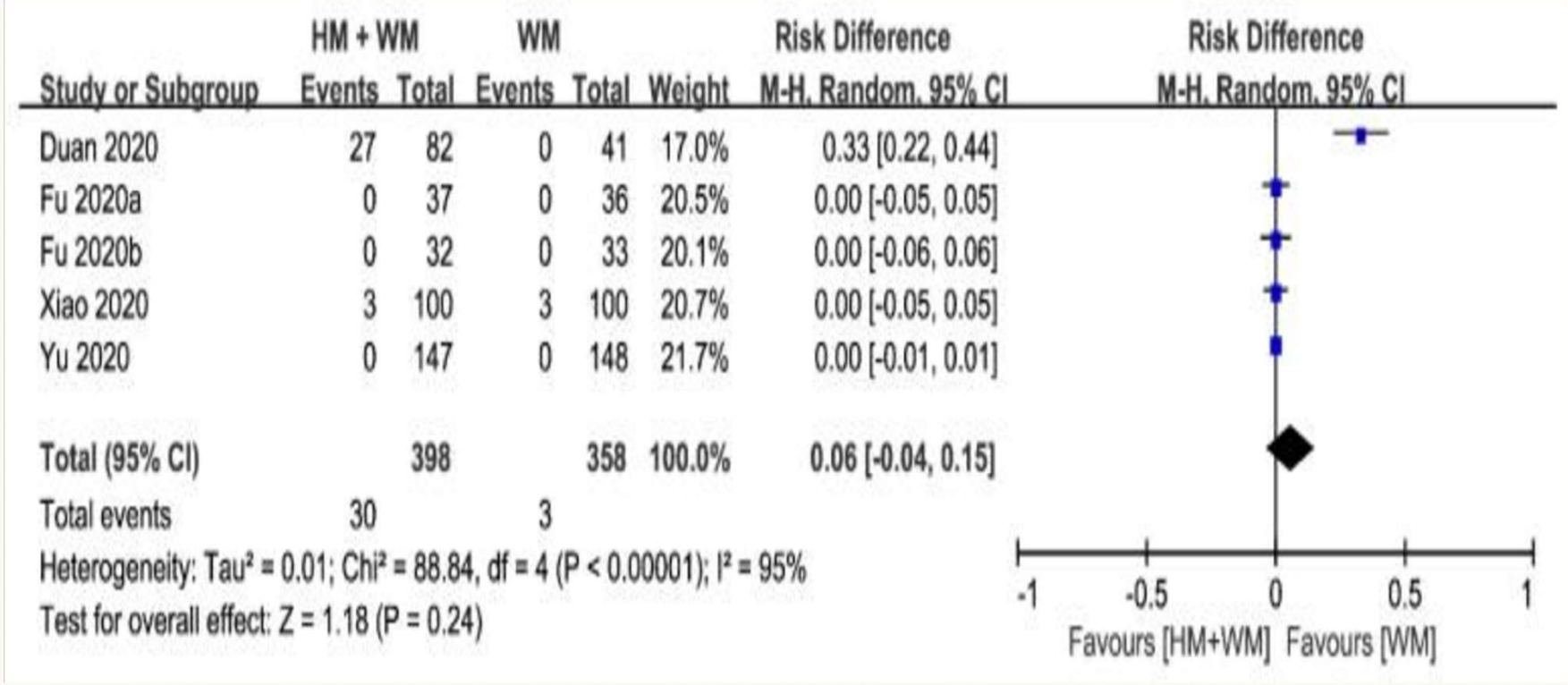
Comparison of herbal medicine and Western medicine (HM + WM) vs. Western medicine (WM) on (**A**) the total effective rate; (**B**) symptom disappearance rate of cough; and (**C**) sputum production.

J Clin Med. 2020;9(5):1583. Published 2020 May 23. doi:10.3390/jcm9051583



Comparison of herbal medicine and Western medicine (HM + WM) vs. Western medicine (WM) on TCM syndrome score of (**A**) cough; (**B**) fever; (**C**) dry and sore throat; (**D**) fatigue.

J Clin Med. 2020;9(5):1583. Published 2020 May 23. doi:10.3390/jcm9051583



Comparison of herbal medicine and Western medicine (HM + WM) vs. Western medicine (WM) on occurrence of adverse events.

J Clin Med. 2020;9(5):1583. Published 2020 May 23. doi:10.3390/jcm9051583

TCM herb formula used for Immune strengthening against SARS-CoV infection

- Yu Ping Feng:
  - San Astragali radix, **Astragalus** membranaceus, **Atractylodes** macrocephala, and Saposhnikoviae Radix
- Actions: Tonifying qi" to protect from external pathogens"
- Antiviral, anti-inflammatory and immunoregulatory effects

Yang Yang, Md Sahidul Islam, Jin Wang, Yuan Li and Xin Chen; Traditional Chinese Medicine in the Treatment of Patients Infected with 2019-New Coronavirus (SARS-CoV-2): A Review and Perspective Int. J. Biol. Sci. 2020; 16(10): 1708-1717. doi: 10.7150/ijbs.45538

Traditional Chinese Medicine Used for Prevention of Corona Virus Disease 2019 (COVID-19)? A Review of Historical Classics, Research Evidence and Current Prevention Programs

- There were 3 studies using TCM for prevention of SARS and 4 studies for H1N1 influenza. None of the participants who took TCM contracted SARS in the 3 studies.
- The main principles of TCM use were to tonify qi to protect from external pathogens, disperse wind and discharge heat, and resolve dampness.
- The most frequently used herbs included Radix astragali (Astragalus), Radix glycyrrhizae (Licorice), Rhizoma Atractylodis Macrocephalae (Atractylodes), Lonicerae Japonicae Flos (Honeysuckle), and Fructus forsythia (Forsythia).

Chin J Integr Med. 2020;26(4):243–250. doi:10.1007/s11655-020-3192-6

Traditional Chinese Herbal Medicine (TCM) for Prevention of Corona Virus Disease 2019 - A Review of Historical Classics, Research Evidence and Current Prevention Programs

- The use of TCM to prevent epidemics of infectious diseases was traced back to ancient Chinese practice cited in Huangdi's Internal Classic (Huang Di Nei Jing) where preventive effects were recorded.
- There were 3 studies using TCM for prevention of SARS and 4 studies for H1N1 influenza.
- None of the participants who took TCM contracted SARS in the 3 studies.
- The infection rate of H1N1 influenza in the TCM group was significantly lower than the non-CM group (relative risk 0.36, 95% confidence interval 0.24-0.52; n=4).

Luo H, Tang QL, Shang YX, et al. Can Chinese Medicine Be Used for Prevention of Corona Virus Disease 2019 (COVID-19)? A Review of Historical Classics, Research Evidence and Current Prevention Programs. *Chin J Integr Med*. 2020;26(4):243-250. doi:10.1007/s11655-020-3192-6

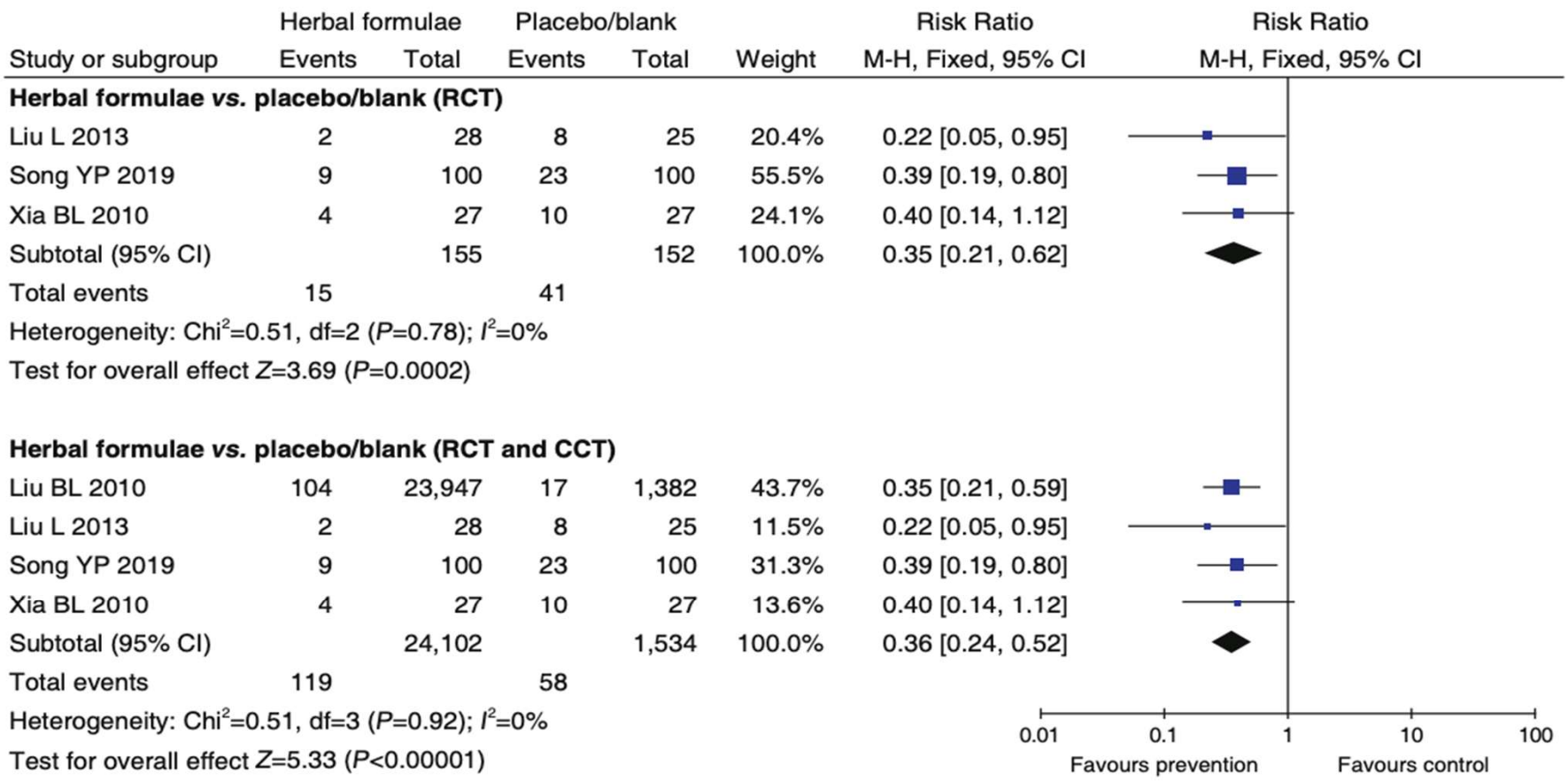


Figure 1. Meta-Analysis of Comparison between Chinese Medicine Prevention and Control (Blank or Placebo) on Infection Rate of H1N1 Influenza

Luo H, Tang QL, Shang YX, et al. Can Chinese Medicine Be Used for Prevention of Corona Virus Disease 2019 (COVID-19)? A Review of Historical Classics, Research Evidence and Current Prevention Programs. *Chin J Integr Med*. 2020;26(4):243-250. doi:10.1007/s11655-020-3192-6

- Of those, they selected six that “directly inhibited” SARS and Swine Flu (H1N1) infection. Not a single participant in the studies contracted SARS, and the rate of Swine Flu infection was significantly lower in the group that was treated with the following herbs:

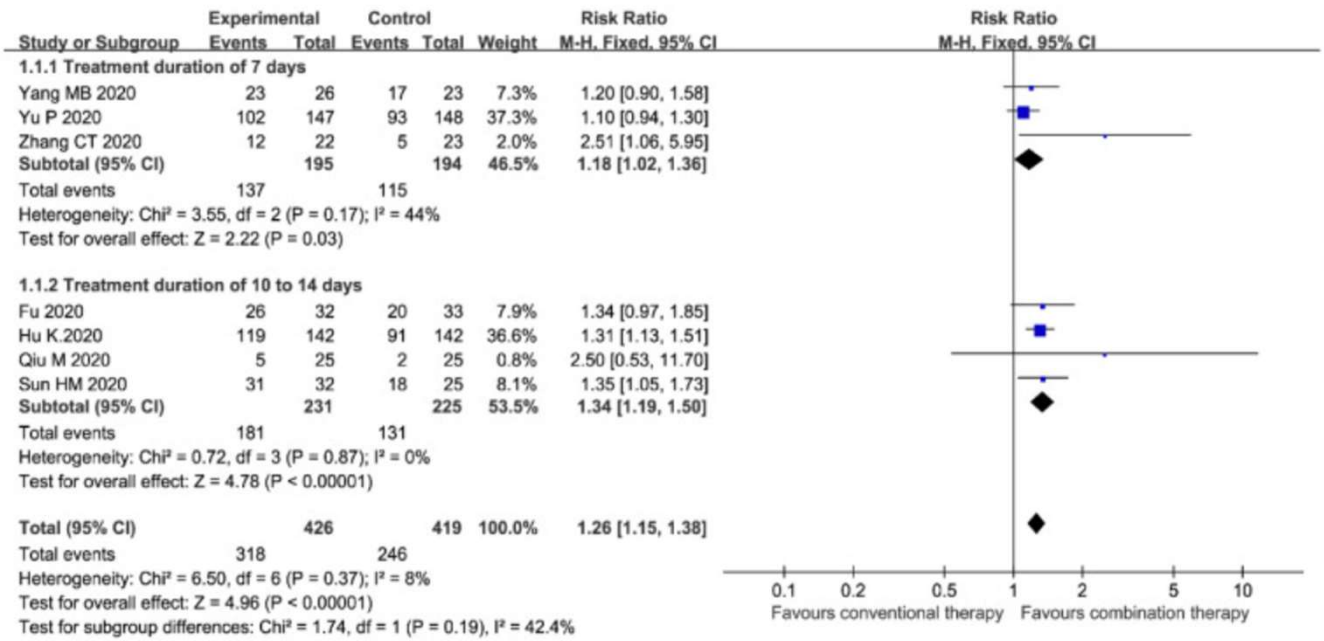
- **Radix astragali (Huangqi)**
- **Radix glycyrrhizae (Gancao)**
- **Radix saposhnikoviae (Fangfeng)**
- **Rhizoma Atractylodis Macrocephalae (Baizhu)**
- **Lonicerae Japonicae Flos (Jinyinhua)**
- **Fructus forsythia (Lianqiao)**

Luo H, Tang QL, Shang YX, et al. Can Chinese Medicine Be Used for Prevention of Corona Virus Disease 2019 (COVID-19)? A Review of Historical Classics, Research Evidence and Current Prevention Programs. *Chin J Integr Med*. 2020;26(4):243-250. doi:10.1007/s11655-020-3192-6

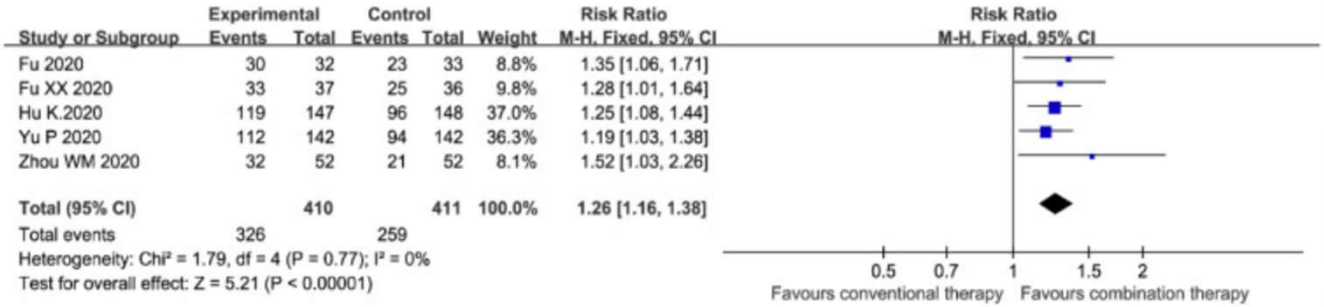
Chinese herbal medicine as an add-on in the treatment of mild to moderate COVID-19: A systematic review and meta-analysis

- Chinese herbal medicine (CHM) has played an indispensable role in treating COVID-19
- Twelve eligible RCTs including 1393 participants were included in this meta-analysis
- Chinese herbal medicine combined with conventional therapy was found to be effective and safe in the treatment of mild to moderate COVID-19

Du X, Shi L, Cao W, Zuo B, Zhou A. Add-on effect of Chinese herbal medicine in the treatment of mild to moderate COVID-19: A systematic review and meta-analysis. PLoS One. 2021 Aug 20;16(8):e0256429. doi: 10.1371/journal.pone.0256429.

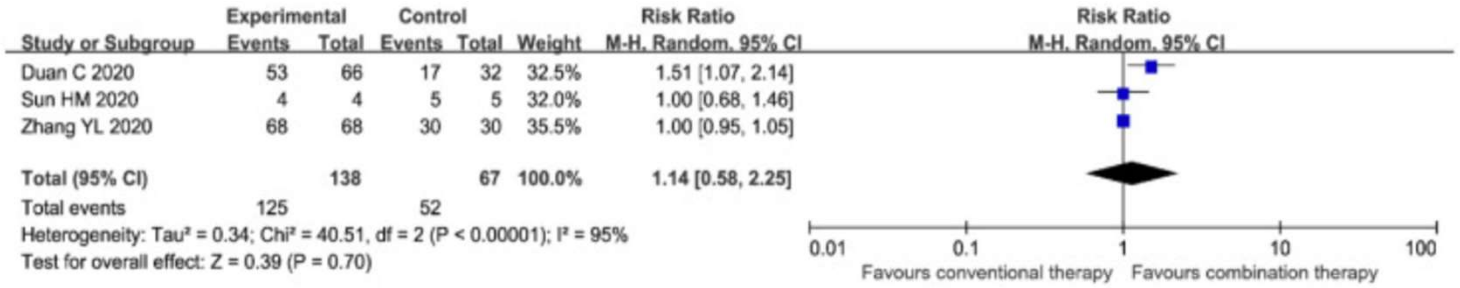


(a) Lung CT.

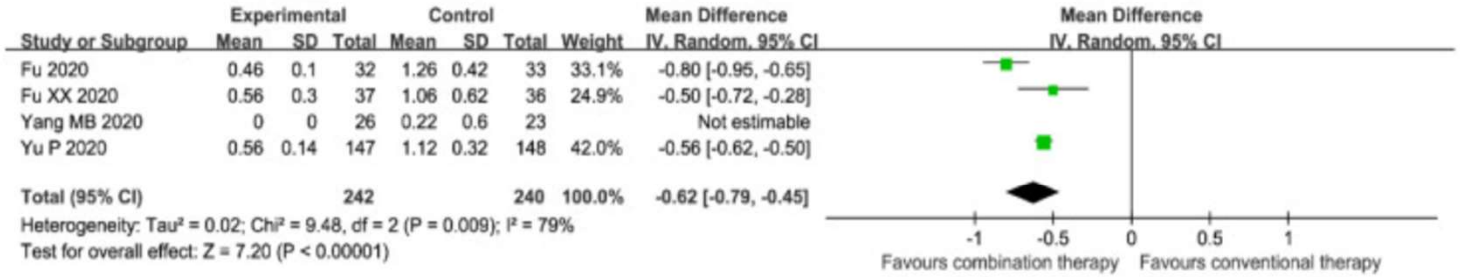


(b) Clinical cure rate.

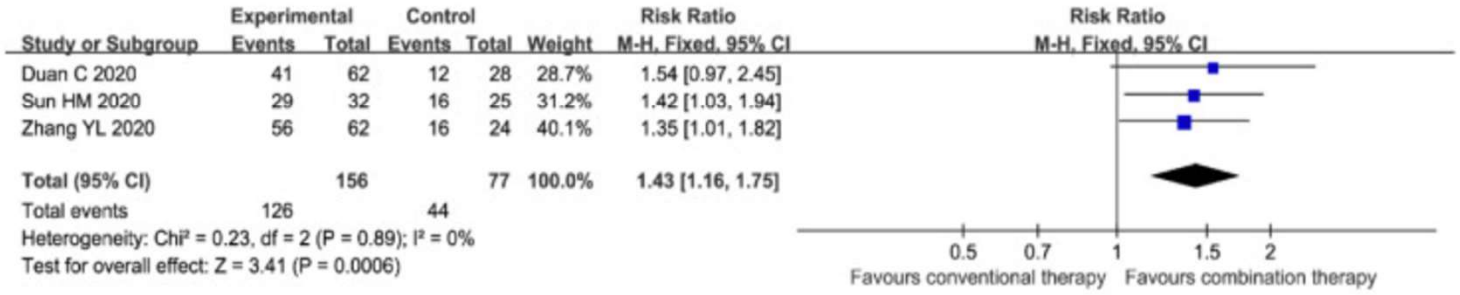
PLoS One. 2021 Aug 20;
16(8):e0256429.
doi: 10.1371/journal.pone.0256429.



(a) Fever reduction cases.

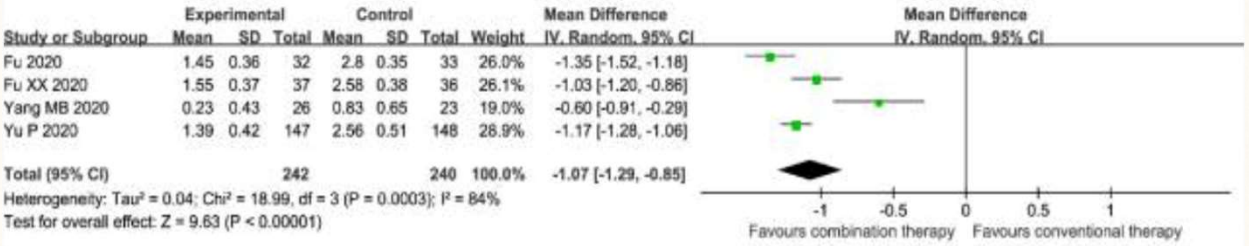


(b) TCM symptom score of fever.

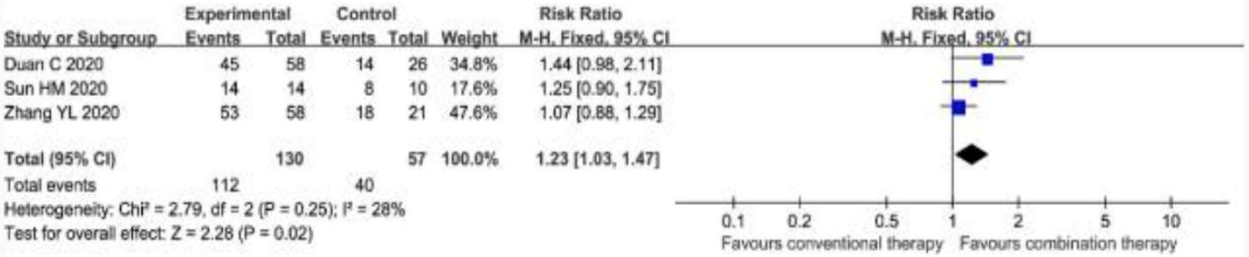


PLoS One. 2021 Aug 20;16(8):e0256429. doi: 10.1371/journal.pone.0256429.

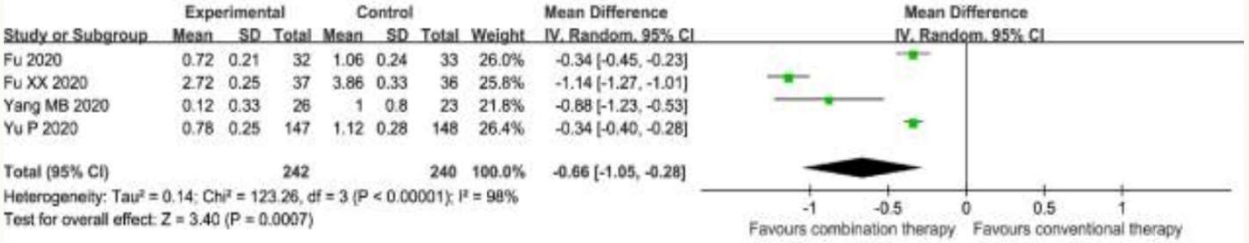
(c) Cough reduction cases.



(d) TCM symptom score of cough.



(e) Fatigue reduction cases.



(f) TCM symptom score of fatigue.

PLoS One. 2021 Aug 20;16(8):e0256429. doi: 10.1371/journal.pone.0256429.

Soshihotang herbal formula may be a new treatment option for COVID-19

- Soshihotang (SSHT, *Xiao Chai Hu Tang* in Chinese) has been prescribed to treat various viral diseases and is used in combination with other herbal medicines depending on the patient's symptoms
- SSHT is made up of Bupleuri Radix, Scutellariae Radix, Pinelliae Tuber, Ginseng Radix, Zingiberis Rhizoma Recens, Zizyphi Fructus, Glycyrrhizae Radix et Rhizom
- In a number of recent COVID-19 clinical studies, treatment with SSHT improved the infection status of the respiratory and hepatobiliary systems, and experimental studies demonstrated the antiviral effect of SSHT and its components

Kwon S, Lee W, Jin C, et al. Could herbal medicine (Soshihotang) be a new treatment option for COVID-19?: a narrative review. *Integr Med Res*. 2020;9(3):100480. doi:10.1016/j.imr.2020.100480

Herbal medicine (Xuanfei Baidu decoction) combined with conventional drug highly effective in treating COVID-19

- Forty-two patients with COVID-19 were randomly assigned to XBD plus conventional medicine (n = 22) and conventional medicine alone (n = 20). Both groups were treated for 1 week
- XBD combined with conventional medicine may significantly improve patient's clinical symptoms, increase the number of white blood cells and lymphocytes to improve immunity, and also significantly reduce C-reactive protein and erythrocyte sedimentation rate to play an anti-inflammatory effect

Xiong WZ, Wang G, Du J, Ai W. Efficacy of herbal medicine (Xuanfei Baidu decoction) combined with conventional drug in treating COVID-19:A pilot randomized clinical trial. *Integr Med Res*. 2020;9(3):100489. doi:10.1016/j.imr.2020.100489

IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Medical Sciences

2021; 18(3): 646-651. doi: 10.7150/ijms.52664

Research Paper

Clinical characteristics and impacts of traditional Chinese medicine treatment on the convalescents of COVID-19

Ya-Wen An[1], Bo Yuan[2], Jian-Chun Wang[1], Cheng Wang[2], Ting-Ting Liu[3], Shuo Song[1]✉, Han-Qing Liu[1]✉

- A total of 372 COVID-19 convalescents from February 21 to May 3 in Shenzhen, China were retrospectively analyzed, 291 of them accepted clinically examined at least once and 191 convalescents accepted TCM.
- The beneficial effects included balanced immune response, improved hematopoiesis and coagulation systems, enhanced functions of liver and heart, increased nutrient intake and lipid metabolism.

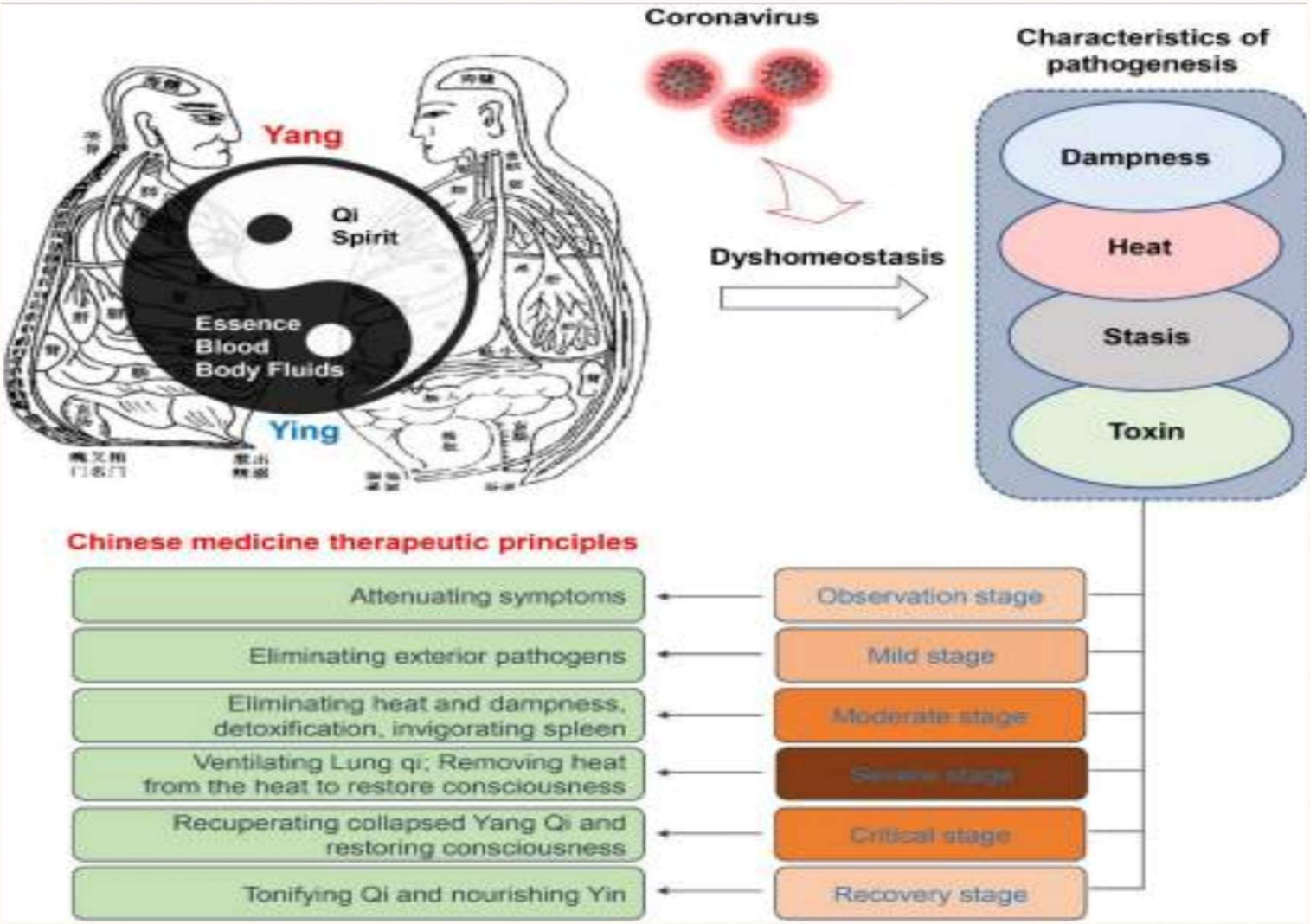
EDITORIAL

Touting Traditional Knowledge and Herbal Medicine to Combat and Prevent COVID-19

Selvaraj Arokiaraj[1,†], Savariar Vincent[2,†,*] and Dinesh K. Vannam[2]

[1]*Department of Food Science & Biotechnology, Sejong University, Seoul 05006, Republic of Korea;* [2]*Centre for Environmental Research and Development (CERD), Loyola College, Nungambakkam, Chennai 600 034, India*

- During the outbreak of SARS in China, 50 ± 10 % infected patients were given the traditional Chinese medicine along with modern medical procedures, at some stages of their therapy.
- This synergistic administration was approved and supported by the Chinese Center for Disease Control and Prevention, and further information on the herbal treatment were recommended to other practitioners



Luo H, Gao Y, Zou J, Zhang S, Chen H, Liu Q, Tan D, Han Y, Zhao Y, Wang S. Reflections on treatment of COVID-19 with traditional Chinese medicine. Chin Med. 2020 Sep 3;15:94. doi: 10.1186/s13020-020-00375-1. PMID: 32905189; PMCID: PMC7468089.

Clinical Nutrition ESPEN 44 (2021) 50–60

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Narrative Review

Dietary supplements and herbal medicine for COVID-19: A systematic review of randomized control trials

Zitong Feng [a, 1], Juan Yang [b, 1], Mingzhu Xu [c, 1], Run Lin [d], Huijun Yang [d], Liting Lai [a], Yixiao Wang [c], Dietlind L. Wahner-Roedler [b], Xuan Zhou [e], Kyung-Min Shin [b], Manisha Salinas [f], Molly J. Mallory [b], Chunzhi Tang [a], David C. Patchett [g, h, ***], Brent A. Bauer [b, **], Shaoyang Cui [a, d, *]

- **Results:** Out of 9402 records identified in the initial search, twelve RCTs were included in this review. Risk of bias of these RCTs was deemed high. Most of the trials were of low methodologic quality.
- Nine studies showed herbal supplements were beneficial to the recovery of COVID-19 patients; zinc sulfate could shorten the duration of loss of smell but not total recovery from COVID-19. No severe adverse events were reported.
- **Conclusion:** Herbal supplements may help patients with COVID-19, zinc sulfate is likely to shorten the duration of olfactory dysfunction.
- Dietary Supplements therapy and herbal medicine appear to be safe and effective adjuvant therapies for patients with COVID-19.

β-glucan (Medicinal mushroom) Restores Tumor-Educated Dendritic Cell Maturation to Enhance Immune Responses

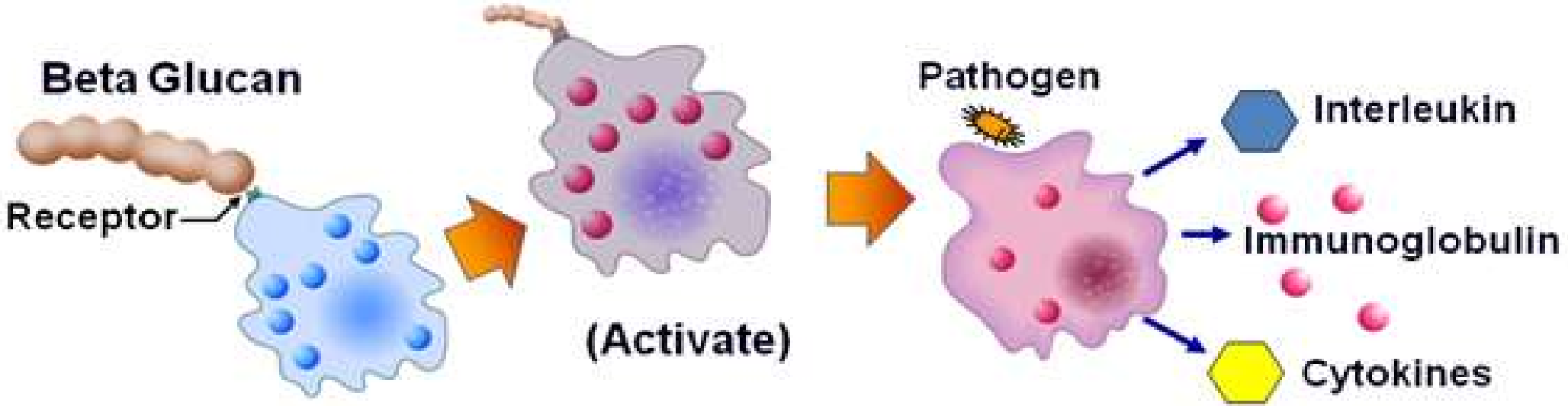
- Although dendritic cell-based cancer vaccines can initiate antitumor immune responses, tumor-educated dendritic cells (TEDCs) involved in the tolerance induction have attracted much attention recently
- Treatment with β-glucan drastically decreased the levels of regulatory T (Treg) cells, but increased the infiltration of macrophages, granulocytes and DCs in tumor masses, thus elicited Th1 differentiation and cytotoxic T-lymphocyte responses and led to a delay in tumor progression.

Reishi (*Ganoderma lucidum*)



Ning Y, Xu D, Zhang X, Bai Y, Ding J, Feng T, Wang S, Xu N, Qian K, Wang Y, Qi C. β-glucan Restores Tumor-Educated Dendritic Cell Maturation to Enhance Antitumor Immune Responses, Int J Cancer. 2016 Jun 1;138(11):2713-23. doi: 10.1002/ijc.30002. Epub 2016 Feb 8.

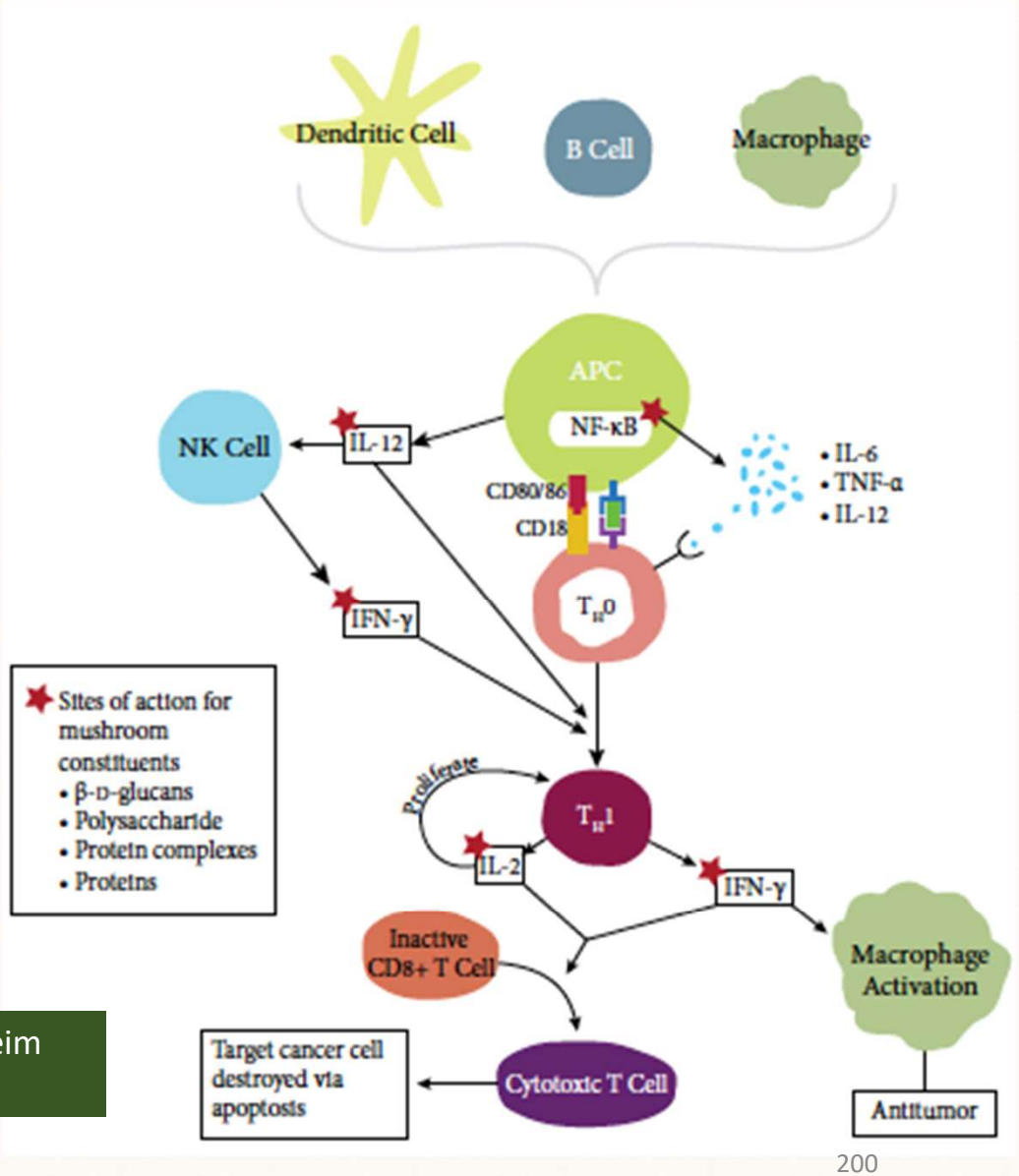
Beta Glucan Leading a Helping Hand to Immune cells



Macrophage activation via cell surface receptor

Eur J Immunol. 2013 May;43(5):1220-30.

- Daily prophylactic oral dosing of Beta-glucan has shown to have a protective effect against flu virus
- Beta glucan increases host immune defenses, activates white blood cells, which in turn can recognize and kill viruses and tumor cells, corrects oxidative damage, and speeds up the recovery of damaged tissue.



Integrative M 38 Medicine • Vol. 13, No. 1 • February 2014 Guggenheim —Mushrooms and Integrative Oncology

Cordyceps Sinensis



- Found in the highlands of China, Tibet, and Nepal, above 10,000 feet
- Called “winter worm, summer herb, & caterpillar mushroom”
- Traditional uses:
  - Kidney/Lung Tonic with immune modulating/enhancing actions
  - Long term Kidney support
  - Used to treat impotence as well as soreness and weakness of the lower back (deficient kidney [yang])
  - Builds vitality during recovery from stress, illness, or physical challenges (cancer/chemotherapy/chronic lung or kidney disease)

Zhu JS, Halpern GM, Jones K. The scientific rediscovery of an ancient Chinese herbal medicine: Cordyceps sinensis: part I. J Altern Complement Med. 1998 Fall;4(3):289-303.

Cordycepin (*Cordyceps militaris*) Anti-inflammatory effects



- Cordycepin enhanced immunity, inhibited the proliferation of viral RNA, and suppressed cytokine storms, thereby suggesting its **potential to treat COVID-19** and other viral infections
- Cordycepin regulates the NF-κB, RIP2/Caspase-1, Akt/GSK-3β/p70S6K, TGF-β/Smads, and Nrf2/HO-1 signaling pathways among others
- Cordycepin has been found to produce rapid, robust imipramine-like antidepressant effects in animal models of depression, and these effects, similarly to those of imipramine, are dependent on enhancement of AMPA receptor signaling

Tan L, Song X, Ren Y, Wang M, Guo C, Guo D, Gu Y, Li Y, Cao Z, Deng Y. Anti-inflammatory effects of cordycepin: A review. Phytother Res. 2020 Oct 8. doi: 10.1002/ptr.6890.

Li, Bai; Hou, Yangyang; Zhu, Ming; Bao, Hongkun; Nie, Jun; Zhang, Grace Y.; Shan, Liping; Yao, Yao; Du, Kai; Yang, Hongju; Li, Meizhang; Zheng, Bingrong; Xu, Xiufeng; Xiao, Chunjie; Du, Jing (2016). "3'-Deoxyadenosine (Cordycepin) Produces a Rapid and Robust Antidepressant Effect via Enhancing Prefrontal AMPA Receptor Signaling Pathway". *International Journal of Neuropsychopharmacology*. **19** (4): pyv112. doi:10.1093/ijnp/pyv112.



Medicinal Herbs and Mushrooms Antiviral, Anti-Inflammatory Effects and SARS-CoV-2 Infection

- Natural substances such as herbs and mushrooms have previously demonstrated both great antiviral and anti-inflammatory activity.
- One of the potential candidates against the SARS-CoV-2 virus may be ***Inonotus obliquus***, also known as chaga mushroom.
- It has been suggested that Inonotus obliquus mushrooms possess a powerful enzymatic system and a strong system of defense, due to their parasitic mode of life.
- Extracts from this fungus have been used for its antitumor, antioxidant, hepatoprotective and anti-inflammatory properties

Shahzad F, Anderson D, Najafzadeh M. The Antiviral, Anti-Inflammatory Effects of Natural Medicinal Herbs and Mushrooms and SARS-CoV-2 Infection. Nutrients. 2020 Aug 25;12(9):2573. doi: 10.3390/nu12092573.

Tulsi (*Ocimum sanctum*) Improves Immune System Response and Possesses Stress Protective Adaptogenic Effects, as well



- Enhances non-specific vitality
- Enhanced immune response reported in five clinical studies
- A randomized double-blind, and placebo-controlled trial found increased immune response with increased NK and T-helper cells in healthy adult participants compared to placebo volunteers after 4 weeks of 300 mg or ethanolic tulsi leaf extract daily taken before food

Evidence-Based Complementary and Alternative Medicine Volume 2017, Article ID 9217567, 13 pages http://dx.doi.org/10.1155/2017/9217567;
Sci Rep. 2018 Mar 22;8(1):5075. doi: 10.1038/s41598-018-23419-x.

Shatavari (*Asparagus Racemosus*)



- Improved the stress tolerance swimming endurance test compared to stress control group
- Stress-induced variations in levels of lipid peroxidation, nitric oxide, protein and glutathione content in mouse brain were significantly ameliorated by pretreatment with extract
- The extract attenuated the elevated weight of adrenal glands and increased the reduced weight of the spleen during stress.
- Inhibits stress-induced pro-inflammatory cytokines
- Gastric protective effects and anti-ulcer effects; Inhibited gastric ulcers in animals given indomethacin

Indian J Exp Biol. 2012 Jun;50(6):419-24; Phytother Res. 2010 Oct;24(10):1562-6 J Postgrad Med. 1990 Apr;36(2):91-4.

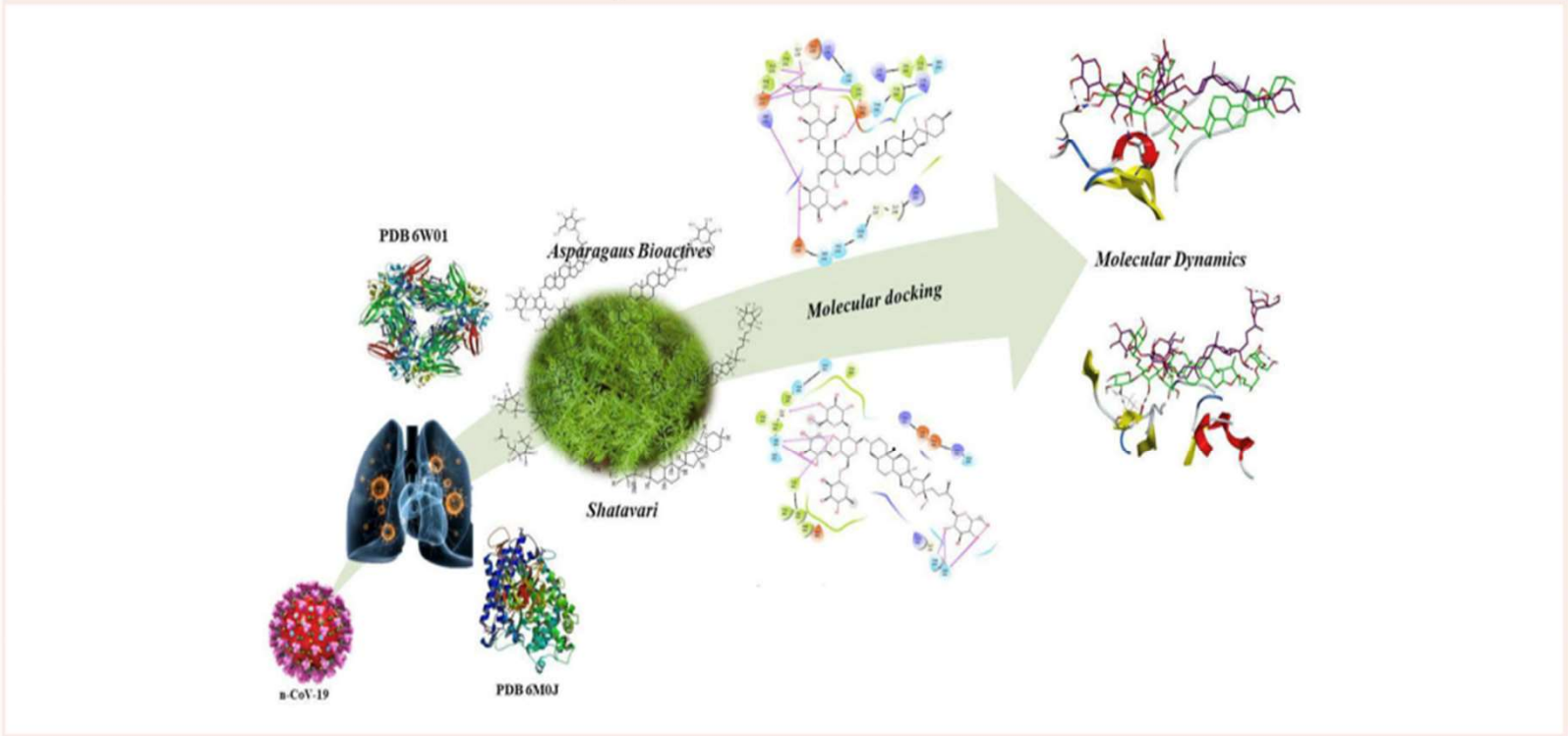
JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS
https://doi.org/10.1080/07391102.2020.1784289

Taylor & Francis
Taylor & Francis Group

Check for updates

In-silico investigation of phytochemicals from *Asparagus racemosus* as plausible antiviral agent in COVID-19

Rupesh V. Chikhale[a], Saurabh K. Sinha[b], Rajesh B. Patil[c], Satyendra K. Prasad[d], Anshul Shakya[e], Nilambari Gurav[f], Rupali Prasad[d], Suhas R. Dhaswadikar[d], Manish Wanjari[g] and Shailendra S. Gurav[h]



Astragalus Membranaceus

- Nourishes Bone marrow, enhances and balances Th1 and Th2
- Classified as a Vital Force-Spleen-Immune System tonic and Secondary Adaptogen
- Increases and strengthens NK and Cytotoxic T cells
- Increases IFN gamma and IL-2
- Anti-tumor & anti-angiogenic activity
- Down regulates TGF-B1 (Kidney C), EGFR (TN-Breast C)
- Protects Liver, Kidney, Heart





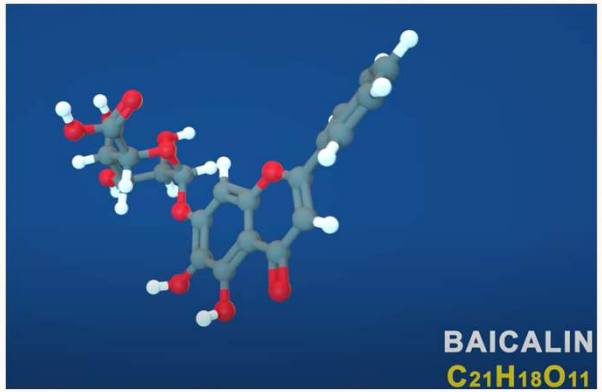
Zhongguo Zhong Xi Yi Jie He Za Zhi 2001; 21(3): 171-173, *Immunopharmacology* 2005; 5(7-8): 1225-1233, Clin Invest Med. 2012 Feb 1;35(1):E1.

Astragalus (AM) Regulates the Toll-Like Receptor 4 Meditated Signal Transduction of Dendritic Cells (DCs) to Restrain Stomach Cancer Cells.

- AM is effective in treating human stomach cancer and the mechanism might be regulated by TLR4 mediated signal transduction of DCs
- AM can precipitate DCs maturation by upregulating TLR4
- AM can greatly reduce the amount of cell lines by MTT assay and induce apoptosis
- Animal studies show that AM can delay tumor development from the diameter and weight of the tumor, prolong life-span and improve life-quality



Afr J Tradit Complement Altern Med. 2014 Apr 3;11(3):92-6.



Baicalin from *Scutellaria baicalensis*



- Is known to have antiviral activity against influenza A,28,29 HIV-1,30,31 respiratory syncytial virus (RSV),32 dengue,33 chikungunya,34 duck hepatitis virus (DHV),35,36 enterovirus,37 and HBV.38
  Another component of Scutellariae Radix, wogonin, also has an antiviral effect against the influenza virus39 and HBV.40

2 S. Kwon, W. Lee, C. Jin et al. / Integrative Medicine Research 9 (2020) 100480

Scutellaria baicalensis anti-COVID-19 activity

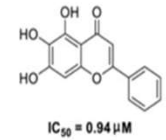
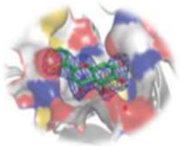
- Scutellariae radix (Huangqin in Chinese), the root of *Scutellaria baicalensis* Georgi, has been reported for widely used in TCM for heat clearing, fire purging, detoxification, and haemostasis.
- Its anti-tumor, antiviral, anti-microbial, and anti-inflammatory activities have been reported. Remarkably, the extracts of *S. baicalensis* have exhibited broad spectrum anti-viral activities, including ZIKA, H1N1, HIV, and DENV.
- *S. baicalensis*, whose major component is baicalein, exerts a marked anti-SARS-CoV-2 effect (IC50 of 0.94 μM, and SI > 212).

Zandi K, Lim TH, Rahim NA, et al. Extract of *Scutellaria baicalensis* inhibits dengue virus replication. BMC Complement Altern Med 2013;13:91.
Liu, H.; Ye, F.; Sun, Q.; Liang, H.; Li, C.; Li, S.; Lu, R.; Huang, B.; Tan, W.; Lai, L. Scutellaria baicalensis extract and baicalein inhibit replication of SARS-CoV-2 and its 3C-like protease in vitro. J. Enzym. Inhib. Med. Chemother. 2021, 36, 497–503

S. baicalensis anti-COVID-19 activity

- Both the ethanol extract of *S. baicalensis* and baicalein effectively inhibit the replication of SARS-CoV-2 in cell assay.
- All the active compounds and the *S. baicalensis* extract also inhibit the SARS-CoV 3CL^{pro}, demonstrating their potential as broad-spectrum anti-coronavirus agents.

