MONTREAL HEART INSTITUTE

THE HESPERIDIN STUDY

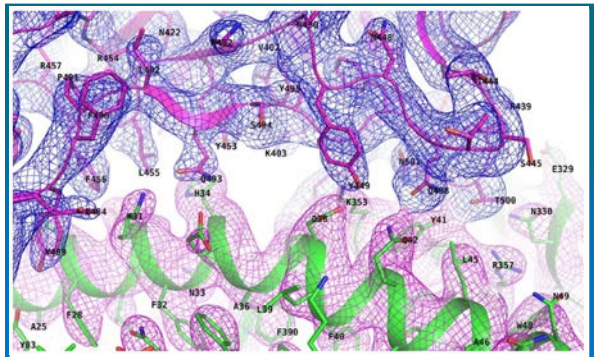
Hesperidin to reduce the severity of illness and requirement for hospitalization

A randomized, double-blind, placebo-controlled study of hesperidin therapy on COVID-19 symptoms

Inhibit Entry/Replication of SARS-CoV-2
AND
Modulate Cytokine Storm

ingenew

Based on an Extensive Review of Recent and Historical Scientific/Medical Literature
Focused on SARS-CoV/SARS-CoV-2/COVID-19



Spike(S) Protein and hACE2 Receptor

Shang, J., Ye, G., Shi, K. et al. Nature 581, 221–224 2020

Scientific Rationale

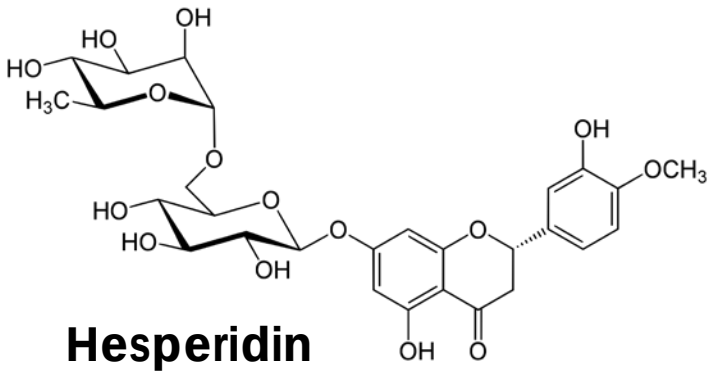
Comprehensive

Montreal, February 16 , 2020

The Hesperidin Study

Overview

A Double-Blind Placebo-Controlled Study Evaluating the Ability of Hesperidin to Reduce the Severity of Illness and Requirement for Hospitalization in COVID-19



Hesperidin

To reduce SARS-CoV-2 viral load and Cytokine Storm for 14 days

https://www.cbc.ca/news/world/wuhan-health-officials-raise-death-toll-linked-to-covid-19-by-50-1.5535543

The Hesperidin Study to Reduce the Burden on the Healthcare System

The objective of the search was to find a compound capable of reducing the severity of illness and requirement for hospitalization in COVID-19

Reduce the viral load, inflammation and potential cytokine storm to reduce risk of hospitalization

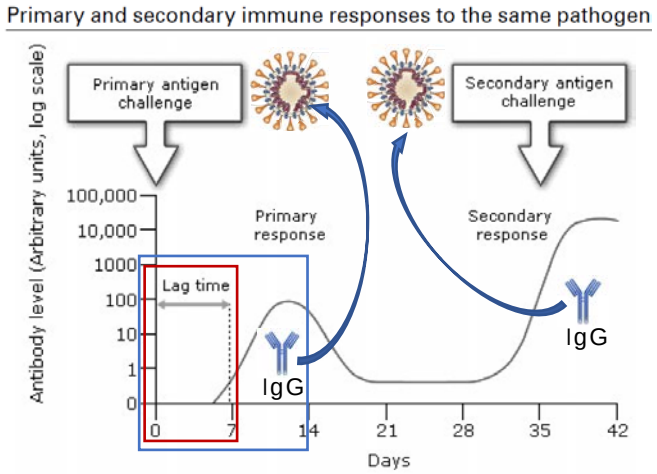
Assumptions: **1** **2** **3**

COVID-19 pandemic

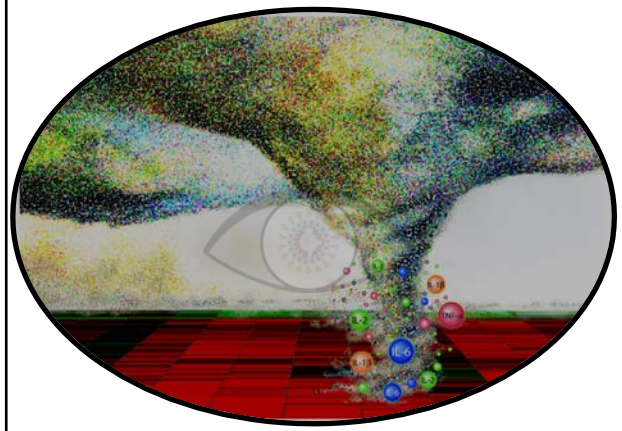
A non-controlled infection/immunization/ vaccination program on a global scale using SARS-CoV-2 as the immunogen

Adaptive Immune Response

The lag time period plays a key role



Inflammation and Cytokine Storm



Objectives: Treat the infection, inflammation and cytokine storm for 14 days starting on the day of onset:

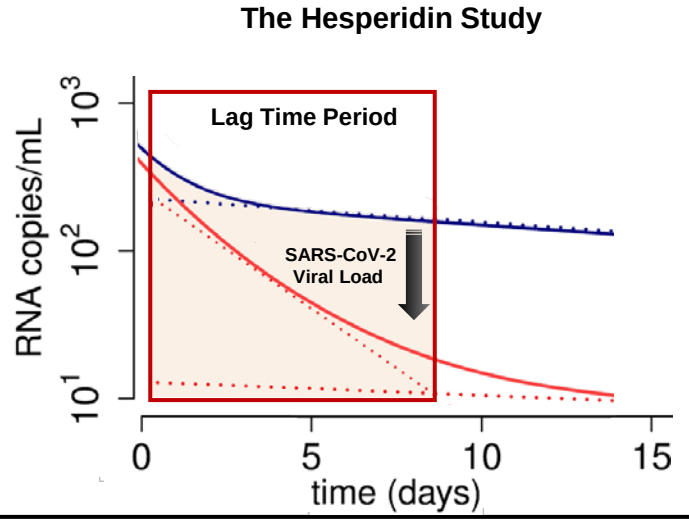
- **To reduce the viral load during the post-incubation stages of the infection, especially the lag time period, in COVID-19 patients**
  - By inhibiting the entry and replication of SARS-CoV-2
- **To reduce the requirement for hospitalization of COVID-19 patients**
  - By decreasing the levels of inflammatory mediators, cytokine storm and potential cardiovascular, lungs and/or neurological injuries

https://www.cbc.ca/news/world/wuhan-health-officials-raise-death-toll-linked-to-covid-19-by-50-1.5535543
Mort M. et al.; 2013 WHO Vaccine Safety Basics; Learning Manual 207 pages
Tisoncik J.R.,et al.; Microbiol Mol Biol Rev. 2012 Mar; 76(1): 16–32

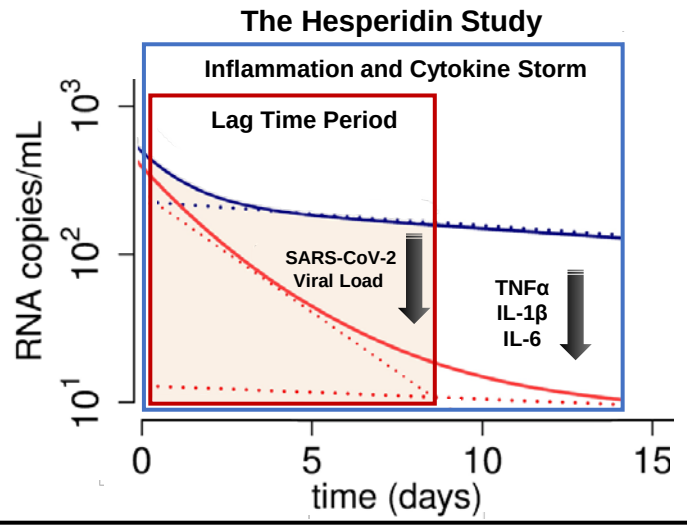
Hesperidin: Two independent mechanisms which may reduce the severity of illness in COVID-19 patients infected with SARS-CoV-2

Multiple scientific papers presented evidences of the 2 mechanisms…with >80 papers on the benefits in inflammation

To reduce the viral load during the initial stages of the infection by inhibiting the entry of SARS-CoV-2 into cells and its subsequent replication, thereby gaining time for the patient to mount an effective immune response