Registered clinical trials relating to traditional Chinese medicine prescriptions containing baicalein (active ingredient of Huangqin) for treatment of COVID-19 patients (Chinese Clinical Trial Registry, www.chictr.org/cn/ (accessed on 31 January 2021).

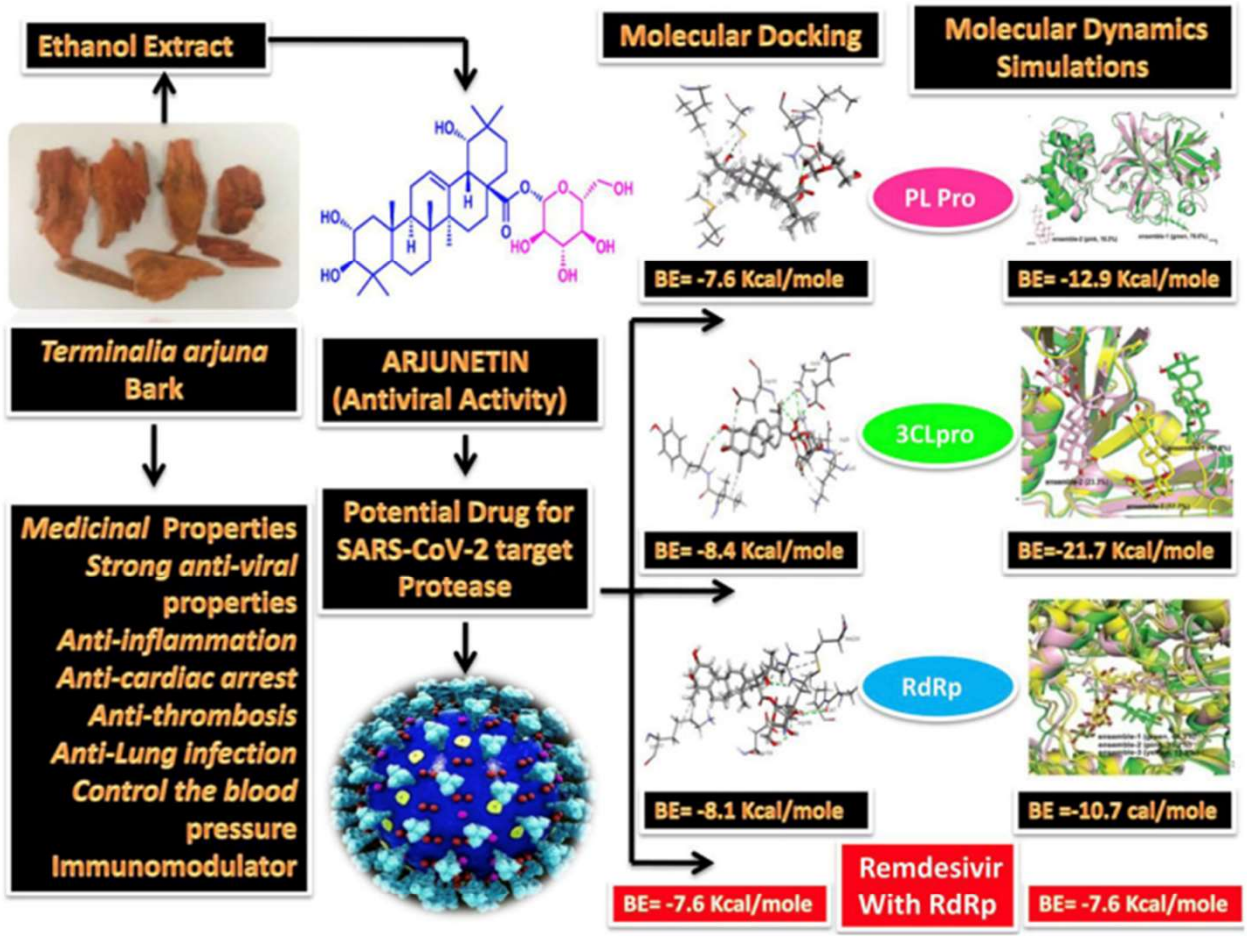
Baicalein (The Active Ingredient of Huangqin)	Molecular Mechanisms of Baicalein	Herbal Formula Containing Huangqin	Registration Number	Sample Size of the Control Group
 IC_{50} = 0.94 μM  PDB ID: 6M2N	RdRp inhibitor via noncovalent incorporation [73], potent antagonists against TMPRSS2 [70], improving respiratory function, decreasing IL-1β and TNF-α levels, and inhibiting cell infiltration [71,72].	Qingfei Paidu decoction	ChiCTR2000029433	120
			ChiCTR2000030883	100
			ChiCTR2000032767	782
		Xinguan I decoction	ChiCTR2000029637	50
		Tanreqing capsules	ChiCTR2000029813	36
		Tanreqing injection	ChiCTR2000029432	72
		Kegan Liyan oral liquid	ChiCTR2000033720	240
			ChiCTR2000033745	240
			ChiCTR2000031982	240
		Shuanghuanglian oral liquid	ChiCTR2000033133	30
			ChiCTR2000029605	100
		Toujie Quwen granule	ChiCTR2000031888	150

Liu H, Ye F, Sun Q, Liang H, Li C, Li S, Lu R, Huang B, Tan W, Lai L. *Scutellaria baicalensis* extract and baicalein inhibit replication of SARS-CoV-2 and its 3C-like protease *in vitro*. J Enzyme Inhib Med Chem. 2021 Dec;36(1):497-503. doi: 10.1080/14756366.2021.1873977. PMID: 33491508; PMCID: PMC7850424.Yang L, Wang Z. Natural Products, Alone or in Combination with FDA-Approved Drugs, to Treat COVID-19 and Lung Cancer. Biomedicines. 2021 Jun 18;9(6):689. doi: 10.3390/biomedicines9060689. PMID: 34207313; PMCID: PMC8234041.

Arjunetin a promising candidate against SARS-CoV-2

- Stem and bark of the tree *Terminalia arjuna* (Combretaceae) has been documented to exhibit therapeutic properties like cardiotonic, anticancer, antiviral, antibacterial, antifungal, hypercholesterolemia, hypolipidemic, and anti-coagulant.
- Molecular docking and molecular dynamics studies showed that arjunetin binds to the binds to key targets of SARS-CoV-2 (namely, 3CLpro, PLpro, and RdRp) with a higher binding energy values than the FDA approved protease inhibitor drugs to Lopinavir and Remdesivir.

Arumugam GS, Sen A, Dash SS, Mitra K, Doble M, Rajaraman G, Gummadi SN. Arjunetin as a promising drug candidate against SARS-CoV-2: molecular dynamics simulation studies. J Biomol Struct Dyn. 2021 Sep 17:1-22. doi: 10.1080/07391102.2021.1970627.



Abbreviations: 3CLpro: protease 3C-like preotease; PLpro: papin like protease; RdRP: RNA dependent RNA polymerase; DPPH: 2,2-Diphenyl-1-picryl hydrazyl radical; RMSD: root-mean-square deviation

J Biomol Struct Dyn. 2021 Sep 17:1-22. doi: 10.1080/07391102.2021.1970627.

The Polyphenols baicalein, resveratrol and neptetin effectively inhibit IL-1β

- **Baicalein** and **resveratrol** exhibited the most significant inhibitory effects on ATP/P2X7R signaling
- Baicalein significantly inhibited ATP-induced inflammation, including interleukin-1β secretion, through inhibition of the ATP/P2X7R signaling
- **Nepetin**, found in the medicinal herb boneset (*Eupatarium perfoliatum*) to alleviate the inflammatory responses of ARPE-19 cells induced by IL-1β

Scutellaria baicalensis



Eupatarium perfoliatum



PLOS ONE | https://doi.org/10.1371/journal.pone.0204229 September 24, 2018; Biomed Pharmacother, 101, 87-93 May 2018

Phytomedicine 85 (2021) 153361

Contents lists available at ScienceDirect

Phytomedicine

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

Review

Herbal immune-boosters: Substantial warriors of pandemic Covid-19 battle

Kanika Khanna [a], Sukhmeen Kaur Kohli [a], Ravdeep Kaur [a], Abhay Bhardwaj [b], Vinay Bhardwaj [b], Puja Ohri [c], Anket Sharma [a,d], Ajaz Ahmad [e], Renu Bhardwaj [a], Parvaiz Ahmad [f,*]

- There is a wide scope of herbal medicines that have been used since traditional times. They have been considered as potent clinical agents against wide array of viral diseases due to their anti-viral properties.
- Medicinal plants and their natural ingredients proved to be the most promising alternatives to prevent or cure the infection and spread of this disease since its outbreak.

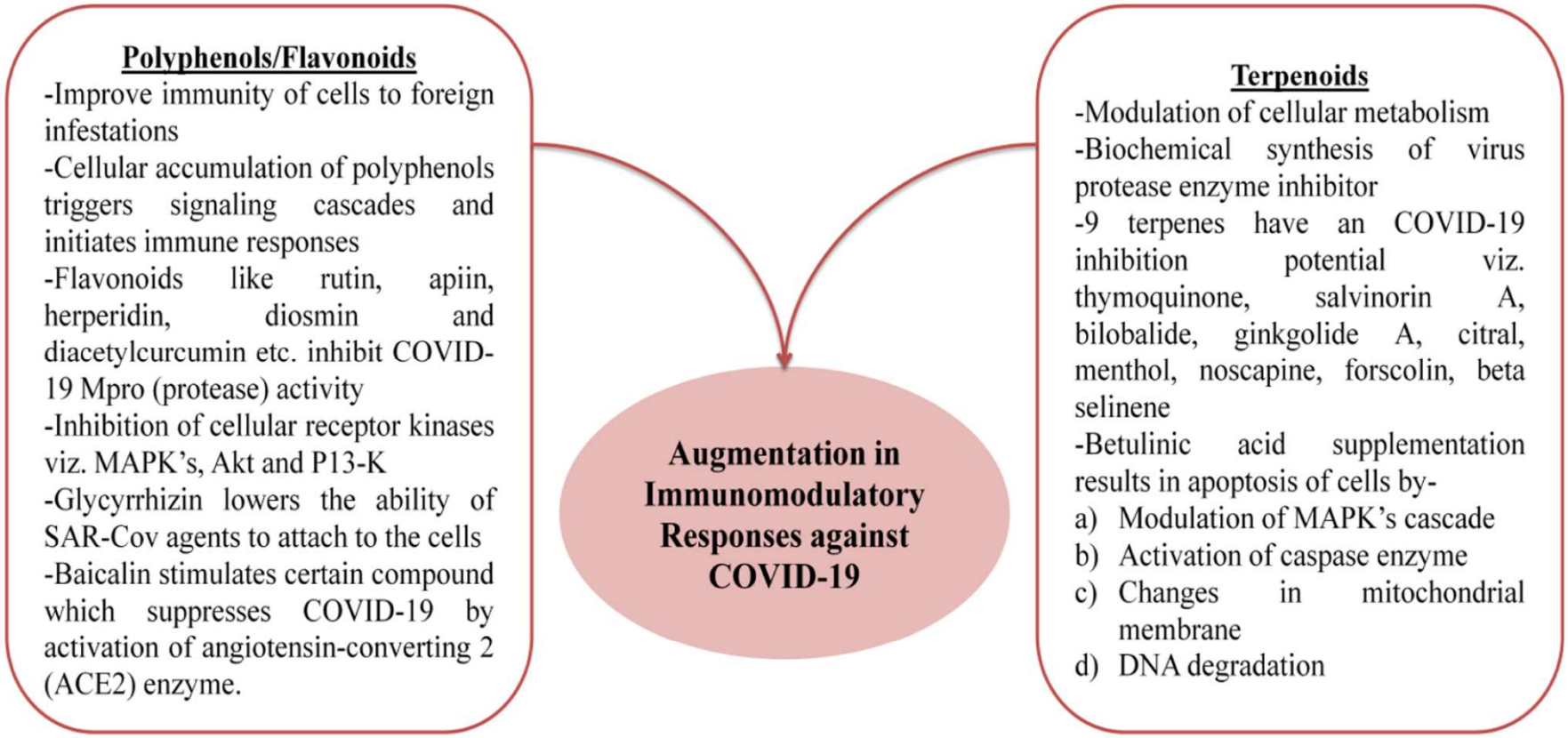


Fig. 2. Prospects of Augmentation in Immuno-Modulatory Responses against COVID-19 by Polyphenols/Flavonoids and Terpenoids.

Biomedicine & Pharmacotherapy 131 (2020) 110622

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

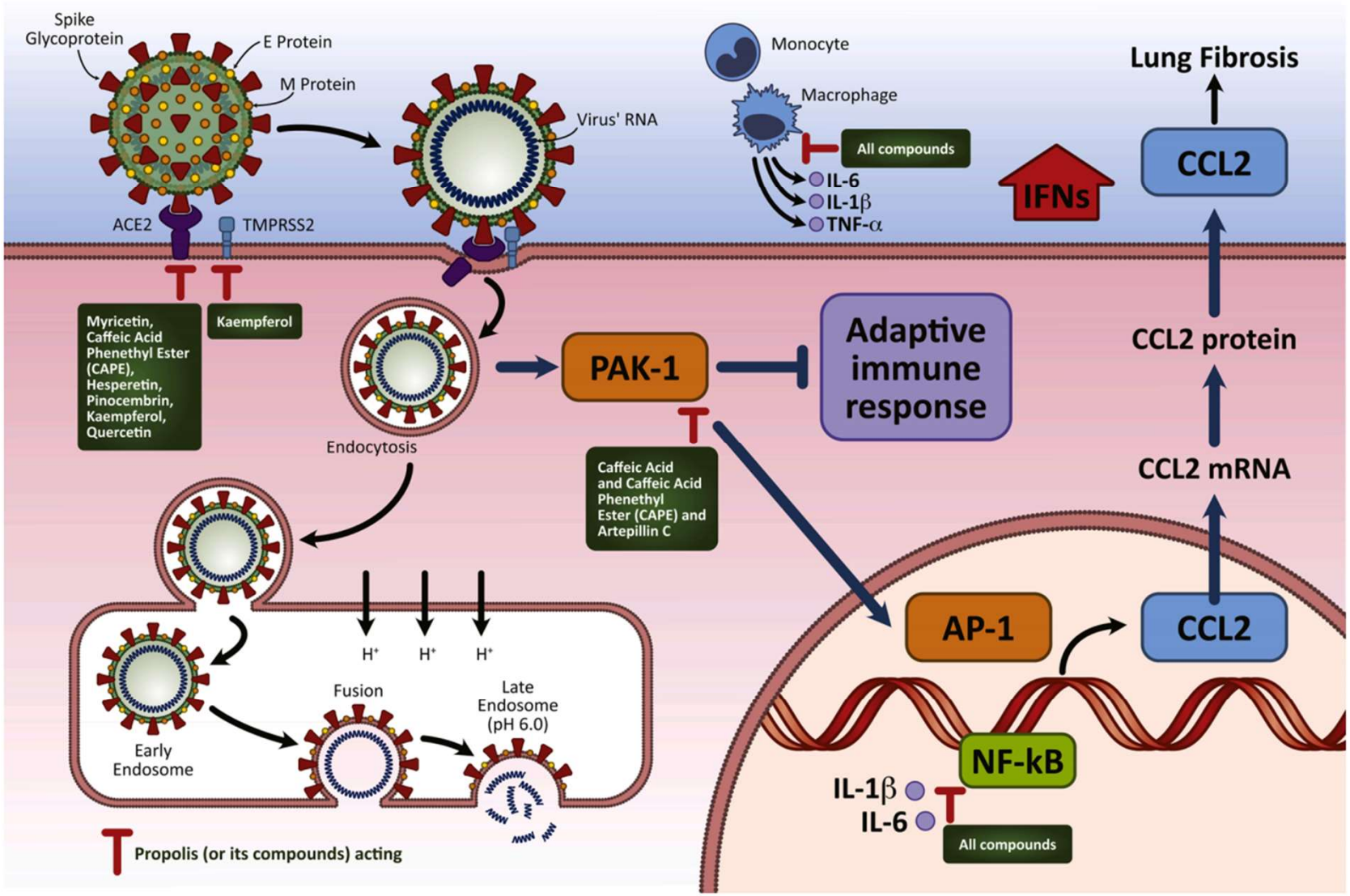
journal homepage: www.elsevier.com/locate/biopha

Review

Propolis and its potential against SARS-CoV-2 infection mechanisms and COVID-19 disease

Running title: Propolis against SARS-CoV-2 infection and COVID-19

Andresa Aparecida Berretta [a], Marcelo Augusto Duarte Silveira [b], José Manuel Cóndor Capcha [c], David De Jong [d,*]


Spike Glycoprotein
E Protein
M Protein
Virus' RNA
ACE2
TMPRSS2
Myricetin, Caffeic Acid Phenethyl Ester (CAPE), Hesperetin, Pinocembrin, Kaempferol, Quercetin
Kaempferol
Endocytosis
Monocyte
Macrophage
All compounds
IL-6
IL-1β
TNF-α
IFNs
Lung Fibrosis
CCL2
CCL2 protein
CCL2 mRNA
PAK-1
Adaptive immune response
Caffeic Acid and Caffeic Acid Phenethyl Ester (CAPE) and Artepillin C
H+
H+
H+
Fusion
Late Endosome (pH 6.0)
Early Endosome
AP-1
CCL2
NF-kB
IL-1β
IL-6
All compounds
Propolis (or its compounds) acting

Archives of Microbiology
https://doi.org/10.1007/s00203-021-02351-1

ORIGINAL PAPER

Investigation of potential inhibitor properties of ethanolic propolis extracts against ACE-II receptors for COVID-19 treatment by molecular docking study

Halil Ibrahim Guler[1] · Gizem Tatar[2] · Oktay Yildiz[3] · Ali Osman Belduz[4] · Sevgi Kolayli[5]

Received: 20 July 2020 / Revised: 22 April 2021 / Accepted: 24 April 2021
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- **Conclusion**: This study shows that the high binding constants for the ACE-II receptors of flavanones in the ethanolic propolis extract make it a good competitive inhibitor and protective natural agents for the treatment of COVID-19.

foods

MDPI

Review

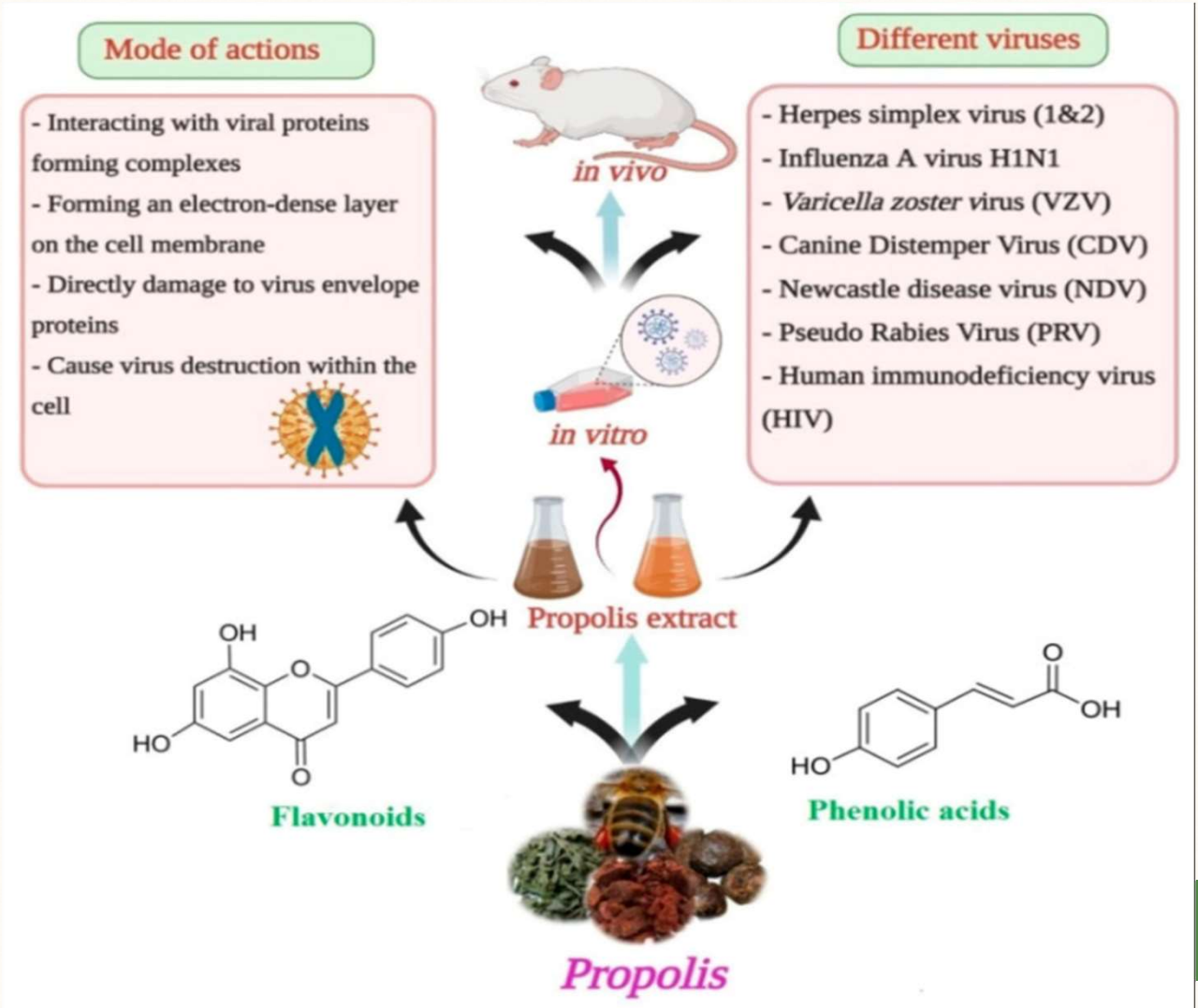
Anti-Viral and Immunomodulatory Properties of Propolis: Chemical Diversity, Pharmacological Properties, Preclinical and Clinical Applications, and In Silico Potential against SARS-CoV-2

Nermeen Yosri [1,2], Aida A. Abd El-Wahed [3], Reem Ghonaim [2], Omar M. Khattab [2], Aya Sabry [2], Mahmoud A. A. Ibrahim [4], Mahmoud F. Moustafa [5,6], Zhiming Guo [1], Xiaobo Zou [1], Ahmed F. M. Algethami [7], Saad H. D. Masry [8,9], Mohamed F. AlAjmi [10], Hanan S. Afifi [11], Shaden A. M. Khalifa [12,*] and Hesham R. El-Seedi [2,13,14,*]

- Propolis and its constituents have demonstrated potential efficacy against SARS-CoV-2 by modulating multiple pathogenic and antiviral pathways. Molecular docking studies have demonstrated high binding affinities of propolis derivatives to multiple SARS-CoV-2 proteins

Foods. 2021 Jul 31;10(8):1776. doi: 10.3390/foods10081776.

Anti-viral • mode of action of propolis extracts/constituents against viruses.



Foods. 2021 Jul 31;10(8):1776.
doi: 10.3390/foods10081776.

Propolis plus Hyoscyamus n. extract improves clinical symptoms in patients with COVID-19 acute respiratory syndrome

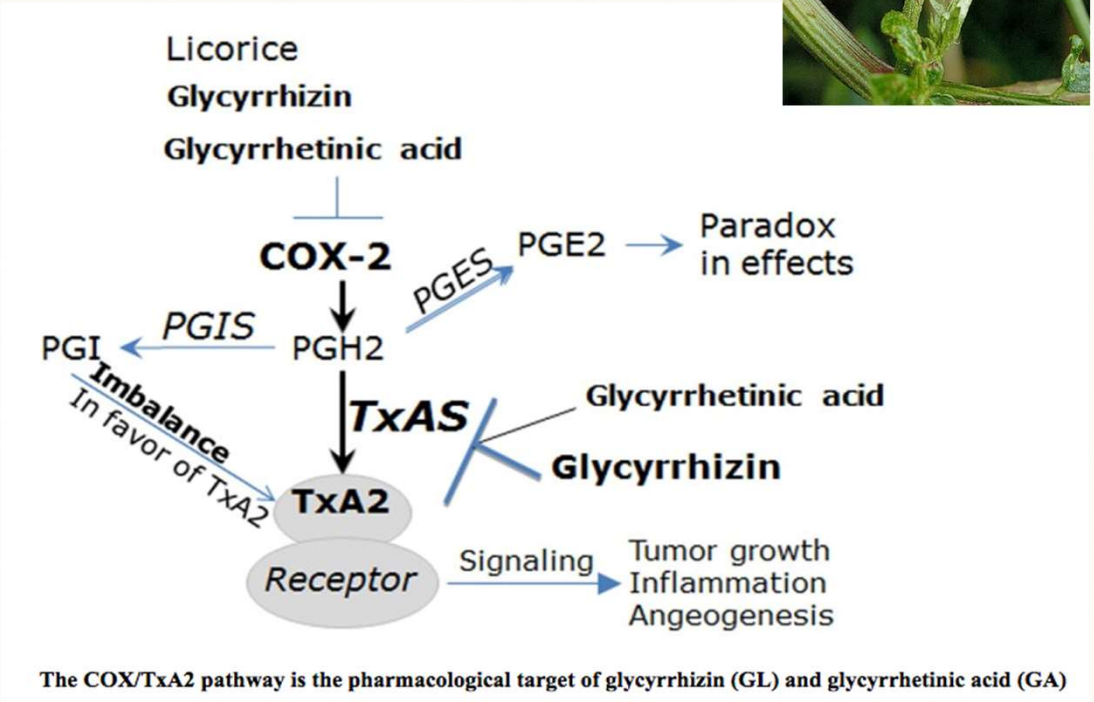
- This randomized clinical trial was conducted on 50 cases referred to Akhavan and Sepehri Clinics, Kashan university of medical sciences, Iran
- This syrup (containing 1.6 mg of methanolic extract along with 450 mg of propolis per 10 mL) was administered three times a day to each patient for 6 days.
- The clinical symptoms of COVID-19 such as: dry cough, shortness of breath, sore throat, chest pain, fever, dizziness, headache, abdominal pain, and diarrhea were reduced with propolis plus Hyoscyamus niger L. extract than the placebo group

Kosari M, Noureddini M, Khamechi SP, Najafi A, Ghaderi A, Sehat M, Banafshe HR. The effect of propolis plus Hyoscyamus niger L. methanolic extract on clinical symptoms in patients with acute respiratory syndrome suspected to COVID-19: A clinical trial. Phytother Res. 2021 Jul;35(7):4000-4006. doi: 10.1002/ptr.7116.

Licorice: Immune-Modulator



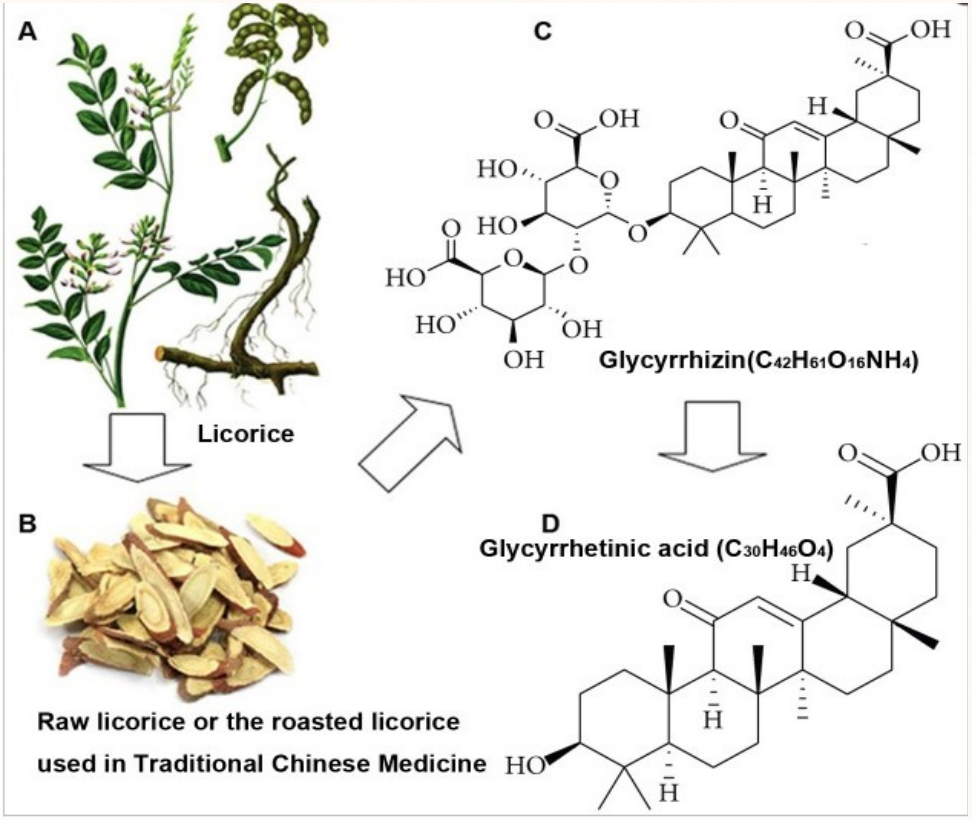
- Supports adrenal stress and inflammatory response
- Protects the thymus and adrenal glands from the stress
- Immunoregulatory effects of glycyrrhizic acid include modulation of Th1/Th2 cytokines and CD4(+)CD25(+)Foxp3+ regulatory T cells



The COX/TxA2 pathway is the pharmacological target of glycyrrhizin (GL) and glycyrrhetinic acid (GA)

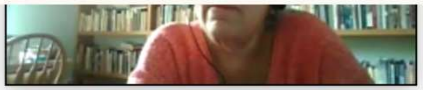
Anticancer Agents Med Chem. 2016 Aug 17; Sci Rep. 2015 Sep 15;5:14046;Zhongguo Zhong Xi Yi Jie He Za Zhi. 2001 Jul;21(7):501-3.

Licorice (*Glycyrrhiza Glabra*)



- Supports the HPA axis, sparing cortisol
- Helps convert cortisol to cortisone on demand
- Assists in the restoration of healthy DHEA levels
- Enhances the actions of other herbs,
  - ➢do not use as a soloist.

Kee Chang Huang, *The Pharmacology of Chinese Herbs*, chap. 34; 364-69; 1999 CRC Press.



Science of the Total Environment 725 (2020) 138277

Contents lists available at ScienceDirect

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



Review

COVID-19: A promising cure for the global panic

Balachandar Vellingiri [a,1,*], Kaavya Jayaramayya [b,1], Mahalaxmi Iyer [b], Arul Narayanasamy [c], Vivekanandhan Govindasamy [d], Bupesh Giridharan [e,f], Singaravelu Ganesan [g], Anila Venugopal [a], Dhivya Venkatesan [a], Harsha Ganesan [a], Kamarajan Rajagopalan [a], Pattanathu K.S.M. Rahman [h], Ssang-Goo Cho [i], Nachimuthu Senthil Kumar [j], Mohana Devi Subramaniam [k]

Table 4
AYUSH recommended medicinal plant extracts for treating COVID-19
(Ref: AYUSH Ministry of Health Corona Advisory – D.O. No. S. 16030/18/2019 – NAM; dated: 06th March, 2020).

Indian medicinal plant	Form of extract	Trade name	Indian traditional medical practice	Preparation	Recommended usage	Effective against
Preventive and prophylactic						
Tinospora cordifolia	Aqueous	Samshamani Vati	Ayurveda	Samshamani Vati 500 g with warm water	Twice a day for 15 days	Chronic fever
Andrographis paniculata	Aqueous	Nilavembu kudineer	Siddha	Nilavembu kudineer 60 ml decoction	Twice a day for 14 days	Fever and cold
Cydonia oblonga *Zizyphus jujube* *Cordia myxa*	Aqueous	Behidana Unnab Sapistan	Unani	Behidana – 3 g Unnab – 5 Nos Sapistan – 9 Nos Boil these 3 in 250 ml water, boil it until it remains half and filter it	Twice a day for 14 days	Antioxidant, immune-modulatory, anti-allergic, smooth muscle relaxant, anti-influenza activity
Arsenicum album 30	Tablet	Arsenicum album 30	Homeopathy	–	Daily once in empty stomach for 3 days (Should be repeated after 1 month till the infection persist).	Effective against SARS-CoV-2, immune-modulator.
Symptomatic Management for COVID-19						

Symptomatic Management for COVID-19						
AYUSH -64	Tablet	–	Ayurveda	–	2 tablets twice a day	Respiratory infections
Agastya Haritaki	Powder	Agasthya Rasayanam	Ayurveda	5 g in warm water	Twice a day	Upper respiratory infections
Anuthaila	Oil	Sesame oil	Ayurveda	–	2 drops in each nostril daily morning	Respiratory infections
Adathodai Manapagu	Aqueous	Adathodai Manapagu	Siddha	–	10 ml twice a day	Fever
Bryonia alba	Tablet	Bryonia	Homeopathy	–	–	Reduce lung inflammation
Rhus toxico dendron	Tablet	Rhus tox	Homeopathy	–	–	Viral infections
Atropa belladonna	Tablet	Belladonna	Homeopathy	–	–	Asthma and chronic lung diseases
Bignonia sempervirens	Tablet	Gelsemium	Homeopathy	–	–	Asthma
Eupatorium perfoliatum	Tablet	Eupatorium perfoliatum	Homeopathy	–	–	Respiratory symptoms
Add on interventions to the conventional care						
Vishasura kudineer	Tablet	Poly-herbal formulation	Siddha	Decoction 60 ml	Twice a day	Fever
Kaba sura kudineer	Tablet	Poly-herbal formulation	Siddha	Decoction 60 ml	Twice a day	Fever, cough, sore throat, shortness of breath

This table depicts the Indian Medicinal plants and its usage provided by the AYUSH, Government of India as a therapeutic approach for COVID-19.

Autumn crocus (*Colchicum autumnale*)



Colchicum autumnale, commonly known as autumn crocus, meadow saffron or naked ladies, is a autumn-blooming flowering plant that resembles the true crocuses, but is a member of the plant family Colchicaceae The plants of the Colchicum family were known during the archaic period in Greece for their deleterious properties.

- The treatment was introduced by the ancient Greek physicians and passed on to the Byzantine and Arabian physicians to endure until nowadays.
- As the most common member of the family blossoms in autumn, the plant was named *Colchicum autumnale*.

Tsoucalas G, Papaioannou T, Panayiotakopoulos G, Saridaki Z, Vrachatis DA, Karamanou M. Colchicum Genus in the Writings of Ancient Greek and Byzantine Physicians. Curr Pharm Des. 2018;24(6):648-653. doi: 10.2174/1381612824666180115111546. PMID: 29336250..

JAMA Network Open

Original Investigation | Infectious Diseases

Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019

The GRECCO-19 Randomized Clinical Trial

- SARS 2 infection has evolved into a global pandemic. Low-dose colchicine combines anti-inflammatory action with a favorable safety profile.
- In this randomized clinical trial, participants who received colchicine had statistically significantly improved time to clinical deterioration.
- There were no significant differences in high-sensitivity cardiac troponin or C-reactive protein levels.

JAMA Network Open. 2020;3(6):e2013136. doi:10.1001/jamanetworkopen.2020.13136

Colchicine and Covid-19

- The actions of colchicine, one of the oldest anti-inflammatory therapies, target multiple targets associated with excessive COVID-19 inflammation.
- Colchicine is easily administered, generally well tolerated, and inexpensive.
- Low-dose colchicine may be considered safe and effective for the treatment and prevention of cytokine storm in patients with SARS-CoV-2 infection, particularly as an adjunctive remedy to other therapeutic agents.

Vitiello A, Ferrara F. Colchicine and SARS-CoV-2: Management of the hyperinflammatory state. Respir Med. 2021 Feb 1;178:106322. doi: 10.1016/j.rmed.2021.106322. Epub ahead of print. PMID: 33550151.

Colchicine reduces need for oxygen therapy and length of hospitalization in patients with moderate-to-severe COVID-19: Study

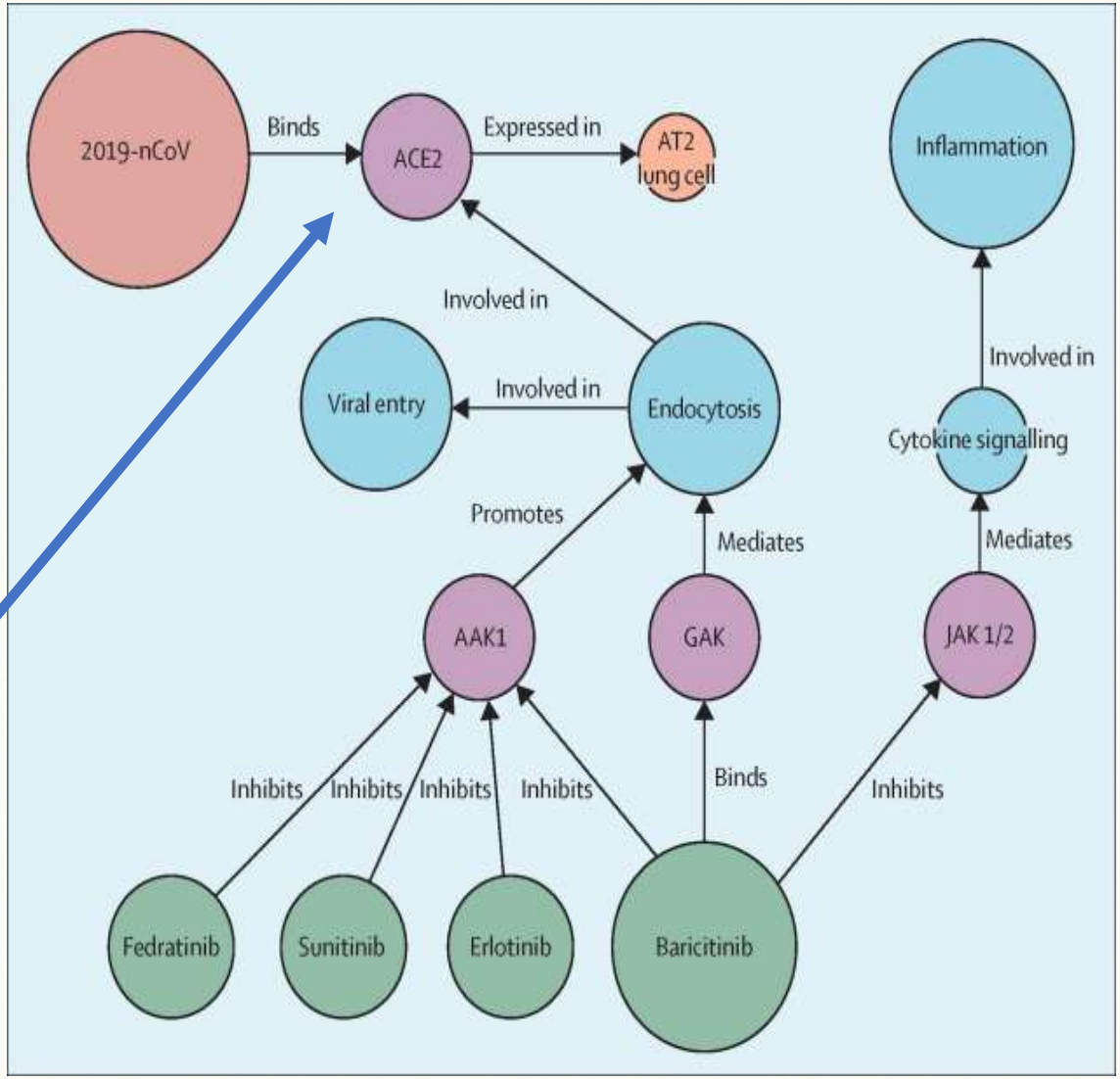
- From April 11 to August 30, 2020, a total of 72 patients were randomly assigned to receive either colchicine (n = 36) or placebo (n = 36). Colchicine was administered at 0.5 mg thrice daily for 5 days, followed by 0.5 mg twice daily for 5 days.
- All patients received the institutional protocol treatment with hydroxychloroquine, azithromycin and heparin. Meanwhile, 25 and 24 patients, respectively, in colchicine and placebo groups also received methylprednisolone.

Lopes MI, Bonjorno LP, Giannini MC, Amaral NB, Menezes PI, Dib SM, Gigante SL, Benatti MN, Rezek UC, Emrich-Filho LL, Sousa BAA, Almeida SCL, Luppino Assad R, Veras FP, Schneider A, Rodrigues TS, Leiria LOS, Cunha LD, Alves-Filho JC, Cunha TM, Arruda E, Miranda CH, Pazin-Filho A, Auxiliadora-Martins M, Borges MC, Fonseca BAL, Bollela VR, Del-Ben CM, Cunha FQ, Zamboni DS, Santana RC, Vilar FC, Louzada-Junior P, Oliveira RDR. Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial. RMD Open. 2021 Feb;7(1):e001455. doi: 10.1136/rmdopen-2020-001455. PMID: 33542047.

- The researchers found that the median time of need for supplemental oxygen was shorter among patients who received colchicine compared with patients who received placebo (4.0 vs 6.5 days; *P*<0.001).
- At day 2, 67% of patients in the colchicine group maintained the need for supplemental oxygen compared to 86% of patients in the placebo group, while at day 7, the proportion of patients requiring supplemental oxygen
- “Patients who received colchicine in this randomized, double-blinded, placebo-controlled clinical trial presented better evolution in terms of the need for supplemental oxygen and the length of hospitalization,” concluded Maria Isabel Lopes, University of Sao Paulo, Ribeirão Preto, Brazil, and colleagues.

RMD Open. 2021 Feb;7(1):e001455. doi: 10.1136/rmdopen-2020-001455. PMID: 33542047.

- The host receptor for CoV-2019, ACE2 is the same as the host receptor of SARS-CoV
- Targeting ACE2 holds promise for preventing CoV-2019 infection
- <u>Herbal compounds that target ACE2 that may be useful for treating infection of 2019-nCoV</u>:
  - **Baicalin** and Scutellarin (Skullcap root),
  - Hesperetin (citrus fruit),
  - Nicotianamine (traditional soy foods) and
  - glycyrrhizin (licorice root)



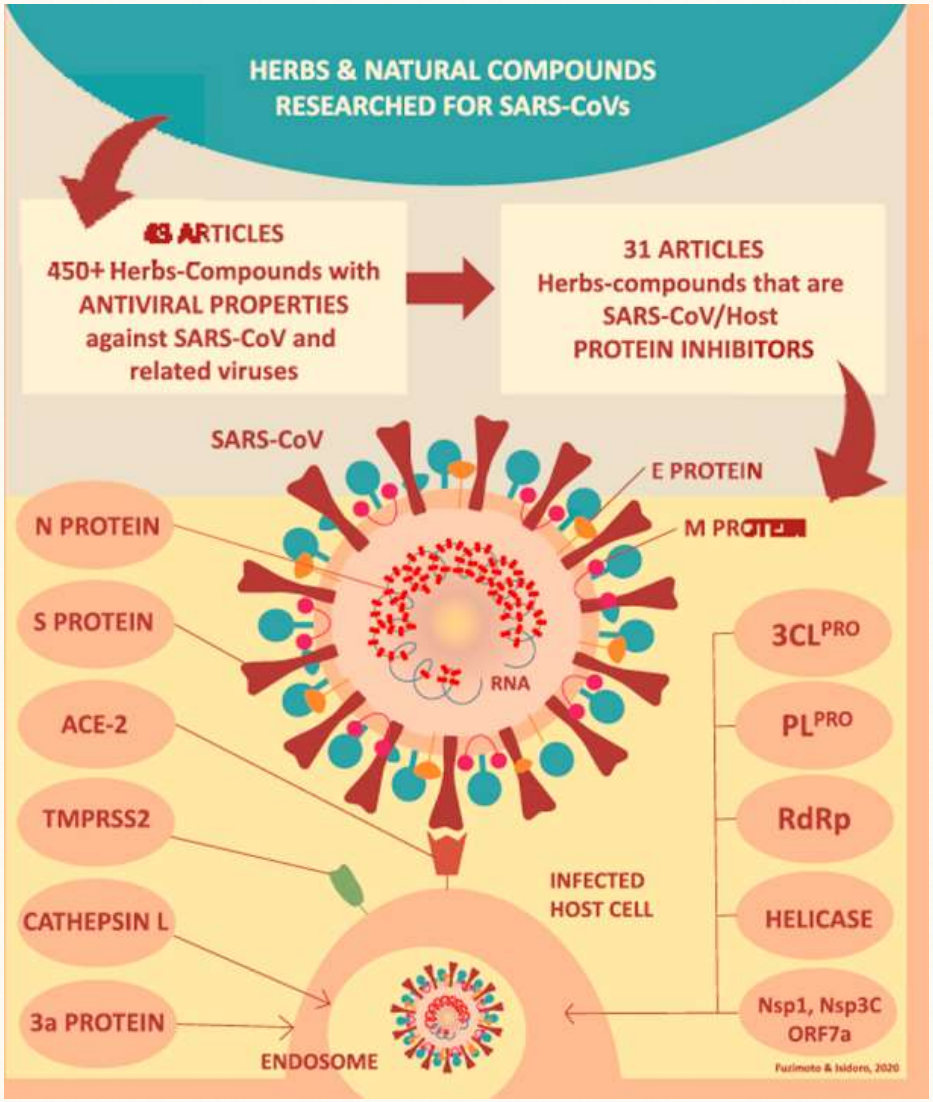
Hansen Chen, Qiaohui Du, Potential natural compounds for preventing 2019-nCoV infection, Department of Neurosurgery, School of Medicine, Stanford University, (www.preprints.org) | NOT PEER-REVIEWED | Posted: 30 January 2020

Specific Natural compounds that exhibit strong anti-SARS-CoV effects

- **Betulinic acid (Chaga-birch)** and **savinin (a lignan From *Pterocarpus spp*.)** were competitive inhibitors of SARS-CoV
- **Niclosamide**, an FDA-approved anthelminthic drug, was found to be effective against various viral infections with nanomolar to micromolar potency such as SARS-CoV, MERS-CoV, ZIKV, HCV, and human adenovirus, indicating its potential as an antiviral agent
- Niclosamide exerts its anticestodal effect by inhibiting oxidative phosphorylation and stimulating adenosine triphosphatase activity in the mitochondria.

Wen CC, Kuo YH, Jan JT, et al. Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus. *J Med Chem*. 2007;50(17):4087–4095. doi:10.1021/jm070295s

Xu, Jimin et al. "Broad Spectrum Antiviral Agent Niclosamide and Its Therapeutic Potential." *ACS infectious diseases*, acsinfecdis.0c00052. 10 Mar. 2020, doi:10.1021/acsinfecdis.0c00052



J Tradit Complement Med. 2020 Jul; 10(4): 405–419. PMCID: PMC7260130 Published online 2020 May 30.
PMID: 32691005 doi: 10.1016/j.jtcme.2020.05.003: 10.1016/j.jtcme.2020.05.003

Received: 29 July 2020 | Revised: 9 December 2020 | Accepted: 28 December 2020

DOI: 10.1096/fj.202001792R

HYPOTHESES

THE FASEB JOURNAL

A small molecule compound berberine as an orally active therapeutic candidate against COVID-19 and SARS: A computational and mechanistic study

Zhen-Zhen Wang[1,2] | Kun Li[3] | Anish R. Maskey[2] | Weihua Huang[4] | Anton A. Toutov[5] | Nan Yang[2,6] | Kamal Srivastava[2,6] | Jan Geliebter[2,7] | Raj Tiwari[2,7] | Mingsan Miao[1] | Xiu-Min Li[2,7]

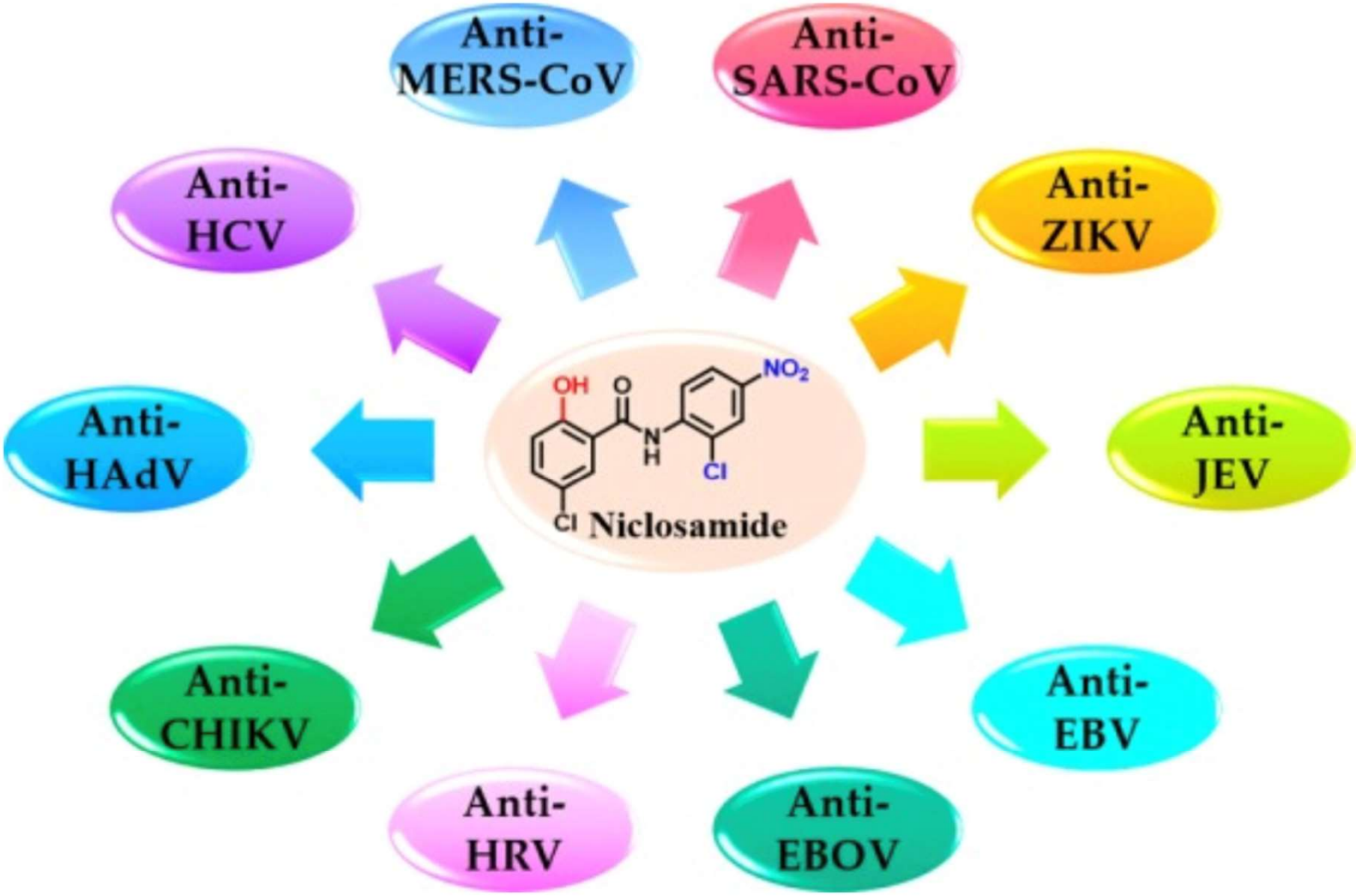
As an ingredient recommended in guidelines issued by the China National Health Commission for COVID-19 to be combined with other therapy, berberine is a promising orally administered therapeutic candidate against SARS-CoV and SARS-CoV-2. The current study comprehensively evaluates the potential therapeutic mechanisms of berberine in preventing and treating COVID-19 and SARS

Pterocarpus spp.

- The major bioactive compounds present in the heartwood of **Pterocarpus** santalinus are santalin A and B, **savinin**, calocedrin, pterolinus K and L, and pterostilbenes
- These compounds can act as antioxidants, enzyme inhibitors and inducers, inhibitors of receptor activities, and inducers and inhibitors of gene expression, among other actions
- **Savinin (a lignan From *Pterocarpus spp*.)** is competitive inhibitors of SARS-CoV



J Med Chem. 2007;50(17):4087–4095. doi:10.1021/jm070295s



ACS infectious diseases, acsinfecdis.0c00052. 10 Mar. 2020, doi:10.1021/acsinfecdis.0c00052

Inhibition of SARS-CoV by flavonoids

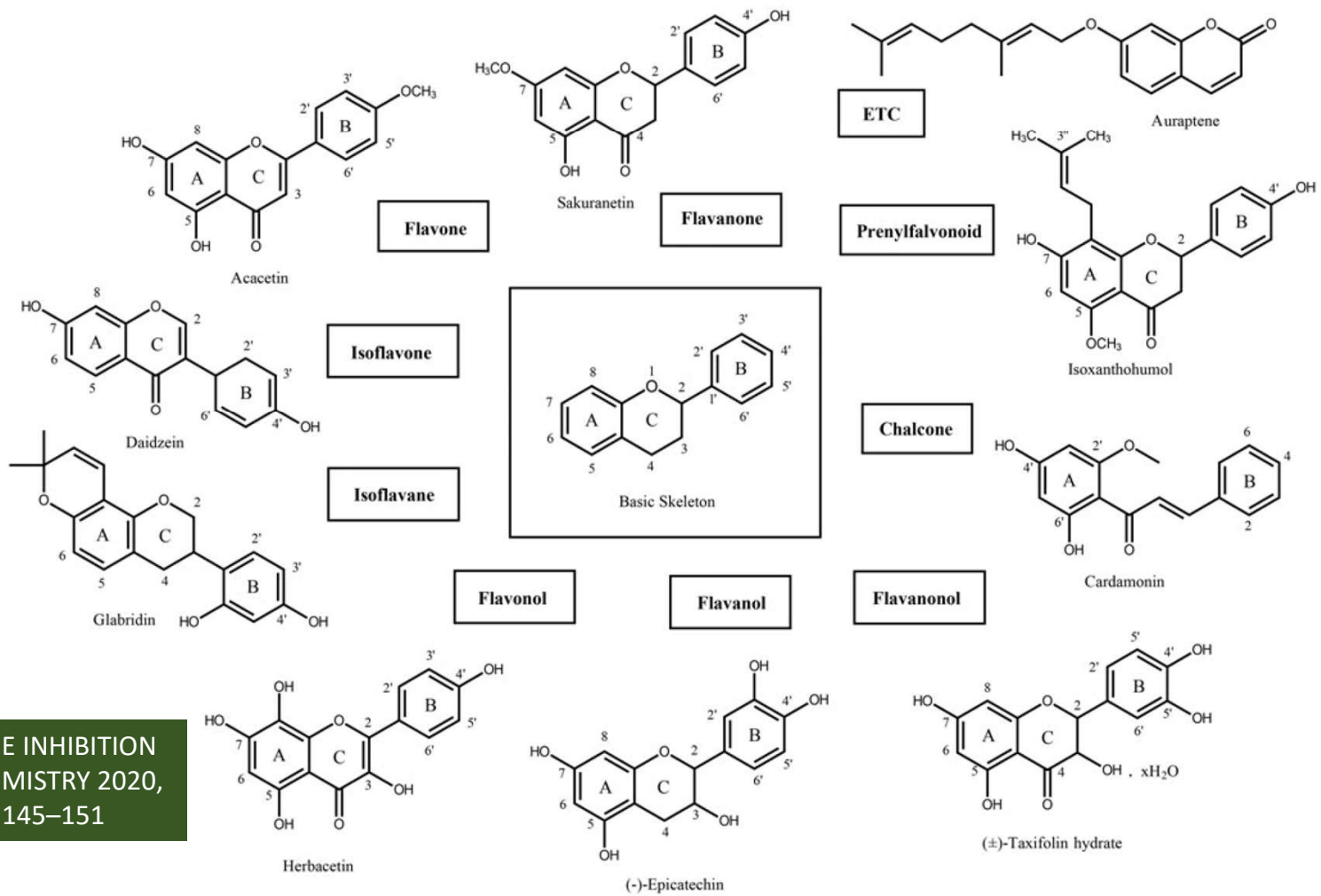
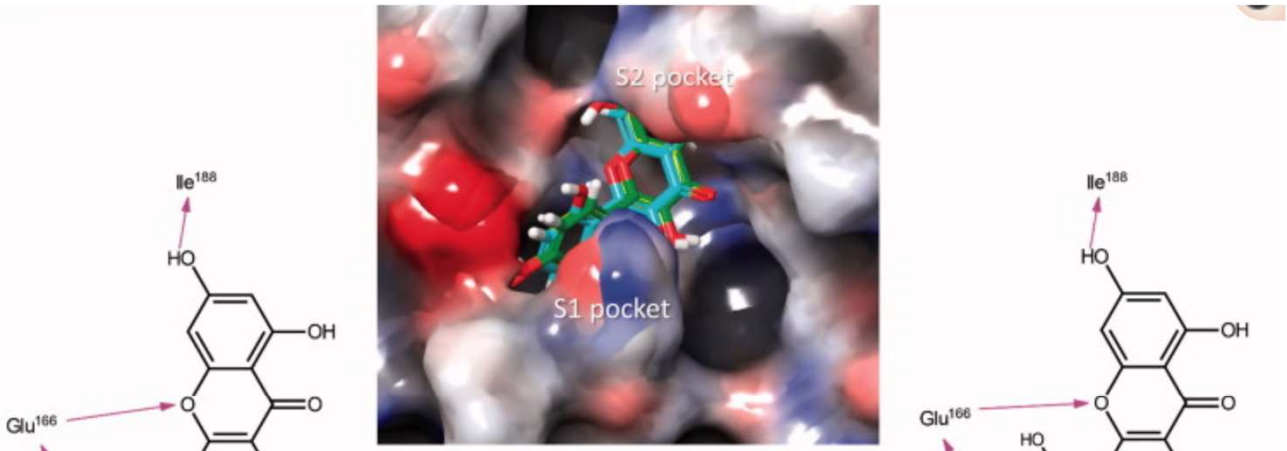


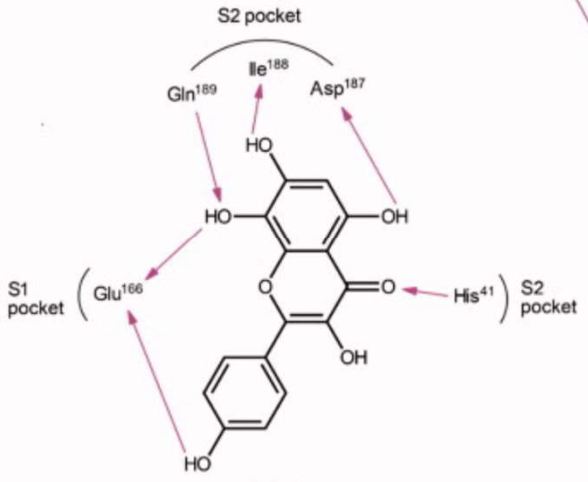
Figure 1. The basic skeleton structures of flavonoids and their scaffolds. Basic representative structures of the most common flavonoids classified in this study were drawn with rings and numbered positions.

JOURNAL OF ENZYME INHIBITION AND MEDICINAL CHEMISTRY 2020, VOL. 35, NO. 1, 145–151

Herbacetin, rhoifolin and pectolinarin were the best inhibitory compounds against SARS-CoV 3CLpro in the flavonoid library.



Kaempferol



Herbacetin

Morin

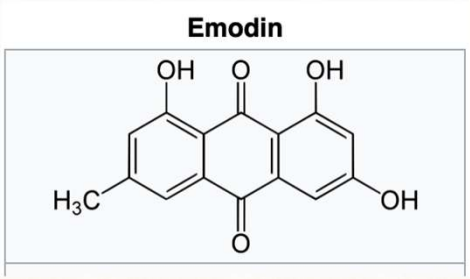
JOURNAL OF ENZYME INHIBITION AND MEDICINAL CHEMISTRY 2020, VOL. 35, NO. 1, 145–151

Herbacetin, Rhodionin, Rhiofolin, Pectolinarin

- **Herbacetin** is found mainly in **flax seeds** (the outer hulls)
- Rhodiolin, a flavonolignan, is the product of the oxidative coupling of **herbacetin**.
- It can be found in the rhizome of the adaptogenic plant **Rhodiola rosea**.
- **Rhiofolin** comes from **citrus peels** - The rhiofolin flavonoid identified earlier is actually part of a patent called “Surface Sterilization by Misting with a Bioflavonoid Solution.”
- **Pectolinarin** has been reported to be major compounds in *Cirsium setidens* (**Korean thistle**).

JOURNAL OF ENZYME INHIBITION AND MEDICINAL CHEMISTRY 2020, VOL. 35, NO. 1, 145–151
Biochemical and Biophysical Research Communications Volume 493, Issue 1, 4 November 2017, Pages 765-772

Emodin



- Derived from *Rheum Palmatum* (rhubarb), *Polygonum cuspidatum* (Japanese knotweed) and **Rhamnus alnifolia** (Buckthorn)
- Is one of the major active components of the antiviral TCM formulation **Lianhua Qingwen**
- Inhibit interaction of SARS-CoV Spike protein and ACE2

Rhubbarb



Ho T, Wu S, Chen J, Li C, Hsiang C. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antiviral Res. 2007; 74: 92-101; Schwarz S, Wang K, Yu WJ, Sun B, Schwarz W. Emodin inhibits current through SARS-associated coronavirus 3a protein. Antiviral res. 2011; 90: 64-9; Luo W, Su X, Gong S, Qin Y, Liu W, Li J, et al. Anti-SARS coronavirus 3C-like protease effects of Rheum palmatum L. extracts. BioScience Trends. 2009; 3; Runfeng L, Yunlong H, Jicheng H, Weiqi P, Qinhai M, Yongxia S, Chufang L, Jin Z, Zhenhua J, Haiming J, Kui Z, Shuxiang H, Jun D, Xiaobo L, Xiaotao H, Lin W, Nanshan Z, Zifeng Y. Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2). *Pharmacol Res*. 2020 Mar 20:104761

JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS
https://doi.org/10.1080/07391102.2020.1775129

Taylor & Francis
Taylor & Francis Group

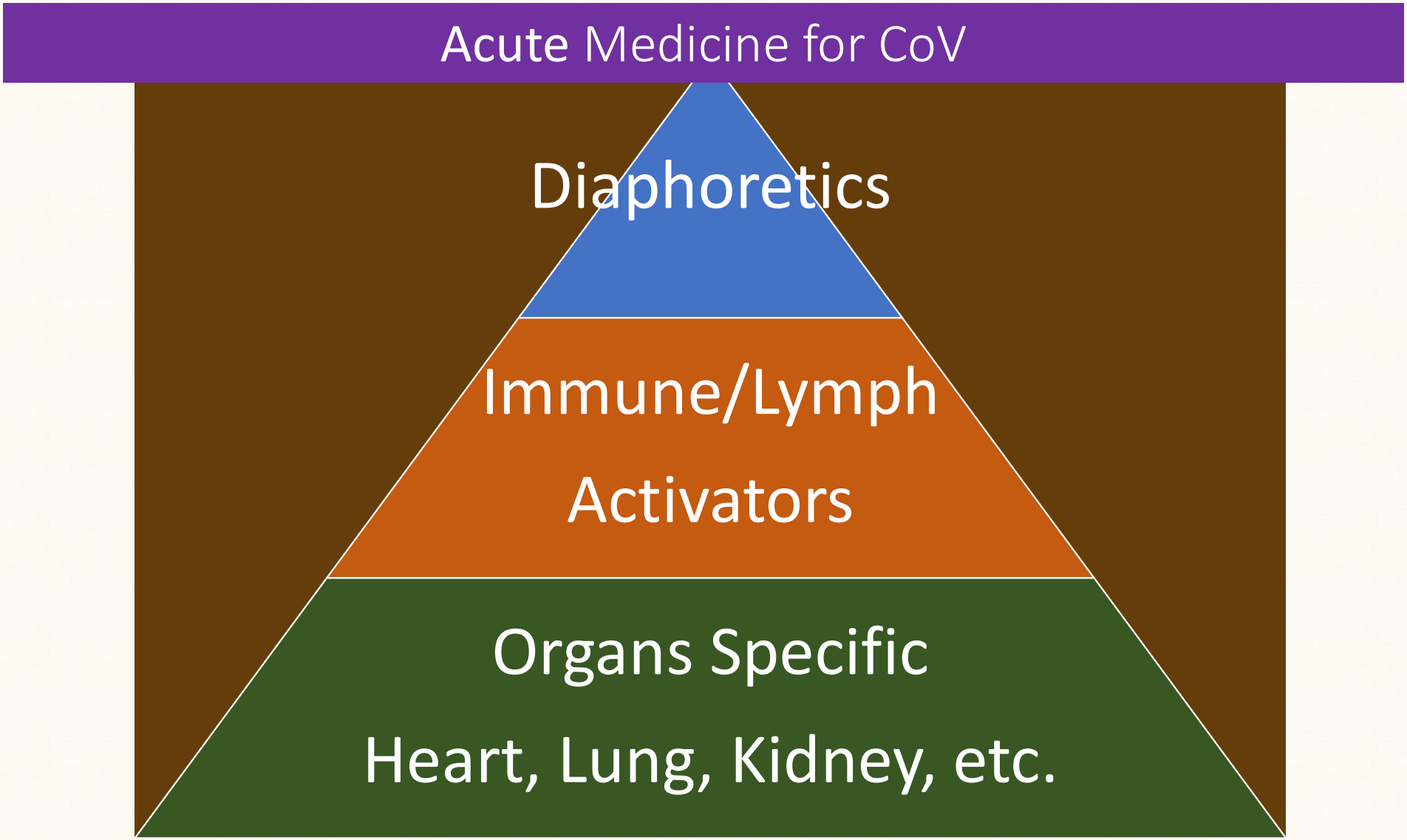
Check for updates

Molecular docking, simulation and MM-PBSA studies of *nigella sativa* compounds: a computational quest to identify potential natural antiviral for COVID-19 treatment

Sajjad Ahmad[a], Hyder Wajid Abbasi[b], Sara Shahid[b], Sana Gul[c] and Sumra Wajid Abbasi[c]

[a]National Center of Bioinformatics, Quaid-i-Azam University, Islamabad, Pakistan; [b]Pakistan Institute of Medical Sciences, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, Pakistan; [c]Department of Biological Sciences, National University of Medical Sciences, Rawalpindi, Pakistan

- N. sativa compound, **dithymoquinone**, has the high potential of binding at SARS-CoV-2:ACE2 interface and thus could be predicted as a plausible inhibitor to disrupt viral-host interactions.


Acute Medicine for CoV
Diaphoretics
Immune/Lymph
Activators
Organs Specific
Heart, Lung, Kidney, etc.

Diaphoretics, Lymphatics, Immune and Anti-viral Botanicals

- Influence the cellular and lymphatic system
- Promote the enhancement of glandular secretions and eliminative capacity, as well as enhance and warm the digestive system, improving the assimilative and eliminative processes
- Enhance immune response, and improve lymphatic drainage - are trophorestorative to these systems

Poke Weed (*Phytolacca*)
A chief anti-viral, lymphatic herb



Don’t Fear A Fever: The Importance of Working WITH, Not Against the Immune System in Warding off Infection

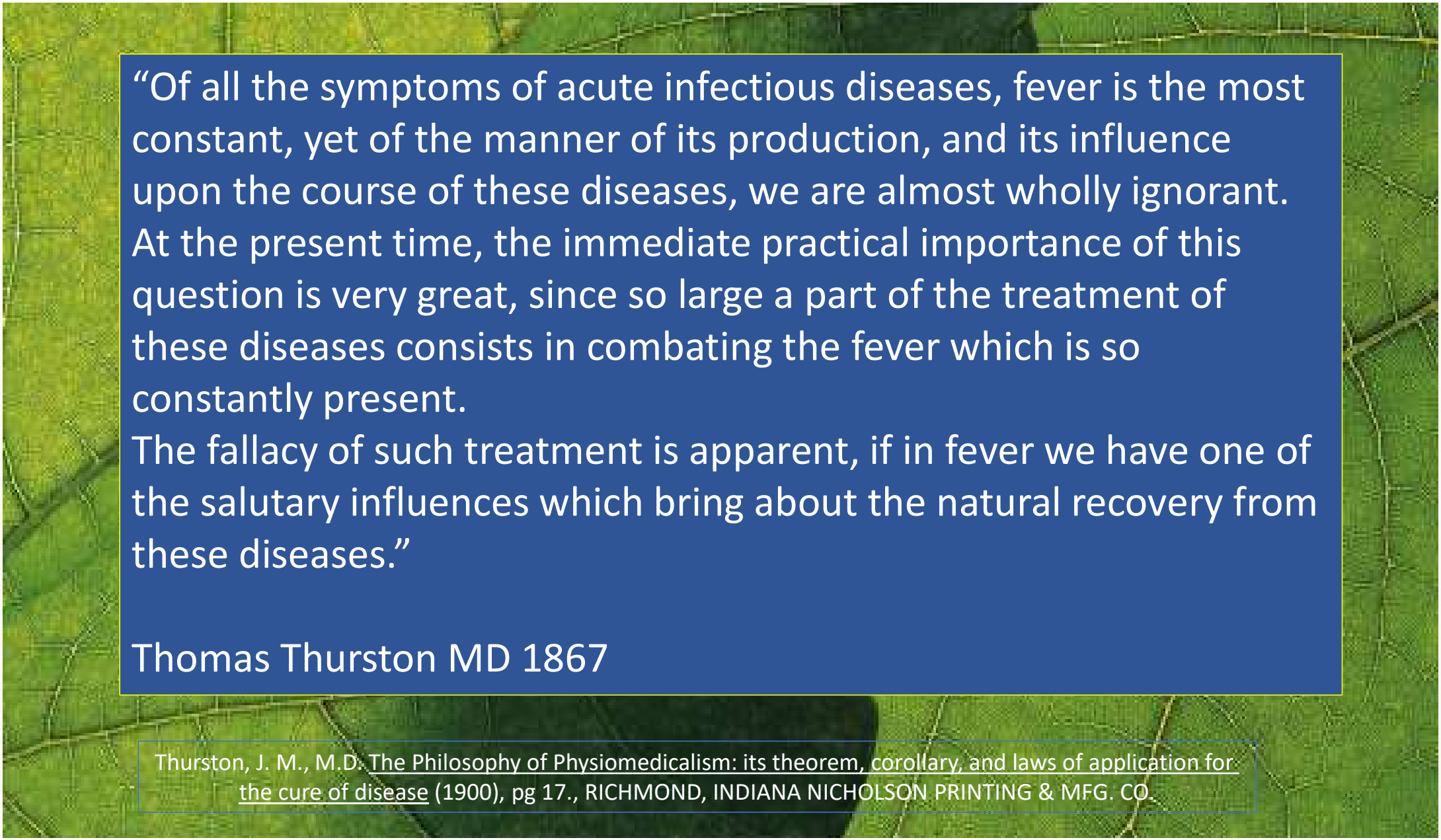
- Fever stimulates white blood cells and other “fighter” cells to fight and destroy viruses and bacteria, other pathogens, and even cancer cells.
- An elevated body temperature triggers cellular mechanisms that ensure the immune system takes appropriate action against the offending virus
- Fever reduces the growth of viral replication, even killing viruses and bacteria directly
- A fever helps to shuttle iron to your liver so that it is not readily available to fuel the growth of invading pathogens
- Fever promotes detoxification through the skin (Diaphoresis), kidneys, liver, and bowels

Coronavirus May be Killed by a Higher Body Temperature

The SARS 2003 CoV and the COVID-2019 share the following characteristics:

1. It is highly infectious, because it infects by being air-borne.
2. Many people lose their sense of smell (need for zinc)
3. If the body temperature is below 36C, it grows very fast.
4. The destructive immune reaction will take some time (? 7-10 days) to develop patients then start to have high fever and progress.
5. During this period, if the body temperature is above 36.5C, and better still, above 37C, the virus is attenuated or killed.

Tsang KW, et al. *A cluster of cases of severe acute respiratory syndrome in Hong Kong.* N Engl J Med 2003 Apr 1, http://content.nejm.org/cgi/reprint/NEJMoa030666v2.pdf (accessed 7 Apr 2003)*M Chan-Yeung, Outbreak of severe acute respiratory syndrome in Hong Kong Special Administrative Region: case report BMJ 2003; 326 doi: https://doi.org/10.1136/bmj.326.7394.850 (Published 19 April 2003) Cite this as: BMJ 2003;326:850*



Thurston, J. M., M.D. The Philosophy of Physiomedicalism: its theorem, corollary, and laws of application for the cure of disease (1900), pg 17., RICHMOND, INDIANA NICHOLSON PRINTING & MFG. CO.

Treating Fever with Botanical Medicine

1. Diaphoretics (gentle diffusive)
   Stimulate or Relax, or a little of both
2. Reduce excess heat, relieve inflammation
3. Heroics (very strong) for very high fevers with specific presenting symptoms and physical signs

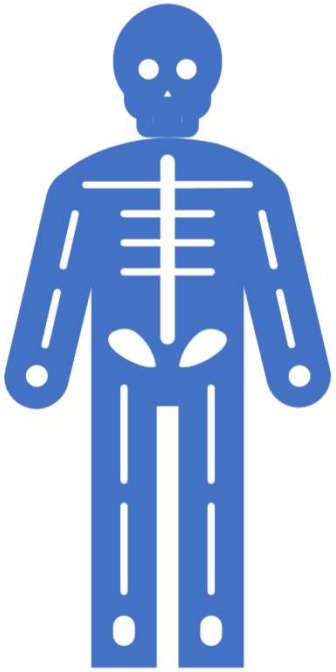
Eclectic/Physiomedicalism Theory

The underlying philosophy of Traditional Herbal Medicine expresses the basic premise that healing comes from the wisdom of God, and it is inherently found in Nature (Gaia).
This spiritual wisdom (Life Force) dwells within all human beings.

- As part of the energetic diagnostic system of Eclectic medicine, somewhat similar to the TCM concept of Yin and Yang, was the concept of Asthetic and Sthetic
- Patients' constitutions and organ systems were seen as either Asthenic (hypoactive, deficient - parasympathetic) or Sthetic (hyperactive, excess - sympathetic)

STHENIC OR ASTHENIC FOR FEVERS

- **STHENIC**: When the vital force has gone into over-drive, and the nervous system, and cardiovascular/circulatory system has gone beyond the range of healthy stability – excess heat (cytokine storm that often occurs in young adults and children in early stage of the fever). This calls for relaxing, and depressing remedies to these systems
- **ASTENIC**: When the vital force is deficient, and depressed, and the class of remedies must be, or include specific stimulates and tonics. The vital force must be nourished and strengthened. This is more common in older and weaker patients



A TABULATED SUMMARY AND COMPARISON OF THE ACTION OF FEVER REMEDIES.

	ACONITE	GELSEMIUM	VERATRUM	BRYONIA	RHUS TOXICODENDRON
WHEN INDICATED	(a) At the onset of fevers, and during fevers in sthenic patients. (b) In small doses in protracted fevers, in asthenic cases.	In sthenic cases. When nervous irritation is present and spasm threatens, or acute cerebral engorgement; in neuralgic pains.	Only in sthenic cases and in convulsions or threatened convulsions with rapid heart action.	In either sthenia or asthenia, when indications exist.	In either sthenia or asthenia. Most often indicated in the latter.
AGE OF PATIENT	Emphatically the child sedative, but equally applicable in middle life; less prompt in the aged.	Excellent in infancy. The remedy in full doses for strong adults; less frequently indicated in the aged.	The agent for strong adults, and women at childbirth; more difficult to adapt to infants; seldom indicated in the aged.	A remedy applicable any time of life; weak and strong; to infants, and to the aged.	Applicable to all by proper adjustment of dosage and by careful study of indications.
GENERAL CONDITIONS, OR LOCATION OF DISEASE	In all acute fevers and inflammations with increased temperature.	In acute cerebral engorgement; acute nervous irritation, and nervous excitability.	Threatened local engorgement; threatened convulsions.	In inflammations of serous, or of the synovial membranes, or of the organs covered by serous membranes; pulmonary and intestinal structures.	In local inflammation, where the skin structure is involved with redness, circumscribed tenderness and heat or pain. In typhoid conditions or low protracted fevers.
HEART AND PULSE INDICATIONS	Heart strong and rapid. Pulse rapid, quick, sharp, hard; in asthenia soft, small, feeble, but regular; given then in very small doses.	Heart strong, irritable, violent in action, increased in muscular power; exalted nerve force in heart disease; contraindicated in feeble heart.	Heart strong and rapid; pulse full, large, hard; or small, hard, very rapid; contraindicated in feeble heart.	Heart may be either weak or strong, if other indications are present, pulse quick. Is not a heart depressant in proper medicinal doses.	Quick and rapid pulse. Usually soft, feeble, compressible, or may be hard or wiry.
TEMPERATURE	Fever always present in acute cases. In chronic adaptation heart and pulse must guide.	Fever usually present, of a nervous type.	Fever usually present; heart's action rather than temperature to be considered.	Fever present	Fever present
SKIN, FACE AND EYES	Skin dry and hot; capillary circulation actively engorged; eyes bright.	Skin dry and hot, usually; face flushed, bright red; eyes bright, pupils contracted.	Skin may be cool, bright red, or dull red, or even dusky colored.	Usually hot, either moist or dry; red spot on one or both cheeks.	Skin usually very hot. Especially in circumscribed area, which is bright red.
MOUTH AND TONGUE	Mouth dry and parched; tongue pale, soft, white coat, moist, or dry and harsh with brown stripe.	Red tongue, dry or moist; in protracted nerve irritation dry and dark red.	Mouth moist, full membranes, tongue dry, red stripe in center.	Tongue dry, usually coated, membranes dark.	Membranes dark, tongue dark, pointed red tip and edges; elongated papillae.
SECRETIONS	May be abruptly suppressed.	Usually suppressed. Of immediate importance, in full, frequent doses, in anuria, especially if from infection	Skin and kidneys usually free in action; in uremic convulsions secretions deficient.	Usually deficient.	Usually suppressed.
PAIN	General distress, and headache; local pain in inflamed organs.	Severe headache with extreme restlessness; local pain of nervous origin, acute neuralgias.	Pain depends upon cause, may be local; may be bursting headache as in puerperal convulsions.	Quick, shooting, darting pains; local soreness and tenderness on pressure; general muscular aching.	Pain in inflamed area; general muscular aching.

BRYONIA

In either sthenia or asthenia, when indications exist.

A remedy applicable any time of life; weak and strong; to infants, and to the aged.

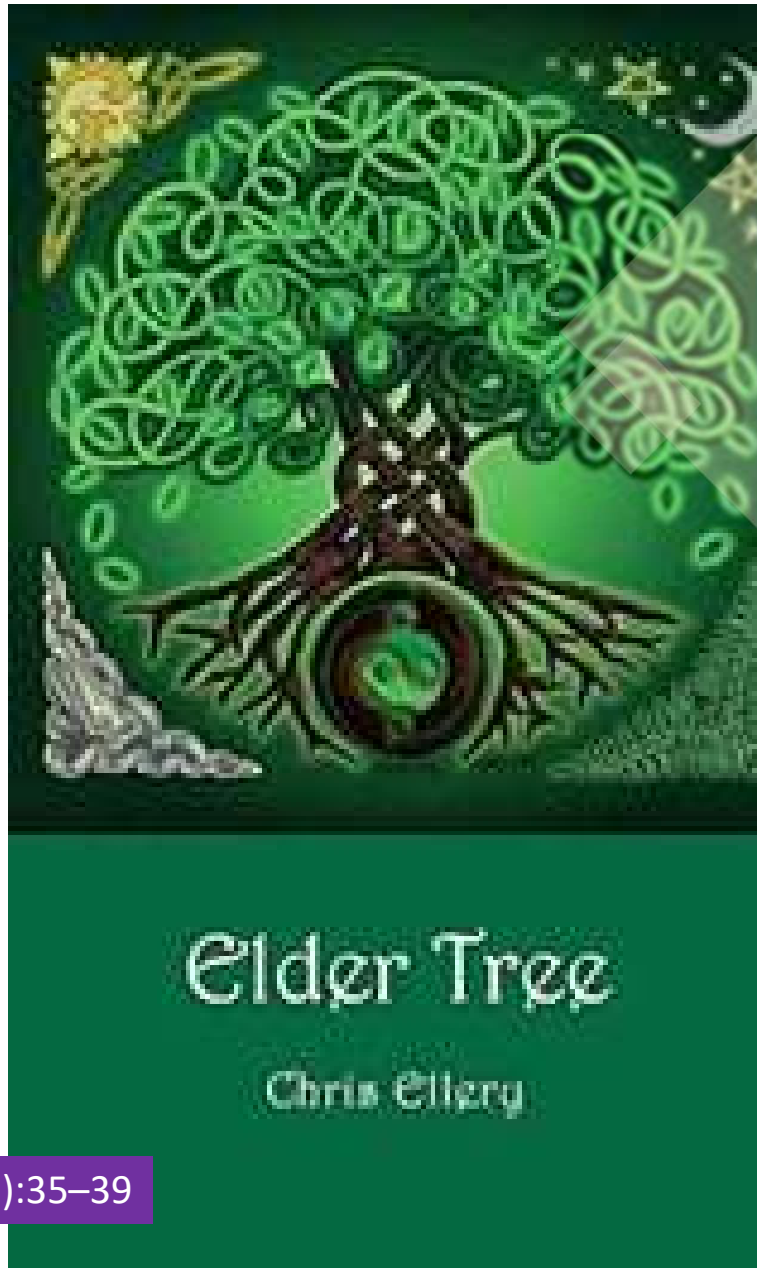
In inflammations of serous, or of the synovial membranes, or of the organs covered by serous membranes; pulmonary and intestinal structures.

Heart may be either weak or strong, if other indications are present, pulse quick. Is not a heart depressant in proper medicinal doses.

Fever present

The Elder Tree (Berry, Leaf and Flower)

- Embodies a lifetime of experience and observation, dream and fantasy, quest and discovery in the shape of the mystical elder
- The Elder tree is a medicinal tree, source of many folk remedies. Its energies are feminine and is committed to the blessings and beauties of eternal life
- If you go and sit under Her, you may experience renewal and healing



A lectin called *Sambucus nigra* fruit specific agglutinin was identified as a minor protein in ripe elderberry fruits. This lectin components might inhibit spike protein function during entry at the binding step

FEBS Lett. 1998 Mar 20;425(1):35–39



The Truth about Elderberry (Sambucus nigra)

Posted by Donnie on Mar 23, 2020 in Botanical Supplements, Detoxification, Healing Medicine, Healthy Living, Herbs and Nutrients, Immune Support, Recent Post | 1 comment

False information can spread like wildfire, particularly during times of fear and uncertainty. Right now, there is misinformation circulating about elderberry (*Sambucus nigra)* and COVID-19.

Elderberry extract is being falsely accused of triggering a cytokine storm or cytokine release syndrome (CRS), an intense inflammatory response that can be deadly. During the SARS epidemic, CRS caused severe lung damage and was a driving factor in many fatalities.

Elderberry (*Sambucus nigra*) extract effective for acute respiratory viral infections: a rapid review of clinical studies

- Collectively the evidence obtained from across five clinical studies involving 936 adults indicate that *Sambucus nigra* L. berry (*S.nigra*), when taken within 48 hours of onset of acute respiratory viral infection, may reduce the duration and severity of common cold and influenza symptoms in adults.
- Given the body of evidence from preclinical studies demonstrating the antiviral effects of *S.nigra* berry, alongside the results from clinical studies involving influenza viral infections included in this review, pre-clinical research exploring the potential effects of *S.nigra* berry on COVID-19 are encouraged.

Harnett J, Oakes K, Carè J, Leach M, Brown D, Cramer H, Pinder TA, Steel A, Anheyer D. The effects of *Sambucus nigra* berry on acute respiratory viral infections: a rapid review of clinical studies. Adv Integr Med. 2020 Aug 22. doi: 10.1016/j.aimed.2020.08.001. Epub ahead of print. PMID: 32864330; PMCID: PMC7443157.

Wieland *et al. BMC Complementary Medicine and Therapies* (2021) 21:112
https://doi.org/10.1186/s12906-021-03283-5

BMC Complementary Medicine and Therapies

RESEARCH ARTICLE Open Access

Elderberry for prevention and treatment of viral respiratory illnesses: a systematic review

L. Susan Wieland[1*], Vanessa Piechotta[2], Termeh Feinberg[3,4,5], Emilie Ludeman[6], Brian Hutton[7,8], Salmaan Kanji[7,9], Dugald Seely[9,10,11] and Chantelle Garritty[7]

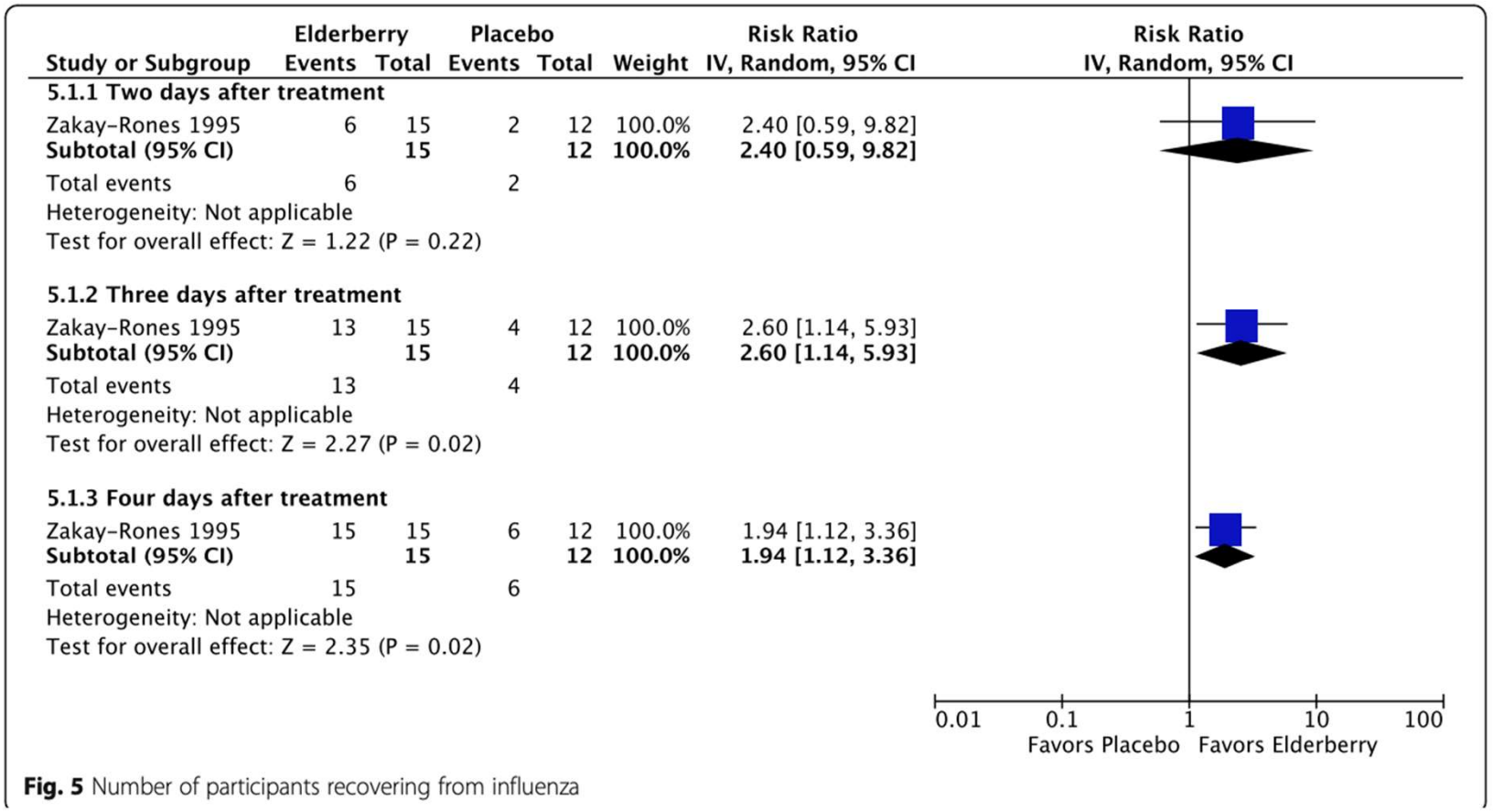


Fig. 5 Number of participants recovering from influenza

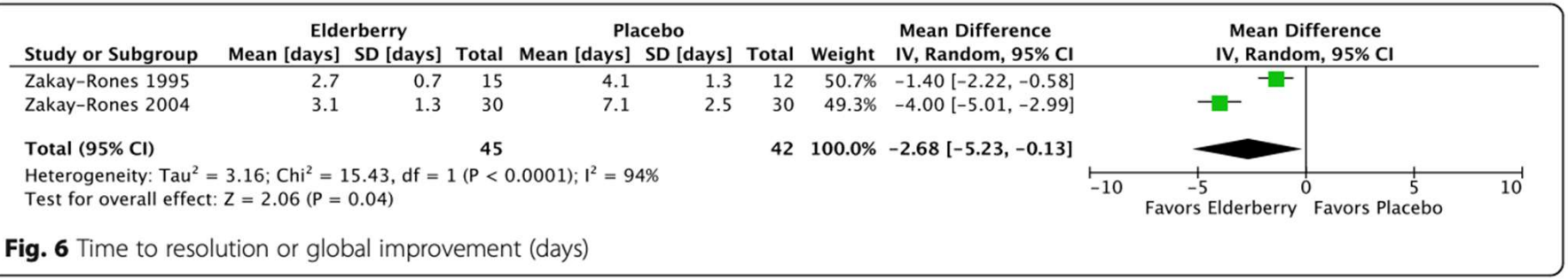


Fig. 6 Time to resolution or global improvement (days)





Boneset (Eupatorium Perfoliatum) Monograph

Posted by Donnie on Mar 17, 2020 in Botanical Supplements, Detoxification, Healing Medicine, Healthy Living, Herbs and Nutrients, Immune Support, Recent Post | 0 comments

“I go into my library and all history unrolls before me.” Alexander Smith

In Western tradition, boneset is perhaps the single most important herb for combating the flu. There have been six major influenza pandemics (worldwide outbreaks) since 1889. The 1918 influenza pandemic (“Spanish flu”) was the deadliest pandemic in history. Approximately 5% of the world’s population was infected, and the number of deaths has been estimated at 50 million (CDC).

TCM herb formula used for the Treatment of Acute SARS-CoV infection

- Yin Qiao San:
  - Fructus **Forsythiae**, Flos **Lonicerae**, Herba **Menthae**, Radix Platycodonis, Herba Lophatheri, Radix Glycyrrhizae, Herba Schizonepetae, Fermented soybean, Fructus arctii, and Rhizoma Phragmitis
- TCM Actions: “Disperses wind-heat, clears heat, and relieves toxicity”
- Usage: Treatment of upper respiratory tract infection. Improvement of the function of upper respiratory mucosal immune system

Yang Yang, Md Sahidul Islam, Jin Wang, Yuan Li and Xin Chen; Traditional Chinese Medicine in the Treatment of Patients Infected with 2019-New Coronavirus (SARS-CoV-2): A Review and Perspective Int. J. Biol. Sci. 2020; 16(10): 1708-1717. doi: 10.7150/ijbs.45538

Forsythia (*Fructus Forsythia*) and Honeysuckle (*Lonicera*)

- Forsythia and Lonicera are often used together in Chinese medicinal for acute respiratory conditions
- They are in the category of herbs that Clear Heat and Clean Toxins
- Forsythia protects the heart from excess Heat in the Lungs
- Lonicera can address even a deeper layer of Heat
- It is not only useful for the sore throat, fever, thirst, and perspiration associated with an external disease, but is also beneficial for internal trapped Heat and Toxins manifesting with high fever, strong thirst, and more severe sore throat



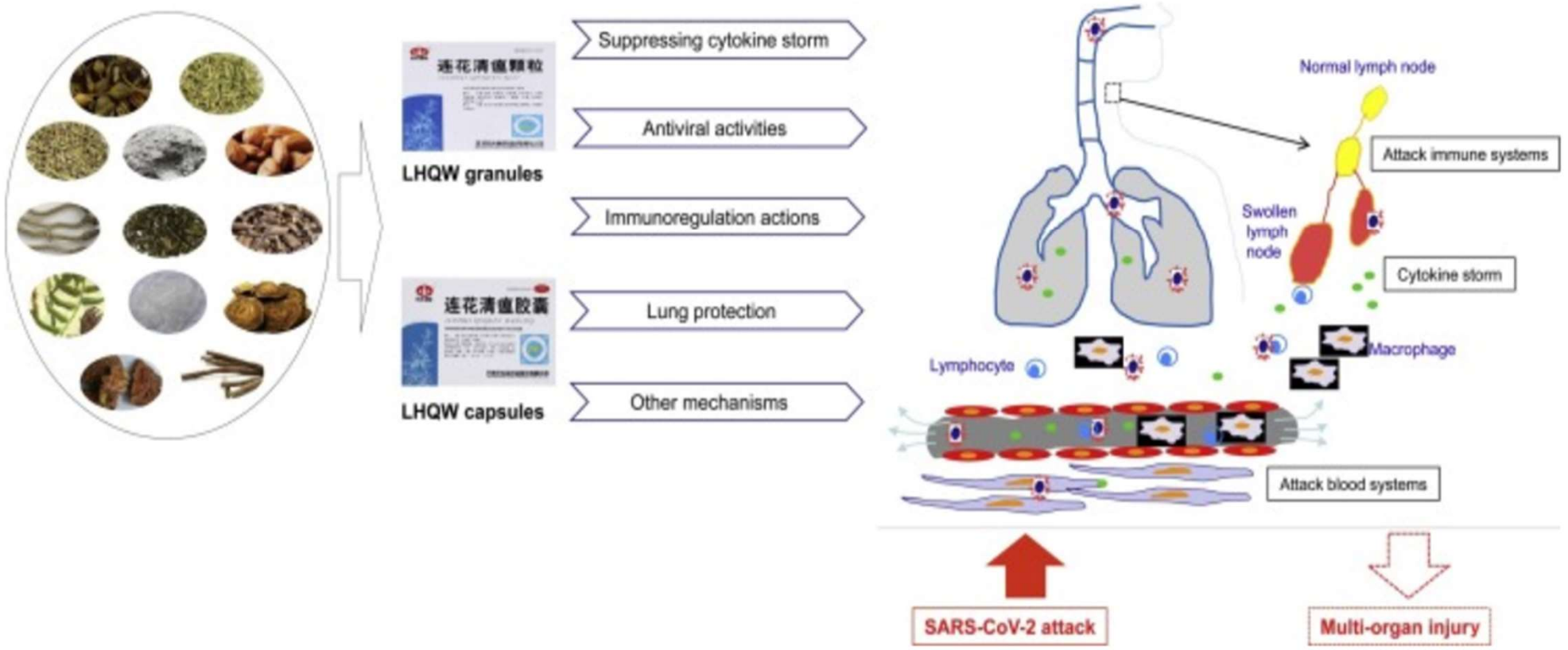


Ke Yan Tong Xun (Journal of Science and Research), 1982 (3):35; Jiang Xi Xin Yi Yao (Jiangxi New Medicine and Herbology); 1960; (1):34; Guang Dong Zhong Yi (Guang Dong Chinese Medicine), 1962 5:25

Forsythia and Lonicera based TCM formula (LHQW) and Covid-19 treatment

- Lianhua Qingwen (LHQW) is a commonly used Chinese medical preparation to treat viral influenza, including in the fight against SARS in 2002-2003 in China.
- The research data were obtained from the academic databases (up to August 8, 2020) including Pubmed, CNKI and Web of Science, on ethnobotany and ethno medicines.
- The collected evidence demonstrated that LHQW exhibited benefits against COVID-19. Impressively, LHQW in conjunction with conventional treatment could significantly improve COVID-19 patients as a synergetic strategy.

Li LC, Zhang ZH, Zhou WC, Chen J, Jin HQ, Fang HM, Chen Q, Jin YC, Qu J, Kan LD. Lianhua Qingwen prescription for Coronavirus disease 2019 (COVID-19) treatment: Advances



Role of LHQW in the treatment of COVID-19. LHQW: Lianhua Qingwen.

Li LC, Zhang ZH, Zhou WC, Chen J, Jin HQ, Fang HM, Chen Q, Jin YC, Qu J, Kan LD. Lianhua Qingwen prescription for Coronavirus disease 2019 (COVID-19) treatment: Advances

Gelsemium (Yellow Jasmine)

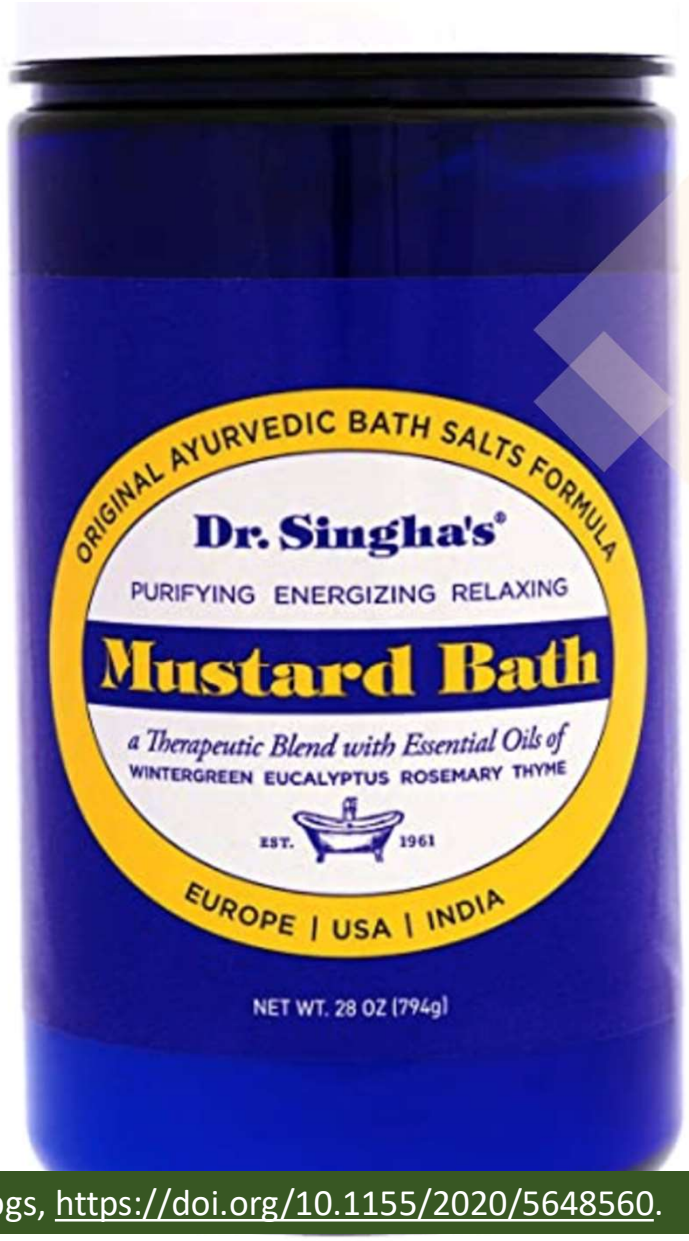


- Sedative and pain killer - especially early stages of fever when there is severe muscle and head pain
- Gelsemium extract serve a variety of biological functions, including **neurobiological, immunosuppressive and antitumor effects**, and have traditionally been used to treat pain, neuralgia, anxiety, insomnia, asthma, respiratory ailments and cancers
- **Indications:** Increased arterial and nervous tension; conditions with bright eyes, flushed face, great heat and restlessness, mental irritability, insomnia, excitation, hysteria, head pain, nerve pain, and convulsions
- Useful for muscle twitching, facial neuralgias, trigeminal neuralgias, intercostal neuralgias (herpes zoster), headaches and sciatica
- Add low dose belladonna with peripheral stagnation/coldness/spasm
- Drop doses (1-5 drops up to 3x daily)

Ellingwood F: *American Materia Medica, Therapeutics and Pharmacognosy*. Sandy, 1919, Eclectic Medical Publications.
Grieve, M. *Gelsemium.* http://www.botanical.com/botanical/mgmh/g/gelsem07.html. (1995). Fitoterapia. 2015 Jan;100:35-43.

Donnie's Bath Therapy for Respiratory Tract Infections (RTI)

- A recent study (103 participants) concluded that mustard foot baths improved the symptoms of patients with RTI.
- I typically recommend full body mustard baths, using 1-3 tablespoons of mustard seed powder such as Dr. Singha's Mustard Bath, which includes aromatic essential (EOs), together with 1 cup of Epsom salts, 1 tablespoon of baking soda. (You can add EOs separately)
- The Epsom salts (magnesium sulfate) and the baking soda (sodium bicarbonate) can really help relieve the bone and muscle achiness.
- Drink a cup of Flew B Gone Tea (Mederi Center) before and/or during the bath with 1-3 lemon slices and raw honey (1 tsp).



Evidence-Based Complementary and Alternative Medicine Volume 2020, Article ID 5648560, 6 pgs, https://doi.org/10.1155/2020/5648560.

Essential Oils may be able to prevent the spread of Co-19



Eucalyptus leaves

Curr Microbiol, 56 (1), 89-92 Jan 2008

Effect of Eucalyptus Essential Oil on Respiratory Bacteria and Viruses

Claudio Cermelli [1], Anna Fabio, Giuliana Fabio, Paola Quaglio

Affiliations



Effects of Essential; oil (EO) of Lavender on Anxiety: A Systematic Review & Meta-Analysis (65 RTCs)

Lavender EO proves to be effective in the treatment of anxiety

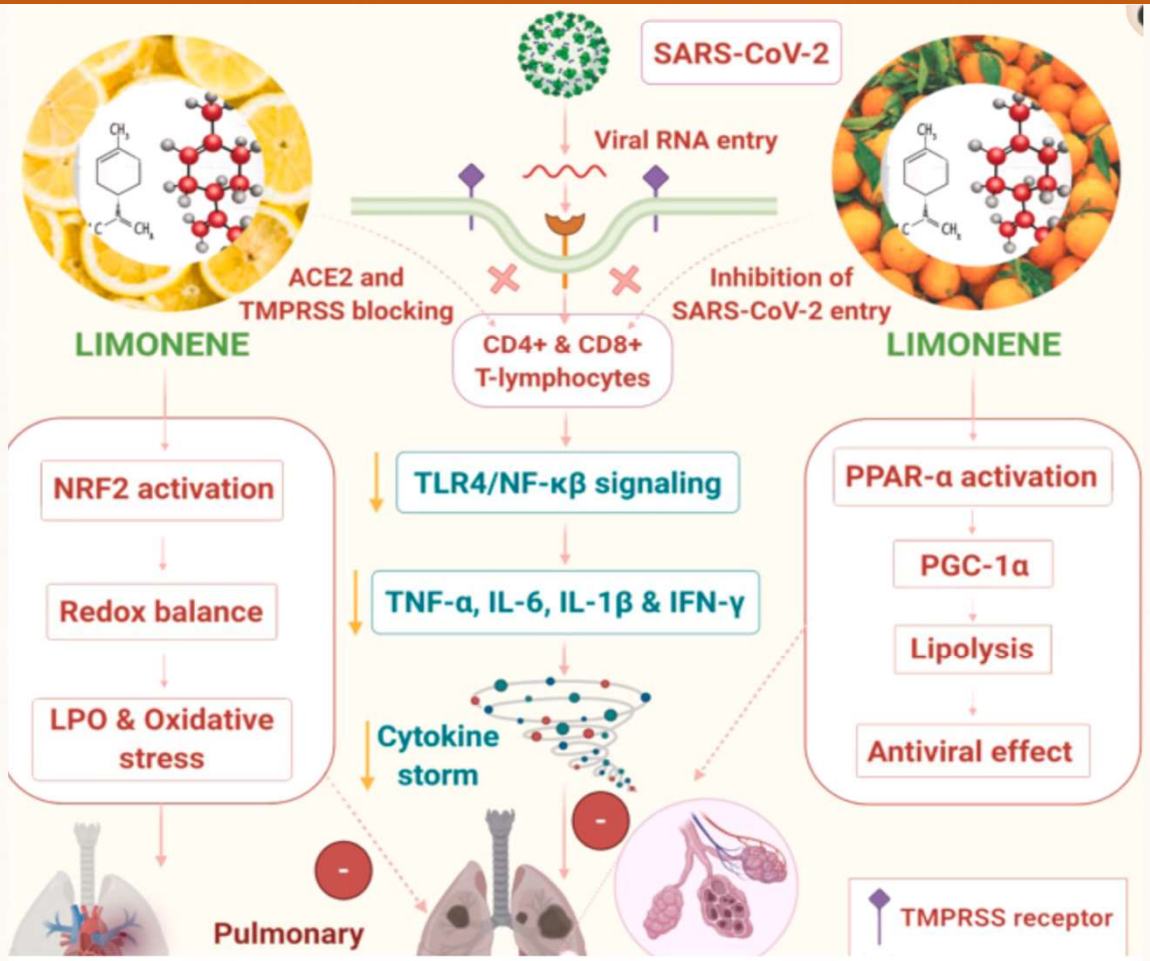
Phytomedicine, 65, 153099 Dec 2019

Geranium and Lemon Essential Oils Downregulate ACE2, a SARS-CoV-2 Spike Receptor-Binding Domain, in Epithelial Cells

- ACE2 inhibitory effects of 10 essential oils was studied. Among them, geranium and lemon oils displayed significant ACE2 inhibitory effects
- Geranium and lemon oils possess potent ACE2 inhibitory effects
- 22 compounds in geranium oil and 9 compounds in lemon oil
- Citronellol, geraniol, and neryl acetate were the major compounds of geranium oil and limonene that represented major compound of lemon oil.
- Treatment with **citronellol** and **limonene** significantly downregulated ACE2 expression in epithelial cells.