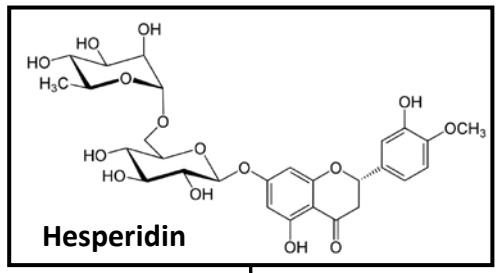


Reduce the incidence and severity of cytokine storm by modulating the inflammatory mediators in COVID-19



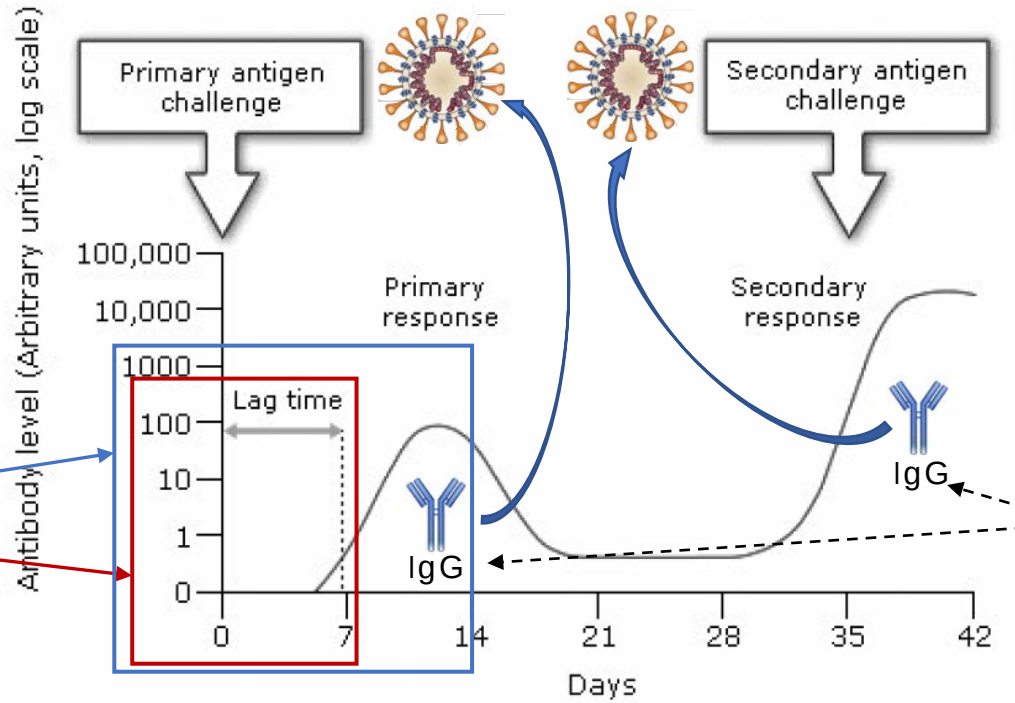
Hesperidin (1g/BID) provides a plasma concentration anticipated to inhibit SARS-CoV-2, thus reducing its viral load and cytokine storm in COVID-19 patients

Allows for the primary immune response to develop antibodies and mount an effective response to SARS-CoV-2



Clinical trial Product
Hesperidin:500mg/capsule

Primary and secondary immune responses to the same pathogen



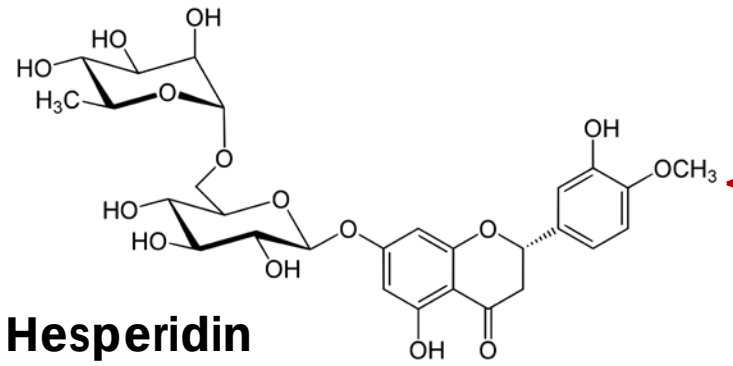
Antibodies are integral components in an effective immune response to SARS-CoV-2

Du L. et al.;Nat Rev Microbiol 7, 226–236 (2009)
Mort M. et al.; 2013 WHO Vaccine Safety Basics; Learning Manual 207 pages

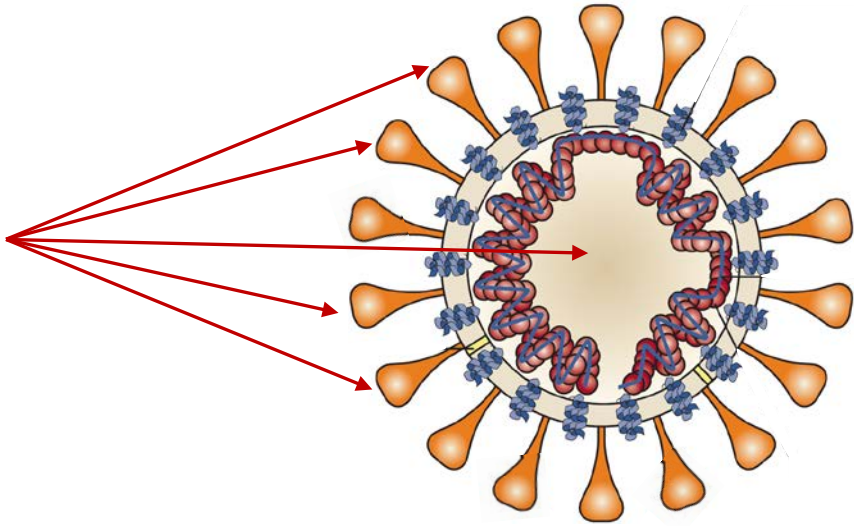
The Hesperidin Study

Part I

Hesperidin to inhibit entry and replication of SARS-CoV-2 by targeting the entry protein Spike(S) and replication protein 3CLpro



Hesperidin



SARS-CoV-2

Du L. et al.;Nat Rev Microbiol 7, 226–236 (2009)

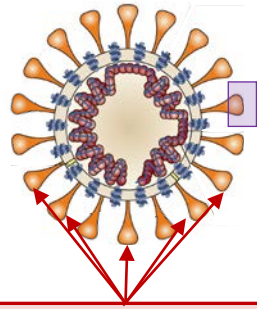
Hesperidin is anticipated to prevent the infection by inhibiting SARS-CoV-2 protein responsible for cellular entry: Spike(S)

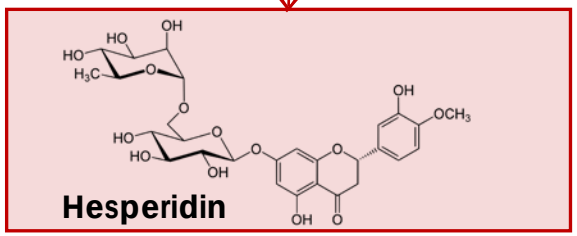
Hesperidin is anticipated to inhibit Spike(S) protein RBD preventing binding to ACE2 receptors