Plants (Basel). 2020;9(6):E770. Published 2020 Jun 19. doi:10.3390/plants9060770

Limonene ,a main compounds found in many citrus plants. may be a possible agent or adjuvant against infection, immunity, and inflammation in COVID-19



Nagoor Meeran MF, Seenipandi A, Javed H, Sharma C, Hashiesh HM, Goyal SN, Jha NK, Ojha S. Can limonene be a possible candidate for evaluation as an agent or adjuvant against infection, immunity, and inflammation in COVID-19? Heliyon. 2020 Dec 11;7(1):e05703. doi: 10.1016/j.heliyon.2020.e05703.

Anti-viral Essential Oils (EO)

- **Tea tree** (*Melaleuca Alternifolia*) EO inhibits influenza during the early stages by preventing intracellular processing of the viral particle
- When introduced into cell culture media, **tea tree oil** prevented viral uncoating by interfering with the acidification of the endosomes and membrane fusion
- The ability to prevent endosome acidification was ascribed to the **tea tree oil** constituents terpinen-4-ol, α-terpineol and terpinolene
- **Tea tree** EO, when actively diffused with a nebulizer for two seconds, cleared nearly all airborne influenza viruses at 10 minutes, and showed zero virus at 15 minutes post nebulizer treatment
- **Eucalyptus** EO showed zero virus at 15 minutes following a 15 second period of active diffusion with a nebulizer

Letters in Applied Microbiology, vol. 49, 2009, pp. 806-808. doi:10.1111/j.1472-765X.2009.02740.x; Antiviral Research, vol. 89, 2011, pp. 83-88. doi:10.1016/j.antiviral.2010.11.010; Journal of Aerosol Science, vol. 59, 2013, pp. 22-30. doi:10.1016/j.jaerosci.2013.01.004

Anti-viral Essential Oils (EO)

- **Lemon balm** (*Melissa officinalis*) EO has been used extensively to prevent HSV infection. Likewise, influenza viruses were inhibited as well – **Lemon balm** EO prevented attachment of the virus to host cell surface cell receptors

- Viral induced autophagy was effectively inhibited by **Clove Bud** EO and eugenol in cells infected with 8 separate flu viruses

- Clove bud and **Sweet Orange** (*Citrus sinensis*) essential oils, and this blend inhibited viral protein production

  - Indian Journal of Virology, vol. 27, no. 2, 2016, pp. 170-178. doi:10.1007/s13337-016-0321-0
  - PLoS ONE, vol. 8, no. 4, 2013, pp. 1–16., doi:10.1371/journal.pone.0061026.

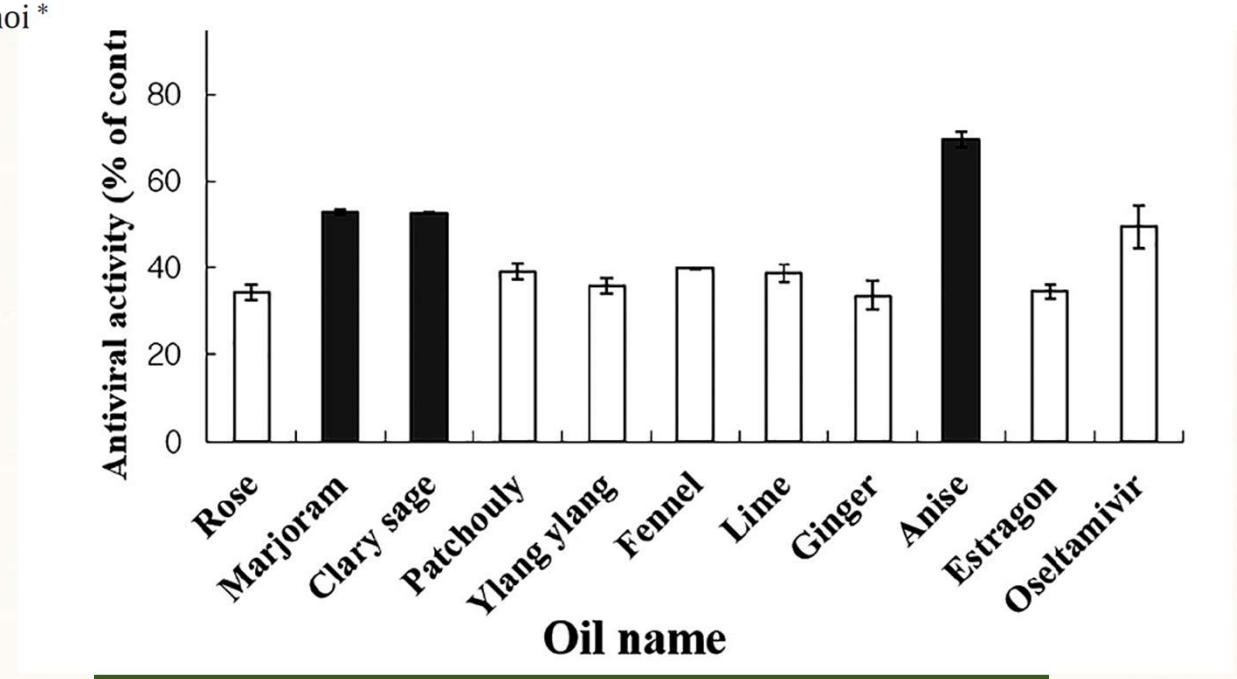
Osong Public Health and Research Perspectives

Journal homepage: http://www.kcdcphrp.org

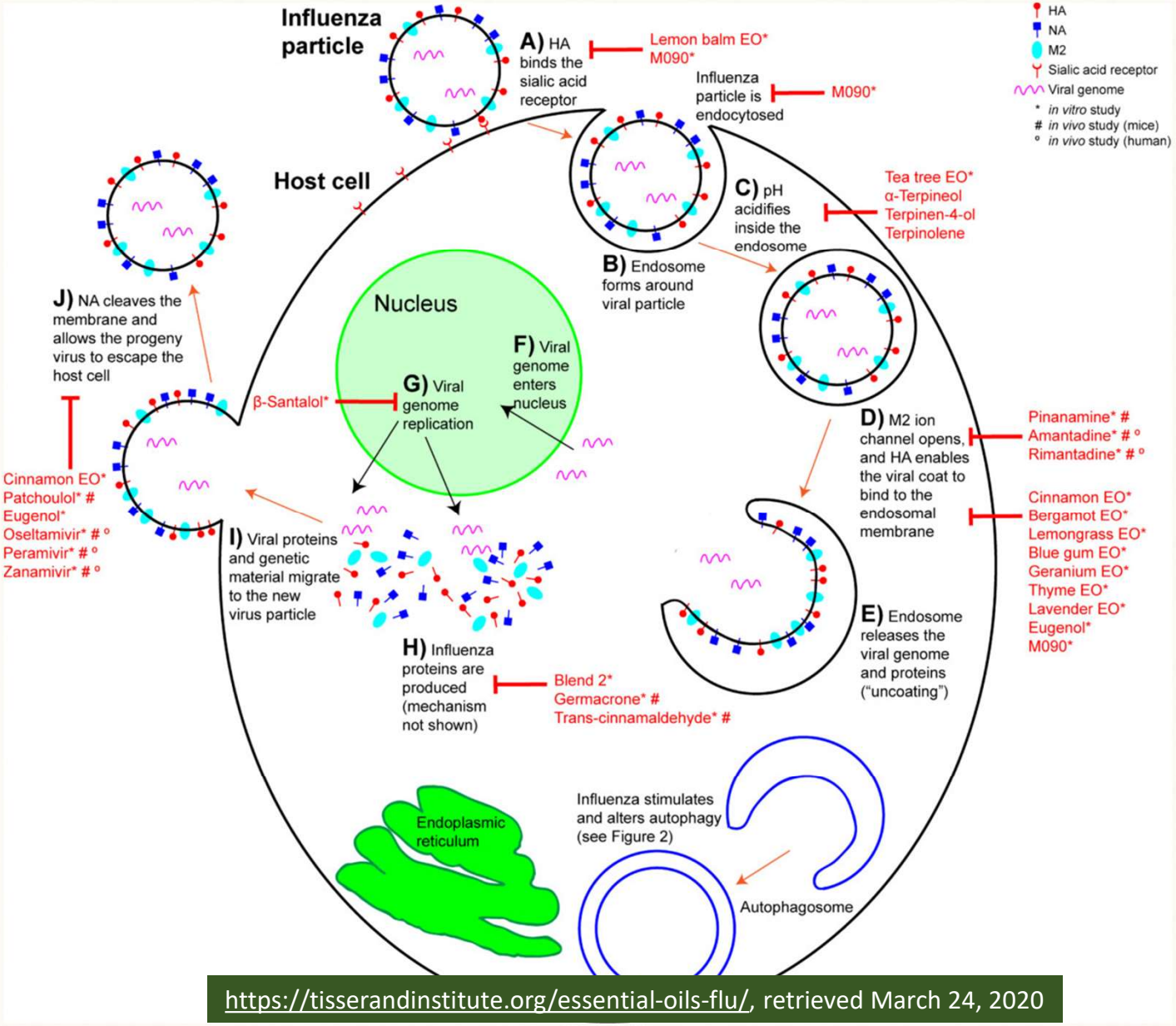
Original Article

Chemical Constituents of Essential Oils Possessing Anti-Influenza A/WS/33 Virus Activity

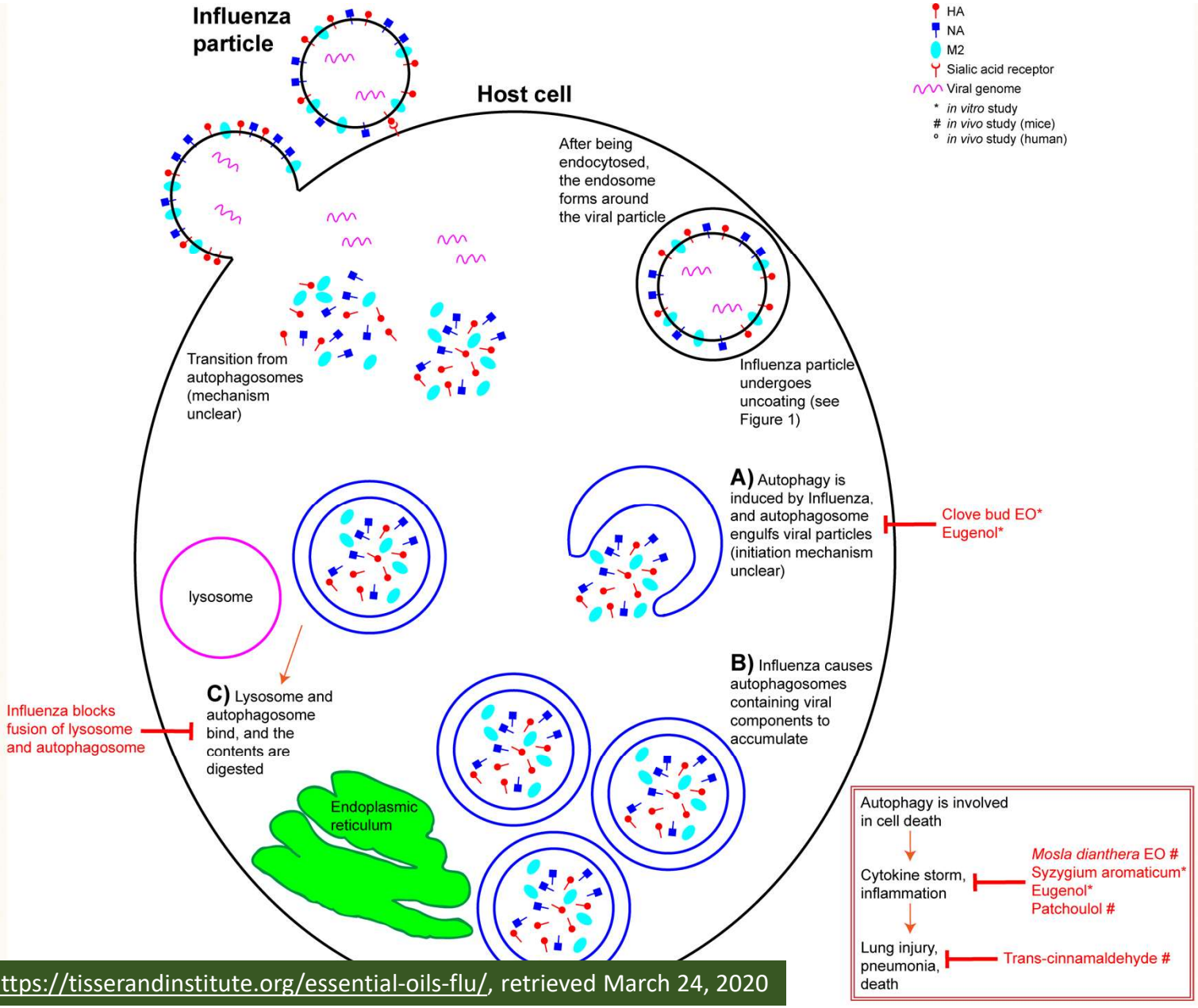
Hwa-Jung Choi *



Osong Public Health Res Perspect 2018;9(6):348–353



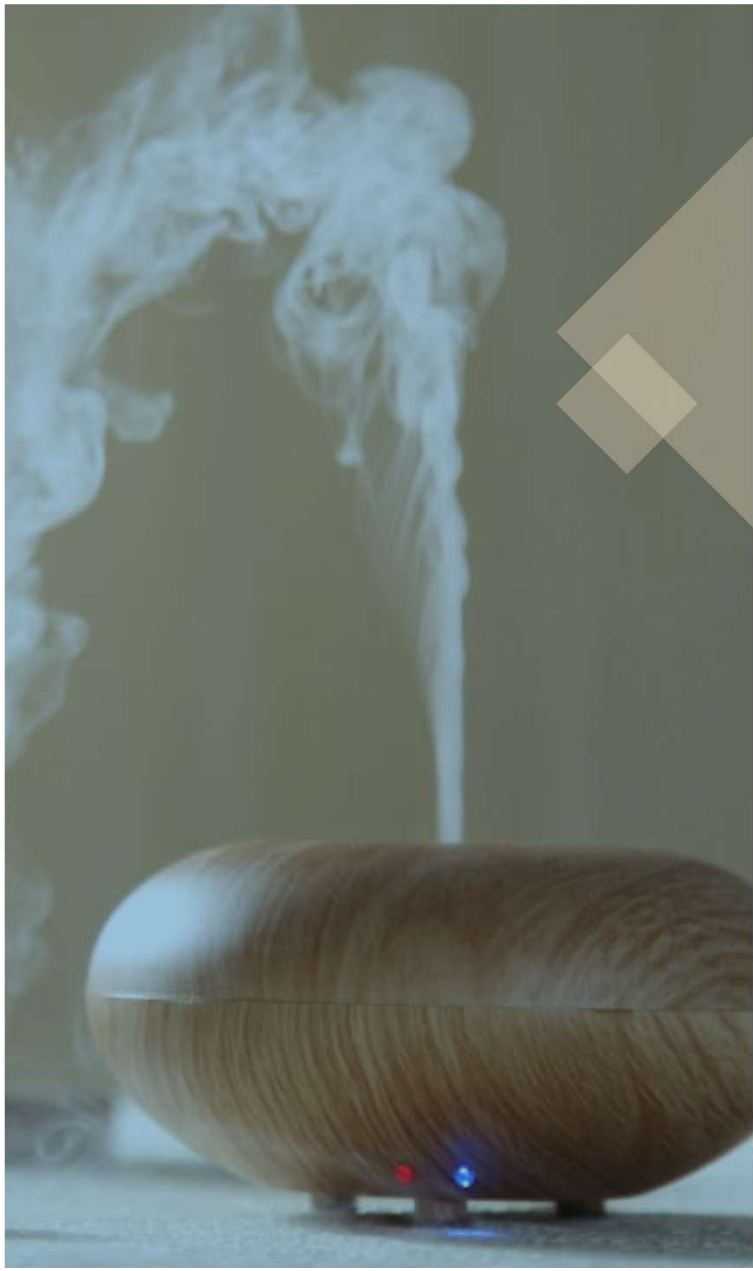
https://tisserandinstitute.org/essential-oils-flu/, retrieved March 24, 2020



https://tisserandinstitute.org/essential-oils-flu/, retrieved March 24, 2020

CoV Prevention in the Home and Office

- CoV particles can spread by airborne droplets, close contact with an infected person, and contact with objects contaminated with the virus
- CoV particles can remain viable on objects for up to 72 hours, but only 24 on cardboard
- Ethanol is effective against most clinically relevant viruses
- Nebulizing Eucalyptus essential and tea tree EO for 15 seconds is a fast and effective method to eliminate airborne influenza droplets within 15 minutes. Additional EOs can include bergamot, thyme, cinnamon, clove, sweet orange, and rosemary



July 23, 2020

Benefits and Safety of Nasal Saline Irrigations in a Pandemic—Washing COVID-19 Away

Nyssa F. Farrell, MD[1]; Cristine Klatt-Cromwell, MD[2]; John S. Schneider, MD, MA[2]

» Author Affiliations | Article Information

JAMA Otolaryngol Head Neck Surg. Published online July 23, 2020. doi:10.1001/jamaoto.2020.1622

- The nasal lining serves an important role in the innate immune system, providing a primary defense against inhaled viruses, bacteria, and other particulates.
- This lining, consisting of a superficial mucus layer atop an aqueous base, traps inhaled particulates that are then propelled by underlying cilia into the nasopharynx.
- They are ultimately driven into the gastrointestinal system, where they are destroyed.
- Topical nasal rinses physically disrupt the viscous surface layer, removing the mucus and its associated particulate matter

Cv-19 can linger in the sinuses for many days before infecting other tissues.

Donnie's Navage Sinus rinse:

- Follow the instructions that come with the device.
- Youtube video demonstration https://www.youtube.com/watch?v=6pvaKzfYvE8
- In addition add 2-3 Sprays of a sinus spray formula to the saline solution
- You can also add a ¼ tsp. of Aromatic Shea Butter (Mederi Center), or 1-5 drops of Clear Airways (Mederi Center)
- Aromatic Shea butter needs to be added to the hot or warm water so it will melt and dissipate in the solution. Can be rubbed on chest and throat as well; and can be added to a hot bath



Shea butter, black cumin seed oil, camphor, Essential oils of eucalyptus, peppermint, thyme, ginger, nutmeg, lavender.

Stinging Nettle (*Urtica dioica*)

- Stinging nettles leaf, my favorite overall super food/herb in the world, is the most nutritive dense plant in the world and is a great tonic for all people, and especially for recovery following an illness and for the chronically sick
- Urtica leaf extract is useful for allergies, and inflammatory diseases, particularly of the lungs and inflammatory bowel diseases
- Use of Stinging Nettle Extract Helps Improve Fasting Glucose, Hepatic Enzyme, and Inflammatory Markers in Patients with Type 2 Diabetes Mellitus
- Urtica leaf extract inhibits 12-lipoxygenase pathway preserving the epithelial integrity and enhancing intestinal steady-state defense



Franciskovic M., et. al. Chemical Composition and Immuno-Modulatory Effects of Urtica dioica L. (Stinging Nettle) Extracts; Phytother Res. 2017 Aug;31(8):1183-1191. doi: 10.1002/ptr.5836;Avicenna J Phytomed. 2016;6(6):686-695.

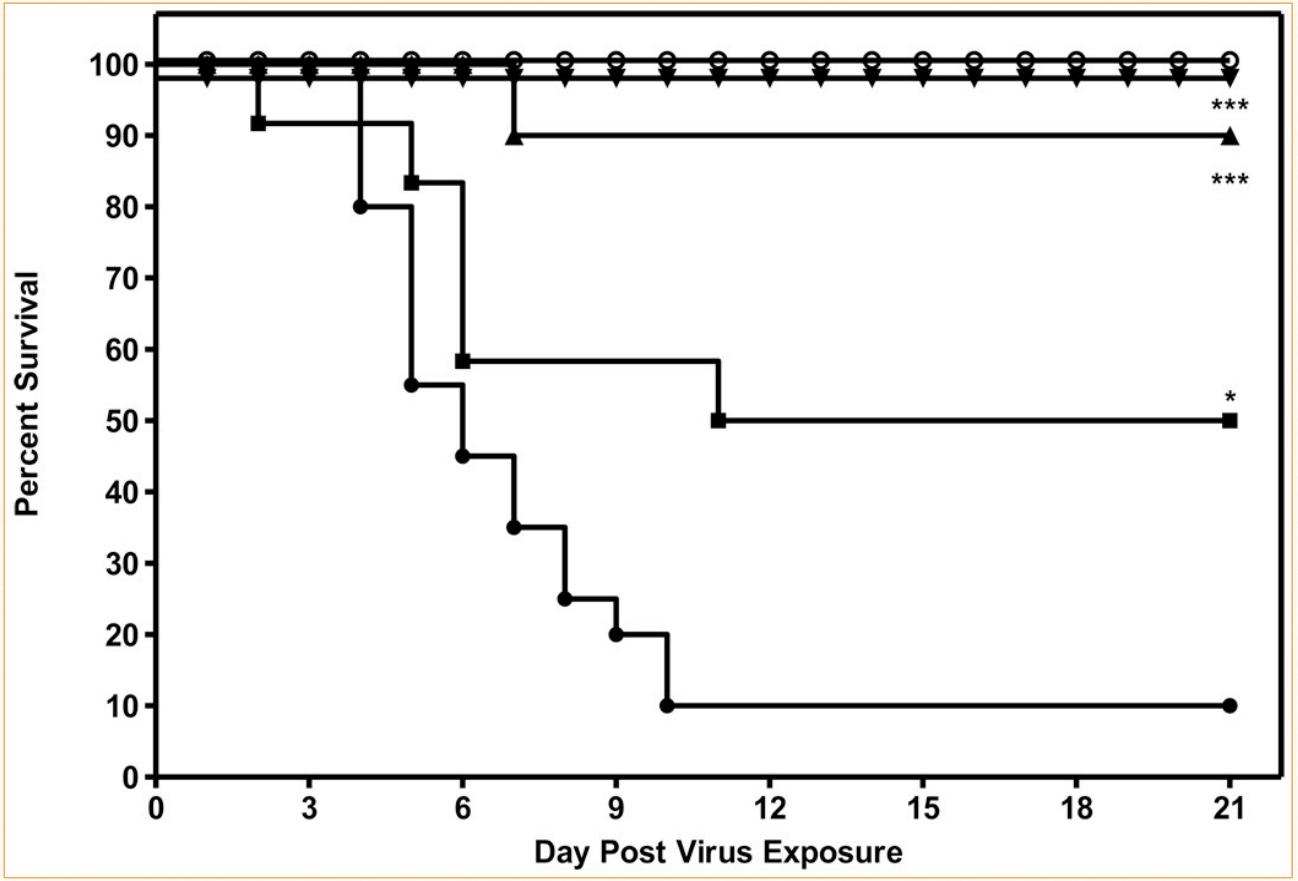
Lectin in Nettles (*Urtica dioica*) Inhibits SARS-CoV Viral Replication

- *Urtica dioica* agglutinin (UDA) is a small plant monomeric lectin with an *N*-acetylglucosamine specificity that inhibits viruses
- UDA likely inhibits SARS-CoV infection by targeting early stages of the replication cycle, namely, adsorption or penetration
- In addition, we demonstrated that UDA neutralizes the virus infectivity, presumably by binding to the SARS-CoV spike (S) glycoprotein

Antiviral Res. 2011 Apr; 90(1): 22–32. Published online 2011 Feb 19. doi: 10.1016/j.antiviral.2011.02.003

Effects of UDA on the Survival of BALB/c Mice Infected with a Lethal Dose of Mouse-Adapted SARS-CoV.

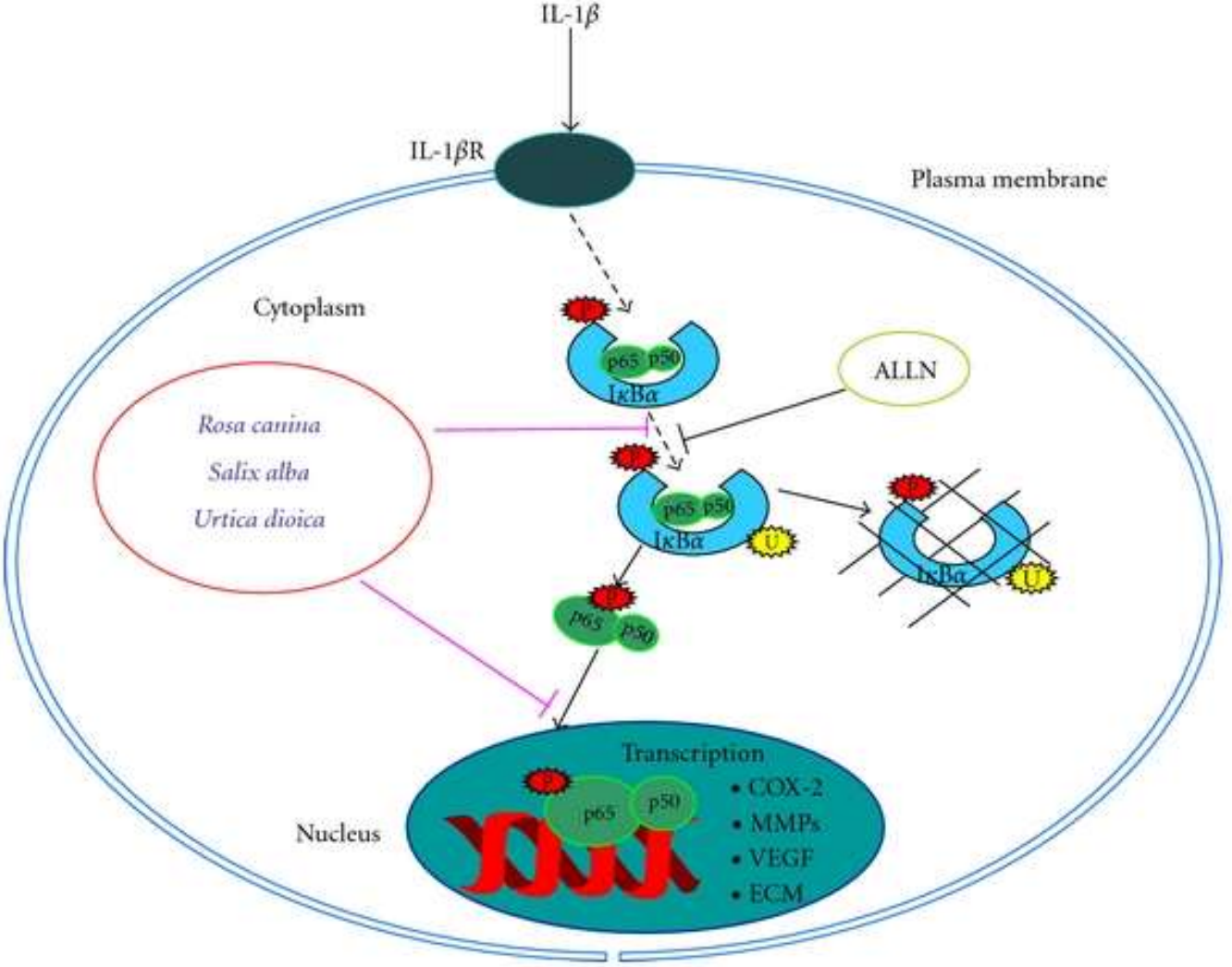
The most significantly efficacious dose of UDA used for treating infected mice was UDA at 5 mg/kg/day.
At this dose, mice were significantly protected against weight loss by day 6 ($p<0.05$) and thereafter, all mice were protected against death due to virus infection ($p<0.001$).



Antiviral Res. 2011 Apr; 90(1): 22–32. Published online 2011 Feb 19. doi: 10.1016/j.antiviral.2011.02.003

Inhibitory Effects of Botanical Extracts on IL-1β-Induced NF-κB Activation

Rose hips
White willow
Nettles



Evid Based Complement Alternat Med. 2012; 2012: 509383. Published online 2012 Mar 14. doi: 10.1155/2012/509383

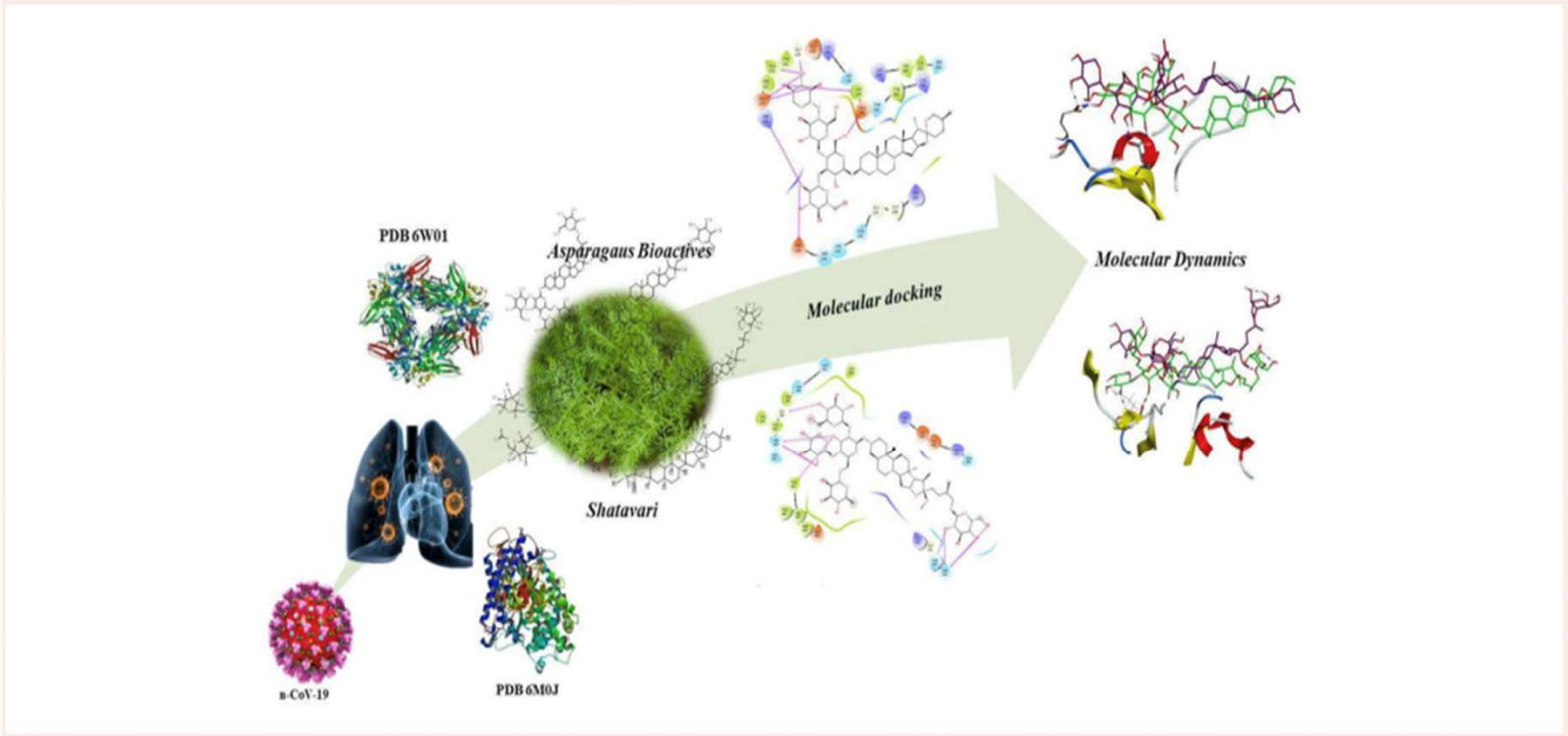
JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS
https://doi.org/10.1080/07391102.2020.1784289

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Taylor & Francis Group

Check for updates

In-silico investigation of phytochemicals from *Asparagus racemosus* as plausible antiviral agent in COVID-19

Rupesh V. Chikhale[a], Saurabh K. Sinha[b], Rajesh B. Patil[c], Satyendra K. Prasad[d], Anshul Shakya[e], Nilambari Gurav[f], Rupali Prasad[d], Suhas R. Dhaswadikar[d], Manish Wanjari[g] and Shailendra S. Gurav[h]



Nigella sativa (NS) for the treatment of COVID-19: An open-label randomized controlled clinical trial

- This trial randomly divided into control or treatment groups, with the latter receiving 500 mg NS oil twice daily for 10 days.
- Symptoms were daily monitored via telecommunication. The primary outcome focused on the percentage of patients who recovered (symptom-free for 3 days) within 14-days. The trial was registered at clinicaltrials.gov (NCT04401202).
- NS oil supplementation was associated with faster recovery of symptoms than usual care alone for patients with mild COVID-19 infection.

Koshak AE, Koshak EA, Mobeireek AF, Badawi MA, Wali SO, Malibary HM, Atwah AF, Alhamdan MM, Almalki RA, Madani TA. Nigella sativa for the treatment of COVID-19: An open-label randomized controlled clinical trial. Complement Ther Med. 2021 Aug 15;61:102769. doi: 10.1016/j.ctim.2021.102769.

Elsevier Public Health Emergency Collection

Public Health Emergency COVID-19 Initiative

Med Hypotheses. 2020 Jun 2 : 109934.

doi: 10.1016/j.mehy.2020.109934 [Epub ahead of print]

PMCID: PMC7265825

PMID: 32512493

The Effects of Allium Sativum on Immunity within the Scope of COVID-19 Infection

Mustafa Metin Donma[a] and Orkide Donma[b]



Med Hypotheses. 2020 Jun 2 : 109934.
doi: 10.1016/j.mehy.2020.109934 [Epub ahead of print]

Figure 2. Some elements in immunological profiles of patients with COVID-19 infection.



Med Hypotheses. 2020 Jun 2 : 109934.
doi: 10.1016/j.mehy.2020.109934 [Epub ahead of print]

Preproofs

Administered Aqueous-Ethanolic Extract of a Mixture of Thuja Occidentalis, Baptisia Tinctoria , Echinacea Purpurea and Echinacea Pallida on the Immune Response in Mice Were Investigated Over the Short and Long Term.

Administration of the extract but initially and over several months also stimulated the splenic forming cells and significantly enhanced antibody response without affecting spleen weight, total cell yield per spleen or white blood cell count.

Bodinet C, Freudenstein J. Effects of an orally applied aqueous-ethanolic extract of a mixture of Thujae occidentalis herba, Baptisia tinctoriae radix, Echinaceae purpureae radix and Echinaceae pallidae radix on antibody response against sheep red blood cells in mice. Planta Med 1999;65:695–699.

Echinacea
Miracle Herb against Aging and Cancer?

- Results of five years of extensive research showed that daily consumption of Echinacea significantly extended lifespan in healthy mice as well as those with leukemia
- Actions: Immune modulation - **enhances NK cells**
- Normalizes Th1 and Th2 cytokine productior
- Anti-Hyaluronidase
- Mediates apoptosis/cytotoxic effects
- Down-regulates TNF-a, and Bcl-2 through caspase
- Neuroprotective



Evidence-based Complementary and Alternative Medicine 2, 309–314.; J. Ethnopharmacol. (2011), doi:10.1016/j.jep.2011.05.017; Journal Ethnopharmacology (2006).

Echinacea and ginger combination alleviates clinical symptoms and hospitalization rate of suspected COVID-19 outpatients: a randomized controlled trial

- A clinical trial with 100 suspected COVID-19 outpatients as participants was conducted.
- The participants were allocated randomly to two groups of 50 members. The intervention group received concurrent Ginger *Zingiber officinale* and Echinacea for seven days in addition to the standard treatment (Hydroxychloroquine).
- After seven days, alleviation of clinical symptoms and hospitalization rate were examined.
- Improvement level as to coughing, dyspnea, and muscle pain was higher in the intervention group (p value <0.05).
- The hospitalization rate in the intervention and control groups were 2 and 6% respectively.

J Complement Integr Med. 2021 Mar 31. doi: 10.1515/jcim-2020-0283. Epub ahead of print. PMID: 33787192.

Echinacea treatment of monocytes promotes tonic interferon signaling, increased innate immunity gene expression and DNA repeat hypermethylated silencing of endogenous retroviral sequences

- Echinaforce® phytochemicals strengthen antiviral innate immunity through tonic IFN regulation of pattern recognition and chemokine gene expression and DNA repeat hypermethylated silencing of HERVs in monocytes.
- Echinaforce® treatment holds promise to reduce symptoms and duration of infection episodes of common cold corona viruses (CoV),
- SARS-CoV, and new occurring strains such as SARS-CoV-2, with strongly impaired IFN response and weak innate antiviral defense.

BMC Complement Med Ther. 2021 May 12;21(1):141. doi: 10.1186/s12906-021-03310-5. PMID: 33980308; PMCID: PMC8114977.

Echinacea supplementation on cytokine levels, a systematic review on the effects: Is there a role in COVID-19?

- The search identified 279 unique publications. After full text screening, 105 studies met criteria for inclusion including 13 human studies, 24 animal studies, and 71 *in vitro* or *ex vivo* studies.
- **The data suggest that *Echinacea* supplementation may be associated with a decrease in the pro-inflammatory cytokines IL-6, IL-8, and TNF, as well as an increase in the anti-inflammatory cytokine IL-10.**

Aucoin M, Cardozo V, McLaren MD, Garber A, Remy D, Baker J, Gratton A, Kala MA, Monteiro S, Warder C, Perciballi A, Cooley K. A systematic review on the effects of *Echinacea* supplementation on cytokine levels: Is there a role in COVID-19? Metabol Open. 2021 Jul 29:100115. doi: 10.1016/j.metop.2021.100115

Echinacea Reduces the Risk of Recurrent Respiratory Tract Infections and Complications by 50%: A Meta-Analysis of Randomized Controlled Trials.

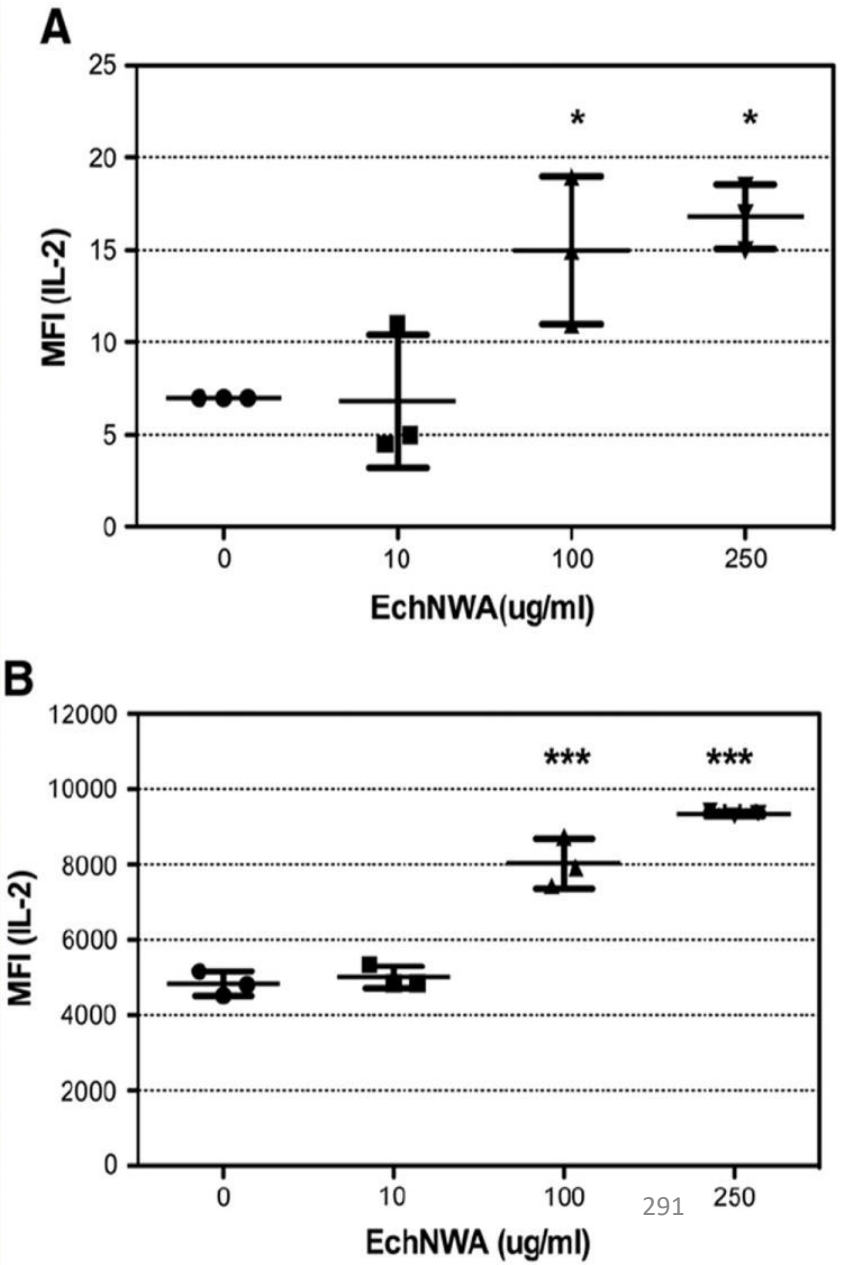
- Six clinical studies with a total of 2458 participants were included in the meta-analysis
- Use of echinacea extracts was associated with reduced risk of recurrent respiratory infections by 50% and increased dosage during acute infections enhanced these effects
- Three studies found that in individuals with higher susceptibility, stress or a state of immunological weakness, had significant benefit from taking echinacea extract



Schapowal A, Klein P, Johnston SL. **Echinacea** reduces the risk of recurrent respiratory tract infections and complications: a meta-analysis of randomized controlled trials. Adv Ther. 2015 Mar;32(3):187-200. doi: 10.1007/s12325-015-0194-4.

Echincea's Immune-Modulatory Effects

- Modulates human cytotoxic T-cell cytokine response: Boost IL-2 and IF-alpha.
- Decreased the number and function of Tregs, in association with the enhanced feeder-function of CD4 antigen-presenting cells



Fonseca FN, Papanicolaou G, Lin H, Lau CB, Kennelly EJ, Cassileth BR, Cunningham-Rundles S. Echinacea purpurea (L.) Moench modulates human T-cell cytokine response. Int Immunopharmacol. 2014 Mar;19(1):94-102; Kim HR, Oh SK, Lim W, Lee HK, Moon BI, Seoh JY. Immune enhancing effects of **Echinacea** purpurea root extract by reducing regulatory **T** cell number and function. Nat Prod Commun. 2014 Apr;9(4):511-4.

Signer *et al. Virology Journal* (2020) 17:136
https://doi.org/10.1186/s12985-020-01401-2

Virology Journal

RESEARCH Open Access

In vitro virucidal activity of Echinaforce®, an *Echinacea purpurea* preparation, against coronaviruses, including common cold coronavirus 229E and SARS-CoV-2

Johanna Signer[1†], Hulda R. Jonsdottir[1*†], Werner C. Albrich[2], Marc Strasser[1], Roland Züst[1], Sarah Ryter[1], Rahel Ackermann-Gäumann[1], Nicole Lenz[1], Denise Siegrist[1], Andreas Suter[3], Roland Schoop[3] and Olivier B. Engler[1*]

Poke – Specific Indications & Uses

- Acute and chronic viral infections with Inflammation of the glandular structures, particularly the lymphatic glands
- Pains of a rheumatic character with increased catabolism
- Irritation, inflammation, ulceration of the mucous membranes
- Extremely valuable in all diseases of the skin and a specific for squamous conditions. Excellent for eczema of a dry character
- To remove catabolic waste and fatty degeneration – it was often totted as a remedy for weight loss
- For adenitis, tonsillitis, parotitis, and enlarged thyroid - it is a specific
- For acute viral conditions combines well with echinacea, red root, propolis, baptisa, thuja, licorice, and lomatium

Toxins **2015**, *7*, 274-298; doi:10.3390/toxins7020274

OPEN ACCESS

toxins

ISSN 2072-6651

www.mdpi.com/journal/toxins

Review

Pokeweed Antiviral Protein, a Ribosome Inactivating Protein: Activity, Inhibition and Prospects

Artem V. Domashevskiy [1,†,*] and Dixie J. Goss [2,†]

- Pokeweed antiviral protein (PAP) from Phytolacca americana is a ribosome inactivating protein (RIP) and is an RNA N-glycosidase that removes specific purine residues from the sarcin/ricin (S/R) loop of large rRNA, arresting protein synthesis at the translocation step.
- PAP is thought to play an important role in the plant's defense mechanism against foreign pathogens.
- PAP has potent antiviral activity.

The Thuja-Based Immune Mixture Immune Enhancing Anti-Viral

- Was administered to mice via their drinking water for 14 days, starting 6 days before intranasal infection with influenza A virus
- The extract induced a statistically significant increase in survival rates, prolonged mean survival time and reduced lung consolidation and virus titers



Bodinet C, Mentel R, Wegner U, Lindequist U, Teuscher E, Freudenstein J. Effect of oral application of an immunomodulating plant extract on influenza virus type A infection in mice. Planta Med 2002;68:896–900..

Int J Biol Macromol. 2017 Dec;105(Pt 1):1105-1116. doi: 10.1016/j.ijbiomac.2017.07.142. Epub 2017 Jul 24.

ELSEVIER FULL-TEXT ARTICLE

Evaluation of anti-inflammatory potential of aqueous extract and polysaccharide fraction of Thuja occidentalis Linn. in mice.

Silva IS[1], Nicolau LAD[2], Sousa FBM[1], Araújo S[1], Oliveira AP[1], Araújo TSL[1], Souza LKM[1], Martins CS[3], Aquino PEA[2], Carvalho LL[2], Silva RO[2], Rolim-Neto PJ[4], Medeiros JVR[5].

- The aqueous extract (AE) and the polysaccharide fraction (PLS) reduced neutrophil infiltration
- Treatment with the AE and PLS (300mg/kg) did not induce gastric toxicity
- AE and PLS reduced the inflammatory response by inhibiting vascular and cellular events, inhibiting proinflammatory cytokine production, and reducing oxidative stress

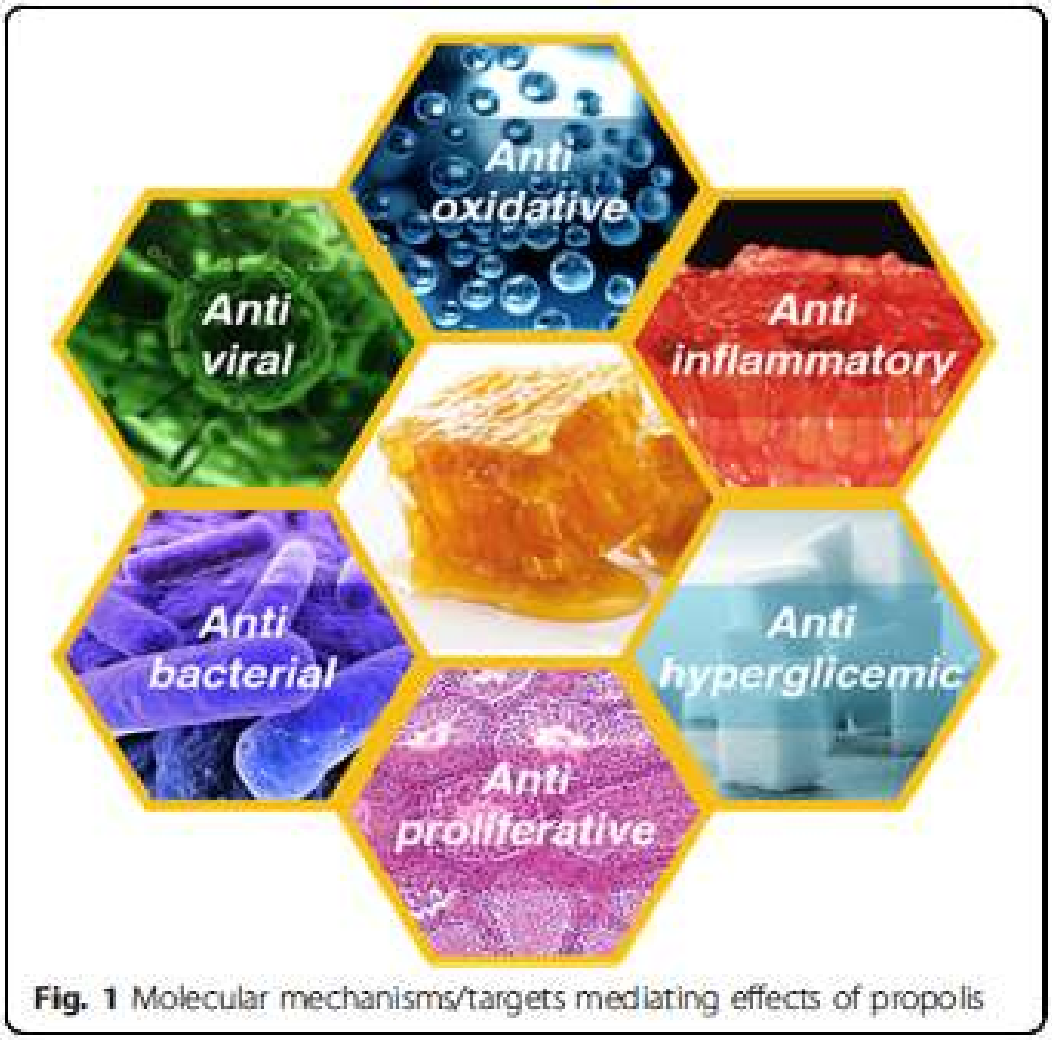


Fig. 1 Molecular mechanisms/targets mediating effects of propolis



Immune System Regulation

Propolis suppresses the IL-6 induced phosphorylation of signal transducer and STAT3, an essential cytokine-activated transcription factor in T helper 17 (Th17). Th17 are a subset of pro-inflammatory T-helper cells defined by their production of interleukin 17 (IL-17).

This effect is instrumental in controlling disturbed cytokine network inflammation.

Martinotti S., Ranzato E., Propolis: a new frontier for wound healing? Burns & Trauma (2015) 3:9
DOI 10.1186/s41038-015-0010-z. Recent Pat Endocr Metab Immune Drug Discov. 2014 Jun 1

Propolis improves cellular immune response

- In cold virus taking propolis is 2.5 times the time to accelerate the healing



- Propolis enhances antibody titer, T lymphocyte proliferation, IL-2 and IL-4 secretion of splenic lymphocyte.
- Propolis could accelerate antibody production.

Otolaryngologia Polska 1989;43(3):180-4.; X. Ma et al. / Cellular Immunology 270 (2011) 13–18

Red Root (*Ceanothus Americanus*)

- A specific 'Spleen remedy' with a favorable influence on the blood, lymph fluids, and structure of the lymph system, improving the tone and action
- North American Indians used to treat sore throats, fevers and problems of the mucous membranes, such as catarrh
- This action can be applied to many problems, such as sprains, bruises, infection, and long-term congestive problems such as varicose veins and swollen glands
- Improves digestion and helps food-related headaches
- Found to have anti-microbial effects and I have found it very useful for raising platelet count in thymbocytopenia

Ellingwood, Finley MD. America Materia Medica Therapeutics and Pharmacognosy, (1919) pg. 326-27, Eclectic Medical Publications, Cincinnati, Ohio; Li XC, Cai L, Wu CD. Antimicrobial compounds from Ceanothus americanus against oral pathogens. Phytochemistry. 1997 Sep;46(1):97-102.

Andrographolide possesses immune enhancing and anti-viral actions

- Andrographolide is a diterpenoid isolated from *Andrographis paniculata*, which has been employed in treating various diseases such as cancer and inflammatory diseases
- Andrographolide exhibits immunomodulatory effect by increasing the level of cytotoxic T cells, NK cells, phagocytic cells, and shows the broad spectral antiviral activity against various deadliest viruses
- Recent computational analysis data suggest that Andrographolide and its derivatives chrysin-7-O-β-glucuronide might produce therapeutic effects against SARS-CoV-2 pneumonia infections

Life Sciences (2020), https://doi.org/10.1016/j.lfs.2020.117765; Arch. Virol., 162 (3) (2017), pp. 611-623 Mar; J. Exp. Ther. Oncol., 3 (3) (2003), pp. 147-158

Thailand Approves Use of Andrographis as Herbal Treatment for COVID-19 - January 4, 2021

Andrographolide inhibit the main proteases of 2019-nCoV and SARS-CoV through covalent linkage

- Andrographolide could be beneficial for attenuating COVID-19 symptoms, extensive investigation of andrographolide on the suppression of 2019-nCoV as well as its application in COVID-19 therapy is suggested
- Human trials showed patient conditions improved within three days of the treatment without side effects if the medicine is administered within 72 hours of testing positive.



Shi TH, Huang YL, Chen CC, Pi WC, Hsu YL, Lo LC, Chen WY, Fu SL, Lin CH. Andrographolide and its fluorescent derivative inhibit the main proteases of 2019-nCoV and SARS-CoV through covalent linkage. Biochem Biophys Res Commun. 2020 Dec 10;533(3):467-473. doi: 10.1016/j.bbrc.2020.08.086. Epub 2020 Aug 25. PMID: 32977949; PMCID: PMC7447262.

Andrographolide as a Potential Compound for Suppressing COVID-19-Induced Cytokine Storm

- We used a "*host response signature network*" consist of 36 genes induced by SARS-CoV-2 infection and associated with cytokine storm
- Andrographolide, naturally present in a medicinal plant *Andrographis paniculata*, has the potential to bind with crucial proteins to block the TNF-induced NFkB1 signaling pathway responsible for cytokine storm in COVID-19 patients.
- The molecular docking method showed the binding of andrographolide with TNF and covalent binding with NFkB1 proteins of the TNF signaling pathway.

Rehan M, Ahmed F, Howladar SM, Refai MY, Baeissa HM, Zughaibi TA, Kedwa KM, Jamal MS. A Computational Approach Identified Andrographolide as a Potential Drug for Suppressing COVID-19-Induced Cytokine Storm. Front Immunol. 2021 Jun 24;12:648250. doi: 10.3389/fimmu.2021.648250. PMID: 34248936; PMCID: PMC8264290.

Curcuma longa (turmeric) and *Andrographis paniculata* against coronavirus (COVID-19)

- The chemical constituents from turmeric like cyclocurcumin and curcumin and from *Andrographis paniculata* like andrographolide and dihydroxy dimethoxy flavone, significantly binding with the active site of SARS CoV-2 main protease, and produce significant activity.

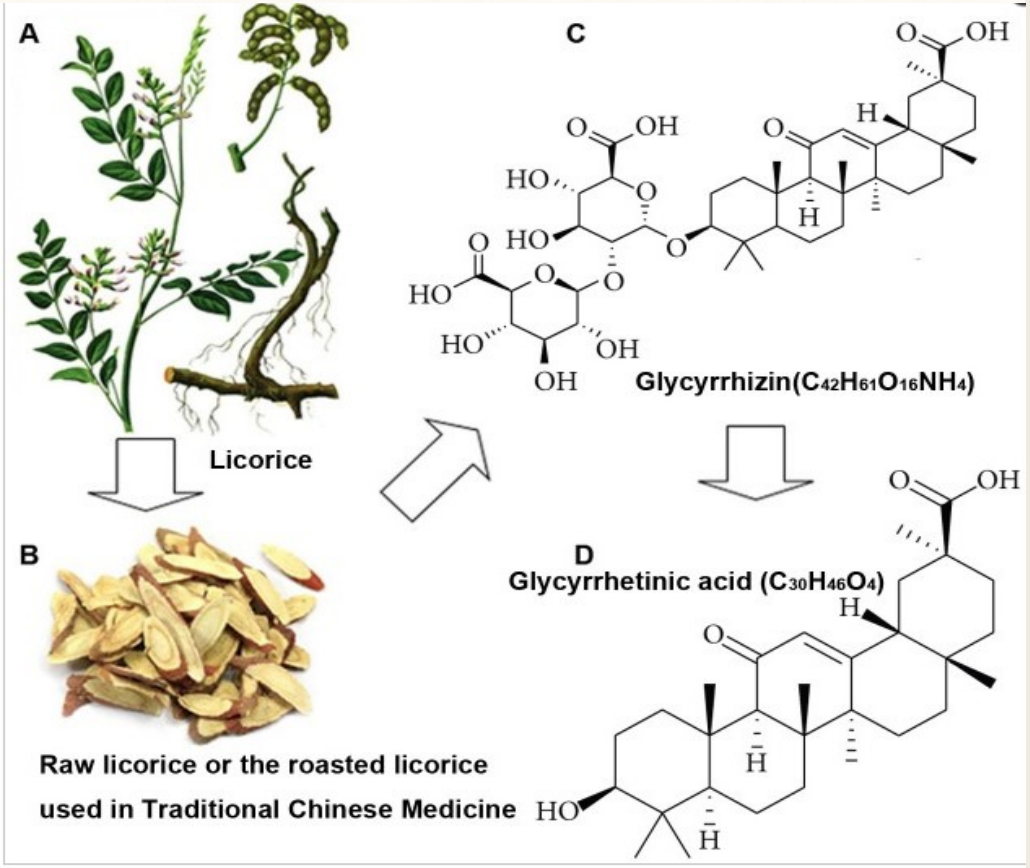
Rajagopal K, Varakumar P, Baliwada A, Byran G. Activity of phytochemical constituents of *Curcuma longa* (turmeric) and *Andrographis paniculata* against coronavirus (COVID-19): an in silico approach. Futur J Pharm Sci. 2020;6(1):104. doi: 10.1186/s43094-020-00126-x. Epub 2020 Oct 16. PMID: 33215042; PMCID: PMC7562761.

Glycyrrhizin, an active component of licorice, inhibits replication of SARS-associated coronavirus

- We assessed the antiviral potential of ribavirin, 6-azauridine, pyrazofurin, mycophenolic acid, and glycyrrhizin against two clinical isolates of coronavirus (FFM-1 and FFM-2) from patients with SARS
- Ribavirin and 6-azauridine were active but not selective inhibitors when assessed with regard to inhibition of cell growth
- Glycyrrhizin had a low selectivity index, but was a significantly potent inhibitor of replication of all the viruses tested
- Glycyrrhizin induces nitrous oxide synthase in Vero cells and that virus replication is inhibited by it.

Lancet, Volume 361, Issue 9374, 14 June 2003, Pages 2045-2046

Licorice (*Glycyrrhiza Glabra*)

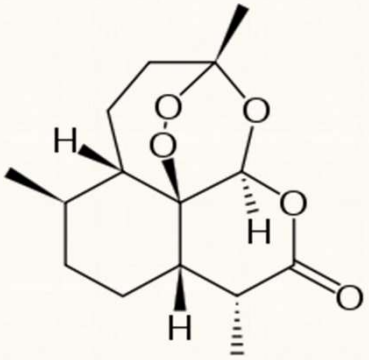


- Supports the HPA axis, sparing cortisol
- Helps convert cortisol to cortisone on demand
- Assists in the restoration of healthy DHEA levels
- Enhances the actions of other herbs

Kee Chang Huang, *The Pharmacology of Chinese Herbs*, chap. 34; 364-69; 1999 CRC Press.

Artemisia Annua is a Plant with Novel Antimalarial Activities





Artemisinin

Artemisia has been used by Chinese herbalists for thousands of years to treat fevers

(TCM docs are using it is specific CoV-2019 cases)

In 1972 the active ingredient, artemisinin, was purified

Nature. **448** (7150): 105–6. 2007.

Artemisia annua and Cov-19



- Initial studies in China showed the alcoholic extract of sweet wormwood (Artemisia annua) was the second most potent herbal medicine used on the 2005 SARS-CoV
- *Artemisia annua* whole plant extract exhibited significant inhibition effects on SARS-CoV strain BJ001
- *Artemisia and it's derrivities have shown to* inhibit several viruses, such as human cytomegalovirus and other members of the *Herpesviridae* family (e.g., herpes simplex virus type 1 and Epstein-Barr virus), hepatitis B virus, hepatitis C virus, and bovine viral diarrhea virus.

https://www.mpg.de/14663263/artemisia-annua-corona-virus, retrieved May 16, 2020
Antiviral Research, Volume 67, Issue 1, July 2005, Pages 18-23; *Clinical Infectious Diseases*, Volume 47, Issue 6, 15 September 2008, Pages 804–811, https://doi.org/10.1086/591195

International Journal of
Molecular Sciences

MDPI

Review

Protective Effect of Epigallocatechin-3-Gallate (EGCG) in Diseases with Uncontrolled Immune Activation: Could Such a Scenario Be Helpful to Counteract COVID-19?

Marta Menegazzi [1,*], Rachele Campagnari [1], Mariarita Bertoldi [1], Rosalia Crupi [2], Rosanna Di Paola [3] and Salvatore Cuzzocrea [3,4]



- Since EGCG can restore the natural immunological homeostasis, we propose here a supplementation therapy with epigallocatechin 3-gallate (EGCG), the main active phenolic compound in green tea, in COVID-19 patients.
- Besides some antiviral and anti-sepsis actions, the major EGCG benefits lie in its anti-fibrotic effect and in the ability to simultaneously downregulate expression and signaling of many inflammatory mediators.
- EGCG can be considered a potential safe natural supplement to counteract hyper-inflammation growing in COVID-19

Liu *et al. Cell Biosci* (2021) 11:168
https://doi.org/10.1186/s13578-021-00680-8

Cell & Bioscience

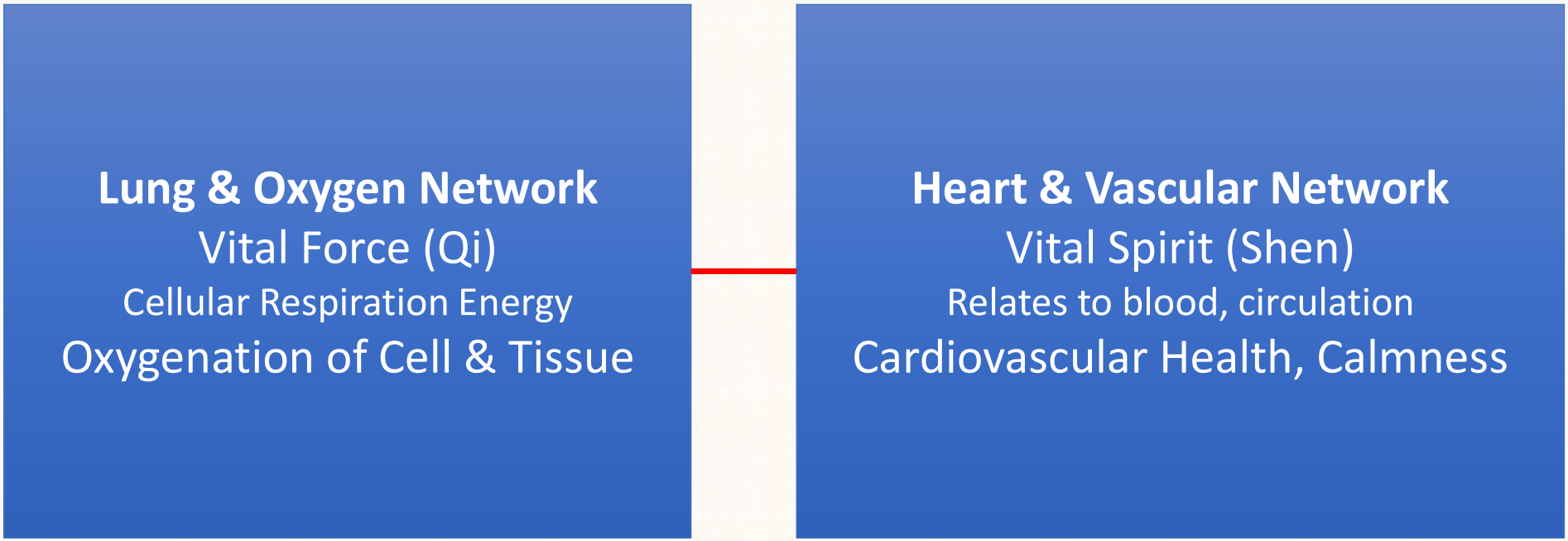
RESEARCH Open Access

Epigallocatechin gallate from green tea effectively blocks infection of SARS-CoV-2 and new variants by inhibiting spike binding to ACE2 receptor

Jinbiao Liu[1,2], Brittany H. Bodnar[1], Fengzhen Meng[1], Adil I. Khan[1], Xu Wang[1], Sami Saribas[1], Tao Wang[3], Saroj Chandra Lohani[3], Peng Wang[1], Zhengyu Wei[1], Jinjun Luo[1], Lina Zhou[1], Jianguo Wu[2], Guangxiang Luo[4*], Qingsheng Li[3*], Wenhui Hu[1*] and Wenzhe Ho[1*]

- Among the 4 active green tea catechins at noncytotoxic doses, EGCG was the most potent in the action against the viruses.
- The highest inhibitory activity was observed when the viruses or the cells were preincubated with EGCG prior to the infection.
- EGCG blocked infection at the entry step through interfering with the engagement of the receptor binding domain of the viral spikes to ACE2 receptor of the host cells.

Lung/Oxygen and Heart/Vascular Networks



Lung-Oxygen Network

- Channels Vital Essence and Vital Force
- Governs the exchange, efficiency and utilization of oxygen throughout the body
- Creates energy through oxygen intake & disperses it to every cell throughout the body
- Essential for producing adequate amounts of ATP necessary for metabolic activities
- Assists in detoxification, removing waste byproducts - breathing out

Aralia racemosa, Elecampane, Cordyceps, Drosera, Colleus f.

Botanical Medicine for Lung Support

Actions of plants:

Antimicrobial, resolves phlegm, relieves cough, expectorant, antispasmodic, relaxes and opens the bronchial network, moistens and nourishes the respiratory system, strengthens the lung network

Some favorite Lung botanicals

- **Elecampane Root** (*Inula helenium*)
- Lobellia (*Lobelia inflata*)
- Mullein Leaf (*Verbascum thapsus*)
- Sundew (*Drosera burmannii*)
- Lungowort (*lobaria Pulmonaria*)
- Plantain Leaf (*Plantago major*)
- Horehound (*Marrubium vulgare L.*)
- Thyme Herb (*Thymus vulgaris*)
- Licorice root (*Glycyrrhiza glabra*)
- Byronia [I often use with Elecampane]

Elecampane Root (*Inula helenium*)

- Has an extended historical use for treatment of colds, flu, respiratory, fungal/bacterial/parasitic infections, pain, animal bites and skin ailments
- It is also categorized as a stimulating expectorant, increasing the activity of the mucociliary escalator by way of its saponin content. This therapy is especially useful in cases of bronchitis, bronchiectasis, and pneumonia
- It not only relieves coughs, but is rejuvenating and strengthening to the entire respiratory system. *Ellingwood* considered Elecampane to, "act directly upon the nutritive functions of the body
- Combined with adaptogens, elecampane is helpful for the person who tends to develop bronchitis or pneumonia

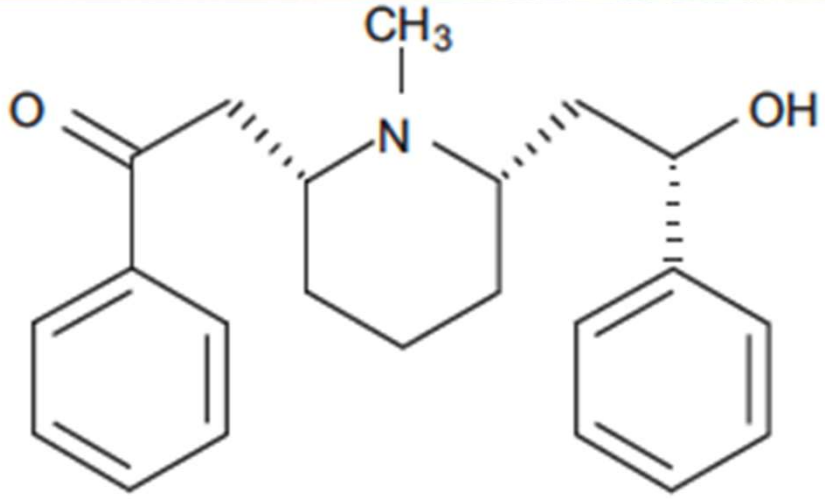


Bull Indian Inst Hist Med Hyderabad. 1998 Jan;28(1):7-11.

Lobelia (*Lobelia inflata*)

- Often combined with cayenne, was without a doubt, the most popular herb used in Thomsonian medicine
- It is anti-spastic, expectorant, anti-asthmatic, emetic, relaxant, sialagogue, and mild sedative
- Lobelia and its alkaloids induce the release of dopamine while inhibiting the re-uptake of dopamine by cells of the central nervous system
- Lobelia is useful for the treatment of drug withdrawal, nicotine addiction, and eating disorders
- Lobeline and alkaloids, are chemically similar to nicotine, which explains in part why it is useful for nicotine withdrawal
- Lobinaline binds to the nicotinic acetylcholine receptor (nicAchR) that has recently demonstrated profound neuroprotective effects





Fitoterapia 111 (2016) 109–123

Fig. 1. Structure of lobeline.

Specific Herbs For Heart & CV System

Herb Type	Herb Examples
Vascular astringent tonics	*Colinsonia*, Horse chestnut (*Aesculus hippocastanum*), Butchers broom (*Ruscus aculeatus*), Witch hazel (*Hamamelis*)
Diffusive stimulants	Prickly ash (*Zanthoxylum*), Ginger (*Zingiber*)
Peripheral (diaphoretic) relaxants	Black cohosh (*Actaea racemosa*), Yarrow (*Achillea millefolium*), Linden (*Tilia*), Elders leaf (*Sambucus*)
Diuretics	Celery seed (*Apium graveolen*), nettles seed & leaf (*Urtica*), dandelion (*Taraxacum*) leaf, juniper (*Juniperus*), water melon seed etc.
Anti-hypertensives	Rauwolfia, Khella, Mistletoe, *Coleus f.*

Specific Herbs For The Heart & CV System (cont.)

- General heart tonics
  - Hawthorn (*Crataegus oxyacantha*) leaf, flower and berry,
  - Chinese salvia (*Salvia miltiorrhiza*),
  - Olive leaf (*Olea europaea*),
  - *Panax Notoginseng*,
  - Arjuna (*Terminalia Arjuna*),
  - Motherwort (*Leonurus cardiaca*),
  - Colleus (*Colleus forskohlii*),
  - *Rhodiola spp*

Specific Herbs For The Heart & CV System (cont.)

Vascular-heart stimulants

- Lily of the valley (*Convallaria majalis)*
- Foxglove (*Digitalis*)
- Scotch broom (*Cytisus scoparius*)
- Squill (*Urginea scilla***)**

Peripheral stimulating tonics

- Night blooming cereus (*Cereus grandiflorus***)**
- *Ginko biloba*
- Periwinkle (*Vinca minor*)
- Gotu cola (*Centella a.*)

Cardiac Glycosides

Indicated for:

- Cardiac insufficiency with reduced cardiac output, especially if associated with a atrial fibrillation
- Supra ventricular rhythm abnormalities, atrial flutter and fibrillation

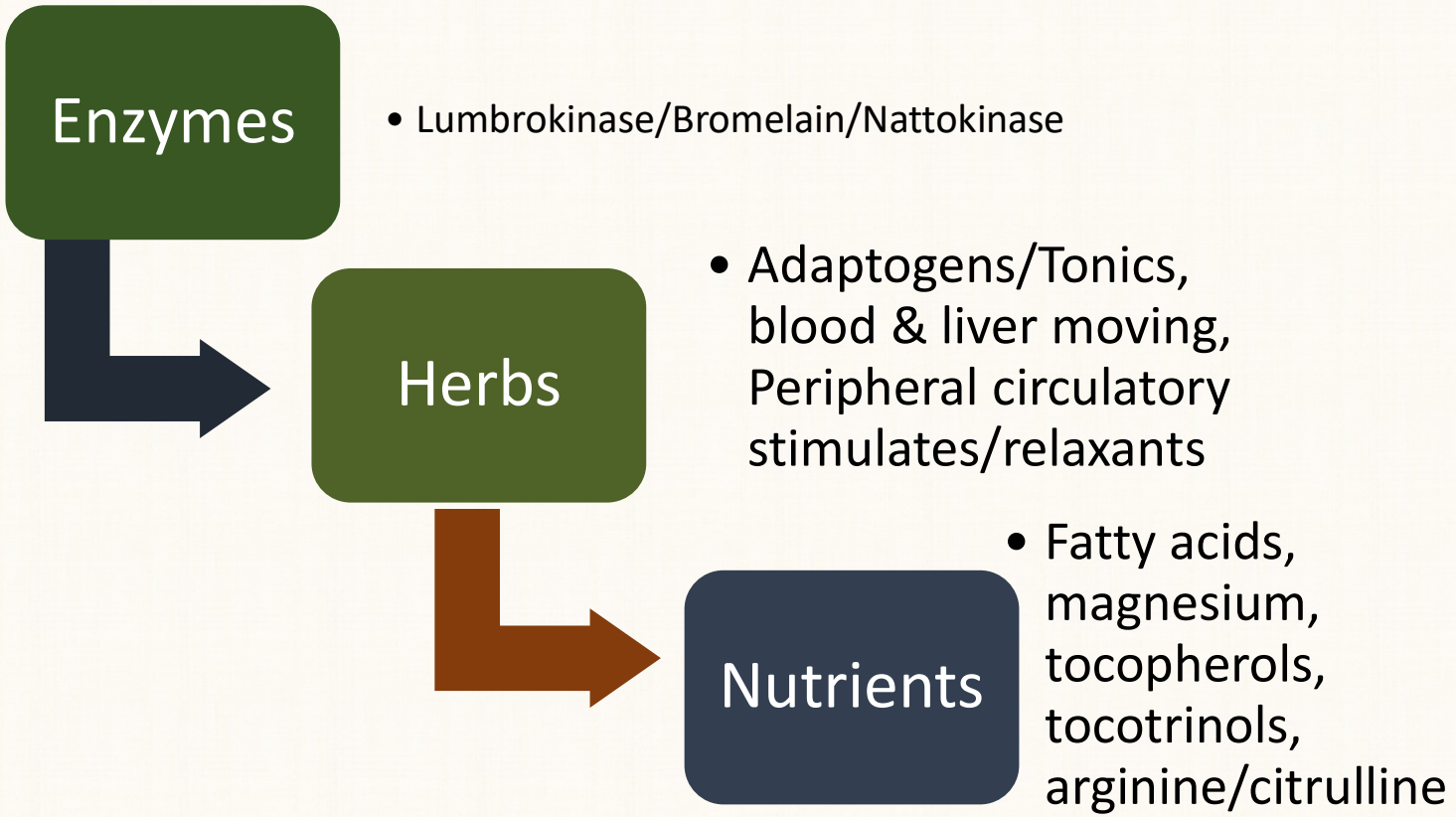
Examples: Foxglove, Lily of the valley, Squills



ETMS Tools for targeting hyper-coagulation in cancer

Botanicals	Compounds	Nutritionals	Enzymes	Drugs
• *Salvia m.* • *Notoginseng* • *Gingko b.* • *Crocus s.* • *Rosmarinus* • *Ganoderma l* • *Angelica s.* • *Paeonia l.* • *Achillea m.*	• RES/Ptero-S • Vinpocetine • Gingerols • Cinnamtannin B-1 • Forskolin • CAPE • Coumarins • Curcumin • Salicin • Berberine • Flavonoids, OPCs, Quercetin	• Fatty acids EPA/DHA/GLA • Amino acids • Magnesium • CoQ 10 • Tocotrinols • Co-enzyme-B vitamins (B-5, 3, 6, 12) • Vitamin D3 • Arginine	• **Lumbro-K** • **Bromelian** • Nattokinase • Serrapeptase	• LMH • (low molecular weight heparins) • Aspirin • Semul-oparin - belongs to the group of LMHs

Enzymes • Herbs (isolates) • Nutrients



Adaptogens - Stress protectors +

antithrombotic • antiplatelet • anticoagulant effects + immune-modulation • anti-cancer • anti-angiogenesis

- *Panax Ginseng* (Rp1 & Rg 2)
- *Panax notoginseng*
- *Rhaponticum carthamoides*
- *Eleutherococcus senticosus*
- *Ocimum sanctum*

- Basic Clin Pharmacol Toxicol. 2007 Mar;100(3):170-5.
- Thromb Res. 2014 Jan;133(1):57-65.
- J. Ethnopharmacol. 2009 Sep 25;125(3):380-6.
- Br J Pharmacol. 2012 Sep;167(1):109-27.
- *Eksperimental'naia i klinicheskaia farmakologiia* 2001; 64(6): 45-47;
- *Drug and Chemical Toxicology* 2008; 31(1): 27-35.
- Eksp Klin Farmakol. 2007 Mar-Apr;70(2):45-7; Patol Fiziol Eksp Ter. 2010 Apr-Jun;(2):43-6.
- J. Ethnopharmacol. 2001 Dec;78(2-3):139-43

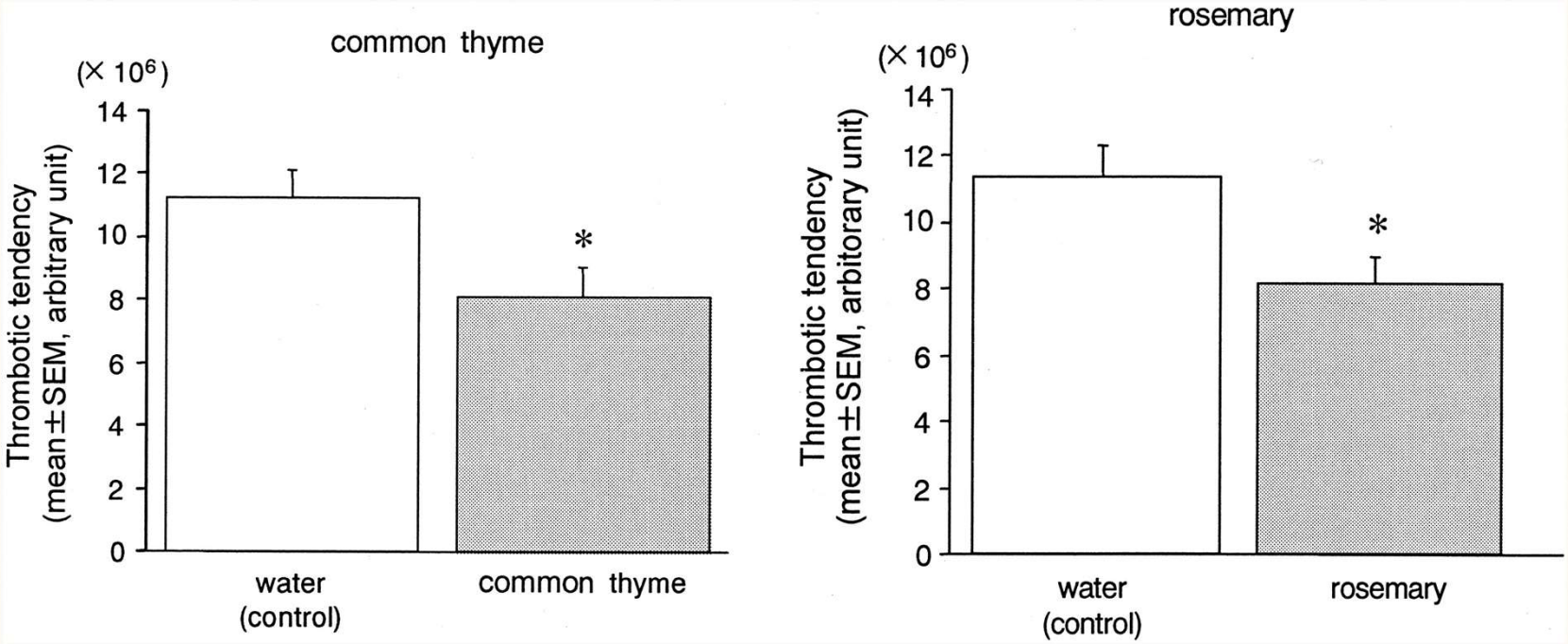
Botanicals positively resolve existing thrombin by accelerating the activity of plasmin, a key enzyme of the fibrinolytic pathway.

Nihon Rinsho. 2014 Jul;72(7):1254-7.

Specific Tonic Herbs for the Heart and Blood Circulation

- Hawthorn (*Crataegus oxyacantha*) leaf, flower & berry,
- Chinese salvia (*Salvia miltiorrhiza*),
- Olive leaf (*Olea europaea*),
- *Panax Notoginseng* (Adaptogen),
- Arjuna (*Terminalia Arjuna*),
- Motherwort (*Leonurus cardiaca*),
- Colleus (*Colleus forskohlii*), - cAMP↑ & PDE4↓
- *Rhodiola spp* (Adaptogen)

Antithrombotic effect of common thyme and rosemary in vivo



Nutrition Volume 21, Issue 5, May 2005, Pages 580–587

Fibrin Digesting Enzymes

Lumbrokinase



Bromelain



Serrapeptase



Nattokinase

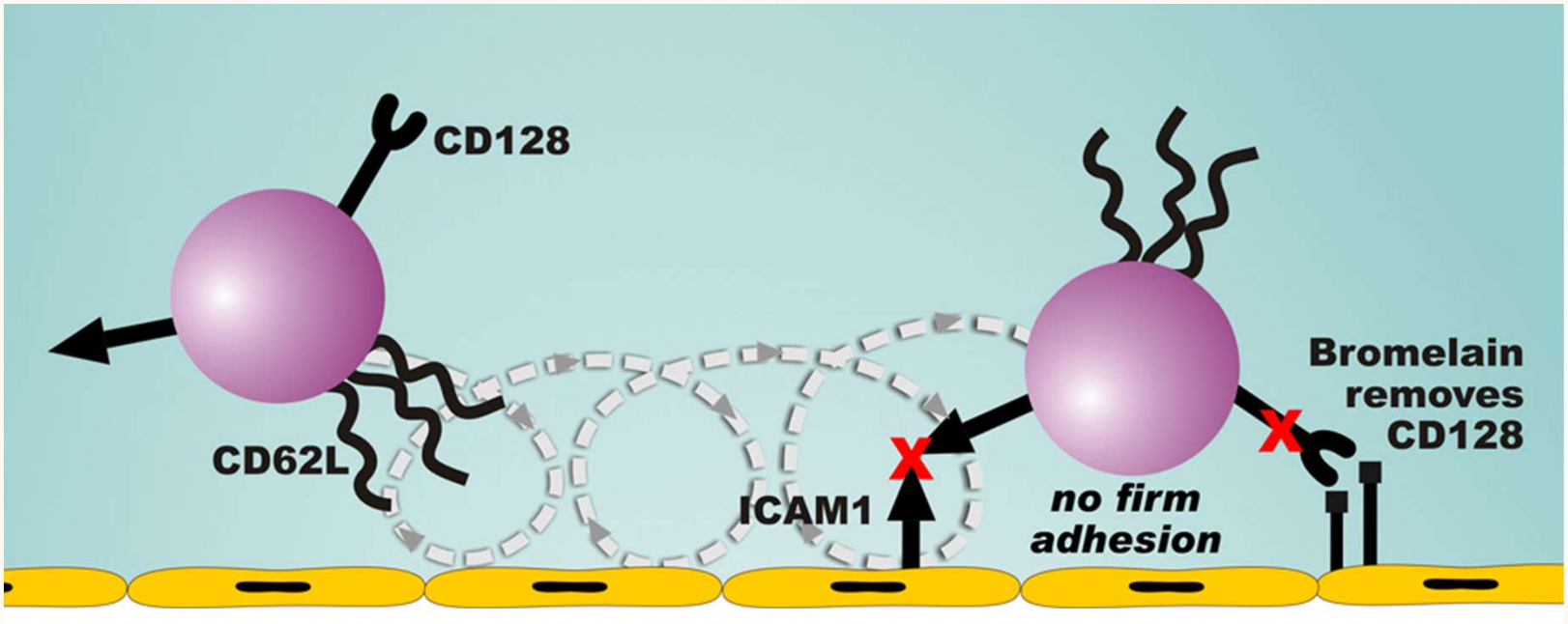


ROLE OF BROMELAN

- Blood fibrolytic activity and reduces the excretion of proinflammatory cytokines and chemokines
- Inhibits COX-2 and effects prostaglandin synthesis inhibiting PG2
- Inhibits fibrinogen synthesis
- Directly degrades fibrin and fibrinogen

Alt Med Rev 1996;1(4):243-257, Cancer Lett. 2009 Aug 21.
Cancer Lett. 2010 Apr 28;290(2):148-56. Epub 2009 Aug 22.

Bromelain decreases Neutrophil Migration to Sites of Inflammation



Bromelain impairs chemokine-mediated changes in integrin affinity, resulting in the observed decrease in firm adhesion.

Clin Immunol. Author manuscript; available in PMC Jul 1, 2009.

International Journal of Surgery 11 (2013) 209–217

Contents lists available at SciVerse ScienceDirect

International Journal of Surgery

journal homepage: www.theijs.com



Review

Serratiopeptidase: A systematic review of the existing evidence

Shivani Bhagat*, Monika Agarwal, Vandana Roy

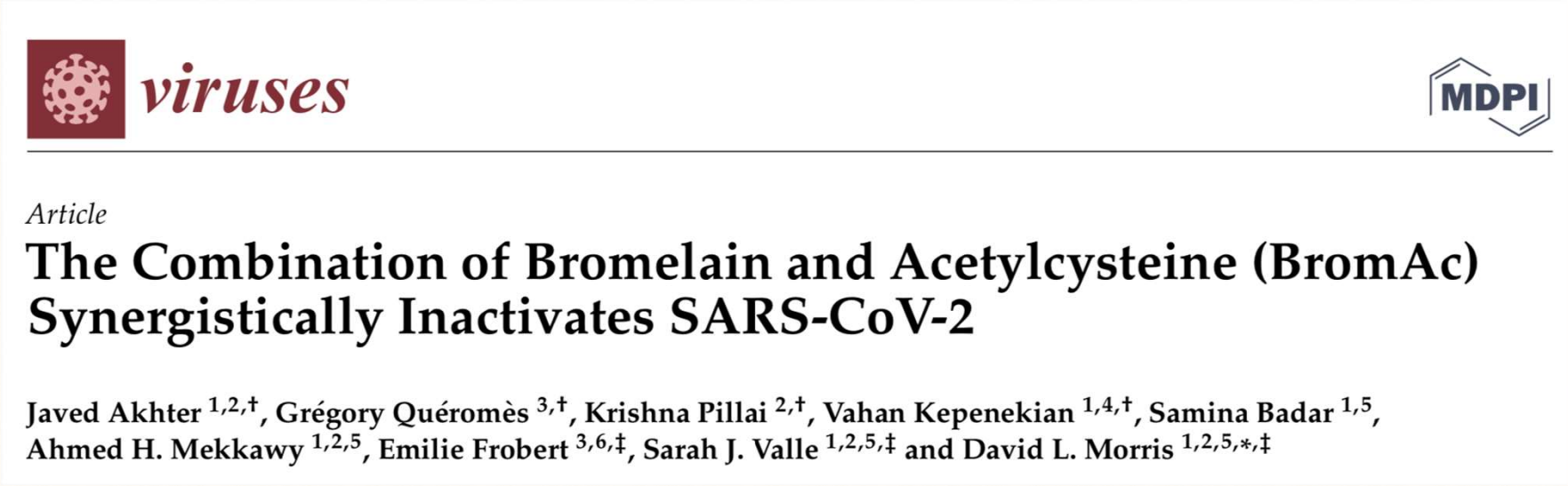
Department of Pharmacology, Maulana Azad Medical College (MAMC), First Floor, Pathology Block, New Delhi 110002, India

- Serrapeptase is thought to work in three ways:
  1. Anti-inflammatory,
  2. Analgesic
  3. Fibrinolytic

Bromelain inhibits SARS-CoV-2 infection via targeting ACE-2, TMPRSS2, and spike protein

- Bromelain can inhibit SARS-CoV-2 infection via targeting ACE-2, TMPRSS2, and SARS-CoV-2 S-protein.
- Since bromelain inhibits SARS-CoV-2 could be used as an antiviral against SARS-CoV-2 and future outbreaks of other coronaviruses

Clin Transl Med. 2021;11(2):e281. doi:10.1002/ctm2.281



viruses

MDPI

Article

The Combination of Bromelain and Acetylcysteine (BromAc) Synergistically Inactivates SARS-CoV-2

Javed Akhter [1,2,†], Grégory Quéromès [3,†], Krishna Pillai [2,†], Vahan Kepenekian [1,4,†], Samina Badar [1,5], Ahmed H. Mekkawy [1,2,5], Emilie Frobert [3,6,‡], Sarah J. Valle [1,2,5,‡] and David L. Morris [1,2,5,*,‡]

Viruses **2021**, *13*, 425. https://doi.org/10.3390/v13030425

nutrients

MDPI

Review

Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections

Philip C. Calder [1], Anitra C. Carr [2], Adrian F. Gombart [3] and Manfred Eggersdorfer [4,*]

1 Faculty of Medicine, University of Southampton and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton SO16-6YD, UK; P.C.Calder@soton.ac.uk

2 Nutrition in Medicine Research Group, Department of Pathology & Biomedical Science, University of Otago, Christchurch, P.O. Box 4345, Christchurch 8140, New Zealand; anitra.carr@otago.ac.nz

3 Linus Pauling Institute, Department of Biochemistry and Biophysics, Oregon State University, 307 Linus Pauling Science Center, Corvallis, OR 97331, USA; adrian.gombart@oregonstate.edu

4 Department of Internal Medicine, University Medical Center Groningen, 9713 GZ Groningen, The Netherlands

* Correspondence: m.eggersdorfer@bluewin.ch

Received: 10 March 2020; Accepted: 18 April 2020; Published: 23 April 2020

check for updates

- Supplementation with Vitamin D, Zinc, Quercetin, Vitamin C, Selenium and omega-3 fatty acids is a safe, effective, and low-cost strategy to help support optimal immune function.

Coenzyme Q10 Supplementation in Fibrosis and Aging

- Is a vitamin-like substance which functions as an electron carrier within the mitochondrial respiratory chain, as well as serving as an important intracellular antioxidant
- Most of the body's CoQ10 requirements are met by endogenous synthesis, although the capacity for CoQ10 production decreases substantially with increasing age
- CoQ10 supplementation has been found to be very effective for the treatment of tissue fibrosis, which has been implicated in the age-related loss of function of various organs including the heart
- Clinical studies have indicated that CoQ10 supplementation may decrease the level of cardiovascular fibrosis to which older individuals are subjected, and thereby improves cardiovascular function and reduce the risk of cardiovascular-associated mortality

Hargreaves IP[1], Mantle D[2]. Coenzyme Q10 Supplementation in Fibrosis and Aging, Adv Exp Med Biol. 2019;1178:103-112. doi: 10.1007/978-3-030-25650-0_6.

Pharmacological Research
Volume 119, May 2017, Pages 128-136



Effects of coenzyme Q10 supplementation on inflammatory markers: A systematic review and meta-analysis of randomized controlled trials

Li Fan [a, 1], Yu Feng [a, b, 1], Guo-Chong Chen [a], Li-Qiang Qin [a], Chun-ling Fu [a], Li-Hua Chen [a]

Seventeen RCTs were selected for the meta-analysis. CoQ10 supplementation significantly reduced the levels of circulating C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α)

JOURNAL OF VIROLOGY, Feb. 2005, p. 1966–1969 Vol. 79, No. 3
0022-538X/05/$08.00+0 doi:10.1128/JVI.79.3.1966–1969.2005
Copyright © 2005, American Society for Microbiology. All Rights Reserved.

Nitric Oxide Inhibits the Replication Cycle of Severe Acute Respiratory Syndrome Coronavirus

Sara Åkerström,[1] Mehrdad Mousavi-Jazi,[2] Jonas Klingström,[1,3] Mikael Leijon,[2] Åke Lundkvist,[1,3] and Ali Mirazimi[1]*

Nitric Oxide (NO) specifically inhibits the replication cycle of SARS CoV, most probably during the early steps of infection, suggesting that the production of NO by iNOS results in an antiviral effect.

Many botanical compound assist in NO production as well as specific nutrients and foods (beet juice and watermelon rind are two that come to mind)

WebMD

Nitric Oxide Investigated as COVID-19 Treatment

By Robert Preidt

HealthDay Reporter

THURSDAY, April 9, 2020 (HealthDay News) -- Doctors at the University of Alabama at Birmingham (UAB) are enrolling patients in an international clinical trial to find out if inhaled nitric oxide benefits those with COVID-19 who have severely damaged lungs.

Arginase, which degrades L-arginine is frequently upregulated in the cancer microenvironment.
Elevated arginase activity decreases cellular availability of nitric oxide by competing with NO synthases.

- **Chlorogenic acid** and **piceatannol** are two potent arginase inhibitors
- **Piceatannol**, an important component in rhubarb extract, is a stilbene (such as **resveratrol**), and potent inhibitor of arginase I and II
- A methanol extract of ***Scutellaria indica*** (common skullcap) showed significant inhibitory effect on arginase II
- Phenolic compounds including the flavonoids fisetin and luteolin inhibit arginase, liberating arginine to act on NO and NK cells

Bordage S[1], Pham TN[1], Zedet A[1], Gugglielmetti AS[1], Nappey M[1], Demougeot C[1], Girard-Thernier C[1]. Investigation of Mammal Arginase Inhibitory Properties of Natural Ubiquitous Polyphenols by Using an Optimized Colorimetric Microplate Assay, Planta Med. 2016 Oct 24; Kim SW[1], Cuong TD, Hung TM, Ryoo S, Lee JH, Min BS. Arginase II inhibitory activity of flavonoid compounds from Scutellaria indica, Arch Pharm Res. 2013 Aug;36(8):922-6. doi: 10.1007/s12272-013-0125-3; Manjolin LC[1], dos Reis MB, Maquiaveli Cdo C, Santos-Filho OA, da Silva ER. Dietary flavonoids fisetin, luteolin and their derived compounds inhibit arginase, a central enzyme in Leishmania (Leishmania) amazonensis infection, Food Chem. 2013 Dec 1;141(3):2253-62.

Japanese Knotweed (*Polygonum cuspidatum*), Hu Zhang

- Richest known source of **resveratrol**
- Traditionally used to treat cancer
- Addresses three underlying factors
  - Phlegm
  - Blood stasis
  - Heat toxins
- Several compounds have shown anti-cancer actions, including resveratrol, emodin and chrysophanol



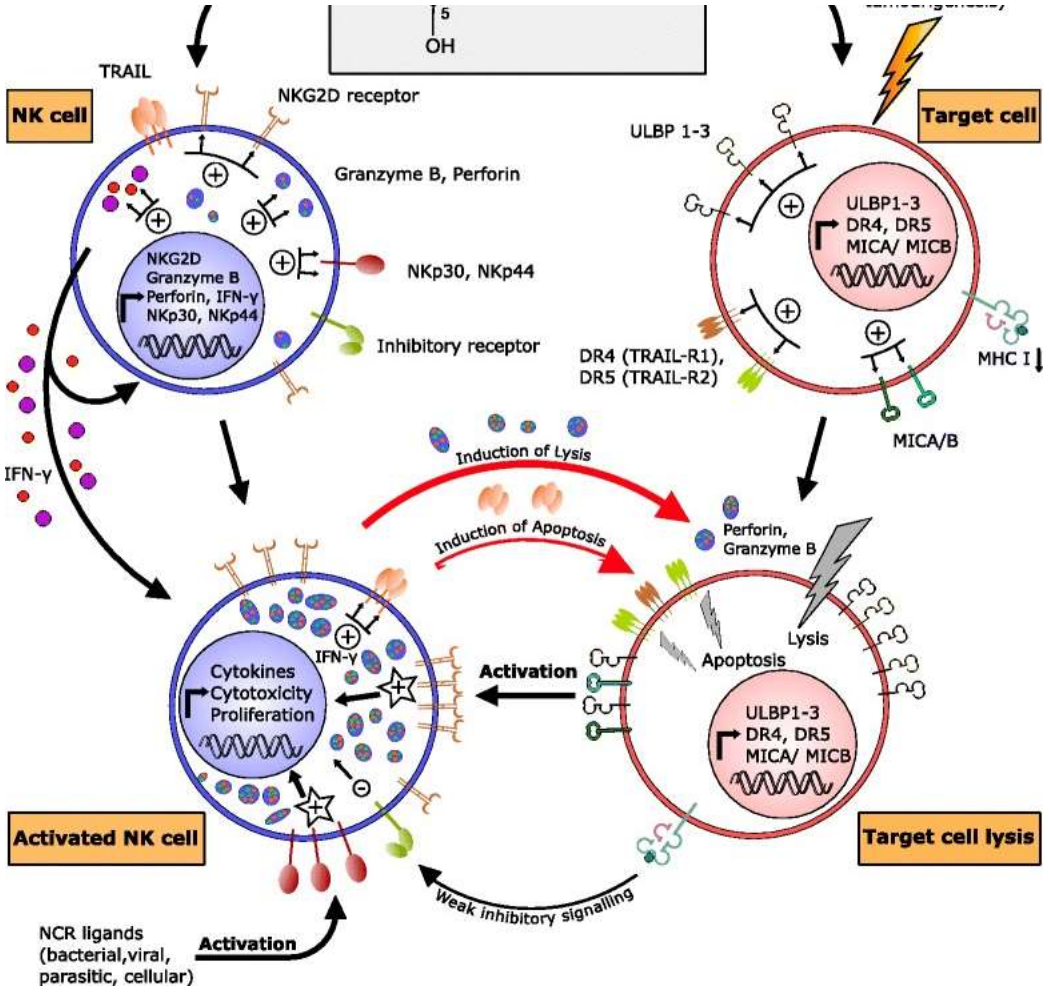
Resveratrol is an Effective Inhibitor of MERS-CoV Infection

- Resveratrol significantly inhibited MERS-CoV infection and prolonged cellular survival after virus infection
- The expression of nucleocapsid (N) protein essential for MERS-CoV replication was decreased after resveratrol treatment
- Resveratrol suppresses interleukin-1beta-induced inflammatory signaling

Lin SC, Ho CT, Chuo WH, Li S, Wang TT, Lin CC. Effective inhibition of MERS-CoV infection by resveratrol. *BMC Infect Dis*. 2017;17(1):144. Published 2017 Feb 13. doi:10.1186/s12879-017-2253-8;
Biochem Pharmacol. 2008 Dec 1;76(11):1426-39. doi: 10.1016/j.bcp.2008.05.029.

Nutritional Immunology: Function of Natural Killer (NK) Cells and Their Modulation by Resveratrol

Resveratrol strongly modulates the immune response including the activity of NK cells.



Leischner C, Burkard M, Pfeiffer MM, Lauer UM, Busch C, Venturelli S: Nutritional immunology: function of natural killer cells and their modulation by resveratrol for cancer prevention and treatment. Nutr J. 2015; 15: 47.

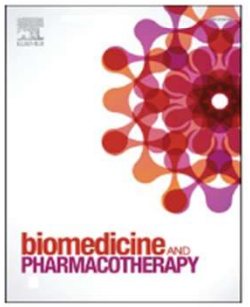
Biomedicine & Pharmacotherapy 139 (2021) 111626



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



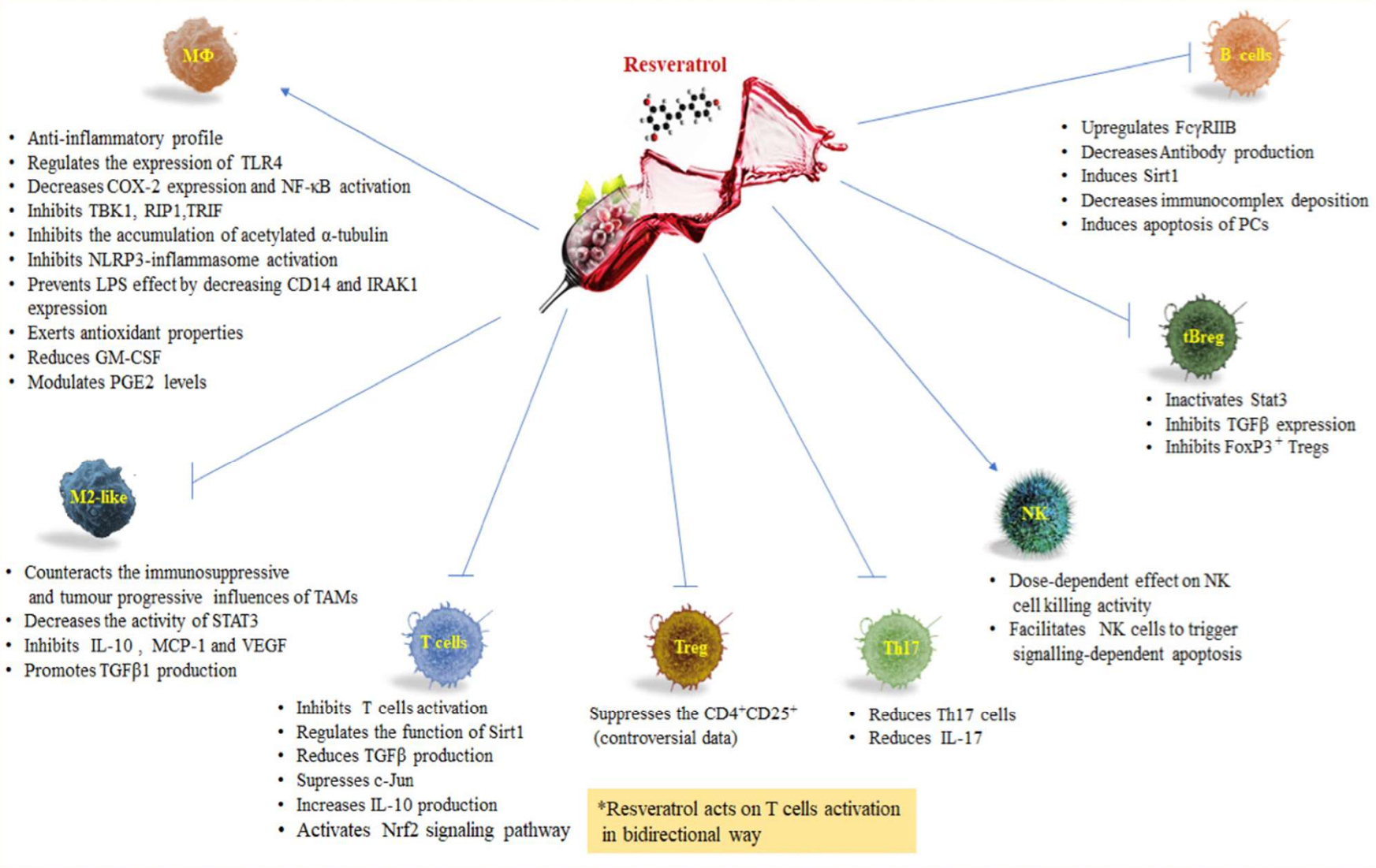


Resveratrol-zinc nanoparticles or pterostilbene-zinc: Potential COVID-19 mono and adjuvant therapy

Mina T. Kelleni [1]

Pharmacology Department, College of Medicine, Minia University, Egypt

Resveratrol is an immune modulator



Nutrients. 2019 May; 11(5): 946.

nutrients

MDPI

Review

Nutraceutical Strategies for Suppressing NLRP3 Inflammasome Activation: Pertinence to the Management of COVID-19 and Beyond

Mark F. McCarty [1], Simon Bernard Iloki Assanga [2], Lidianys Lewis Luján [2], James H. O'Keefe [3] and James J. DiNicolantonio [3,*]

- A consideration of the molecular biology underlying inflammasome priming and activation enables the prediction that a range of nutraceuticals may have clinical potential for suppressing inflammasome activity—antioxidants including phycocyanobilin, phase 2 inducers, melatonin, and N-acetylcysteine, the AMPK activator berberine, glucosamine, zinc, and various nutraceuticals that support generation of hydrogen sulfide

Nutrients 2021, 13, 47. https://dx.doi.org/10.3390/nu13010047

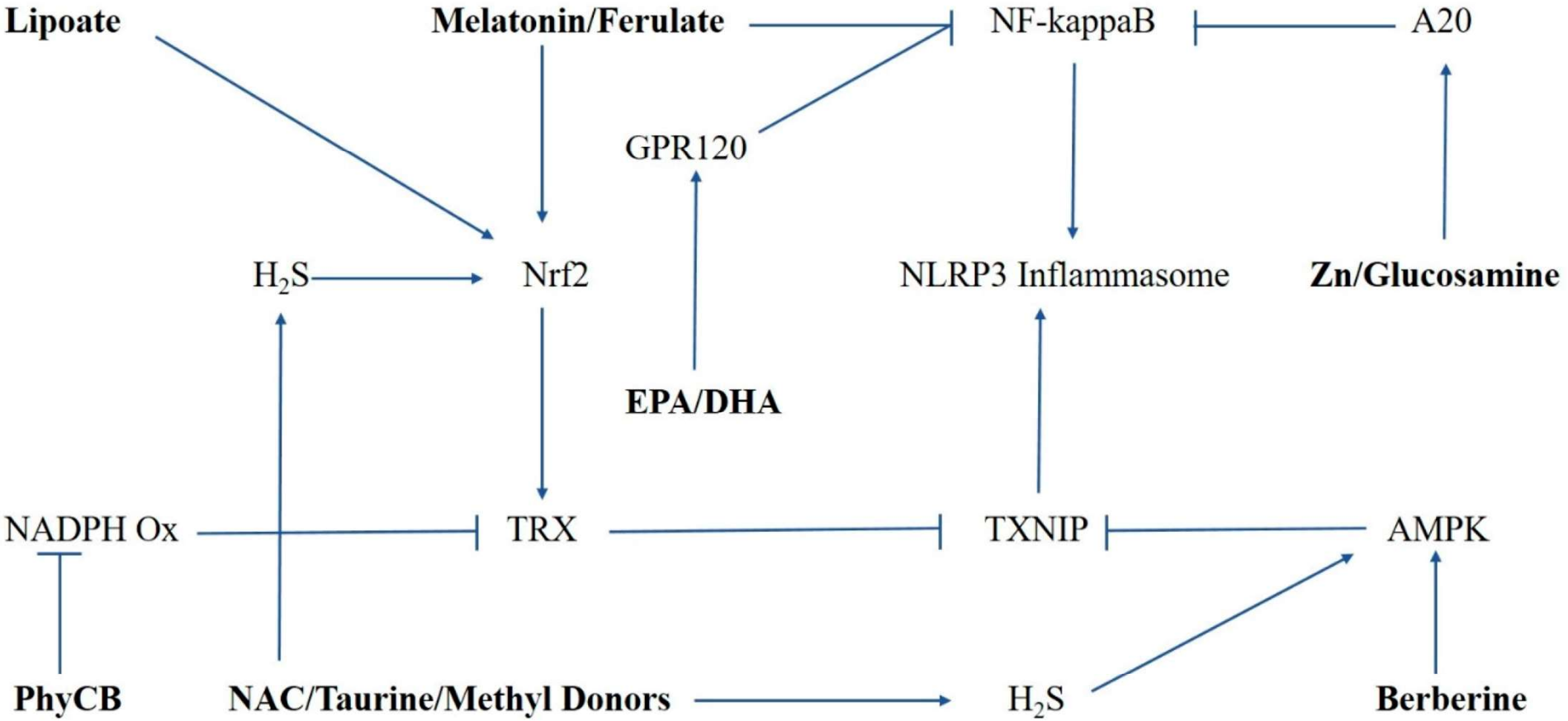


Figure 1. Mechanisms for nutraceutical suppression of NLRP3 inflammasome activation. TRX, thioredoxin; TXNIP, thioredoxin interacting protein.