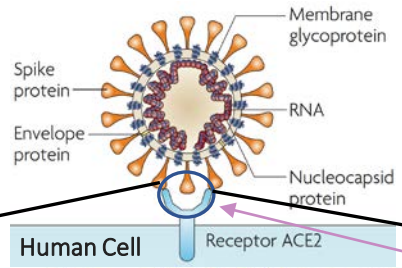
The Hesperidin Study: Mechanism 1a

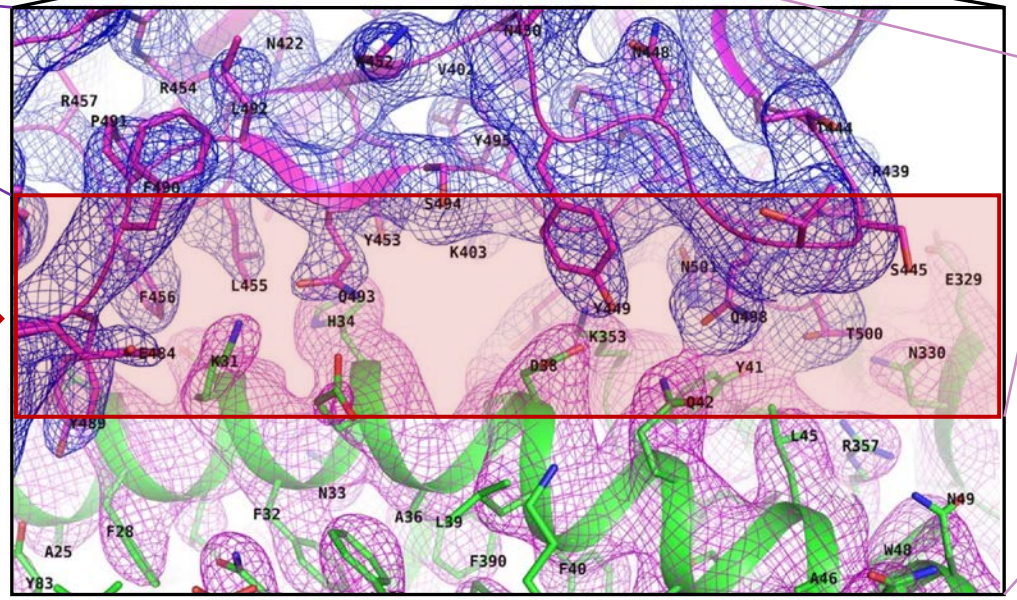
Hesperidin inhibits viral replication

SARS-CoV-2







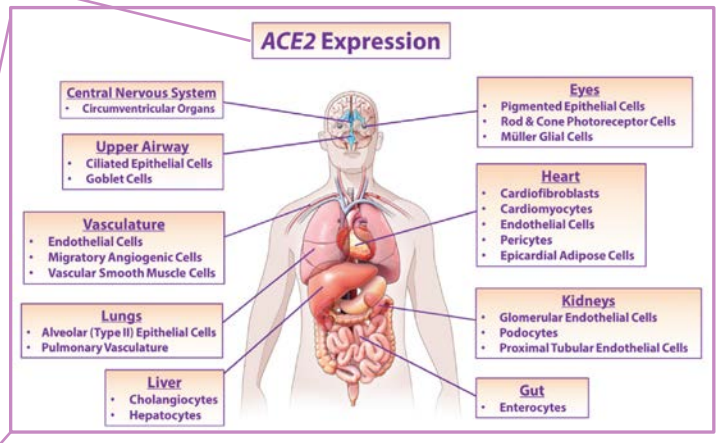


Region Binding Domain (RBD)

Composite map of the interface between Spike(S) and ACE2

Shang, J., Ye, G., Shi, K. et al. Nature 581, 221–224 2020

ACE2 protein allows SARS-CoV-2 to infect humans



Angiotensin Converting Enzyme -2 (ACE2)

Wu C. et al.; Acta Pharmaceutica Sinica B 2020; 10(5): 766-788
Shang, J., Ye, G., Shi, K. et al. Nature 581, 221–224 2020
Gheblawi M. et al.; Circulation Research 2020; 126 1456-1474

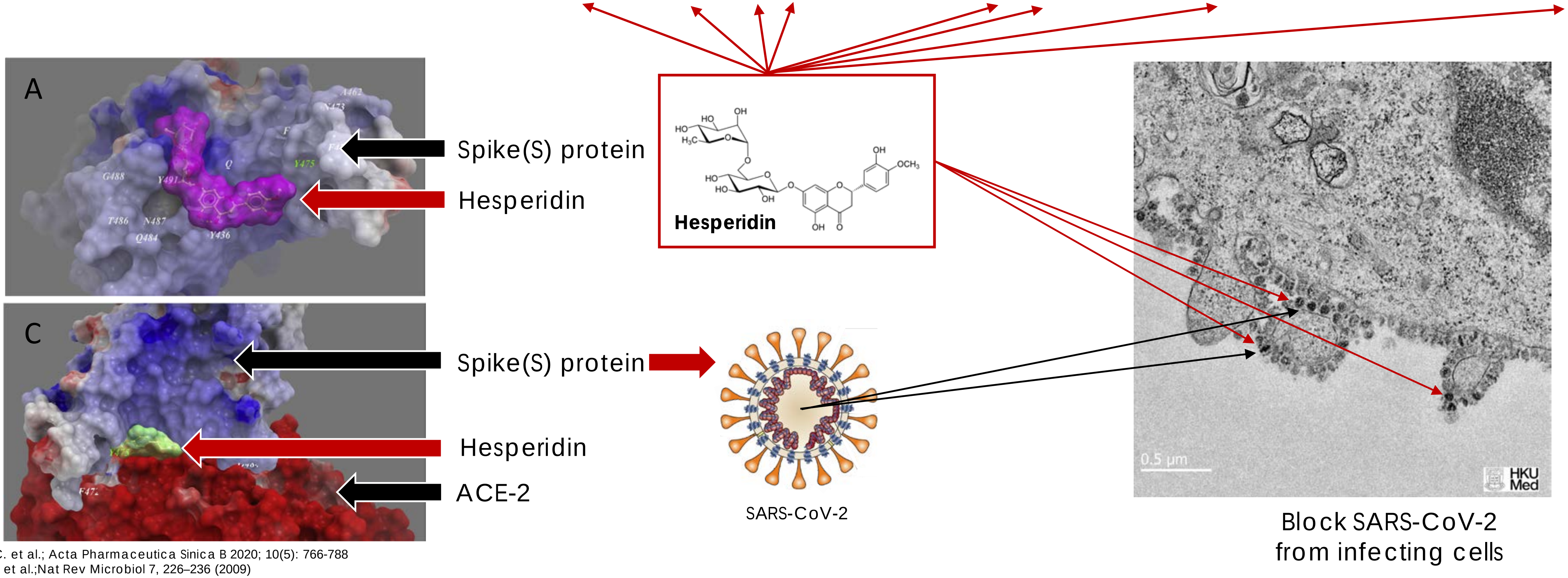
Molecular modelling suggests hesperidin could inhibit SARS-CoV-2 entry process by binding to the RBD of Spike(S) protein

Would dock in a hydrophobic shallow pocket (Tyr436, Tyr440, Leu442, Phe443, Tyr475, Phe476, Tyr481, Tyr491)

Spike(S) protein region binding domain amino acid sequence

The **5 Critical** A.A.												1	
The **14 Key** A.A.		1			2			3			4	5	
Amino Acid Sequence	401	402	403	425	426	427	435	436	437	440	441	442	443
SARS-CoV(2002)/SARS-CoV_Tor-2	Q	T	G	T	R	N	N	Y	N	Y	R	Y	L
SARS-CoV-2 (COVID-19)	Q	T	G	S	N	N	N	Y	N	Y	R	L	F

The **5 Critical** A.A.		2						3								4				5	
The **14 Key** A.A.		6	7		8			9					10		11	12	13			14	
Amino Acid Sequence	471	472	473	474	475	476	478	479	480	481	482	483	484	485	486	487	488	489	490	491	492
SARS-CoV(2002)/SARS-CoV_Tor-2	A	L	N	C	Y	W	L	N	D	Y	G	F	Y	T	T	T	G	I	G	Y	Q
SARS-CoV-2 (COVID-19)	G	F	N	C	Y	F	L	Q	S	Y	G	F	Q	P	T	N	G	V	G	Y	Q



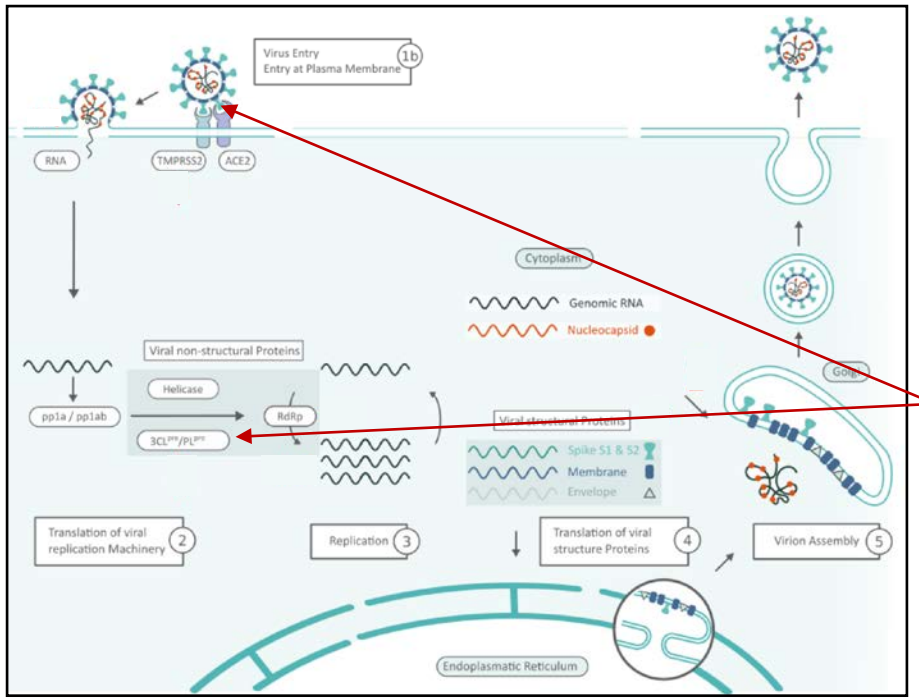
Wu C. et al.; Acta Pharmaceutica Sinica B 2020; 10(5): 766-788
Du L. et al.;Nat Rev Microbiol 7, 226–236 (2009)
Nicholls J., et al : HKUMed on COVID-19 (2020)

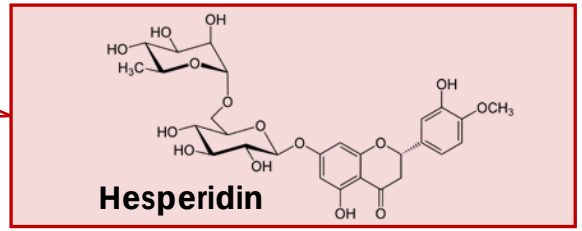
Hesperidin is anticipated to disrupt the replication process by blocking the catalytic domain of 3CLpro, a key replication enzyme