Nutrients 2021, 13, 47. https://dx.doi.org/10.3390/nu13010047

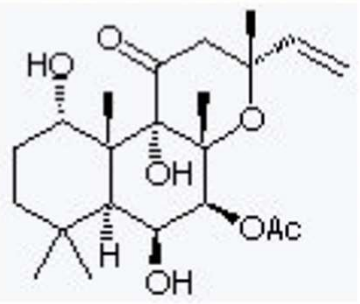
Phosphodiesterase (PDE) 4 & 5 Inhibition

- PDE 4 inhibition, improves lung function in asthmatics
- PDE 4 and 5 down-regulate arginase 1 which helps to release NO
- **Theophylline** and **Forkolin** specifically enhance cAMP and down-regulate PDE4, and enhance all other therapies used against SARS
- **Green tea extract** 40-50% epigallocatechin gallate (EGCG), with theophylline, have a synergistic effect
- Coleus Cardiotonic, smooth-muscle relaxation, anti-hypertensive, anti-depressant, anti-obesity, **insulintrophic**, thyroid-enhancing, anti-allergenic, anti-asthmatic, **anti-cancer**

Coleus Forskolii



Forskolin



Blood, Vol 92, No 7 (October 1), 1998: pp 2484-2494, Biochemical Pharmacology Volume 69, Issue 3, 1 February 2005, Pages 473-483, Leukemia Research, Volume 30, Issue 6, June 2006, Pages 649-650, Leukemia. 2004 Oct;18(10):1605-10.,

Key supplements for the immune system for the prevention of acute viral Respiratory infections

- **Zinc** (Naturized form) 25 (1 cap) to 50 mg. protective dose, 50 to 100 mg. therapeutic dosage. I recommend testing people for zinc status (blood, RBC, and even zinc challenge taste test).
- **Vitamin D** (Naturized DAK form – 5k of vitamin D plus 2 forms of vitamin K and Red Palm oil a rich source of carotenoids) 1 cap daily. I recommend testing both forms of Vitamin D 25 OH and 125 diOH.
- **Quercetin** (Quercetin Plus with Nettles leaf and Naturized Vitamin C) Protective dose 2-3 caps, therapeutic dose 2-3 caps 3x daily.
- **Selenium** (Organic form) 100-200 mcg.
- Naturized Vitamin C
- ? Citruline

Effects of select dietary supplements on the prevention and treatment of viral respiratory tract infections (VTI): a systematic review of randomized controlled trials

- Thirty-nine randomized controlled trials (n = 16,797 participants) were eligible and included.
- **Vitamin D supplementation improves outcome in viral RTIs across cohorts particulate in those with vitamin D deficiency**.
- ***Lactobacillus*** strains were used most commonly with selected prebiotics that showed potentially positive effects on the prevention and treatment of viral RTIs.
- **Ginseng extract** supplementation may effectively prevent viral RTIs as adjuvant therapy.

Shokri-Mashhadi N, Kazemi M, Saadat S, Moradi S. Effects of select dietary supplements on the prevention and treatment of viral respiratory tract infections: a systematic review of randomized controlled trials. Expert Rev Respir Med. 2021 Apr 26:1-17. doi: 10.1080/17476348.2021.1918546.

[Dermato-Endocrinology 1:4, 215-219; July/August 2009]; ©2009 Landes Bioscience

Report

The possible roles of solar ultraviolet-B radiation and vitamin D in reducing case-fatality rates from the 1918–1919 influenza pandemic in the United States

William B. Grant[1,*] and Edward Giovannucci[2]

Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths

- Through several mechanisms, vitamin D can reduce risk of infections.
- Those mechanisms include inducing cathelicidins and defensins that can lower viral replication rates and reducing concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increasing concentrations of anti-inflammatory cytokines.

Nutrients 2020, 12, 988; doi:10.3390/nu12040988

Vitamin D Deficiency and Low Serum Calcium as Predictors of Poor Prognosis in Patients with Severe COVID-19

- This is a prospective study, including 120 severe cases of COVID-19
- This study demonstrates the high frequency of hypocalcemia and hypovitaminosis D in severe COVID-19 patients and provides further evidence of their potential link to poor short-term prognosis.
- It is, therefore, possible that the correction of hypocalcemia, as well as supplementation with vitamin D, may improve the vital prognosis.

Bennouar S, Cherif AB, Kessira A, Bennouar DE, Abdi S. J Am Coll Nutr. 2021 Jan 12:1-11. doi: 10.1080/07315724.2020.1856013.

Vitamin D Deficiency and Low Calcium as Predictors of Poor Prognosis in Patients with Severe COVID-19

- Mean vitamin D serum level of 376 patients
- Serum vitamin D levels could be implicated in the COVID-19 prognosis.
- Patients with poor prognosis (N = 150) had significantly lower serum levels of vitamin D compared with those with good prognosis (N = 161)
- Diagnosis of vitamin D deficiency could be a helpful adjunct in assessing patients' potential of developing severe COVID-19. Appropriate preventative and/or therapeutic intervention may improve COVID-19 outcomes

Munshi R, Hussein MH, Toraih EA, Elshazli RM, Jardak C, Sultana N, Youssef MR, Omar M, Attia AS, Fawzy MS, Killackey M, Kandil E, Duchesne J. J Med Virol. 2021 Feb;93(2):733-740. doi: 10.1002/jmv.26360.

Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results

- A total of 489 patients (mean [SD] age, 49.2 [18.4] years; 366 [75%] women; and 331 [68%] race other than White) had a vitamin D level measured in the year before COVID-19 testing.
- In this single-center, retrospective cohort study, deficient vitamin D(<20 25 OH) status was associated with increased COVID-19 risk

Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results. *JAMA Netw Open*. 2020;3(9):e2019722. Published 2020 Sep 1. doi:10.1001/jamanetworkopen.2020.19722

Vitamin D Sufficiency Reduced Risk for Morbidity and Mortality in COVID-19 Patients

- Hospital medical records were analyzed from inpatient database of Sina Hospital COVID-19 Registry (SHCo-19R).
- Vitamin D sufficiency was defined a serum 25(OH)D evel of at least 30ng/mL.
- The hospital data of 235 patients infected with COVID-19 were analyzed.
- **The significant reduction in serum CRP, an inflammatory marker, along with increased lymphocytes percentage suggest that vitamin D sufficiency also may help modulate the immune response possibly by reducing risk for cytokine storm in response to this viral infection.**

The Lancet, 5/27/20, https://ssrn.com/abstract=3616008 or http://dx.doi.org/10.2139/ssrn.3616008

Vitamin D supplementation and clinical outcomes in COVID-19: a systematic review and meta-analysis

- 13 studies (10 observational, 3 RCTs) pooling data retrieved from 2933 COVID-19 patients.
- Pooled analysis of unadjusted data showed that vitamin D use in COVID-19 was significantly associated with reduced ICU admission/mortality,
- Vitamin D was also found to reduce the risk of adverse outcomes (pooled OR 0.27, 95% CI: 0.08, 0.91, $p = 0.03$, $I^2 = 80\%$, random-effects model).
- Subgroup analysis showed that vitamin D supplementation was associated with improved clinical outcomes only in patients receiving the drug post-COVID-19 diagnosis and not in those who had received vitamin D before diagnosis.

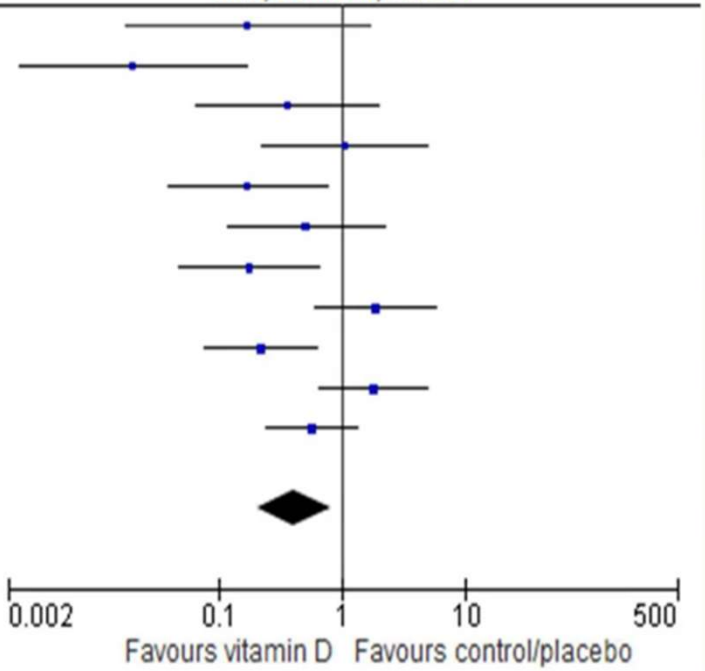
Pal, R., Banerjee, M., Bhadada, S.K. *et al.* Vitamin D supplementation and clinical outcomes in COVID-19: a systematic review and meta-analysis. *J Endocrinol Invest* (2021). https://doi.org/10.1007/s40618-021-01614-4

From: Vitamin D supplementation and clinical outcomes in COVID-19: a systematic review and meta-analysis

Study or Subgroup	Vitamin D Events	Vitamin D Total	Control/Placebo Events	Control/Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Jevalikar et al. (2021)	1	128	3	69	5.6%	0.17 [0.02, 1.70]
Entrenas Castillo et al. (2020)	1	50	13	26	6.1%	0.02 [0.00, 0.17]
Lakkireddy et al. (2021)	2	44	5	43	7.8%	0.36 [0.07, 1.98]
Hernandez et al. (2020)	2	19	20	197	8.5%	1.04 [0.22, 4.84]
Annweiler C et al. (2020)	10	57	5	9	8.8%	0.17 [0.04, 0.75]
Annweiler G et al. (2020)	3	16	10	32	8.9%	0.51 [0.12, 2.19]
Cangiano et al. (2020)	3	20	39	78	9.6%	0.18 [0.05, 0.65]
Murai et al. (2021)	9	119	5	118	10.6%	1.85 [0.60, 5.69]
Alcala-Diaz et al. (2021)	4	79	90	458	11.0%	0.22 [0.08, 0.61]
Cereda et al. (2021)	7	18	40	152	11.1%	1.78 [0.65, 4.91]
Giannini et al. (2021)	14	36	29	55	12.0%	0.57 [0.24, 1.34]
Total (95% CI)		**586**		**1237**	**100.0%**	**0.41 [0.20, 0.81]**
Total events	56		259			

Heterogeneity: $Tau^2 = 0.85$; $Chi^2 = 29.42$, $df = 10$ ($P = 0.001$); $I^2 = 66\%$

Test for overall effect: $Z = 2.56$ ($P = 0.01$)



Forest plot showing the effect (unadjusted) of vitamin D supplementation on clinical outcomes (intensive care unit admission and/or mortality) in patients with COVID-19 as compared to non-use of vitamin D

Pal, R., Banerjee, M., Bhadada, S.K. *et al.* Vitamin D supplementation and clinical outcomes in COVID-19: a systematic review and meta-analysis. *J Endocrinol Invest* (2021). https://doi.org/10.1007/s40618-021-01614-4

Vitamin D Supplementation to Prevent Acute Respiratory Tract Infections: Systematic Review and Meta-Analysis of Individual Participant Data

- 25 eligible randomized controlled trials (total 11 321 participants, aged 0 to 95 years) were identified
- **Conclusions** Vitamin D supplementation was safe, and it protected against acute respiratory tract infection overall
- Patients who were very vitamin D deficient and those not receiving bolus doses experienced the most benefit
- Chronic vitamin D deficiency may induce renin-angiotensin system (RAS) activation lung fibrosis through activation of the RAS; therefore, increasing evidence indicates that 1,25(OH) D may also be a negative endocrine regulator of the RAS, and may exert protective effects on inflammation-induced lung injury

Martineau, Adrian R et al. *BMJ (Clinical research ed.)* vol. 356 i6583. 15 Feb. 2017, doi:10.1136/bmj.i6583;
Mol Med Rep. 2017 Nov; 16(5): 7432–7438.

Serum Vitamin D Level Affect COVID-19 Infection and Its Severity

- This case-control study compared serum 25(OH)D levels and rates of vitamin D deficiency (VDD) between 80 healthy controls and 62 patients diagnosed with COVID-19 and admitted to Guangxi People's Hospital, China, 2/16/2020-3/16/2020.
- **Elderly and people with comorbidities were susceptible to severe COVID-19 infection. VDD was a risk factor for COVID-19, especially for severe/critical cases**

Ye K, Tang F, Liao X, Shaw BA, Deng M, Huang G, Qin Z, Peng X, Xiao H, Chen C, Liu X, Ning L, Wang B, Tang N, Li M, Xu F, Lin S, Yang J. Does Serum Vitamin D Level Affect COVID-19 Infection and Its Severity?-A Case-Control Study. J Am Coll Nutr. 2020 Oct 13:1-8. doi: 10.1080/07315724.2020.1826005.

Evidence related to low levels of vitamin D in T1D, respiratory infection and its putative association with COVID-19.

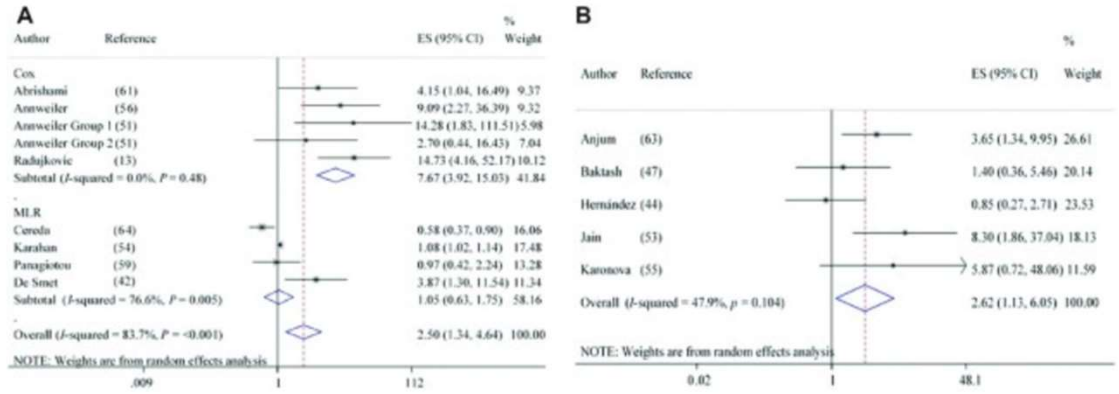
VITAMIN D3		
T1D	**Respiratory Infection**	**Possible Role in COVID-19**
↓ levels of vitamin D3 vitamin D3 supplementation: ✓ ↓ fasting glycemia ✓ ↑ insulin secretion ✓ ↓ autoimmune process	↓ levels of vitamin D3 ↑ adverse outcomes ↑ cytokine storm	↓ levels of vitamin D correlated with COVID-19 severity ↓ levels of vitamin D are associated with anosmia and ageusia

↑: increased; ↓ reduced.

Ricordi C, Pacifici F, Lanzoni G, Palamara AT, Garaci E, Della-Morte D. Dietary and Protective Factors to Halt or Mitigate Progression of Autoimmunity, COVID-19 and Its Associated Metabolic Diseases. *Int J Mol Sci*. 2021;22(6):3134. Published 2021 Mar 19. doi:10.3390/ijms22063134

Vitamin D status associated with SARS-COV-2 infection or COVID-19 severity: a systematic review and meta-analysis.

- Thirty-nine studies were included in the current systematic review.
- Analysis of studies indicated a significant association of vitamin D deficiency with mortality, while in adjusted studies that used logistic regression, no relation was observed.



Relation between vitamin D deficiency and risk of mortality from COVID-19 in studies that adjusted for confounders (adjusted HR) (A) and studies that did not adjust for confounders (crude OR) (B). COVID-19, coronavirus disease 2019; ES, effect size; MLR, multiple logistic regression.

Corrigendum to Kazemi et al. Adv Nutr. 2021 Oct 1;12(5):1636-1658.

All-Trans Retinoic Acid Exhibits Antiviral Effect against SARS-CoV-2

- The 3C-like protease (3CLpro), the major protease of SARS-CoV-2, is one of the most interesting targets for antiviral drug development because it is highly conserved among SARS-CoVs and plays an important role in viral replication
- 91 natural product compounds were tested and it found that **all-trans retinoic acid (ATRA), a derivative of Vitamin A** , and an FDA-approved drug, inhibited 3CLpro activity.
- ATRA inhibited the replication of SARS-CoV-19 of all the current variants.

Morita T, Miyakawa K, Jeremiah SS, Yamaoka Y, Sada M, Kuniyoshi T, Yang J, Kimura H, Ryo A. All-Trans Retinoic Acid Exhibits Antiviral Effect against SARS-CoV-2 by Inhibiting 3CLpro Activity. Viruses. 2021 Aug 23;13(8):1669. doi: 10.3390/v13081669..

Zinc - the most Important Nutrient for Immunity Is the Most Deficient

- Zinc is essential for virtually all processes in the human body
- Observations during zinc deficiency indicate that the absence of zinc severely impairs the immune response
- An abundance of evidence has accumulated over the past 50 years to demonstrate the antiviral activity of zinc against a variety of viruses, and via numerous mechanisms
- SARS coronavirus was inhibited by zinc.

Scott ARead,1,2 Stephanie Obeid,3 Chantelle Ahlenstiel,3 and Golo Ahlenstiel, The Role of Zinc in Antiviral Immunity, American Society for Nutrition 2019. Adv Nutr 2019;10:696–710; doi: https://doi.org/10.1093/advances/nmz013

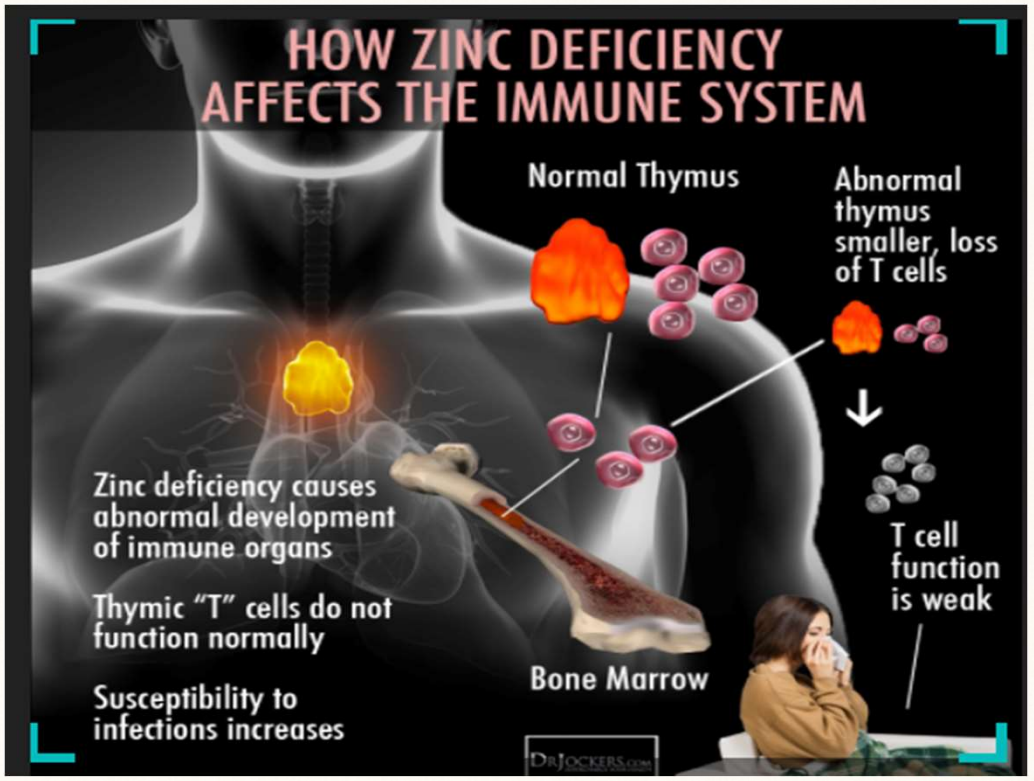
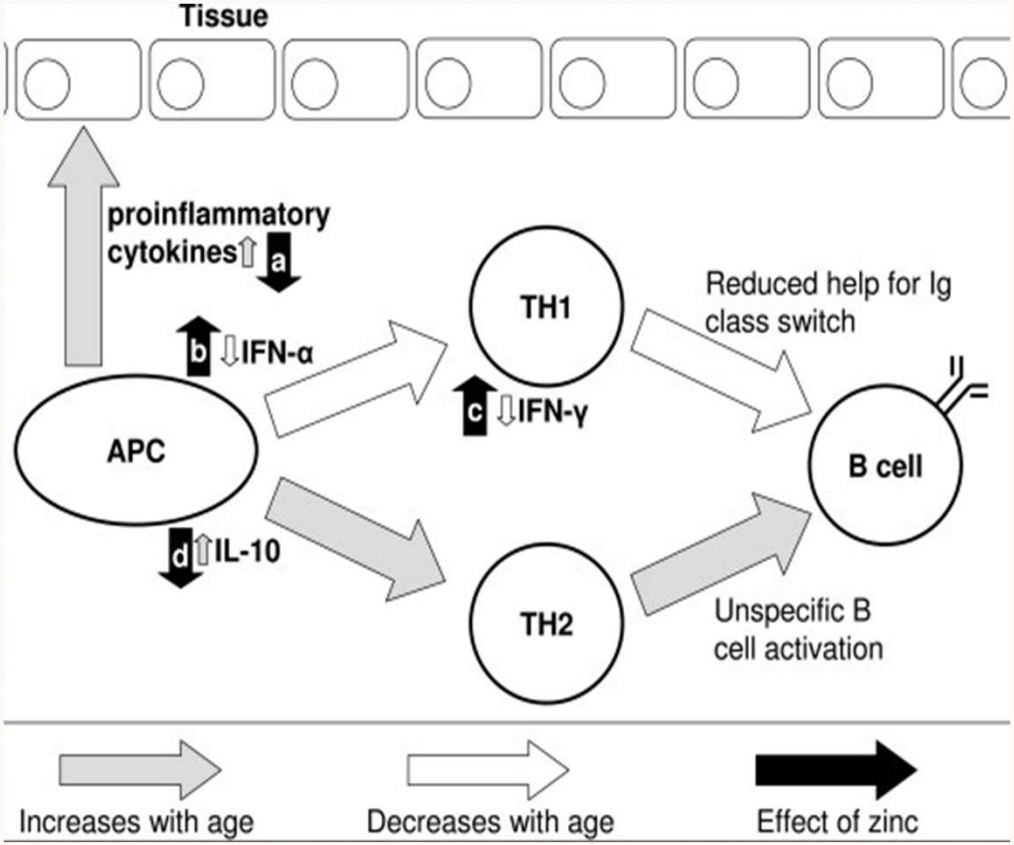


Image Source: https://drjockers.com/15-zinc-deficiency-symptoms/

The Role of Zinc in Antiviral Immunity

- When high doses of ionic zinc are used in clinical studies, a clear reduction in cold duration of 42% was calculated.
- In a review of six randomized DBPC trials including 2216 patients, Zinc given as an adjunct to the treatment of severe pneumonia is effective in reducing the mortality of severe pneumonia, and has no significant effects on treatment failure and change of antibiotic therapy.



Smailhodzic D, van Asten F, et al. The immune system and the impact of **zinc** during aging. Immunity & Aging. **2009**. **6:9**. PLOS ONE. **2014** Nov. 9(11):1-10. 24; Linlin Wang [1], Yuanlin Song, Efficacy of Zinc Given as an Adjunct to the Treatment of Severe Pneumonia: A Meta-Analysis of Randomized, Double-Blind and Placebo-Controlled Trials, Clin Respir J, 12 (3), 857-864 Mar 2018.

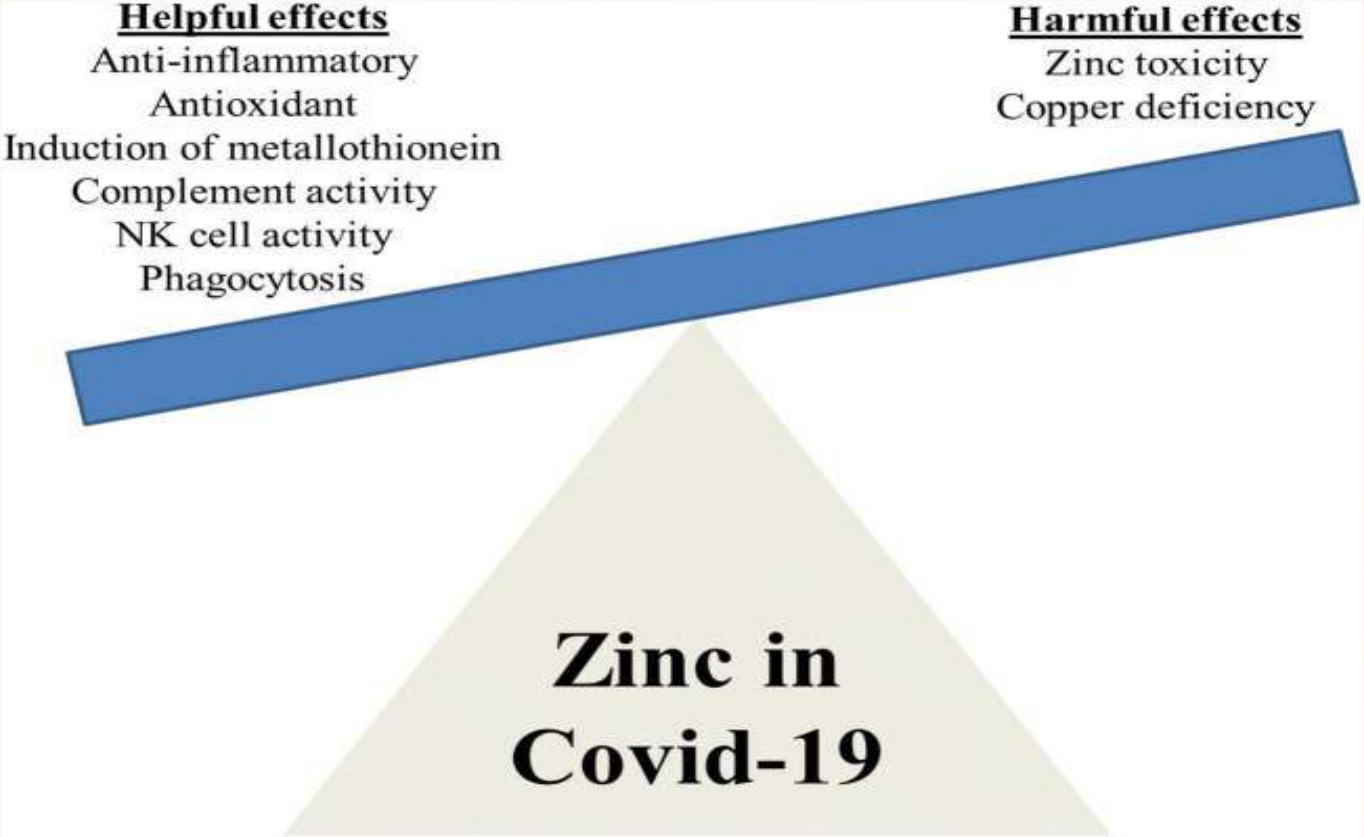
INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE 46: 17-26, 2020

Zinc and respiratory tract infections: Perspectives for COVID-19 (Review)

ANATOLY V. SKALNY[1,2*], LOTHAR RINK[3*], OLGA P. AJSUVAKOVA[2,4], MICHAEL ASCHNER[1,5], VIKTOR A. GRITSENKO[6], SVETLANA I. ALEKSEENKO[7,8], ANDREY A. SVISTUNOV[1], DEMETRIOS PETRAKIS[9], DEMETRIOS A. SPANDIDOS[10], JAN AASETH[1,11], ARISTIDIS TSATSAKIS[1,9] and ALEXEY A. TINKOV[1,2,6*]

- Due to the clearly demonstrated role of zinc in immunity (2), and impaired zinc status in ageing (35), metabolic diseases including diabetes, obesity, and cardiovascular diseases (13), it is speculated that zinc compounds may be used as an adjunct therapy in COVID- 19 treatment (36) for increasing antiviral resistance (37).
- Of note, zinc was earlier suggested as the potential agent for immune support and prevention of H1N1 influenza (‘swine flu’) (38).

A marked neutrophilia is observed in severe COVID-19 patients. Zinc gluconate supplementation is able to reduce airway neutrophil infiltration and TNF-α release by inhibiting NF-kB-dependent transcription of inflammatory genes.



Pal A, Squitti R, Picozza M, et al. Zinc and COVID-19: Basis of Current Clinical Trials. *Biol Trace Elem Res*. 2021;199(8):2882-2892. doi:10.1007/s12011-020-02437-9

Integrative Medicine Research 9 (2020) 100457

Contents lists available at ScienceDirect

Integrative Medicine Research

journal homepage: www.imr-journal.com



Study Protocol

Rapid review protocol: Zinc for the prevention or treatment of COVID-19 and other coronavirus-related respiratory tract infections

Jennifer Hunter [a,*], Susan Arentz [a], Joshua Goldenberg [b], Guoyan Yang [a], Jennifer Beardsley [a,b,c,d], Dominik Mertz [c], Stephen Leeder [d]

Low Zinc Levels associated with Severity of Acute Respiratory Distress Syndrome by New Coronavirus (SARS-CoV-2)

- A total of 269 patients met inclusion criteria
- Critically ill patients infected by SARS-CoV-2 with severe ARDS have a high prevalence of low serum zinc levels.

Gonçalves TJM, Gonçalves SEAB, Guarnieri A, Risegato RC, Guimarães MP, de Freitas DC, Razuk-Filho A, Junior PBB, Parrillo EE. Nutr Clin Pract. 2020 Dec 23. doi: 10.1002/ncp.10612. Epub ahead of print. PMID: 33368619.

COVID-19: Poor outcomes in patients with zinc deficiency

- This was a prospective study of fasting zinc levels in COVID-19 patients at the time of hospitalization.
- An initial comparative analysis was conducted between COVID-19 patients and healthy controls
- The study data clearly show that a significant number of COVID-19 patients were zinc deficient.
- These zinc deficient patients developed more complications, and the deficiency was associated with a prolonged hospital stay and increased mortality

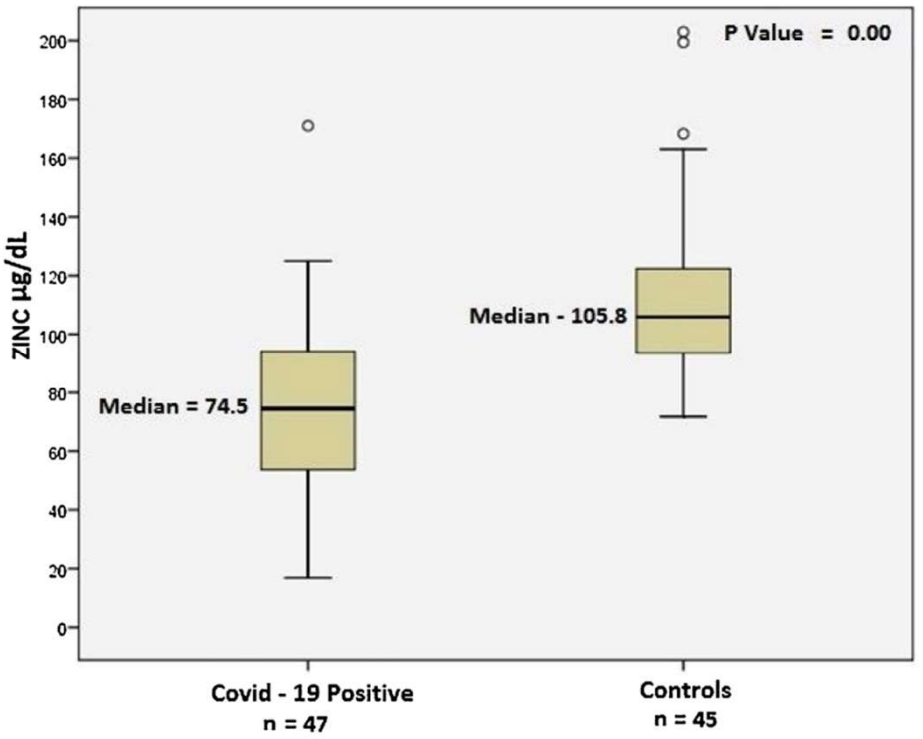


Figure 1. Serum zinc levels in patients with COVID-19 and healthy controls.

Jothimani D, Kailasam E, Danielraj S, Nallathambi B, Ramachandran H, Sekar P, Manoharan S, Ramani V, Narasimhan G, Kaliamoorthy I, Rela M.. Int J Infect Dis. 2020 Nov;100:343-349. doi: 10.1016/j.ijid.2020.09.014.

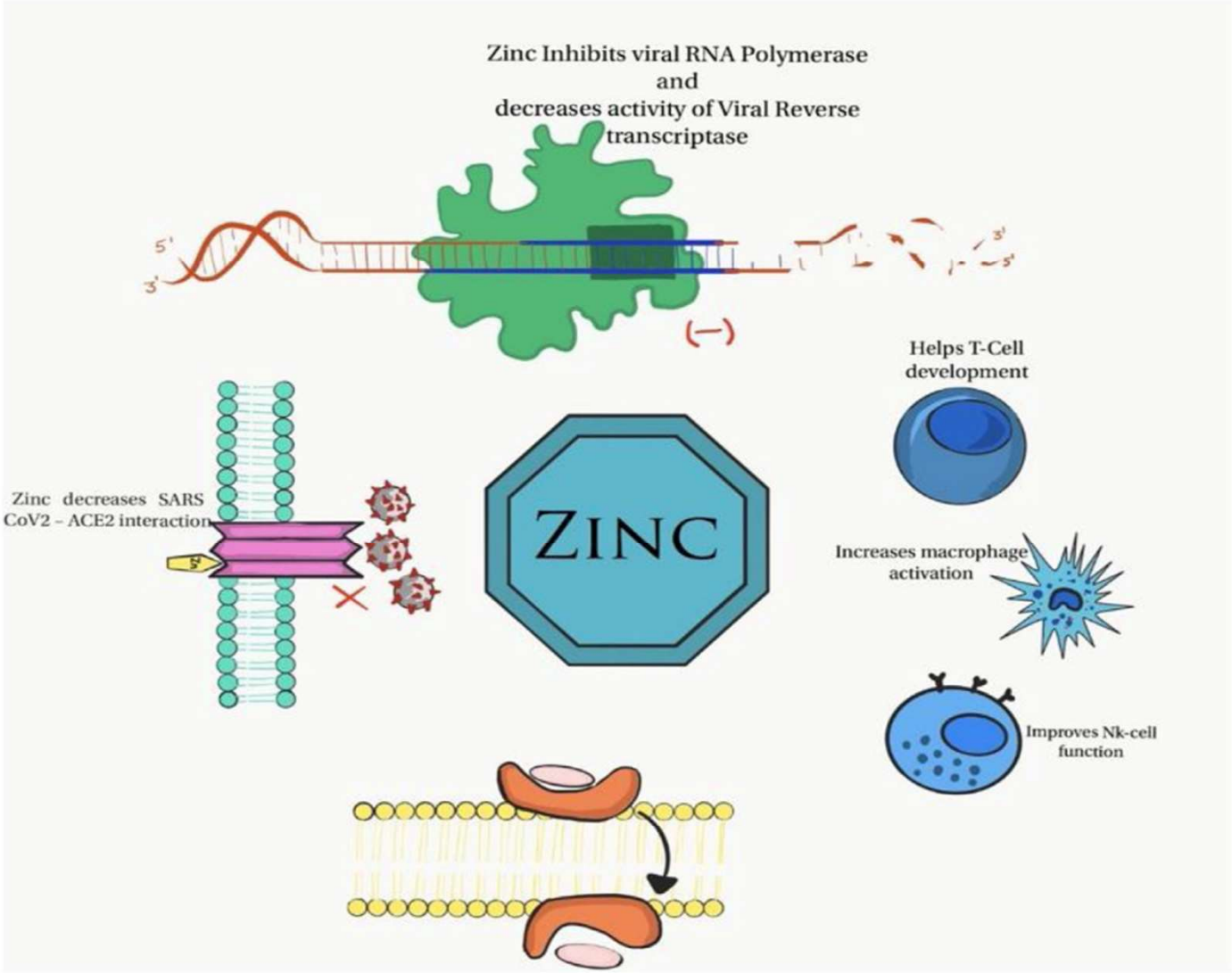
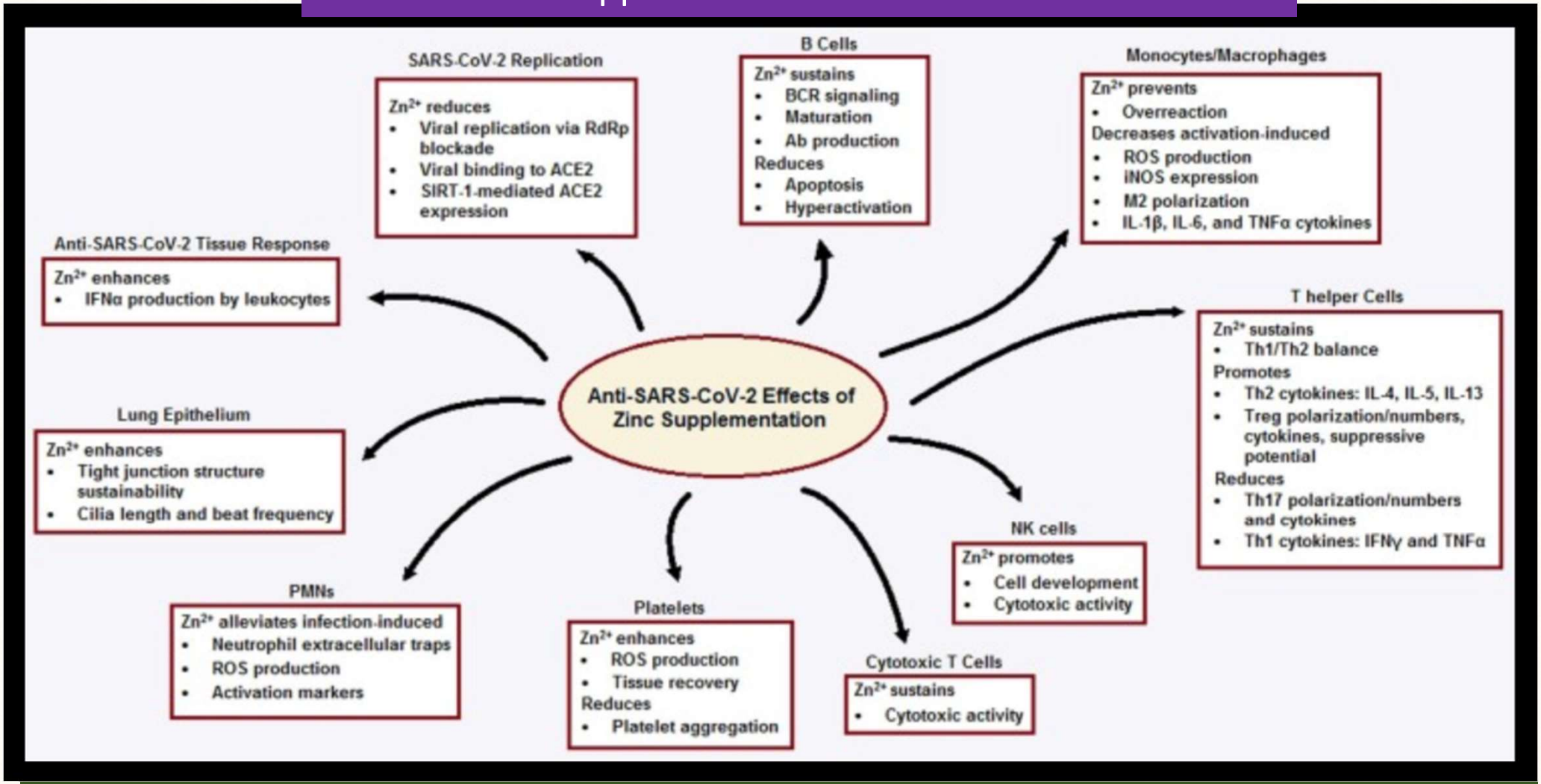


Figure 2. Illustration of antiviral and immunomodulatory properties of zinc in COVID-19.

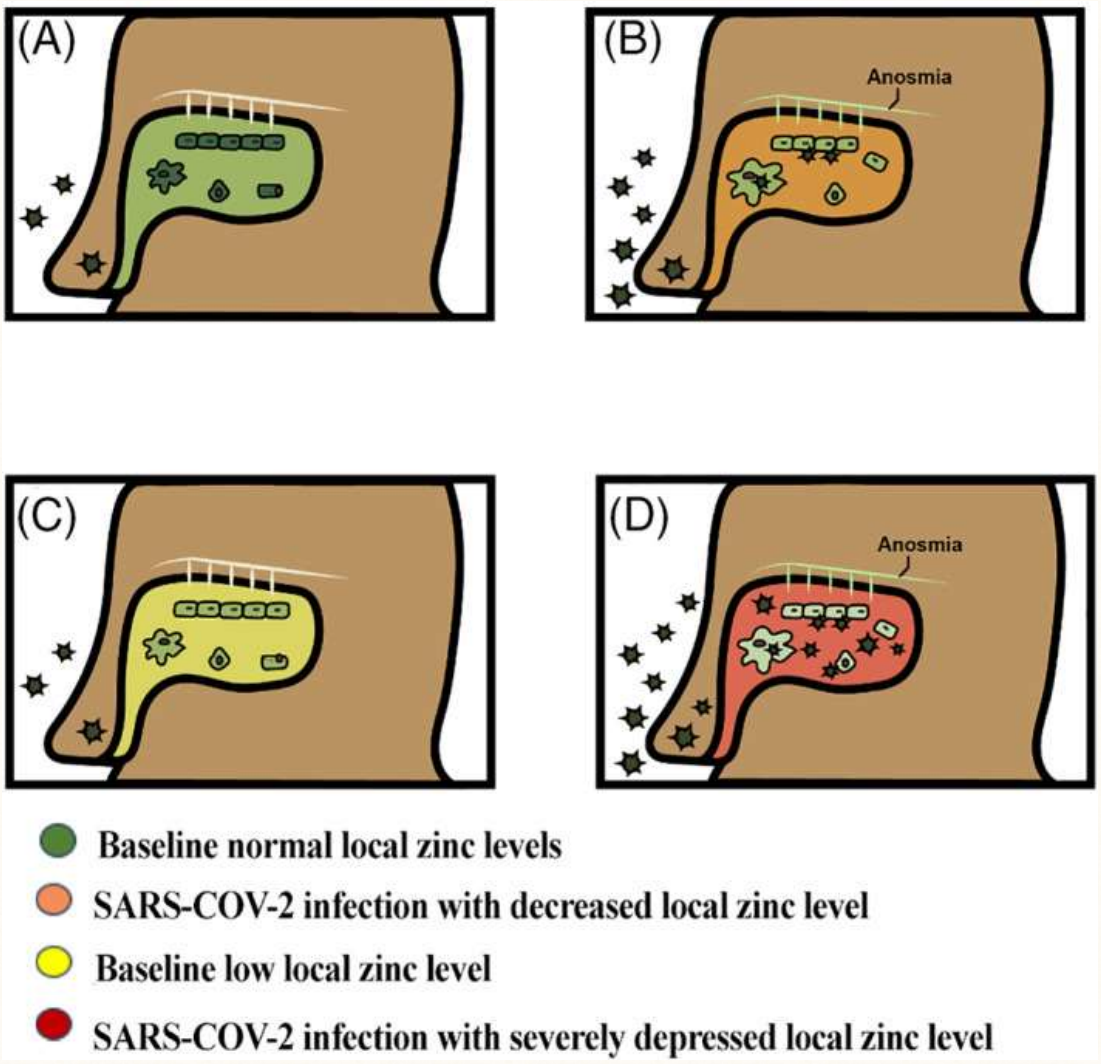
Int J Infect Dis. 2020 Nov;100:343-349. doi: 10.1016/j.ijid.2020.09.014.

Effects of zinc supplementation on SARS-CoV-2 infection.



Asl SH, Nikfarjam S, Majidi Zolbanin N, Nassiri R, Jafari R. Immunopharmacological perspective on zinc in SARS-CoV-2 infection. Int Immunopharmacol. 2021 Apr 1;96:107630. doi: 10.1016/j.intimp.2021.107630. Epub ahead of print. PMID: 33882442; PMCID: PMC8015651.

Intra-nasal zinc level relationship to COVID-19 anosmia



Equils O, Lekaj K, Wu A, Fattani S, Liu G, Rink L. Intra-nasal zinc level relationship to COVID-19 anosmia and type 1 interferon response: A proposal. *Laryngoscope Investig Otolaryngol*. 2020;6(1):21-24. Published 2020 Dec 25. doi:10.1002/lio2.513

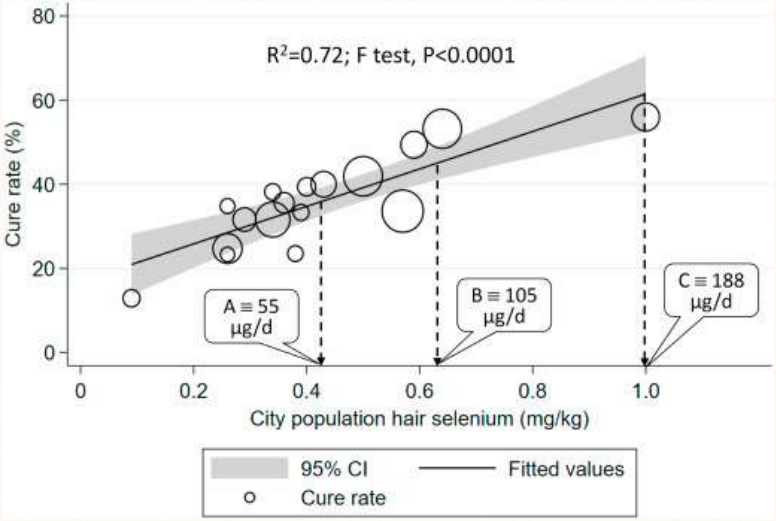
Alpha-Lipoic Acid (LA) Therapeutic Potential in Viral Infections, including COVID-19

- LA is one of the most-studied and used natural compounds, as it is endowed with a well-defined antioxidant and immunomodulatory profile.
- LA has been tested in several chronic immunoinflammatory conditions, such as diabetic neuropathy and metabolic syndrome.
- There emerging literature on the potential use of LA in viral infections, including COVID-19.