Hesperetin inhibits 3CLpro with an IC_{50} of 8.3µM

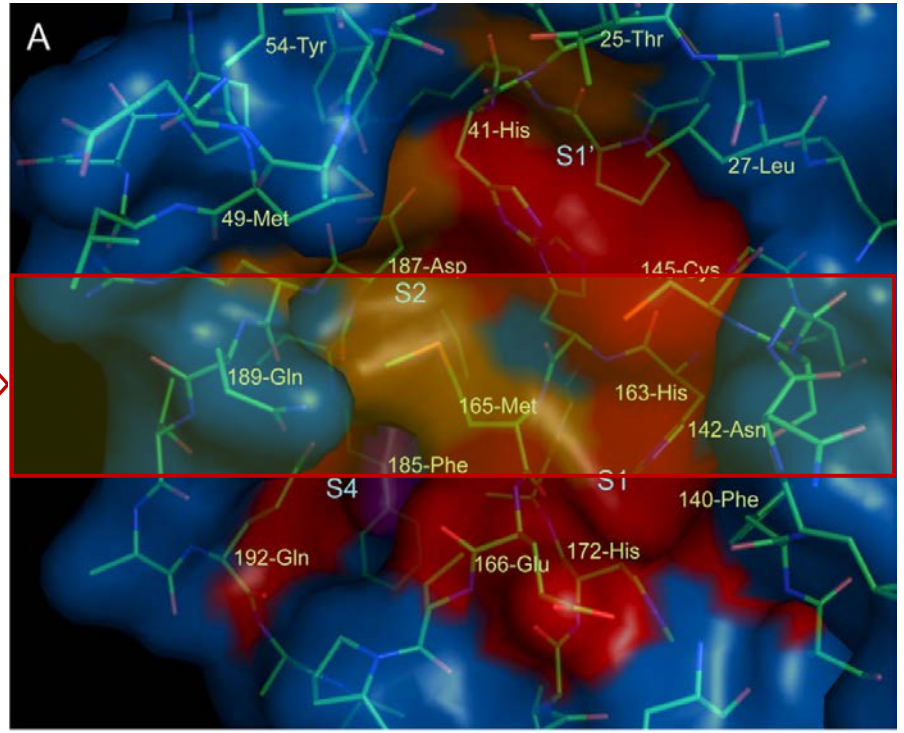
The Hesperidin Study: Mechanism 1b

Hesperidin inhibits viral replication





SARS-COV-2 3CLpro catalytic domain



Lin CW, et al.; Antiviral Res. 2005; 68 (1): 36-42
Yang H, et al.; PLoS Biol. 2005; 3 (10): e324
https://www.antibodies-online.com/resources/18/5410/sars-cov-2-life-cycle-stages-and-inhibition-targets/

SARS-CoV-2 leading to COVID-19 and SARS-CoV (2002) share the highly conserved 3CLpro/Mpro; a key replication protein for β-coronavirus

3CLpro (Mpro) Sequence							Catalytic Domain																																			
	Domain I															Domain II																				Long Loop								
Amino Acid Sequence	24	25	26	27	28	40	41	42	48	49	50	52	53	54	55	139	140	141	142	143	144	145	146	162	163	164	165	166	167	168	169	170	171	172	173	183	184	185	186	187	188	189	190	191	192	193
SARS-CoV(2002)/SARS-CoV_Tor-2	T	T	T	L	N	R	H	V	D	M	L	P	N	Y	E	S	F	L	N	G	S	C	G	M	H	H	M	E	L	P	T	G	V	H	A	G	P	F	V	D	R	Q	T	A	Q	A
"Wuhan Seafood Market"/SARS-CoV-2	T	T	T	L	N	R	H	V	D	M	L	P	N	Y	E	S	F	L	N	G	S	C	G	M	H	H	M	E	L	P	T	G	V	H	A	G	P	F	V	D	R	Q	T	A	Q	A
SARS-CoV(2002)/SARS-CoV BJ01	T	T	T	L	N	R	H	V	D	M	L	P	N	Y	E	S	F	L	N	G	S	C	G	M	H	H	M	E	L	P	T	G	V	H	A	G	P	F	V	D	R	Q	T	A	Q	A

Article

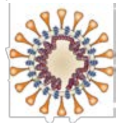
A new coronavirus associated with human respiratory disease in China

Nature | Vol 579 | 12 March 2020 | **265**

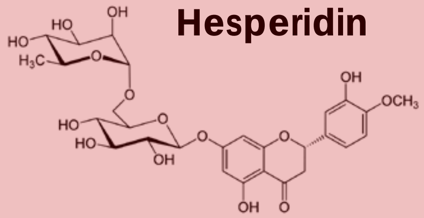
The patient studied was a 41-year-old man with no history of hepatitis, tuberculosis or diabetes. He was admitted to and hospitalized in the Central Hospital of Wuhan on 26 December 2019, 6 days after the onset of disease. The patient reported fever, chest tightness, unproductive cough, pain and weakness for 1 week on presentation

The viral load in the BALF sample was estimated by qPCR to be 3.95×10^{8} copies per ml

395,000,000 copies/ml

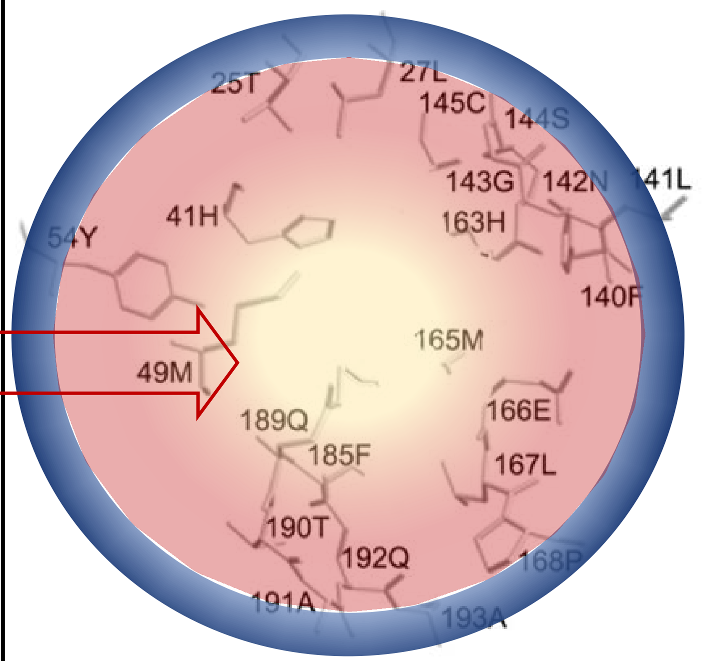


Hesperidin



Inhibit the Catalytic Site

SARS-CoV-2 3CLpro catalytic site



Wu F., det al.; *Nature*. 2020; 579 (7798): 265-269.
Yang H, et al.; PLoS Biol. 2005; 3 (10): e324
Du L. et al.;Nat Rev Microbiol 7, 226–236 (2009)

Multiple computational modeling teams supported hesperidin inhibitory potential against 3Clpro (Mpro)

The inhibitory potential of hesperidin has now been evaluated and published by +5 different scientific teams

BRIEF REPORT

Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CL^{pro}) structure: virtual screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates [version 1; peer review: 3 approved]

Yu Wai Chen [1,2], Chin-Pang Bennu Yiu [3], Kwok-Yin Wong[1,2]

F1000Research 2020, 9:129 Last updated: 17 MAR 2020

Virtual screening

MTiOpenScreen web service[4] was used for screening against its library of 7173 purchasable drugs (Drugs-lib), with 4574 unique compounds and their stereoisomers.

Hesperidin hits showed up multiple times, suggesting it has many modes of binding

Computational Determination of Potential Inhibitors of SARS-CoV-2 Main Protease

J Chem Inf Model. 2020 Jun 12 : acs.jcim.0c00491.

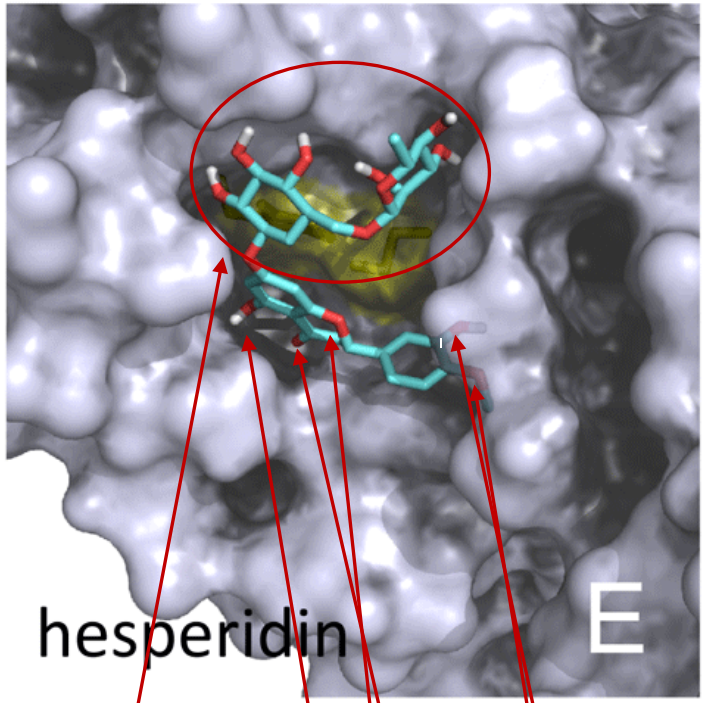
Son Tung Ngo, Ngoc Quynh Anh Pham, Ly Le, Duc-Hung Pham, Van Vu

The binding affinity of top-lead and all compounds to SARS-CoV-2 Mpro is provided in Table S1 of the Supporting Information 1 (SI1) and Supporting Information 2 (SI2)

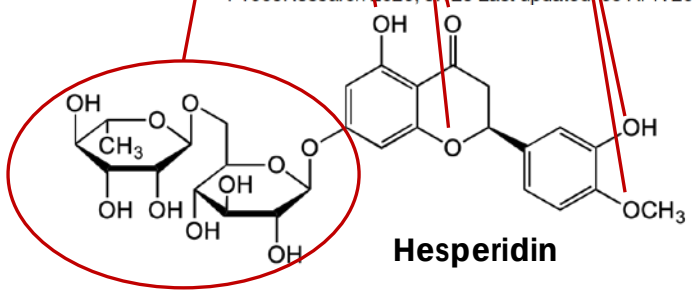
Table S1. Top-lead compounds identified with molecular docking simulations

N°	Pubchem	Compound Name	Vietnamese Herb Name	ΔG_{Dock}[a]
1	10621	Hesperidin	Citrus Aurantium	-9.0

SARS-COV-2 3CLpro catalytic domain



F1000Research 2020, 9:129 Last updated: 09 APR 2020



Hesperidin

Revealing the Potency of Citrus and Galangal Constituents to Halt SARS-CoV-2 Infection

Rohmad Yudi Utomo[1,2], Muthi' Ikawati[1,3], Edy Meiyanto[1,3,*]

doi:10.20944/preprints202003.0214.v1

Abstract

binding to 3 protein receptors. The study was conducted by molecular docking using the MOE 2010 program (licensed from Faculty of Pharmacy UGM, Indonesia). The selected protein targets are RBD-S (PDB ID:6LXT), PD-ACE2 (PDB ID: 6VW1), and SARS-CoV-2 protease (PDB ID:6LU7). The affinities of bonds formed is represented as a docking score. The results show that hesperidin, one of the compounds in Citrus sp., has the lowest docking score for all three protein receptors representing the highest affinity to bind the receptors. Moreover, all of the citrus flavonoids possess good affinity to the

perform inhibitory potential for the viral infection and replication. In general, the results of this study indicate that *Citrus sp*. exhibit the best potential as an inhibitor to the development of the SARS-CoV-2, followed by galangal, sappan wood, and *Curcuma sp*. that can be consumed in daily life as

Potential Unconventional Medicines for the Treatment of SARS-CoV-2

Maurizio Coppola[1] and Raffaella Mondola[2]

Drug Res (Stuttg). 2020 Jun; 70(6): 286.

Potential inhibition properties were studied using the Molegro Virtual Docker Program and some flavonoids, in particular hesperidin, rutin, and diosmin showed a better affinity for the MPro than nelfinavir 1 . Hesperidin showed the highest binding energy at the active site of the MPro with a MoLDock score of −178.5910 (nelfinavir -147.3800) and a HBond of −20.2594 (nelfinavir −6.8731).

Chen YW, et al.; F1000Research. 2020; 9.
https://doi.org/10.12688/f1000research.22457.1.
Vu V, et al; https://doi.org/10.26434/chemrxiv.12111297.v1.
Utomo RY,et al.; https://doi.org/10.20944/preprints202003.0214.v1
Coppola M., et al; Drug Res (Stuttg). 2020 Jun; 70(6): 286.

Hesperidin to inhibit entry and replication of SARS-CoV-2 in COVID-19

Based on review of recent and historical scientific/medical literature focused on SARS-CoV/SARS-CoV-2/COVID-19

Spike(S) protein region binding domain amino acid sequence

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The **14 Key** A.A.		1			2			3			4	5	
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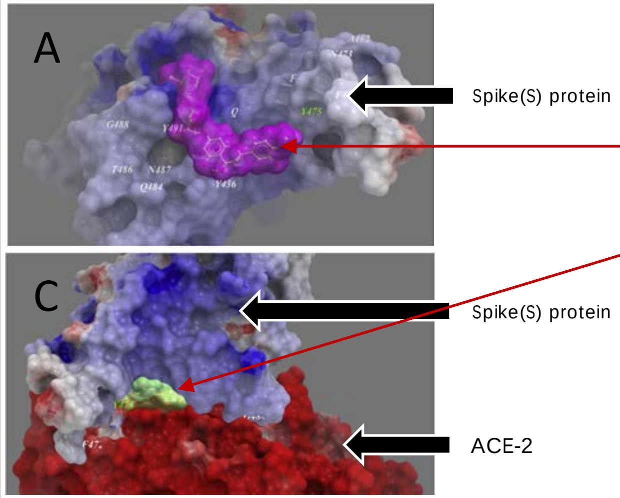
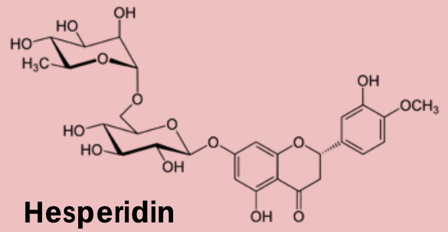
SARS-CoV-2 (COVID-19)	Q	T	G	S	N	N	N	Y	N	Y	R	L	F

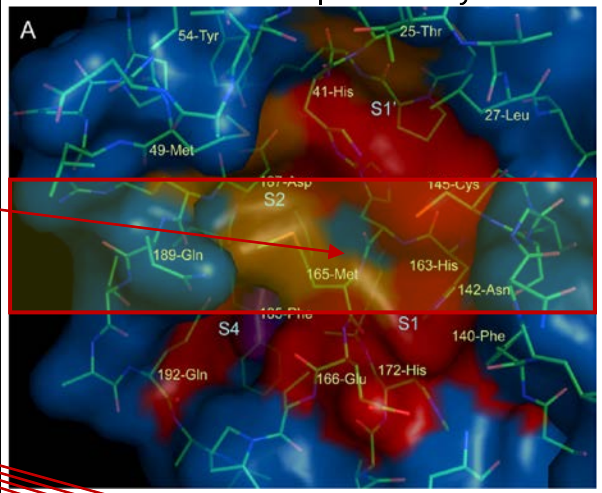
The **5 Critical** A.A.		2						3								4				5	
The **14 Key** A.A.		6	7		8			9					10		11	12	13			14	
Amino Acid Sequence	471	472	473	474	475	476	478	479	480	481	482	483	484	485	486	487	488	489	490	491	492
SARS-CoV(2002)/SARS-CoV_Tor-2	A	L	N	C	Y	W	L	N	D	Y	G	F	Y	T	T	T	G	I	G	Y	Q
SARS-CoV-2 (COVID-19)	G	F	N	C	Y	F	L	Q	S	Y	G	F	Q	P	T	N	G	V	G	Y	Q

Hesperidin inhibiting the binding between Spike(S) protein and ACE2





SARS-CoV-2 3CLpro catalytic



3CLpro (Mpro) Sequence						Catalytic Domain								
	Domain I													
Amino Acid Sequence	24	25	26	27	28	40	41	42	48	49	50	52	53	54	55
SARS-CoV(2002)/SARS-CoV_Tor-2	T	T	T	L	N	R	H	V	D	M	L	P	N	Y	E
"Wuhan Seafood Market"/SARS-CoV-2	T	T	T	L	N	R	H	V	D	M	L	P	N	Y	E
SARS-CoV(2002)/SARS-CoV BJ01	T	T	T	L	N	R	H	V	D	M	L	P	N	Y	E

	Domain II																			
Amino Acid Sequence	139	140	141	142	143	144	145	146	162	163	164	165	166	167	168	169	170	171	172	173
SARS-CoV(2002)/SARS-CoV_Tor-2	S	F	L	N	G	S	C	G	M	H	H	M	E	L	P	T	G	V	H	A
"Wuhan Seafood Market"/SARS-CoV-2	S	F	L	N	G	S	C	G	M	H	H	M	E	L	P	T	G	V	H	A
SARS-CoV(2002)/SARS-CoV BJ01	S	F	L	N	G	S	C	G	M	H	H	M	E	L	P	T	G	V	H	A