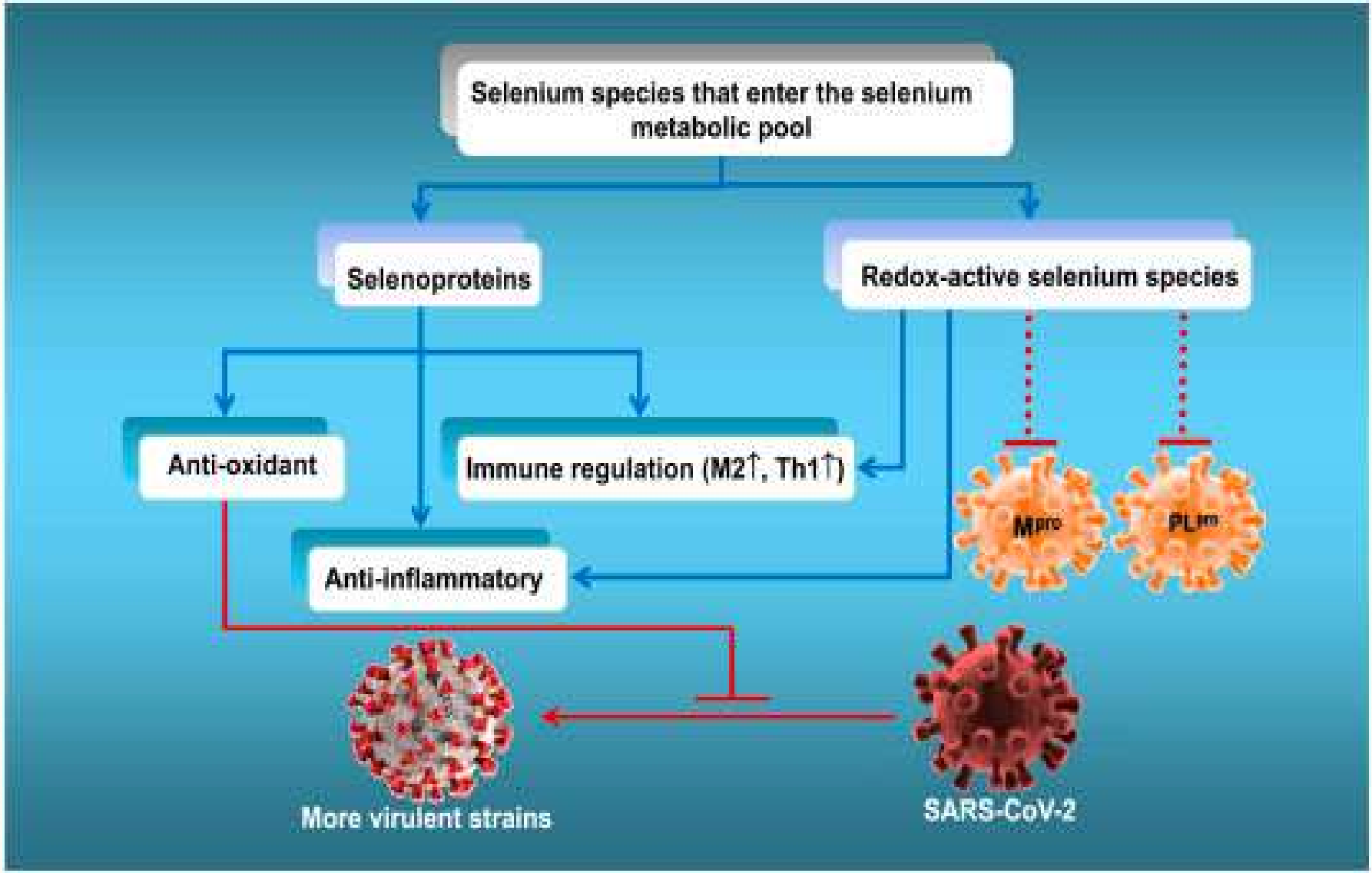
Dragomanova S, Miteva S, Nicoletti F, Mangano K, Fagone P, Pricoco S, Staykov H, Tancheva L. Therapeutic Potential of Alpha-Lipoic Acid in Viral Infections, including COVID-19. Antioxidants (Basel). 2021 Aug 16;10(8):1294. doi: 10.3390/antiox10081294.

Selenium and COVID-19

- Selenium has an ongoing history of reducing the incidence and severity of various viral infections; for example, a German study found selenium status to be significantly higher in serum samples from surviving than non-surviving COVID-19 patients.
- Furthermore, a significant, positive, linear association was found between the cure rate of Chinese patients with COVID-19 and regional selenium status.



Jinsong Zhang, Ramy Saad, Ethan Will Taylor, Margaret P. Rayman, Selenium and selenoproteins in viral infection with potential relevance to COVID-19, Redox Biology, Volume 37, 2020,101715, ISSN 2213-2317, https://doi.org/10.1016/j.redox.2020.101715.



Redox Biology, Volume 37, 2020,101715, ISSN 2213-2317, https://doi.org/10.1016/j.redox.2020.101715.

Prediction of survival odds in COVID-19 by zinc, age and selenoprotein P as composite biomarker

- Several redox-relevant micronutrients are known to contribute to an adequate immune response, including the essential trace elements zinc (Zn) and selenium (Se).
- Data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study were used for comparison.
- This study concluded that Zn and SELENOP status within the reference ranges indicate high survival odds in COVID-19, and assume that correcting a diagnostically proven deficit in Se and/or Zn by a personalized supplementation may support convalescence.

Diegmann J, Pilz M, Bachmann M, Ranjbar A, Moghaddam A, Schomburg L. Prediction of survival odds in COVID-19 by zinc, age and selenoprotein P as composite biomarker. Redox Biol. 2020 Oct 20;38:101764. doi: 10.1016/j.redox.2020.101764. Epub ahead of print. PMID: 33126054; PMCID: PMC7574778.

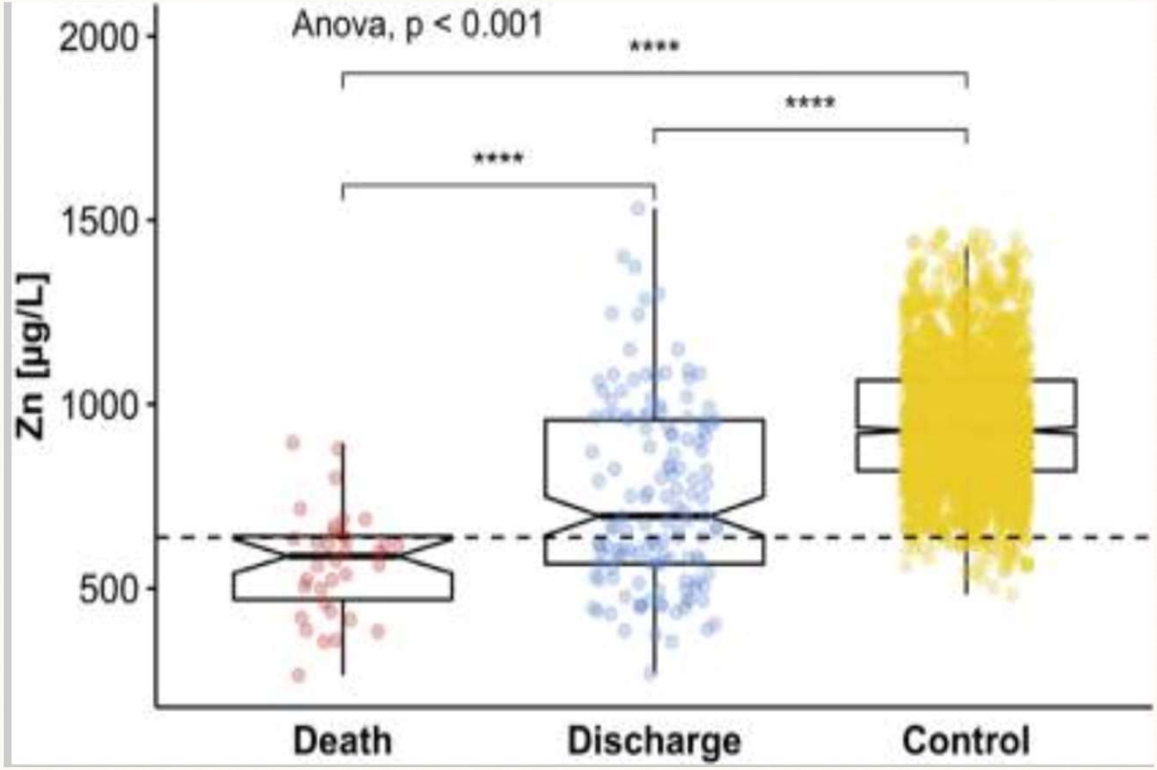


An Exploratory Study of Selenium Status in Normal Subjects and COVID-19 Patients in South Indian population: Case for Adequate Selenium Status: Selenium Status in COVID-19 Patients

Muhammed Majeed, Kalyanam Nagabhushanam, Sujay Gowda, Lakshmi Mundkur
Nutrition, 2020, 111053
ISSN 0899-9007
doi: 10.1016/j.nut.2020.111053.
(http://www.sciencedirect.com/science/article/pii/S0899900720303361)

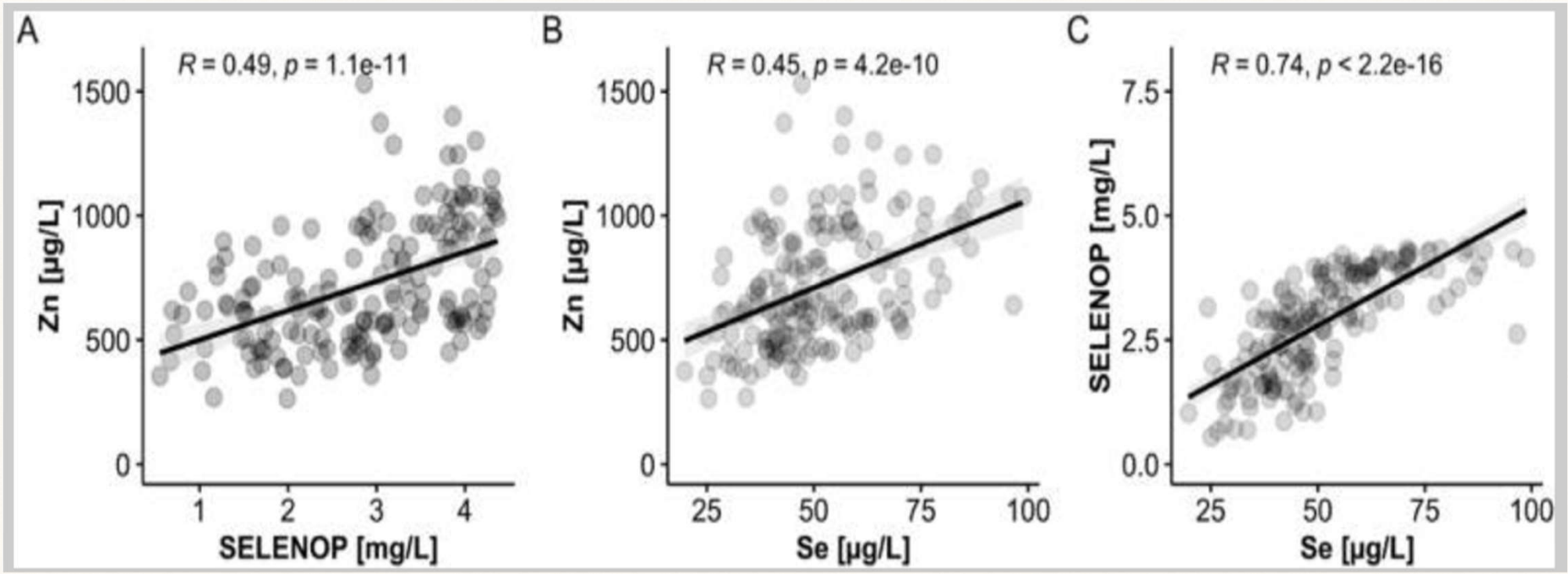
- The blood serum levels in 30 apparently healthy individuals and in 30 patients with confirmed COVID-19 infection was analyzed in the southern part of India.
- The patients showed significantly lower selenium levels of 69.2 ± 8.7 ng/mL than controls 79.1 ± 10.9 ng/mL. The difference was statistically significant (P = 0.0003).

Zn concentrations in patient samples were low as compared to healthy subjects (mean ± SD; 717.4 ± 246.2 vs 975.7 ± 294.0 µg/L, P < 0.0001).



Diegmann J, Pilz M, Bachmann M, Ranjbar A, Moghaddam A, Schomburg L. Prediction of survival odds in COVID-19 by zinc, age and selenoprotein P as composite biomarker. Redox Biol. 2020 Oct 20;38:101764. doi: 10.1016/j.redox.2020.101764. Epub ahead of print. PMID: 33126054; PMCID: PMC7574778.

Se status biomarker and Se transporter selenoprotein P (SELENOP) is also particularly low in COVID-19



Diegmann J, Pilz M, Bachmann M, Ranjbar A, Moghaddam A, Schomburg L. Prediction of survival odds in COVID-19 by zinc, age and selenoprotein P as composite biomarker. Redox Biol. 2020 Oct 20;38:101764. doi: 10.1016/j.redox.2020.101764. Epub ahead of print. PMID: 33126054; PMCID: PMC7574778.

Reproductive Sciences
https://doi.org/10.1007/s43032-020-00400-6

REVIEW

Potential Role of Zinc in the COVID-19 Disease Process and its Probable Impact on Reproduction

Ramya Sethuram[1] · David Bai[1] · Husam M. Abu-Soud[1,2,3]

Received: 18 August 2020 / Accepted: 16 November 2020
© Society for Reproductive Investigation 2021

- Zinc deficiency places the individual at an increased risk of infections and secondary complications, delayed recovery, decreased wound healing, and increased vulnerability to cell damage from the acute phase response.
- There is a considerable overlap between the symptomatology of SARS CoV-2 infection and zinc deficiency.
- Some of the unusual COVID-19 symptoms such as loss of smell and taste are well established in conjunction with zinc deficiency.
- All adults could be supplemented with up to a maximum of 50 mg/day without significant toxic side-effects

Le Infezioni in Medicina, n. 2, 192-197, 2020

Improving the efficacy of chloroquine and hydroxychloroquine against SARS-CoV-2 may require zinc additives - A better synergy for future COVID-19 clinical trials

Mujeeb Olushola Shittu, Olufemi Ifeoluwa Afolami
Biological Science Department, Michigan Technological University, Houghton, Michigan, United States of America

- "We seek to draw the attention of the scientific community to the possibility of drastically reducing the effects of the virus on the affected patients and improving clinical trials outcome through the synergistic action of zinc and chloroquine in patients suffering from the coronavirus disease."

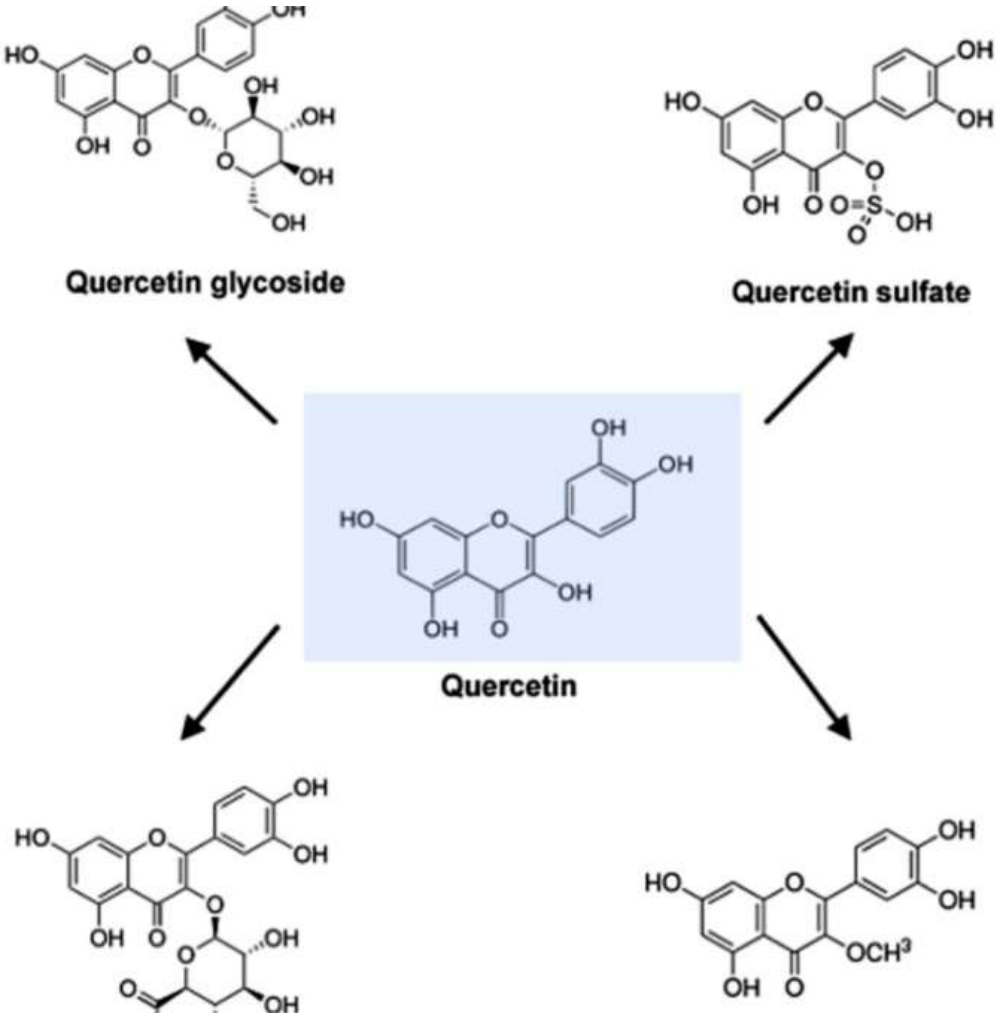
Targeting RAS Components Could Improve Outcomes in Acute Respiratory Distress Syndrome During Mechanical Ventilation (ARDS).

- Recent studies have suggested the renin-angiotensin system (RAS), which consists of the ACE/Ang-II/AT1R axis and ACE2/Ang-(1-7)/MasR axis, plays a dual role in the pathogenesis of ARDS and VILI.
- ACE/Ang-II/AT1R axis has a deleterious action, whereas ACE2/Ang-(1-7)/MasR axis, as well as AT2R, in VILI and ARDS, and the beneficial role.

Wang D, Chai XQ, Magnussen CG, et al. Renin-angiotensin-system, a potential pharmacological candidate, in acute respiratory distress syndrome during mechanical ventilation. *Pulm Pharmacol Ther*. 2019;58:101833. doi:10.1016/j.pupt.2019.101833

Quercetin

Molecular structure of quercetin, quercetin glycoside, quercetin glucuronide, quercetin sulfate and methylated quercetin.



Nutrients 2016 Mar; 8(3): 167.

Quercetin Inhibits Viral Infection

- Quercetin, an aglycone of rutin, is a phytochemical abundant in plants and may diminish the replication of many viruses: highly pathogenic influenza virus, rhinovirus, dengue virus type-2, HSV-1, poliovirus, adenovirus, Epstein-Barr virus, Mayaro virus, Japanese encephalitis virus, respiratory syncytial virus, and HCV

There are five main proposed mechanisms of action:

1. Inhibiting the virus' ability to infect cells
2. Inhibiting replication of already infected cells
3. Reducing infected cells' resistance to treatment with antiviral medication
4. Reduces virus related hyper-responsiveness/inflammation (cytokine storm)
5. Inhibits viral producing heat shock proteins

Shimon Ben-Shabat SB, Antiviral effect of phytochemicals from medicinal plants: Applications and drug delivery strategies, Drug Delivery and Translational Research (2020) 10:354–367, https://doi.org/10.1007/s13346-019-00691-6

Journal of Infectious Diseases & Preventive Medicine

ISSN: 2329-8731

Kinker et al., J Anc Dis Prev Rem 2014, 2:2
DOI: 10.4172/2329-8731.1000111

Review Article Open Access

Quercetin: A Promising Treatment for the Common Cold

Brenton Kinker, Adam T Comstock and Uma S Sajjan*

Department of Pediatrics and Communicable Diseases, University of Michigan, USA

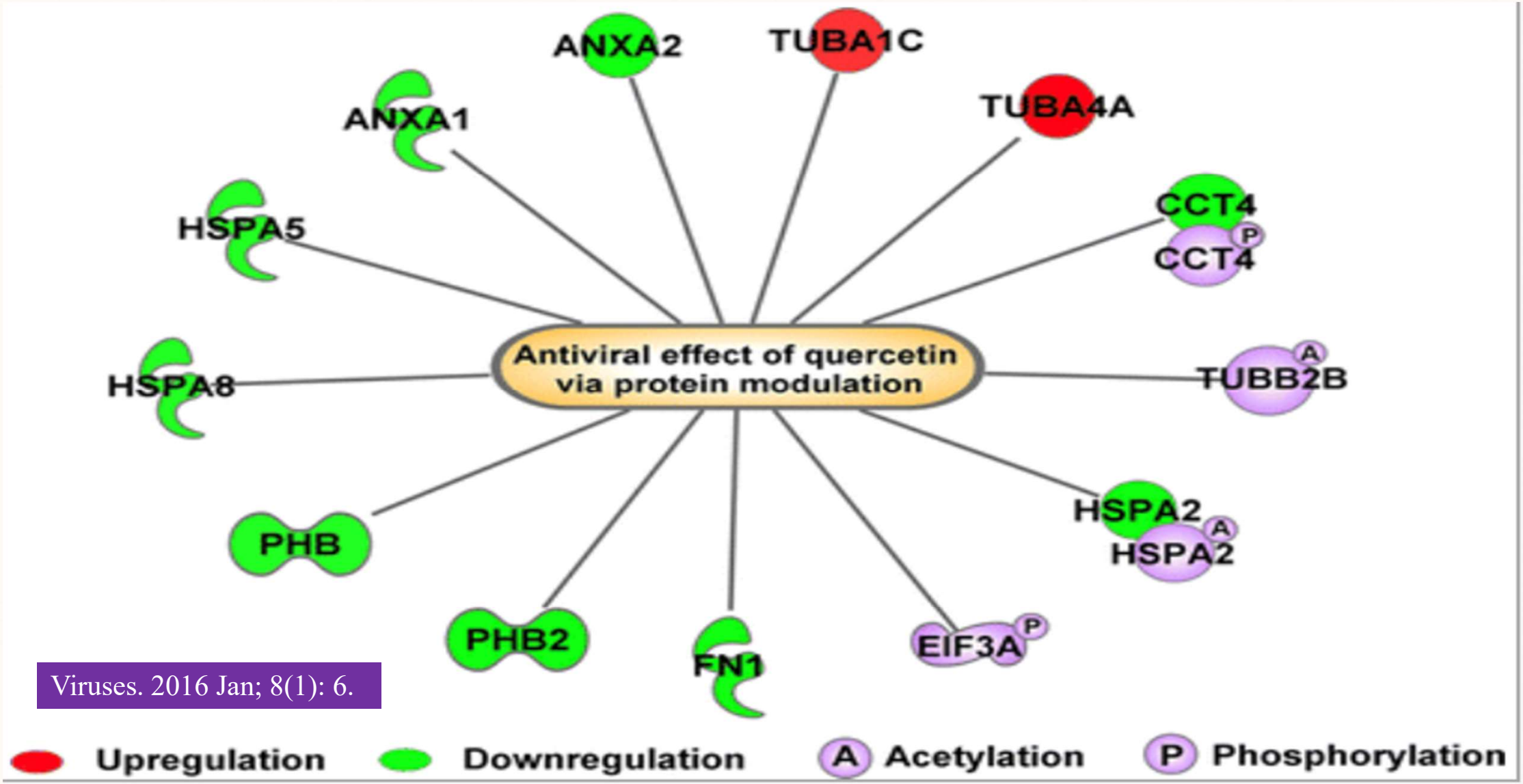
***Corresponding author:** Uma Sajjan, Department of Pediatrics and Communicable Diseases, University of Michigan, 1150 W. Medical Center Dr., Ann Arbor, MI 48109-5688, USA, Tel: (734) 936-4200; Fax: (734) 764-3200; E-mail: usajjan@umich.edu

Rec date: Mar 25, 2014, **Acc date:** May 22, 2014, **Pub date:** May 24, 2014

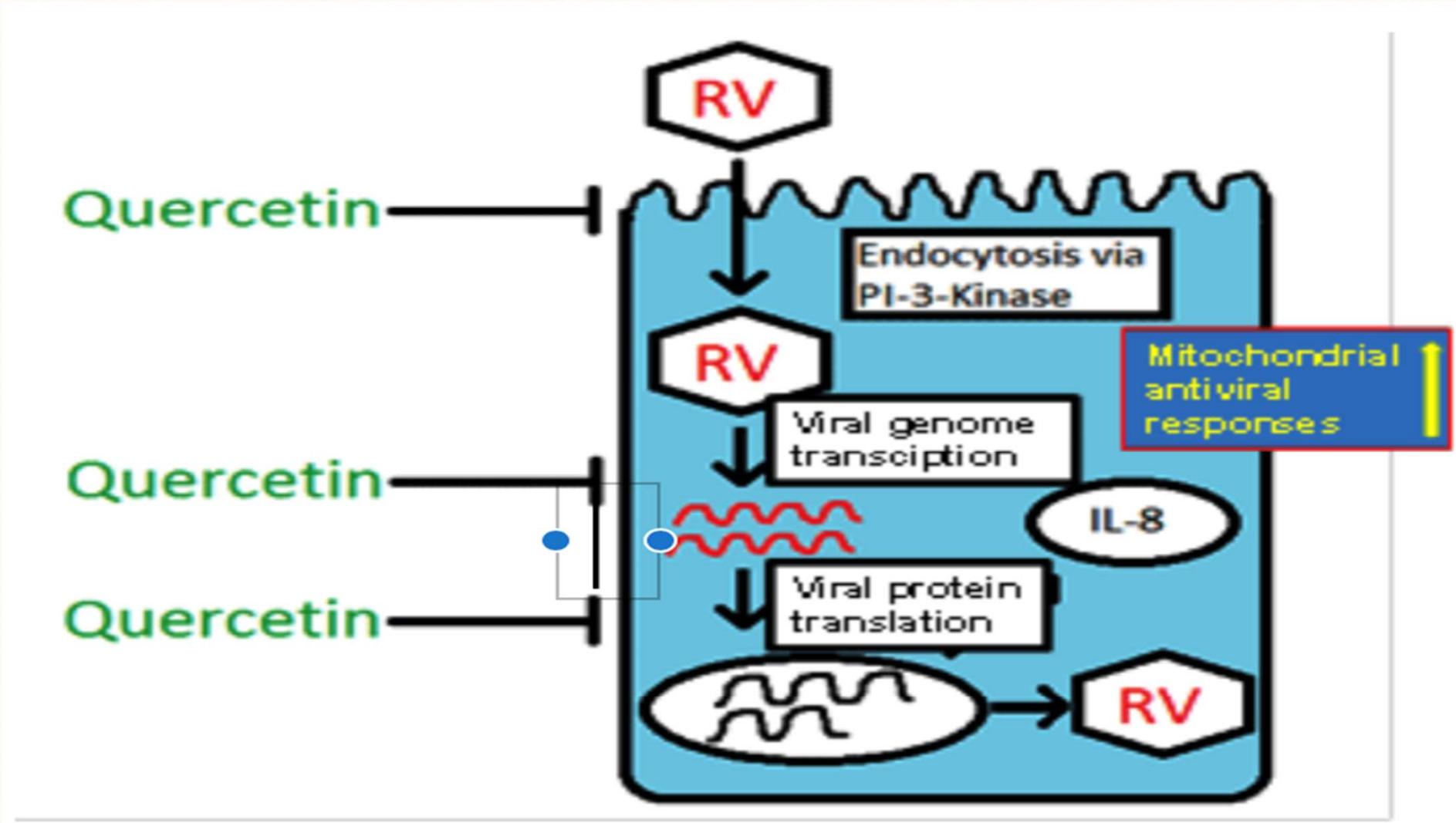
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Abstract

Rhinovirus infections have afflicted humanity since the dawn of civilization, and are difficult to treat even with modern medicine. Throughout the ages many remedies have been used for the common cold, often caused by the rhinovirus. Recent research points to a flavanol anti-oxidant, quercetin, as having therapeutic properties. Quercetin has been shown to reduce viral internalization and replication in vitro, and viral load, lung inflammation and airways hyper-responsiveness in vivo.

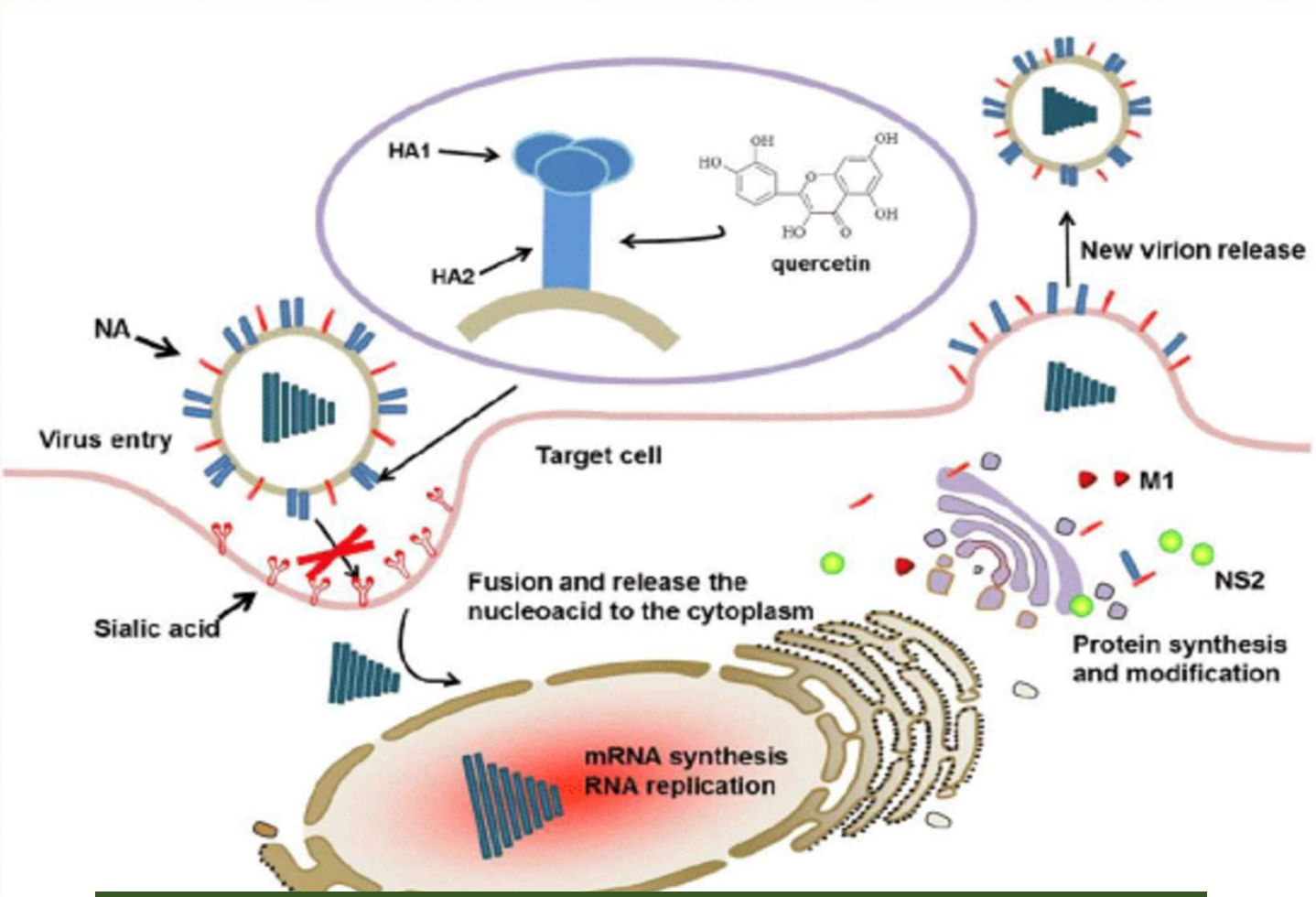


Viruses. 2016 Jan; 8(1): 6.

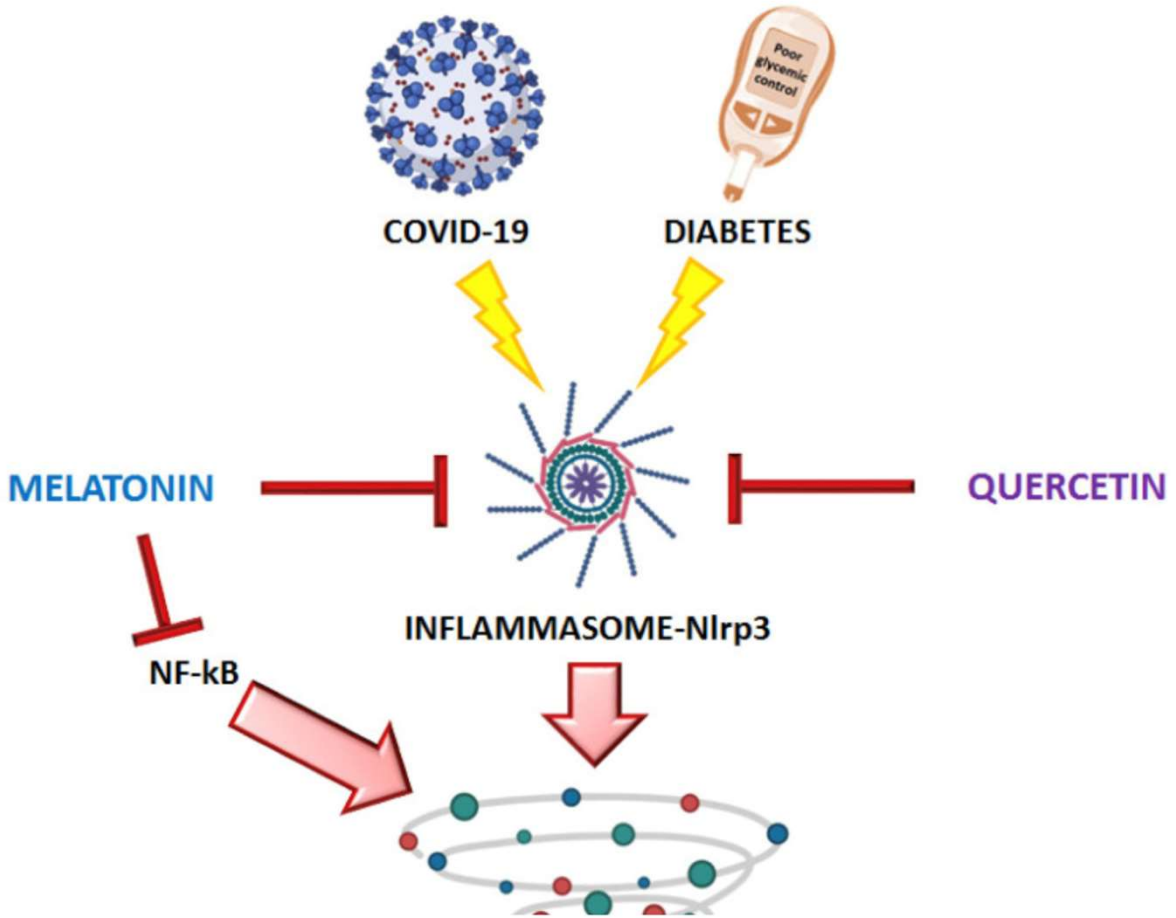


Brenton Kinker, Adam T Comstock and Uma S Sajjan, Quercetin: A Promising Treatment for the Common Cold, Journal of Infectious Diseases and Preventive Medicine May 24, 2014; 2: 111

Quercetin inhibited influenza infection with a wide spectrum of strains



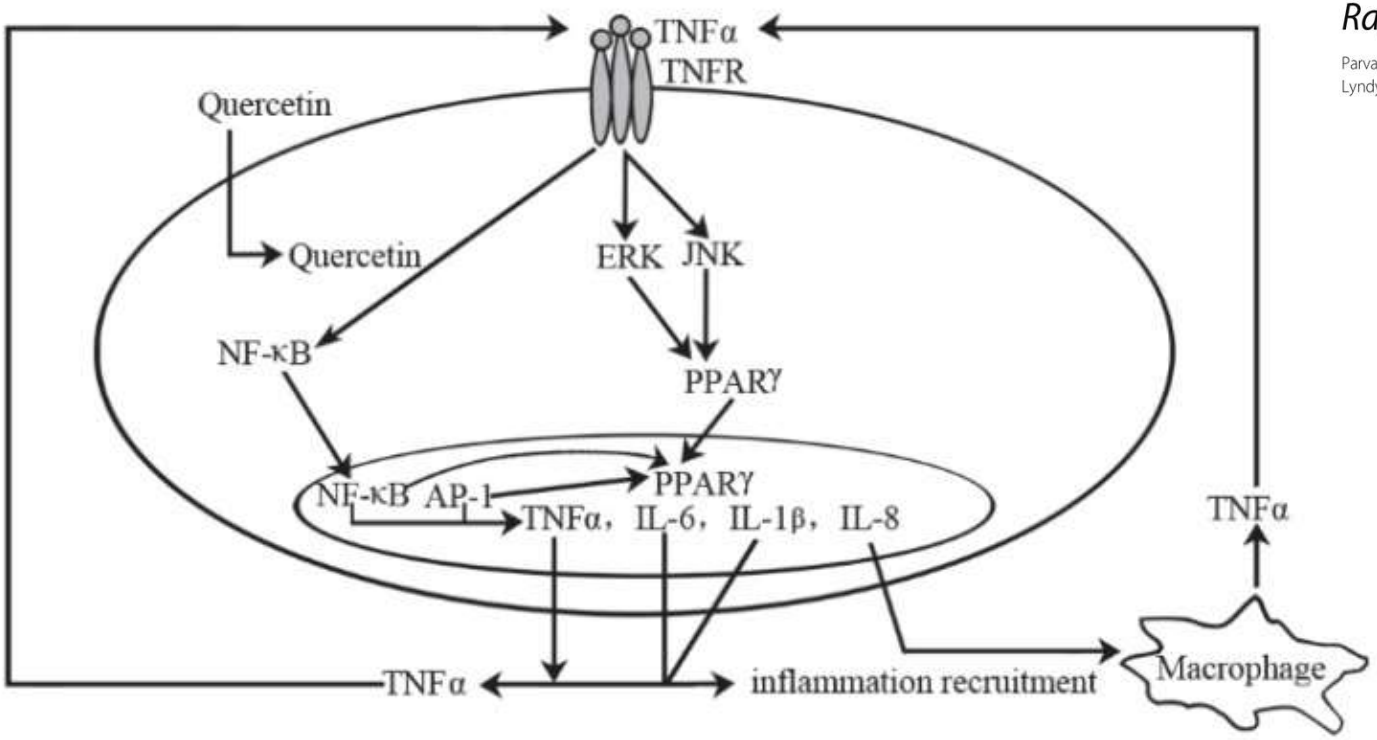
Viruses. 2015;8(1):6. Published 2015 Dec 25. doi:10.3390/v8010006



Proposed protective effects for melatonin and quercetin against SARS-CoV-2 infection. Melatonin and quercetin may blunt the deleterious effects of SARS-CoV-2 by reducing activation of the cytokine storm. Created with BioRender.com.

Ricordi C, Pacifici F, Lanzoni G, Palamara AT, Garaci E, Della-Morte D. Dietary and Protective Factors to Halt or Mitigate Progression of Autoimmunity, COVID-19 and Its Associated Metabolic Diseases. *Int J Mol Sci*. 2021;22(6):3134. Published 2021 Mar 19. doi:10.3390/ijms22063134

Quercetin, Inflammation and Immunity



Mehrbod *et al. BMC Complementary and Alternative Medicine* (2019) 19:346
https://doi.org/10.1186/s12906-019-2774-3

BMC Complementary and Alternative Medicine

RESEARCH ARTICLE Open Access

Experimental validation and computational modeling of anti-influenza effects of quercetin-3-O-α-L-rhamnopyranoside from indigenous south African medicinal plant *Rapanea melanophloeos*

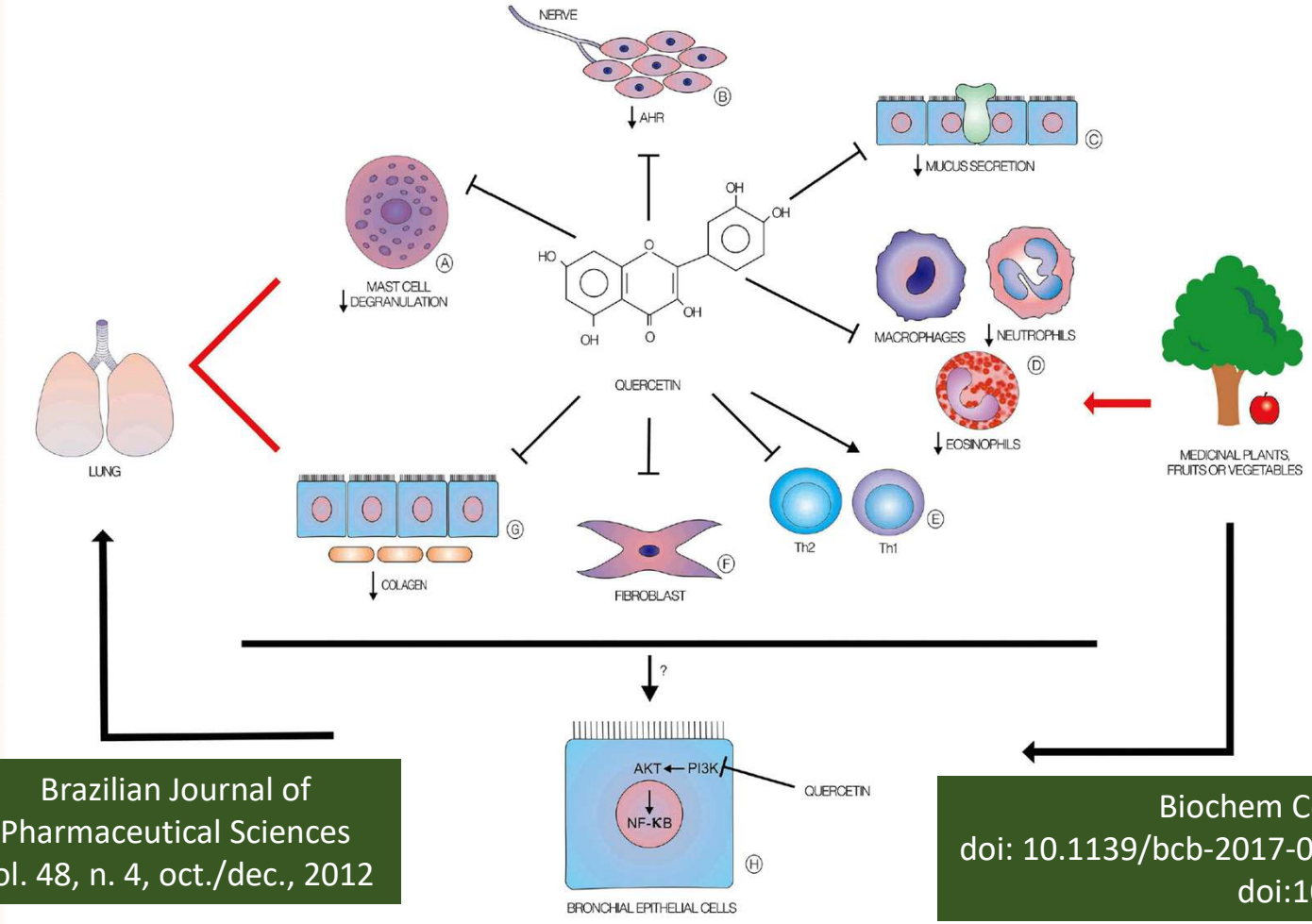
Parvaneh Mehrbod[1,2*], Samad Nejad Ebrahimi[3], Fatemeh Fotouhi[1], Fatemeh Eskandari[1], Jacobus N. Eloff[4], Lyndy J. McGaw[4] and Folorunso O. Fasina[2,5]

Significantly induces the gene expression as well as the production of Th-1 derived interferon-γ (IFN-γ) and down-regulates Th-2 derived interleukin 4 (IL-4) by normal peripheral blood mononuclear cells (PBMC).

Yao Li, Jiaying Yao, Chunyan Han, Jiaxin Yang, Maria Tabassum Chaudhry, Shengnan Wang, Hongnan Liu, Yulong Yin, Nutrients. 2016 Mar; 8(3): 167.

Mechanisms of Quercetin during Asthma

592



Ameliorates pulmonary fibrosis

Anti-fibrotic effect and inflammatory cytokines in pulmonary fibrosis

Brazilian Journal of Pharmaceutical Sciences vol. 48, n. 4, oct./dec., 2012

Biochem Cell Biol. 2018 Dec;96(6):742-751. doi: 10.1139/bcb-2017-0302.; *Eur J Pharmacol*. 2010;642(1-3):134–139. doi:10.1016/j.ejphar.2010.05.019

molecules

MDPI

Review

Mechanistic Aspects and Therapeutic Potential of Quercetin against COVID-19-Associated Acute Kidney Injury

Lúcio Ricardo Leite Diniz [1,*], Marilia Trindade de Santana Souza [2], Allana Brunna Sucupira Duarte [3] and Damião Pergentino de Sousa [3]

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2 Pharmacy Center, Uninassau University, 49075479 Aracaju, SE, Brazil; biomari@hotmail.com
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* Correspondence: luciodiniz@yahoo.com.br; Tel.: +55-75-3286-2268

Academic Editor: H.P. Vasantha Rupasinghe
Received: 10 November 2020; Accepted: 3 December 2020; Published: 7 December 2020

check for updates

Quercetin is effective in blocking or attenuating kidney lesions and dysfunctions caused by sepsis, diabetic nephropathy, ischemia/reperfusion as well as renal damage induced by varied nephrotoxic substances

Science of the Total Environment 801 (2021) 149719

Contents lists available at ScienceDirect

Science of the Total Environment

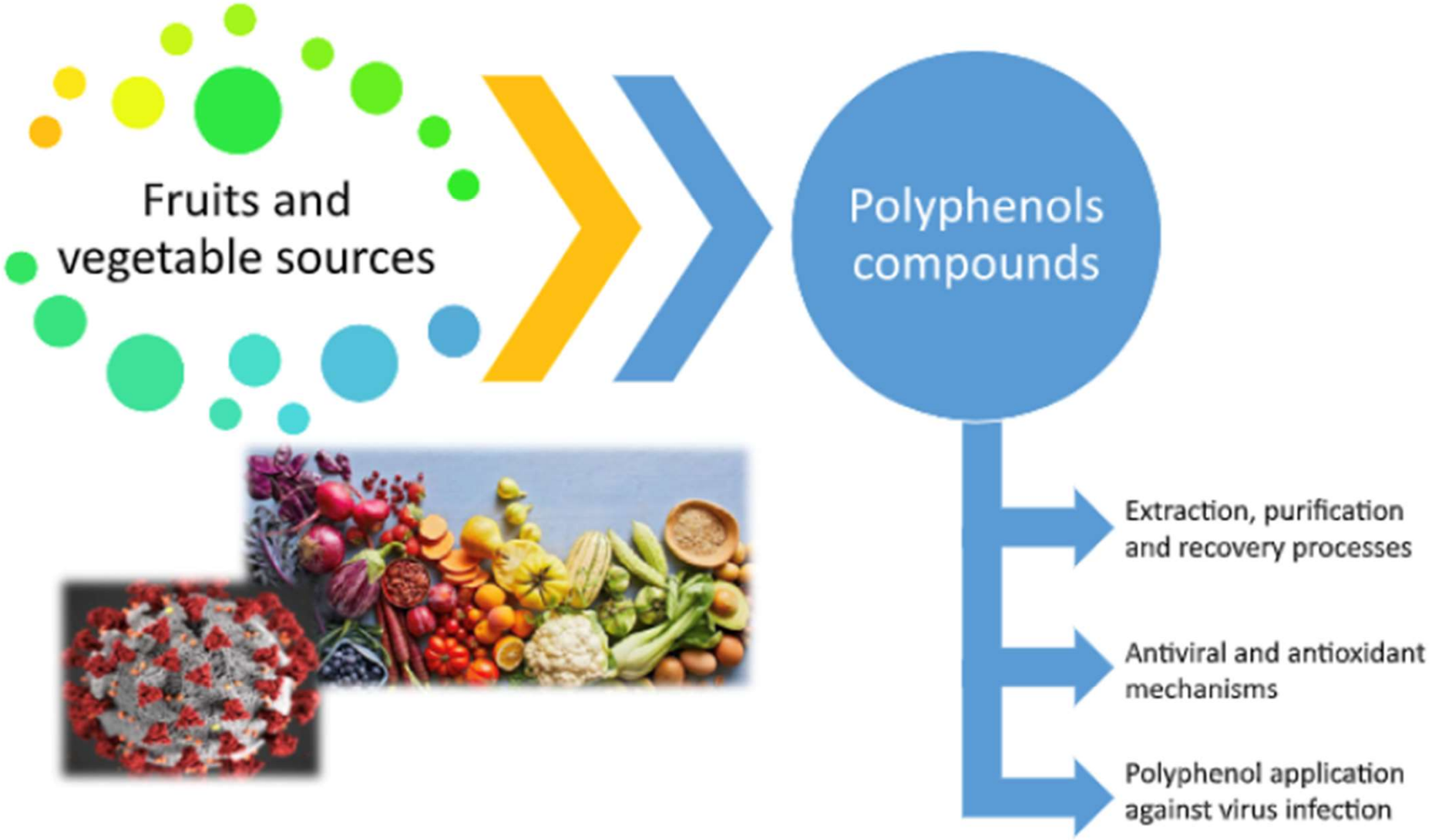
journal homepage: www.elsevier.com/locate/scitotenv



Review

Polyphenols and their potential role to fight viral diseases: An overview

María Fernanda Montenegro-Landívar [a,b], Paulina Tapia-Quirós [a,b], Xanel Vecino [a,b,c], Mònica Reig [a,b], César Valderrama [a,b], Mercè Granados [d], José Luis Cortina [a,b,e,*], Javier Saurina [d]



Sci Total Environ. 2021 Aug 19;801:149719. doi: 10.1016/j.scitotenv.2021.149719.

The action mechanism of hesperidin (citrus fruit) relies on its binding to the key entry or spike protein of SARS-CoV-2



Sci Total Environ. 2021 Aug 19;801:149719.
doi: 10.1016/j.scitotenv.2021.149719.
August 2021Nutrients 13(8):2800, DOI:
10.3390/nu13082800

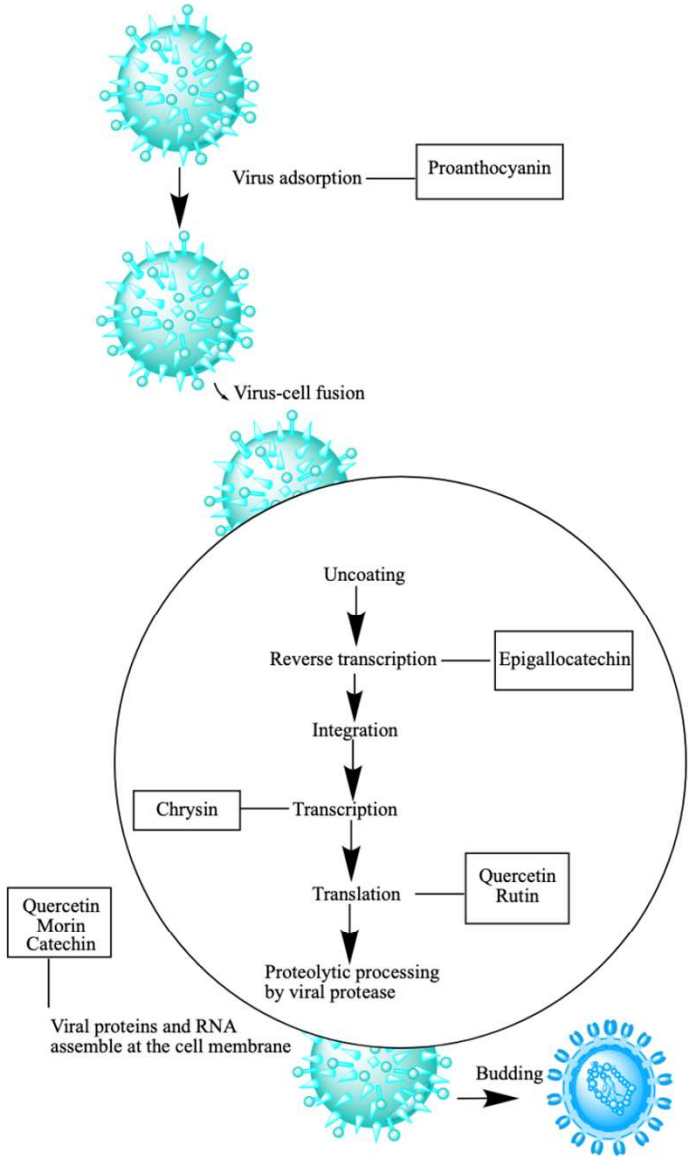


Fig. 1. Virus replication and polyphenol targets (adapted from Pommier et al., 2005; Kamboj et al., 2012).

N-acetylcysteine (NAC) for lung health

- **NAC** is a potent antioxidant that helps to replenish glutathione levels and reduce inflammation in your lungs
- Additionally, it is a protected and endured mucolytic agent that mellows tenacious mucous discharges. It has been used for treatment of various diseases
- NAC is effective at reducing acute attacks of chronic bronchitis
- A 2015 recent meta-analysis study was conducted to clarify the possible role of NAC in the treatment of patients with chronic bronchitis and chronic obstructive pulmonary disease.