			Long loop								
Amino Acid Sequence	183	184	185	186	187	188	189	190	191	192	193
SARS-CoV(2002)/SARS-CoV_Tor-2	G	P	F	V	D	R	Q	T	A	Q	A
"Wuhan Seafood Market"/SARS-CoV-2	G	P	F	V	D	R	Q	T	A	Q	A
SARS-CoV(2002)/SARS-CoV BJ01	G	P	F	V	D	R	Q	T	A	Q	A

3CLpro catalytic domain amino acid sequence

Wu C. et al.; Acta Pharmaceutica Sinica B 2020; 10(5): 766-788
Yang H, et al.; PLoS Biol. 2005; 3 (10): e324

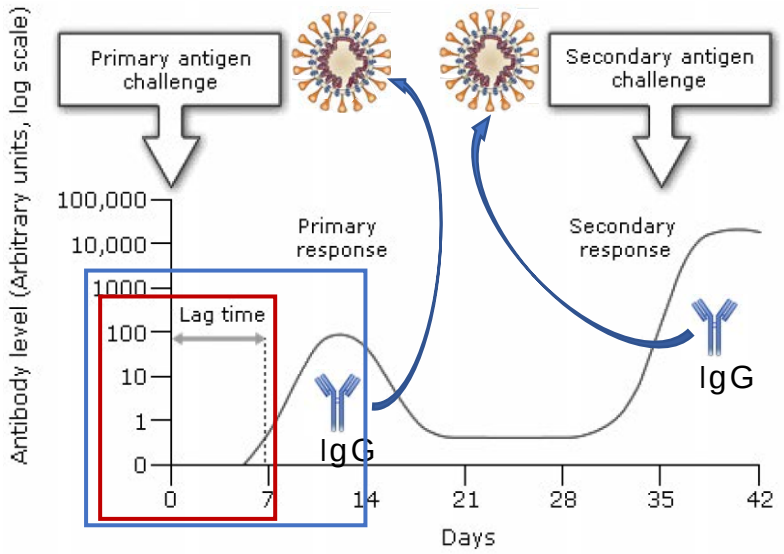
The Hesperidin Study

Part II

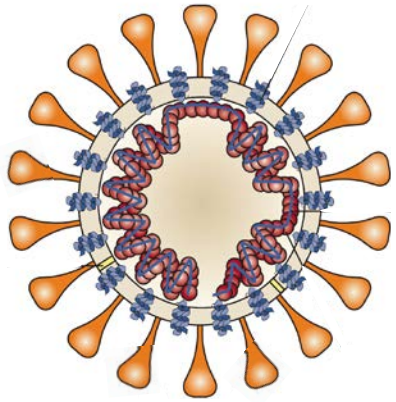
Reduce the Incidence and Severity of Cytokine Storm

by Modulating the Inflammatory Mediators in COVID-19 for 14 days

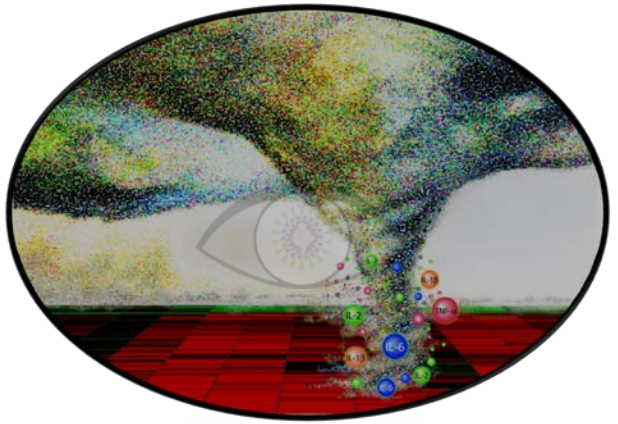
Primary Immune Response



SARS-CoV-2



Cytokine Storm

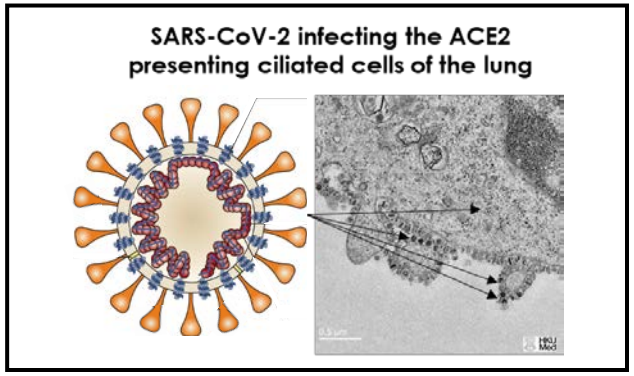


Keeping the Infection and Cytokine Storm Balanced within COVID-19 Patients

Mort M., et al.; 2013 WHO Vaccine Safety Basics; Learning Manual 207 pages
Du L., et al.; Nat Rev Microbiol 7, 226–236 (2009)
Tisoncik J.R.,et al.; Microbiol Mol Biol Rev. 2012 Mar; 76(1): 16–32

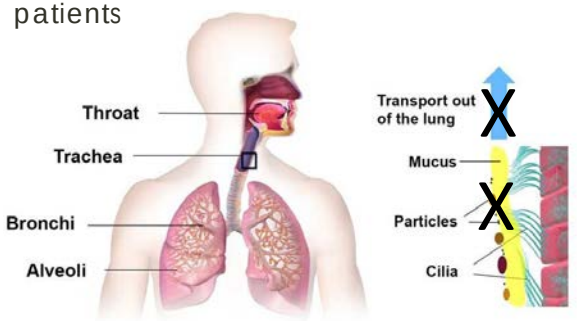
SARS-CoV-2 infection and tissue injury triggers the release of mediators of inflammation which initiate and amplify the inflammatory response

Cytokines TNF, IL-1 and IL-6 are important markers of acute inflammation and leading cause of fever on day 1 of onset



Cilia beat continuously to remove mucus, traps inhaled pollutants and pathogens like SARS-CoV-2…much like a conveyor belt

Infection by SARS-COV-2 reduce the cilia's function and lead to cough in COVID-19 patients



Inflammatory cells
Mast cells
Eosinophils
Th2 cells
Basophils
Platelets

Structural cells
Epithelial cells
Smooth muscle cells
Endothelial cells
Fibroblast
Nerves

Mediators
Histamine
Leukotrienes
Prostanoids
PAF
Kinins
Adenosine
Endothelins
Nitric oxide
Cytokines
Chemokines
Growth factors

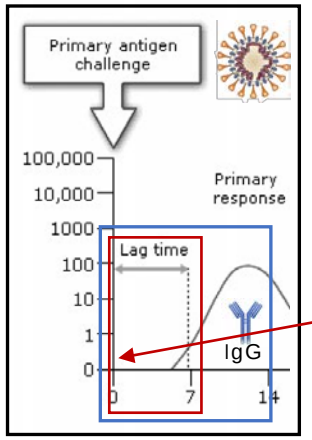
Cytokines in Acute Inflammation

Cytokine	Principal Source	Principal role in acute inflammation
TNF	• Macrophages • Mast cells • T lymphocytes	• Leukocyte activation • Endothelial activation • **Systemic acute phase response (next lecture)**
IL-1	• Macrophages • Endothelial cells • Some epithelial cells	• **Systemic acute phase response, greater role in fever**
IL-6	• Macrophages	• **Systemic acute phase response**

Understanding the symptoms of the common cold and influenza

Interleukin 1 and interleukin 6 are believed to be the most important cytokines that induce fever.

Lancet Infect Dis 2005; 5: 718–725



Du L., et al.;Nat Rev Microbiol 7, 226–236 (2009)
Nicholls J., et al : HKUMed on COVID-19 (2020)
Vogel V.; Reducing the risk of infection 2020
Arona P., et al; Asthma biological evidences Ed. Pereira C. ISBN: 978-1-83962-246-5
MDTI, Kelly18 Acute inflammation 1/5
Eccles R., Lancet Infect Dis 2005; 5 : 718-725

Fever as: day of onset for COVID-19/day 1 of the protocol/ day 1 of the lag time finds support in vaccination protocols and associated adverse events

Fever can occur 1-2 days post vaccination, but SARS-COV-2 is an airborne pathogen with incubation time and initial viral load as added variable

World Health Organization

VACCINE SAFETY BASICS

© World Health Organization 2013

Minor vaccine reactions

The frequency of vaccine reactions likely to be observed with some of the most commonly used vaccines, and their treatments, are listed below. These reactions typically occur within a day or two of immunization

Common, minor vaccine reactions

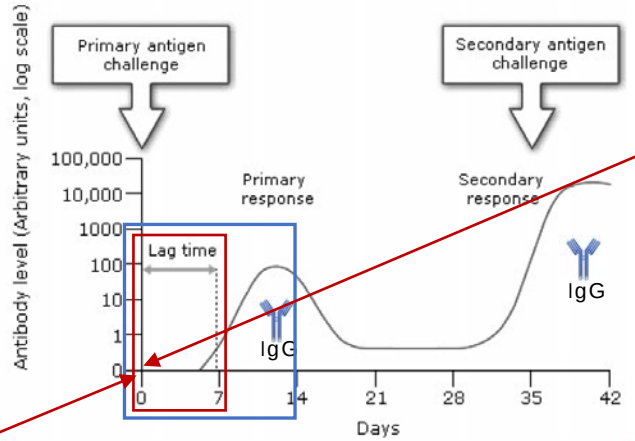
Vaccine	Systemic reactions	
	Fever > 38°C	Irritability, malaise and systemic symptoms
BCG[a]	–	–
Hepatitis B	1–6%	–
Hib	2–10%	
Measles/MR/MMR	5–15%	5% (Rash)
OPV	Less than 1%	Less than 1%[b]
Pertussis (DTwP)[c]	up to 50%	up to 55%
Pneumococcal conjugate[e]	~ 20%	~ 20%
Tetanus/DT/aTd	~ 10%	~ 25%

Primary and secondary immune responses to the same pathogen

World Health Organization

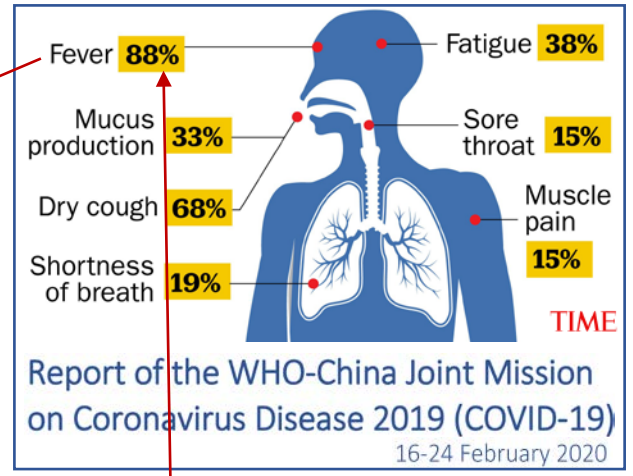
VACCINE SAFETY BASICS

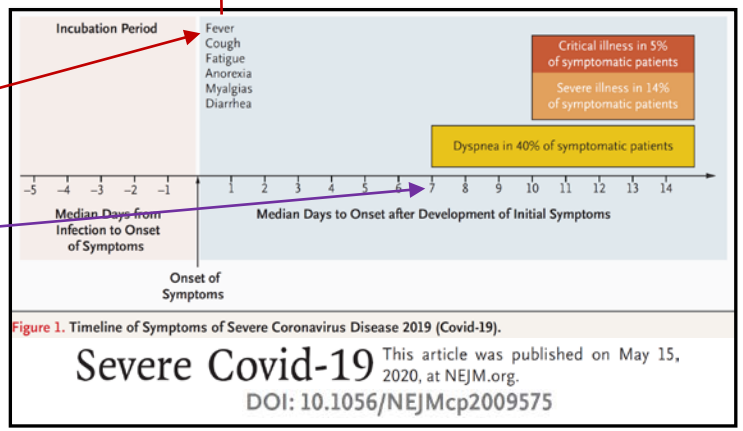
© World Health Organization 2013



	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Demographics and clinical characteristics				
Age, years	56·0 (46·0–67·0)	69·0 (63·0–76·0)	52·0 (45·0–58·0)	<0·0001
Sex	..	..	..	0·15
Female	72 (38%)	16 (30%)	56 (41%)	..
Male	119 (62%)	38 (70%)	81 (59%)	..
Time from illness onset to fever, days	1·0 (1·0–1·0)	1·0 (1·0–1·0)	1·0 (1·0–1·0)	0·16
Time from illness onset to cough, days	1·0 (1·0–3·0)	1·0 (1·0–1·0)	1·0 (1·0–4·0)	0·30
Time from illness onset to dyspnoea, days	7·0 (4·0–9·0)	7·0 (4·0–10·0)	7·0 (4·0–9·0)	0·51
Time from illness onset to sepsis, days	9·0 (7·0–13·0)	10·0 (7·0–14·0)	9·0 (7·0–12·0)	0·22
Time from illness onset to ARDS, days	12·0 (8·0–15·0)	12·0 (8·0–15·0)	10·0 (8·0–13·0)	0·65
Time from illness onset to ICU admission, days	12·0 (8·0–15·0)	12·0 (8·0–15·0)	11·5 (8·0–14·0)	0·88

Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study www.thelancet.com Published online March 9, 2020



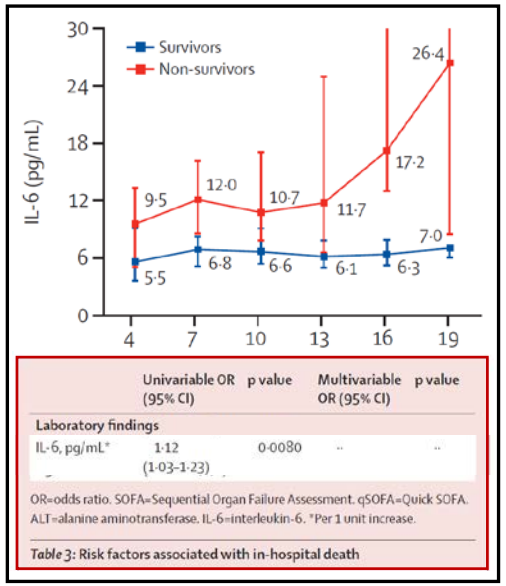


Mort M., et al.; 2013 WHO Vaccine Safety Basics; Learning Manual 207 pages
Zhou F. et al.; Lancet 2020; 395 :1054-1062 supp
Berlin D.A., et al; N Engl J Med 2020 DOI: 10.1056/NEJMcp2009575
Dufay H. WHO-China Joint Mission on COVID-19-Final Report
Time Staff Time Magazine 2020

Levels of IL-6 remained ~75% higher in non-survivors than in survivors and elevated cardiac troponin I (cTnI) had the highest odds ratio (80:1) in death risk factors

Fever starts declining sharply on day of onset +7 for survivors but not for non-survivors and death starts being reported

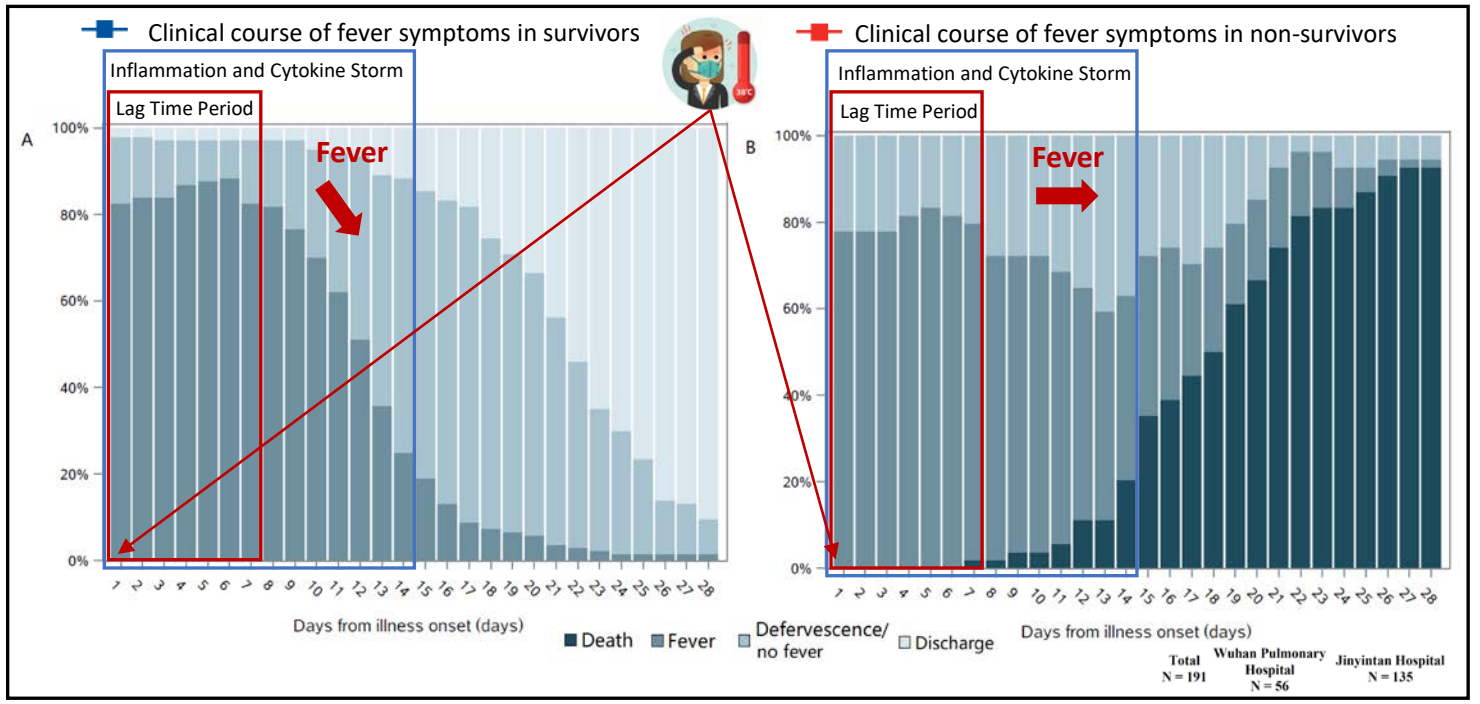
Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study *Lancet* 2020; 395: 1054–62

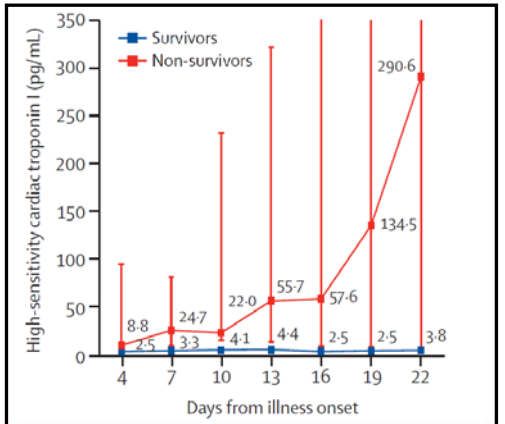


	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Laboratory findings				
IL-6, pg/mL*	1·12 (1·03–1·23)	0·0080	..	..