CELL JOURNAL(Yakhteh), Vol 19, No 1, Apr- Jun (Spring) 2017; *Clinical Therapeutics*, 22(2):209-21; *European Respiratory Journal*, 16:253-62. *Eur Respir Rev*. 2015;24(137):451–461. doi:10.1183/16000617.00002215

Eur Respir J 1997; 10: 1535–1541
DOI: 10.1183/09031936.97.10071535
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European Respiratory Journal
ISSN 0903 - 1936

Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term N-acetylcysteine treatment

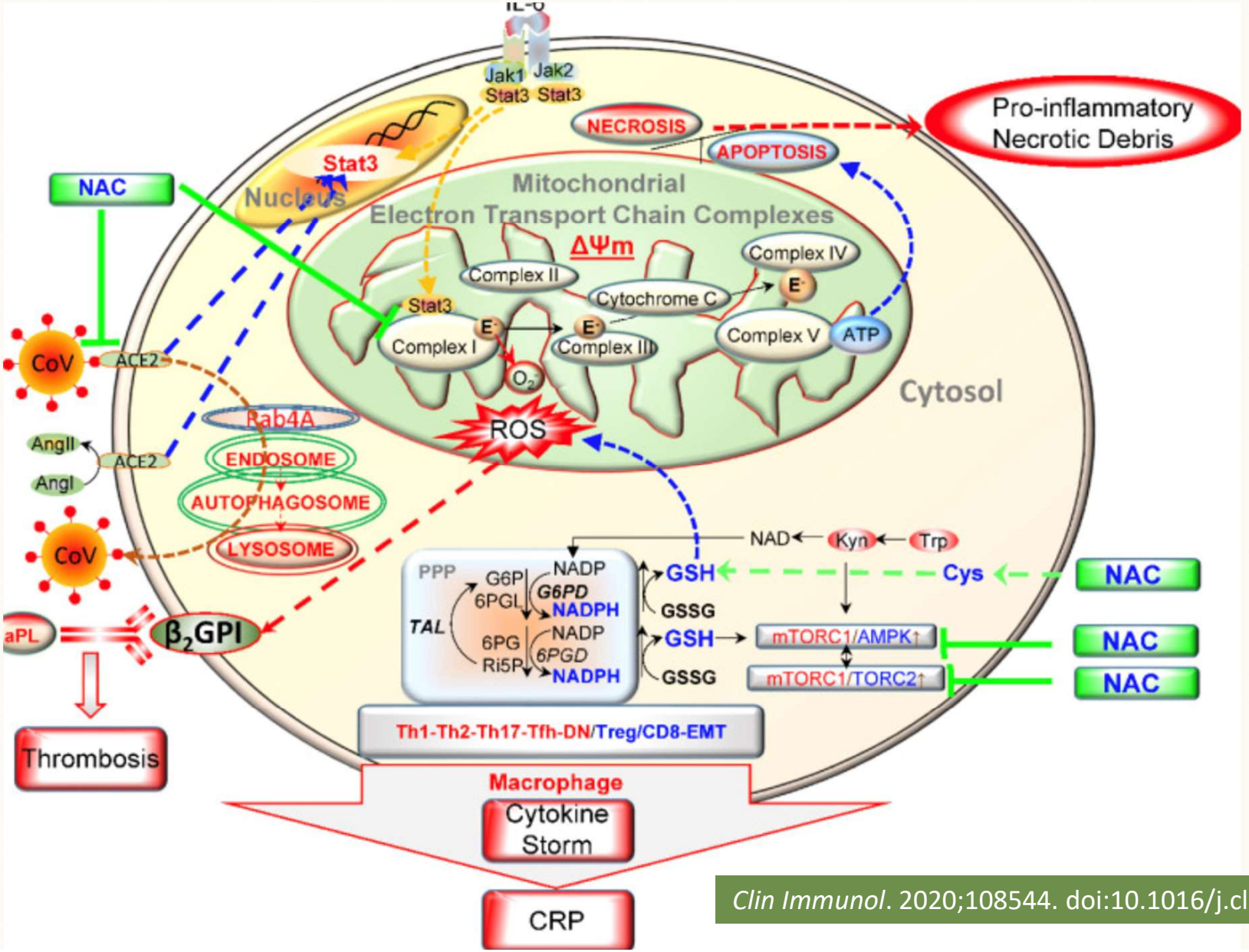
S. De Flora*, C. Grassi**, L. Carati+

- NAC has been in clinical use for more than 30 yrs as a mucolytic drug. It has also been proposed for and/or used in the therapy and/or prevention of several respiratory diseases and of diseases involving an oxidative stress,
- Both local and systemic symptoms of influenza and influenza-like episodes were sharply and significantly reduced in the NAC group.

NAC (n-acetylcysteine) IV - Therapeutic blockade of inflammation in severe COVID-19 infection

- NAC blocked hemolysis and elevation of liver enzymes, C-reactive protein (CRP), and ferritin and allowed removal from respirator and veno-venous extracorporeal membrane oxygenator and full recovery of the G6PD-deficient patient.
- NAC was also administered to 9 additional respirator-dependent COVID-19-infected patients without G6PD deficiency.
- NAC elicited clinical improvement and markedly reduced CRP in all patients and ferritin in 9/10 patients.
- NAC mechanism of action may involve the blockade of viral infection and the ensuing cytokine storm that warrant follow-up confirmatory studies in the setting controlled clinical trials.

Clin Immunol. 2020;108544. doi:10.1016/j.clim.2020.108544



Clin Immunol. 2020;108544. doi:10.1016/j.clim.2020.108544

Luteolin – Citrus Bioflavonoid



- A common flavonoid that exists in many types of foods and medicinal herbs including citrus fruit, cruciferous vegetables, artichoke, celery, thyme, parsley, peppermint, basil, green peppers, and chamomile
- Attenuates neutrophilic oxidative stress and inflammation
- **Inhibits furin and was shown to help in treating dengue virus**
- Induces viral and cancer cell apoptosis.

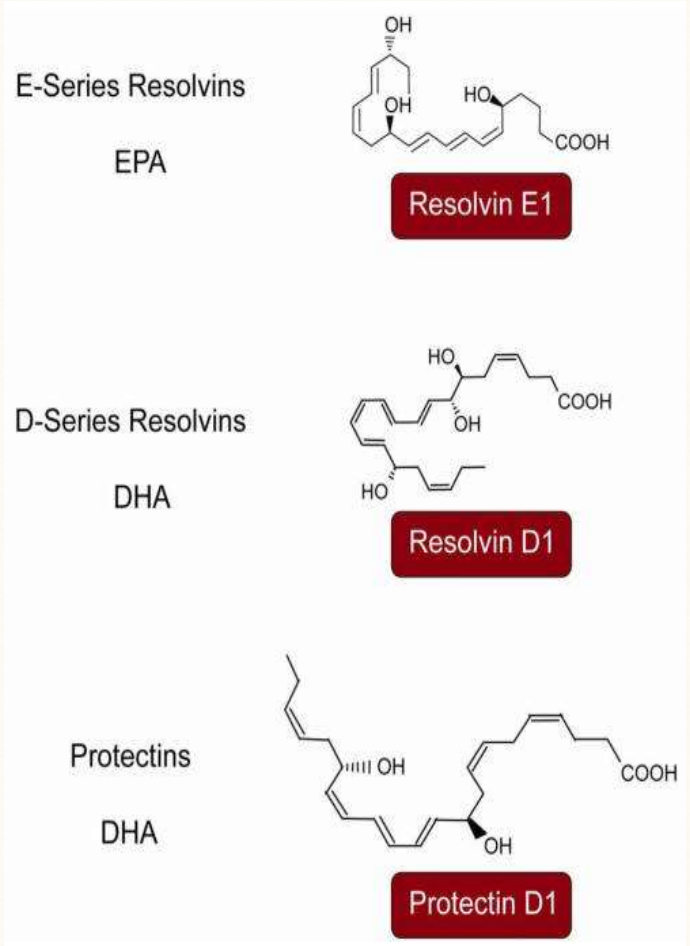
Highlights

- Extracts from 70 traditional Chinese medicine herbs were screened for antiviral activity.
- Luteolin was purified from the Chinese herb belonging to "heat clearing" class.
- Luteolin inhibits DENV 1–4 infection *in vitro* and DENV 2 infection in AG129 mice.
- Luteolin treatment reduces mature DENV particles production.
- The anti-DENV activity of luteolin is due to inhibition of pro protein convertase furin.

Attenuates neutrophilic oxidative stress and inflammation. Biochem Pharmacol 2018, Aug154 384 396, Antiviral Research Volume 143, July 2017, Pages 176-185

Fish oils fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

- Recent years have seen the discovery of a new class of inflammation-dampening and resolution-promoting n-3 PUFA-derived lipid mediators called resolvins and protectins.
- E-series resolvins are from EPA, while D-series resolvins and protectins are from DHA.
- Resolvins and protectins orchestrate inflammation resolution.



Weylandt KH, Chiu CY, Gomolka B, Waechter SF, Wiedenmann B. Omega-3 fatty acids and their lipid mediators: towards an understanding of resolvin and protectin formation. *Prostaglandins Other Lipid Mediat*. 2012;97(3-4):73-82. doi:10.1016/j.prostaglandins.2012.01.005; Bannenberg GL. Resolvins: Current understanding and future potential in the control of inflammation [published correction appears in Curr Opin Drug Discov Devel. 2010 Jan;13(1):136]. *Curr Opin Drug Discov Devel*. 2009;12(5):644-658; Levy BD. Resolvins and protectins: natural pharmacophores for resolution biology. *Prostaglandins Leukot Essent Fatty Acids*. 2010;82(4-6):327-332. doi:10.1016/j.plefa.2010.02.003

Melatonin and Viral Infections

- The immunomodulatory, antioxidant, and neuroprotective effects of melatonin suggest that this indole must be considered as an additional therapeutic alternative to fight viral diseases
- Its role in promoting sleep and circadian rhythms regulation, has important immunomodulatory, antioxidant, and neuroprotective effects suggest that this indole must be considered as a therapeutic alternative against infections
- Consider 1-3 mg. of Melatonin before bed, particularly for older patients

Bonilla E, Valero N, Chacín-Bonilla L, Medina-Leendertz S. Melatonin and viral infections. *J Pineal Res*. 2004;36(2):73–79. doi:10.1046/j.1600-079x.2003.00105.x

Life Sciences 250 (2020) 117583

Contents lists available at ScienceDirect

Life Sciences

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

COVID-19: Melatonin as a potential adjuvant treatment

Rui Zhang[a], Xuebin Wang[a], Leng Ni[a], Xiao Di[a], Baitao Ma[a], Shuai Niu[a], Changwei Liu[a,*], Russel J. Reiter[b,**]

[a] Department of Vascular Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

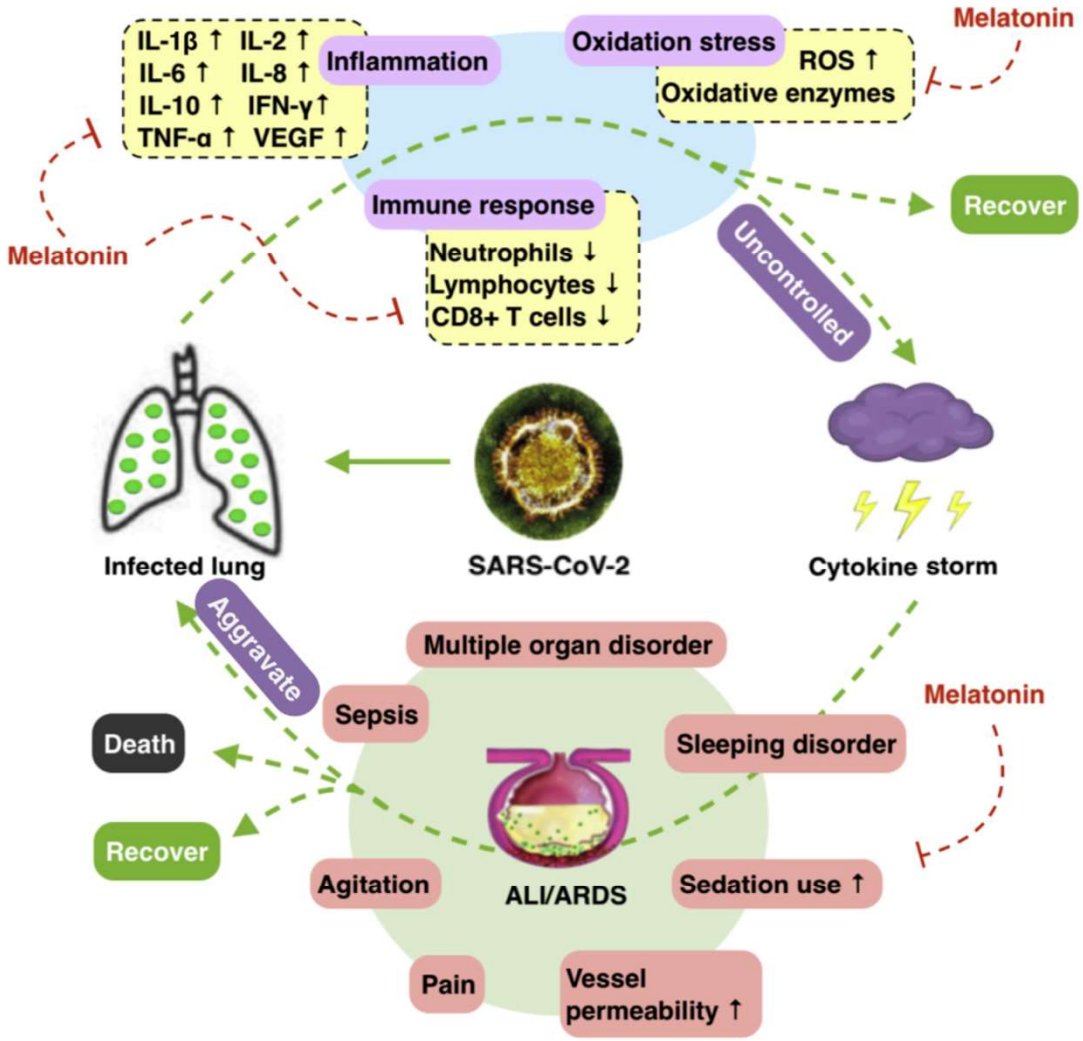
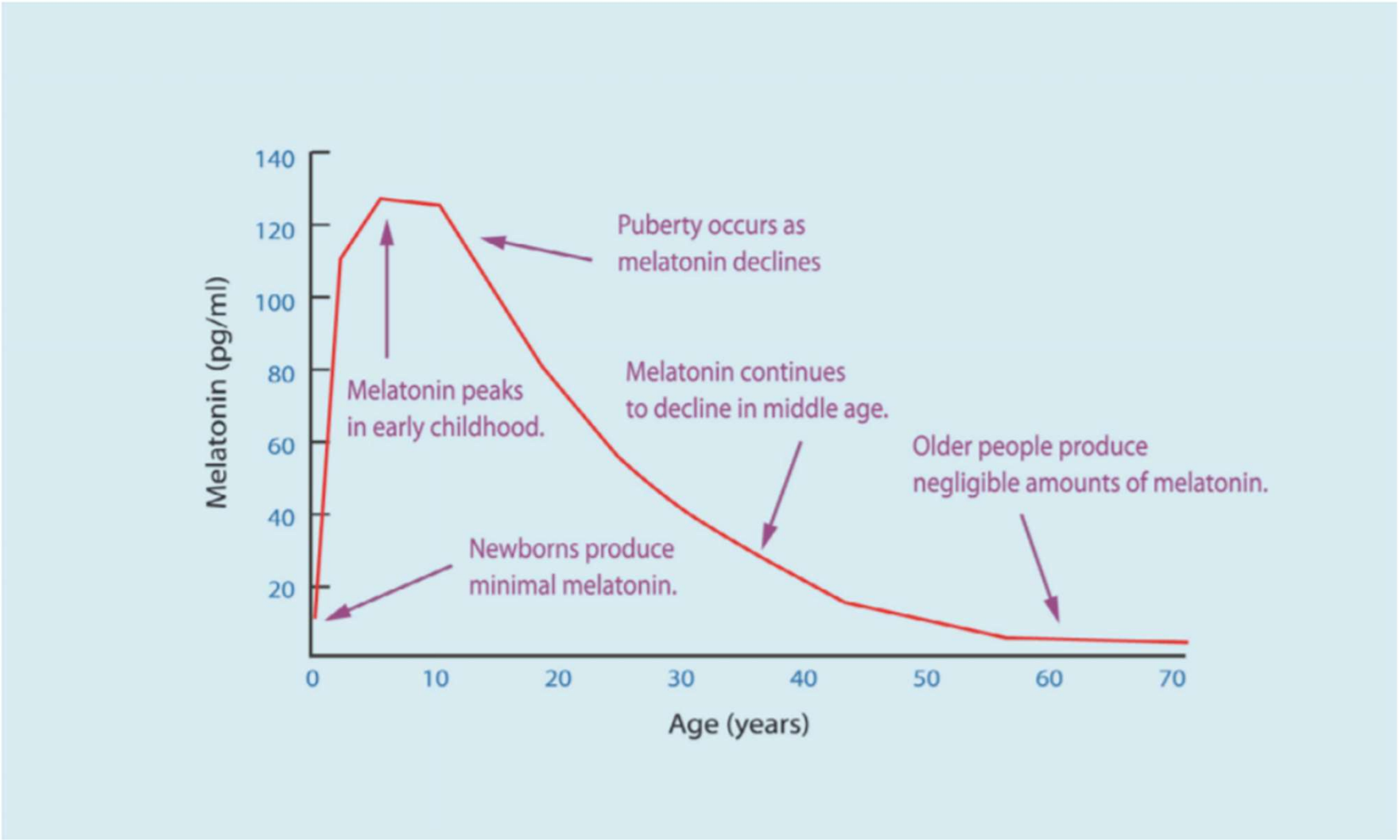


Fig. 1. Pathogenesis of COVID-19 and potential adjuvant use of melatonin. We postulated that lungs infected by SARS-CoV-2, and a suppressed immune response, elevated inflammation and excessive oxidation stress proceed unabated, this results in the activation of the cytokine storm. ALI/ARDS may ensue, accompanied by a series of complications, the outcomes of which vary according to the severity of the disease. Melatonin may play a role of adjuvant medication in the regulation of immune system, inflammation and oxidation stress, and provide support for patients with ALI/ARDS and related complications. ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome.



Grivas TB, Savvidou OD. Melatonin the "light of night" in human biology and adolescent idiopathic scoliosis. Scoliosis. 2007;2:6. Published 2007 Apr 4. doi:10.1186/1748-7161-2-6

Melatonin Inhibits NLRP3 Inflammasomes

- Melatonin might the reason why children under the age of 9 seldom exhibit severe symptoms. In fact, children may exhibit mild or even no symptoms at all, even though they have been infected by SARS-CoV-2
- The NLRP3 inflammasome has an interesting nickname of “Pandora’s Box for Sepsis”
- An excellent study by Volt et al (2016) showed that chronic low doses of melatonin in aged mice could prevent increase in inflammation, ROS and mitochondria impairments reflective of inflammaging
- Melatonin receptor agonist protects against acute lung injury induced by ventilator through up-regulation of IL-10 production

Inflammasomes: Pandora’s box for sepsis https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6294171/ | Respiratory Research | Full Text https://respiratory-research.biomedcentral.com/articles/10.1186/s12931-020-1325-2

van de Veerdonk and Netea *Critical Care* (2020) 24:445
https://doi.org/10.1186/s13054-020-03166-0

Critical Care

REVIEW Open Access

Blocking IL-1 to prevent respiratory failure in COVID-19

Frank L. van de Veerdonk[1*] and Mihai G. Netea[1,2*]

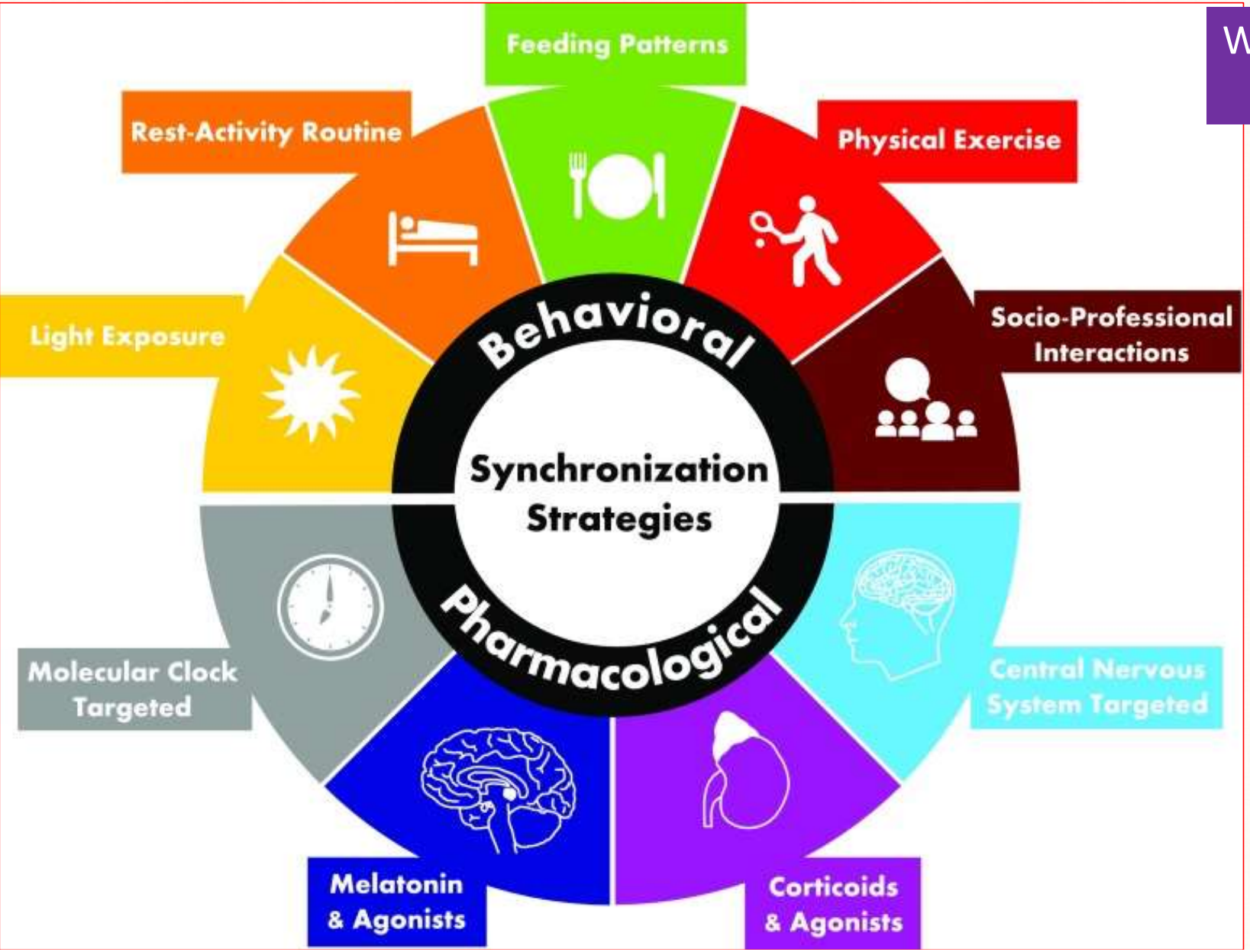
Received: 29 June 2020 | Revised: 1 July 2020 | Accepted: 2 July 2020

DOI: 10.1002/prp2.631

REVIEW

Hypothesis: Pentoxifylline is a potential cytokine modulator therapeutic in COVID-19 patients

Bruce M. Hendry[1] | Nina Stafford[2] | Ahran D. Arnold[3] | Arvind Sangwaiya[2] | Vijay Manglam[2] | Stuart D. Rosen[3] | Jayantha Arnold[2]



Ways to Boost and Restore Circadian Rhythms

- A nutritiously-rich and balanced breakfast
- Get early morning sun, or use a light box
- **Vitamin D (DAK)**
- **Melatonin (1-3 mg.)**
- Exercise
- Fresh air
- Limit (Wi-Fi) screen time in the evening
- Set a bedtime between 10-12
- Sleep at night in the dark

Important Foods and Recipes for Immune Health

- Allium family of vegetables, specific onions, leeks, and garlic
- Horse radish – a specific food I recommend
- Fermented foods – Hard cheeses, kimchi, sauerkraut, Miso
- Beets, cooked greens (nettles is #1), carrots, celery, celery root, artichoke, asparagus
- Fruit: pears (poached with ginger, honey, orange slices and a cinnamon stick), tomato (sauce), citrus fruit – lemon, orange, tangerine, lime etc. Fruit and peel) ; pomegranate
- Fresh OJ is rich in vitamin c, hesperetin and luteolin.
- Whole grains (bread), and Potatoes (Potato leek soup)
- Apple cider drink – to make combine ¼ cup vinegar, ¼ lemon juice, ¼ raw honey, 1 tsp. ginger juice [can also add ½ tsp. Horse radish juice], and 1-quart water, or a tea-blend Drink 3-4 oz with before or during meals
- Omega-3 rich fish, nuts and seeds rich in ALA
- Raw honey and black strap molasses
- Hot and Sour soup and Immune Bone Marrow soup
- Herbs: fresh ginger, and dried oregano, thyme and mustard

Foods for the Lung-Oxygen Network

- Foods rich in carotenoids and Chlorophyll
- Persimmon is one such food that moistens the lungs. The carotenoids lutein and zeaxanthin enhance lung function. High carotenoid intake appears to reduce the signs of lung aging by about one to two years, according to a population-based study
- Another study showed that from the six major serum carotenoids studied, alpha-carotene, beta-carotene, and lycopene were positively associated with lung function in the elderly

Pears cooked with ginger, orange peel and honey

Am J Epidemiol. 2002 Mar 1;155(5):463-71; (Am J Respir Crit Care Med. 2000 Mar;161(3 Pt 1):790-5.

Horse Radish
(*CochlleariaArmoracia* or *Armorac ia Rusticana*)

- Horseradish was one of the five bitter herbs (along with coriander, horehound, lettuce, and nettle) eaten historically during the feast of the Passover; in present times, horseradish is still commonly used in the Passover Seder.
- Is rich in vitamins, minerals, and isothiocyanates. (27 all together); The vitamin C content of horseradish can be up to 350 mg per 100 g of fresh horseradish root
- Effective for respiratory and sinus health and also shown to help in managing hypertension and promotes the metabolism – reducing excess body weight.
- Try some horse radish mustard in salad dressing or with artichokes, I use it daily myself.



International Scholarly and Scientific Research & Innovation 6(4) 2012;https://fdc.nal.usda.gov/fdcapp.html#/?query=ndbNumber:2055

Emerging Microbes & Infections
2021, VOL. 10
https://doi.org/10.1080/22221751.2021.1957720



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Lentil lectin derived from *Lens culinaris* exhibit broad antiviral activities against SARS-CoV-2 variants

Wenbo Wang[a], Qianqian Li[b,c], Jiajing Wu[b,d], Yu Hu[e,f], Gang Wu[a], Chuanfei Yu[a], Kangwei Xu[g], Xumei Liu[a,h], Qihui Wang [e], Weijin Huang[b], Lan Wang[a] and Youchun Wang[b]

- The Lens culinaris-derived lentil lectin shows potent and broad antiviral
- activity against a panel of mutant strains and variants, including the artificial mutants at N-/O-linked glycosylation site, natural existed amino acid mutants, as well as the epidemic variants B.1.1.7, B.1.351, and P.1.
- Lentil lectin also showed antiviral activity against SARS-CoV and MERS-CoV.
- Lentil lectin could block the binding of ACE2 to S trimer and inhibit SARS-CoV-2 at the early steps of infection.

Beetroot Juice (BRJ) for Hypertension: A Systematic Review

- A review of 11 studies found that BRJ supplementation is a cost-effective strategy that might reduce blood pressure in different populations, probably through the nitrate/nitrite/nitric oxide (NO3/NO2 /NO) pathway and secondary metabolites found in Beta vulgaris
- Nitric oxide enhancement aids in antiviral immunity as well
- Fresh grated beet root with horse radish (eaten during Passover and Lent) could be an effective "food as medicine" for Cardio health, organ protection and detoxification, and as immune system support
- The ratio of horseradish to **beets** is generally 1 to 3



Biomolecules 2018, 8, 134; doi:10.3390/biom8040134

Antiviral Activities of Mulberry (*Morus alba*) Juice and Seed against Acute Respiratory Viruses (ARV)



- Mulberry juice suppressed several ARV (A/Brisbane/59/2007 (H1N1) (BR59), pandemic A/Korea/01/2009(H1N1) (KR01), A/Brisbane/10/2007(H3N2) (BR10), and B/Florida/4/2006)
- Pre- and cotreatment of virus, MAJ showed antiviral effects against BR59, KR01, and FL04 in a dose-dependent manner. In particular, MAJ at 4% concentration exhibited 1.3 log inhibition in the pre- and cotreatment of the virus against FL04, a type B virus
- Mulberry contains Morin, a bioflavanol that has demonstrated a potent anti-inflammatory effect against gout and other inflammatory diseases
- Morin specific reduces IL-1B, IL-6 and TNF-Alpha.

Evid Based Complement Alternat Med. 2018 Nov 1;2018:2606583. doi: 10.1155/2018/2606583. eCollection 2018;
European Journal of Pharmacology 786 (2016) 116–127

Biomedicine & Pharmacotherapy 133 (2021) 110974

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

Review

Kefir: A protective dietary supplementation against viral infection

Reham Samir Hamida [a], Ashwag Shami [b], Mohamed Abdelaal Ali [c], Zakiah Nasser Almohawes [b], Afrah E. Mohammed [b,*], Mashael Mohammed Bin-Meferij [b,*]

- The antiviral mechanisms of kefir involve enhancement of macrophage production, increasing phagocytosis, boosting production of cluster of differentiation-positive ($CD4^+$), $CD8^+$, IgG^+ and IgA^+ B cells, T cells, neutrophils, as well as cytokines (e.g., IL-2, IL-12, interferon gamma-γ). Kefir can act as an anti-inflammatory agent by reducing expression of IL-6, IL-1, TNF-α, and interferon-γ.
- Hence, kefir might be a significant inhibitor of the 'cytokine storm' that contributes to COVID-19.

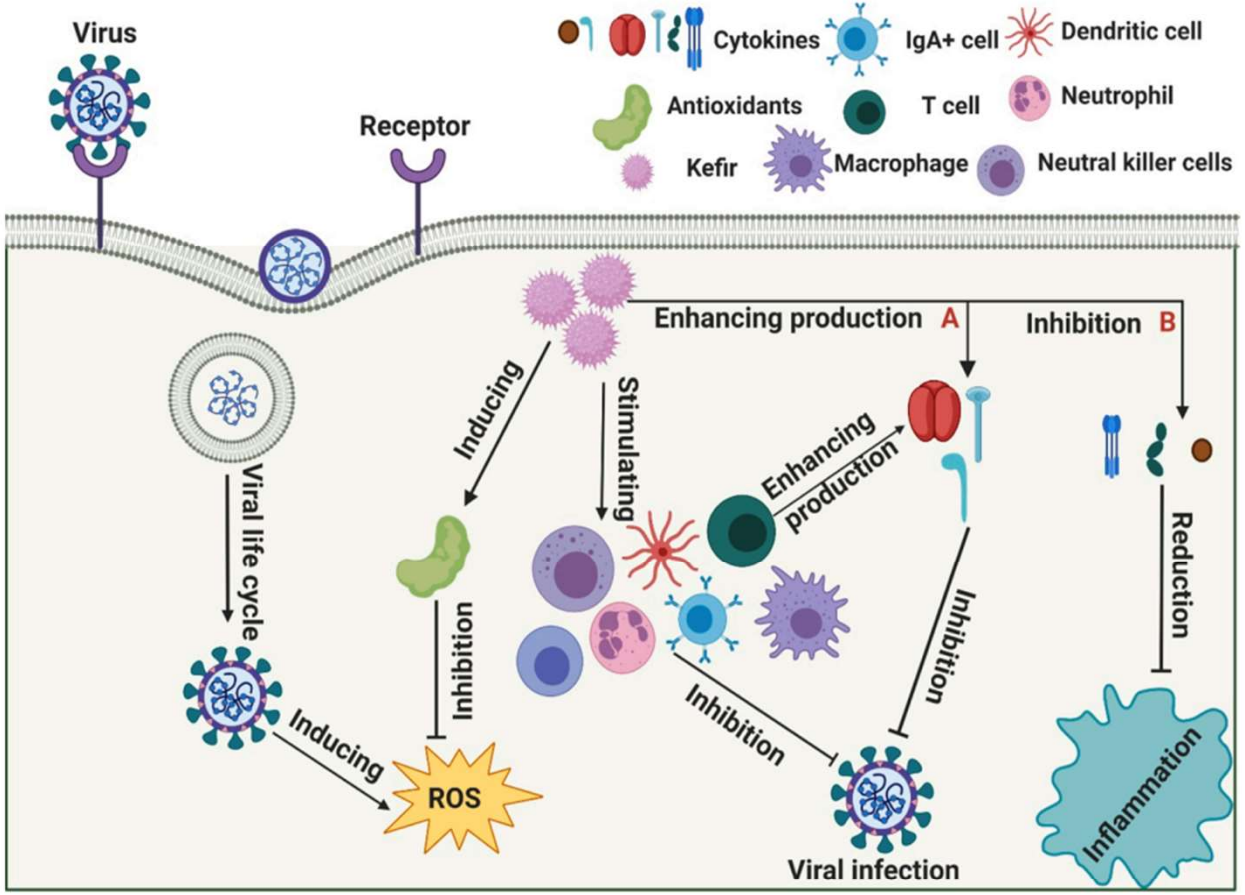


Fig. 3. Potential mechanism of action of kefir against viral infection. (**A**) Kefir enhances the immune response by stimulating cytokine production, including interferon gamma (IFN-γ), interleukin (IL)-2, and IL-12. (**B**) Kefir inhibits the inflammatory response by suppressing cytokine production, such as IL-6, IL-1 and tumour necrosis factor (TNF)-α.

Hamida RS, Shami A, Ali MA, Almohawes ZN, Mohammed AE, Bin-Meferij MM. Kefir: A protective dietary supplementation against viral infection. Biomed Pharmacother. 2021 Jan;133:110974. doi: 10.1016/j.biopha.2020.110974. Epub 2020 Nov 11. PMID: 33186795; PMCID: PMC7655491.

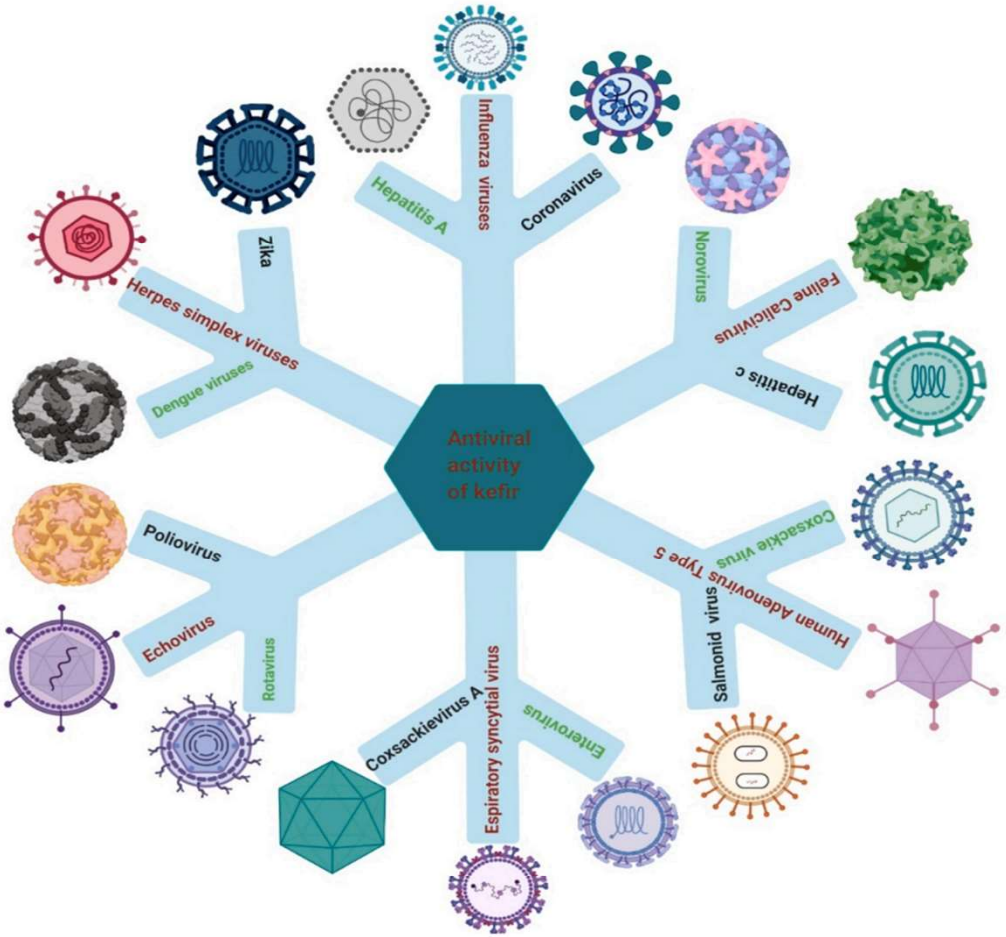


Fig. 4. Antiviral activities of kefir.

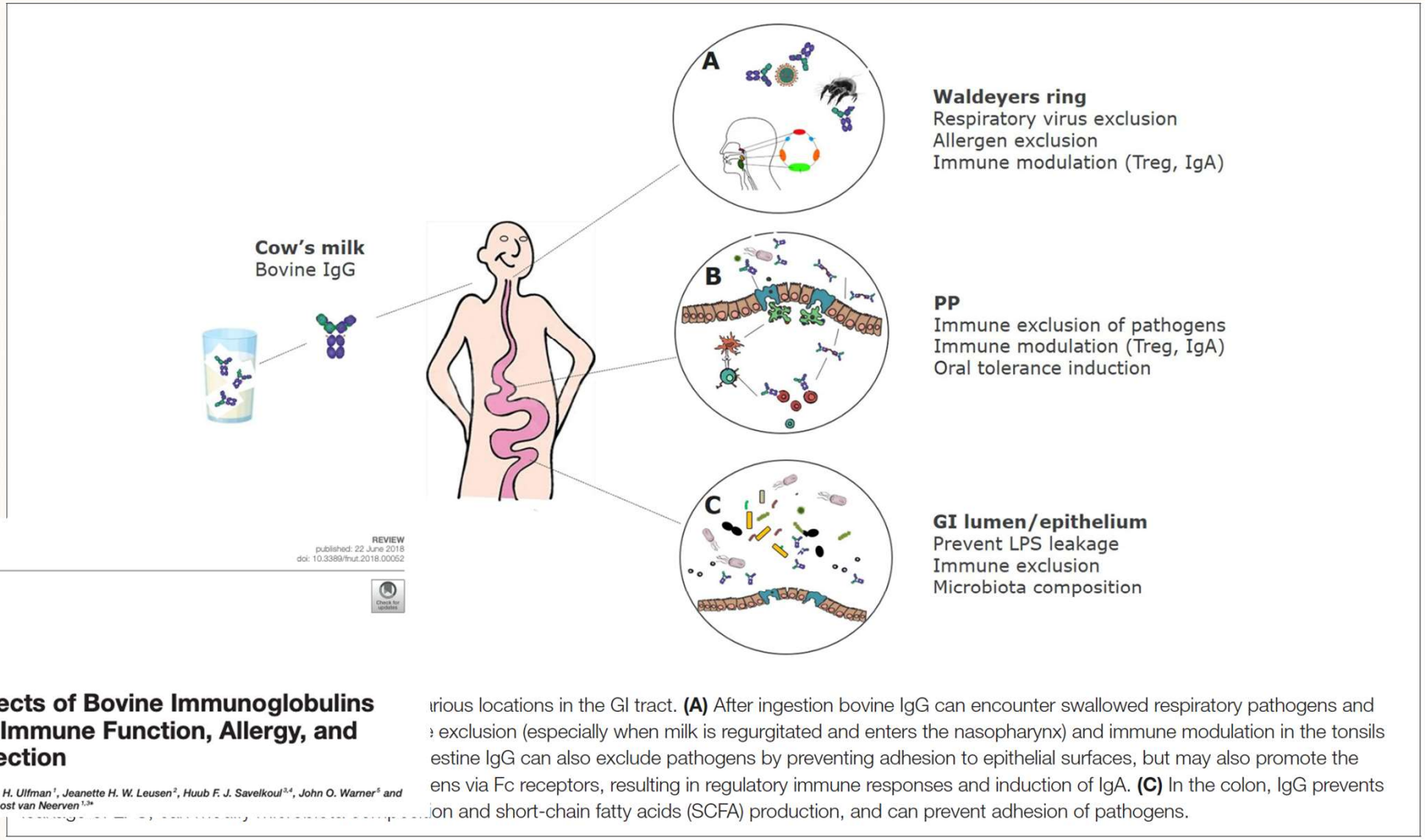
Hamida RS, Shami A, Ali MA, Almohawes ZN, Mohammed AE, Bin-Meferij MM. Kefir: A protective dietary supplementation against viral infection. Biomed Pharmacother. 2021 Jan;133:110974. doi: 10.1016/j.biopha.2020.110974. Epub 2020 Nov 11. PMID: 33186795; PMCID: PMC7655491.

Whey Protein Concentrate (WPC) Supplementation Improves Nutritional Status, Glutathione Levels, and Immune Function in Cancer Patients: A Randomized, Double-Blind Controlled Trial

- A total of 42 cancer patients (41-63 years old) who received intravenous chemotherapy were randomized in a double-blind controlled trial at the National Cancer Institute in Thailand.
- WPC supplementation significantly increased albumin (2.9%) and immunoglobulin G (4.8%) levels compared to the control group at week 12. Controls showed a significantly lower percent change in GSH levels (6.0%), whereas there was a significant time-dependent increase in the intervention group (11.7%).
- WPC supplementation improved nutrition status scores in the intervention group compared to the control.
- These data indicate that whey protein supplementation can increase GSH levels and improve nutritional status and immunity in cancer patients undergoing chemotherapy.

J Med Food. 2018 Jun;21(6):612-616. doi: 10.1089/jmf.2017.4080.

Oral bovine immunoglobulins are a promising approach to support immune function in vulnerable groups such as infants, children, elderly and immunocompromised patients.



frontiers in Nutrition

REVIEW
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Effects of Bovine Immunoglobulins on Immune Function, Allergy, and Infection

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...rious locations in the GI tract. **(A)** After ingestion bovine IgG can encounter swallowed respiratory pathogens and ...e exclusion (especially when milk is regurgitated and enters the nasopharynx) and immune modulation in the tonsils ...estine IgG can also exclude pathogens by preventing adhesion to epithelial surfaces, but may also promote the ...ens via Fc receptors, resulting in regulatory immune responses and induction of IgA. **(C)** In the colon, IgG prevents ...ion and short-chain fatty acids (SCFA) production, and can prevent adhesion of pathogens.

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THE EFFECT OF DIETARY SUPPLEMENTATION WITH n−3 POLYUNSATURATED FATTY ACIDS ON THE SYNTHESIS OF INTERLEUKIN-1 AND TUMOR NECROSIS FACTOR BY MONONUCLEAR CELLS

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Abstract We examined whether the synthesis of interleukin-1 or tumor necrosis factor, two cytokines with potent inflammatory activities, is influenced by dietary supplementation with n−3 fatty acids.

Nine healthy volunteers added 18 g of fish-oil concentrate per day to their normal Western diet for six weeks. We used a radioimmunoassay to measure interleukin-1 (IL-1β and IL-1α) and tumor necrosis factor produced in vitro by stimulated peripheral-blood mononuclear cells. With endotoxin as a stimulus, the synthesis of IL-1β was suppressed from 7.4±0.9 ng per milliliter at base line to 4.2±0.5 ng per milliliter after six weeks of supplementation (43 percent decrease; $P = 0.048$). Ten weeks after the end of n−3 supplementation, we observed a further decrease to 2.9±0.5 ng per milliliter (61 percent decrease; $P = 0.005$). The production of IL-1α and tumor necrosis factor responded in a similar manner. Twenty weeks after the end of supplementation, the production of IL-1β, IL-1α, and tumor necrosis factor had returned to the presupplement level. The decreased production of interleukin-1 and tumor necrosis factor was accompanied by a decreased ratio of arachidonic acid to eicosapentaenoic acid in the membrane phospholipids of mononuclear cells.

We conclude that the synthesis of IL-1β, IL-1α, and tumor necrosis factor can be suppressed by dietary supplementation with long-chain n−3 fatty acids. The reported antiinflammatory effect of these n−3 fatty acids may be mediated in part by their inhibitory effect on the production of interleukin-1 and tumor necrosis factor. (N Engl J Med 1989; 320:265-71.)



frontiers in Human Neuroscience

SYSTEMATIC REVIEW
published: 07 September 2018
doi: 10.3389/fnhum.2018.00353

Check for updates

How Breath-Control Can Change Your Life: A Systematic Review on Psycho-Physiological Correlates of Slow Breathing

*Andrea Zaccaro[1], Andrea Piarulli[1,2], Marco Laurino[3], Erika Garbella[4], Danilo Menicucci[1], Bruno Neri[5] and Angelo Gemignani[1,3,6]**

- Slow breathing techniques enhance autonomic, cerebral and psychological flexibility in a scenario of mutual interactions
- There is evidence that links the parasympathetic activity (increased HRV and Respiratory Sinus Arrhythmia power), and the CNS activities to emotional control and psychological well-being in healthy subjects
- Humming appears to increase nitric oxide concentration in the nasal passages and sinuses

Weitzberg, Eddie, and Jon ON Lundberg. "Humming greatly increases nasal nitric oxide." American journal of respiratory and critical care medicine 166.2 (2002): 144-145.)

Chanting, Hymn Singing, Humming and Even Joyful Energetic Singing all Increase Vagus Nerve and HRV

- Singing, in general seems to promote more well-being
- Choir singing is known to promote wellbeing. One reason for this may be that singing demands a slower than normal respiration, which may in turn affect heart activity.
- Song structure, respiration and HR are connected.
- Unison singing of regular song structures makes the hearts of the singers accelerate and decelerate simultaneously.

Grape C, Sandgren M, Hansson LO, Ericson M, Theorell T. Does singing promote well-being?: An empirical study of professional and amateur singers during a singing lesson. Integr Physiol Behav Sci. 2003 Jan-Mar;38(1):65-74; Björn Vickhoff* Helge Malmgren, Rickard Åström, Gunnar Nyberg, Seth-Reino Ekström, Mathias Engwall, Johan Snygg, Michael Nilsson, and Rebecka Jörnsten Music structure determines heart rate variability of singers, Front Psychol. 2013; 4: 334.









Effect of ‘Rosary Prayer’ and ‘Mantras’ on Autonomic Cardiovascular Rhythms

- Both prayer (reciting the rosary prayer) and mantra caused striking and powerful effects in stabilizes the respiratory rate and cardiovascular rhythms
- Rhythm formulas that involve breathing at six breaths per minute induce favorable psychological and possibly physiological effects

Bernardi L, Sleight P, Bandinelli G, Cencetti S, Fattorini L, Wdowczyc-Szulc J, Lagi A., BMJ. 2001 Dec 22-29;323(7327):1446-9.





Health Benefits of Laughter and Cold Water

- As the saying goes, laughter is the best medicine. Many studies show health benefits from laughing.
- Laughter is capable of stimulating the vagus nerve.
- A study done on yoga laughter found increased HRV in the laughter group.
- Studies show that when your body adjusts to cold, your fight or flight (sympathetic) system declines and your parasympathetic system increases.

Michael Miller, M. D. and William F. Fry, M. D. The Effect of Mirthful Laughter on the Human Cardiovascular System, Med Hypotheses. 2009 Nov; 73(5): 636. Dolgoff-Kaspar R, Baldwin A, Johnson MS, Edling N, Sethi GK. Effect of laughter yoga on mood and heart rate variability in patients awaiting organ transplantation: a pilot study, Altern Ther Health Med. 2012 Sep Oct;18(5):61-6.

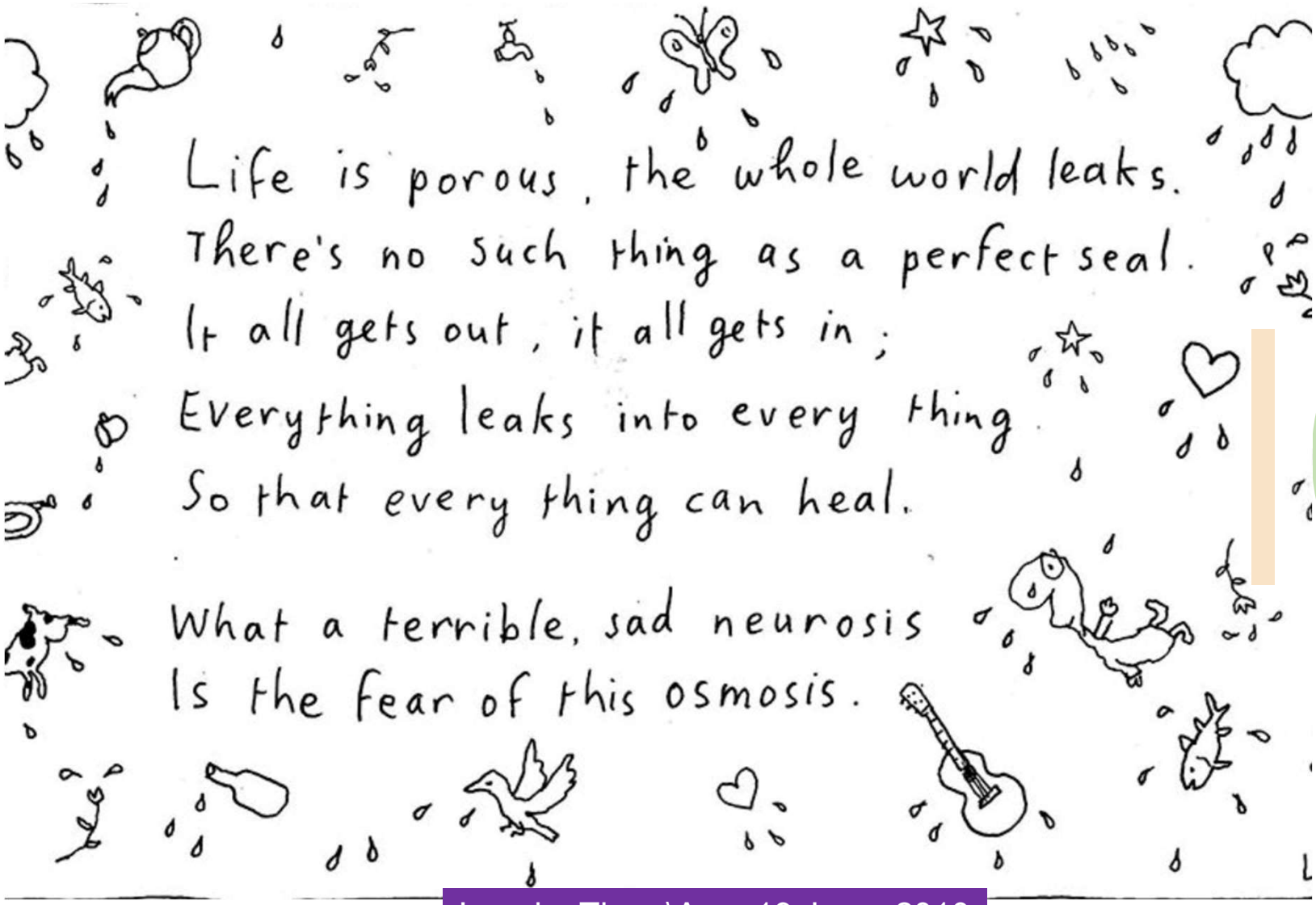
Laughter may help to strengthen the immune system against viruses



- Laughter stimulates the body's organs by increasing oxygen intake to the heart, lungs and muscles, and triggers the release of endorphins
- It also helps people handle stress by easing tension, relaxing the muscles and lowering blood pressure
- Considering the pandemic that our world is currently facing, the most important thing is that laughter increases immune cells and infection-fighting antibodies, thus improving our resistance to disease

Sparks, Dana, Mayo Mindfulness: The health benefit of laughter, July 11, 2018, https://newsnetwork.mayoclinic.org/discussion/mayo-mindfulness-the-health-benefit-of-laughter/ retrieved March 23, 2020.
Lawrence Robinson, Melinda Smith, M.A., and Jeanne Segal, Ph.D. Last updated: November 2019, Laughter is the Best Medicine, https://www.helpguide.org/articles/mental-health/laughter-is-the-best-medicine.htm, retrieved March 23, 2020.


Milton, let's play!
Wake up! It's play time!
Milton, come on! I'm bored!
Quarantine Log Day 4: With the human home all the time I can only get 15 hours of naps in. I fear I am growing delirious from lack of sleep
@meowingtonsco



Leunig: The a\Age, 19 June, 2010

Everything is connected