OR=odds ratio. SOFA=Sequential Organ Failure Assessment. qSOFA=Quick SOFA. ALT=alanine aminotransferase. IL-6=interleukin-6. *Per 1 unit increase.

Table 3: Risk factors associated with in-hospital death





	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Laboratory findings				
High-sensitivity cardiac troponin I, pg/mL				
≤28	1 (ref)	..	..	..
>28	80·07 (10·34–620·36)	<0·0001	..	..

OR=odds ratio. SOFA=Sequential Organ Failure Assessment. qSOFA=Quick SOFA. ALT=alanine aminotransferase. IL-6=interleukin-6. *Per 1 unit increase.

Table 3: Risk factors associated with in-hospital death

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
(Continued from previous page)				
IL-6, pg/mL	7·4 (5·3–10·8)	11·0 (7·5–14·4)	6·3 (5·0–7·9)	<0·0001

Table 1: Demographic, clinical, laboratory, and radiographic findings of patients on admission

Zhou F. et al.; Lancet 2020; 395 :1054-1062

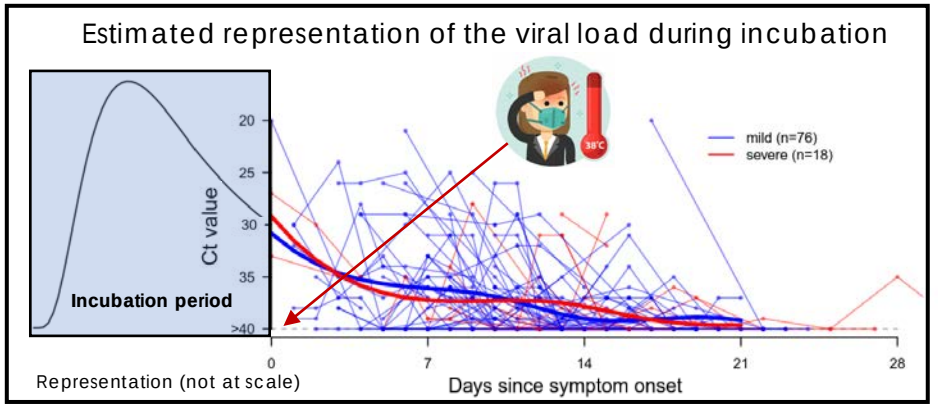
Temporal dynamics in viral shedding of SARS-CoV-2 suggests that the viral load and infectiousness peaked before the day of onset in COVID-19 patients

Fever and cough are the 2 typical manifestations reported on the day of onset

Temporal dynamics in viral shedding and transmissibility of COVID-19

NATURE MEDICINE | VOL 26 | MAY 2020 | 672-675 |

We report temporal patterns of viral shedding in 94 patients with laboratory-confirmed COVID-19 and modeled COVID-19 infectiousness profiles from a separate sample of 77 infector-infectee transmission pairs. We observed the highest viral load in throat swabs at the time of symptom onset, and inferred that infectiousness peaked on or before symptom onset.



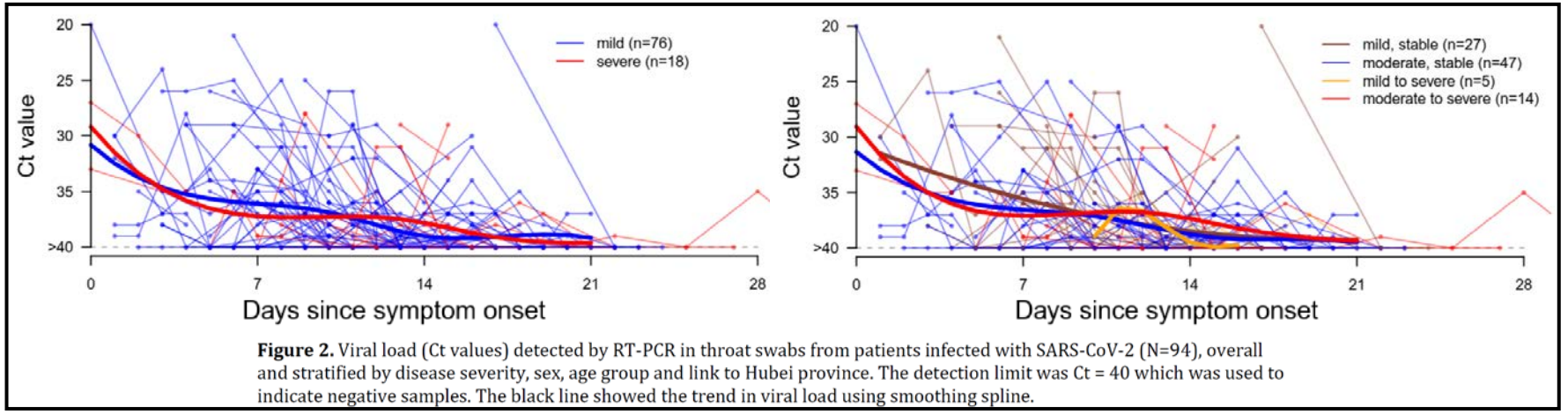


Figure 2. Viral load (Ct values) detected by RT-PCR in throat swabs from patients infected with SARS-CoV-2 (N=94), overall and stratified by disease severity, sex, age group and link to Hubei province. The detection limit was Ct = 40 which was used to indicate negative samples. The black line showed the trend in viral load using smoothing spline.

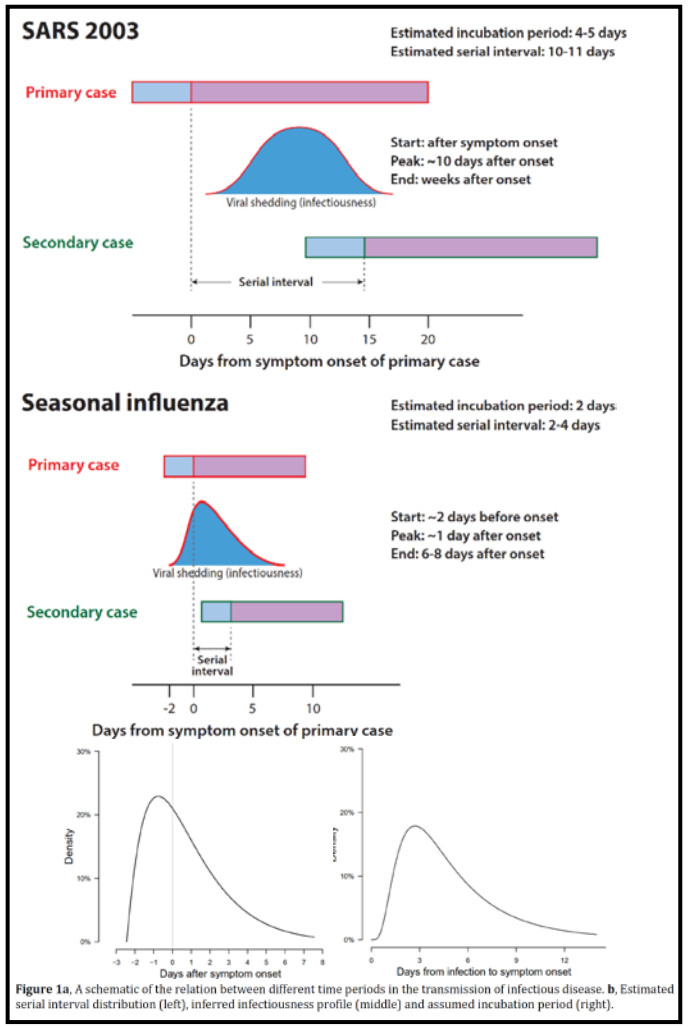


Figure 1a, A schematic of the relation between different time periods in the transmission of infectious disease. **b**, Estimated serial interval distribution (left), inferred infectiousness profile (middle) and assumed incubation period (right).

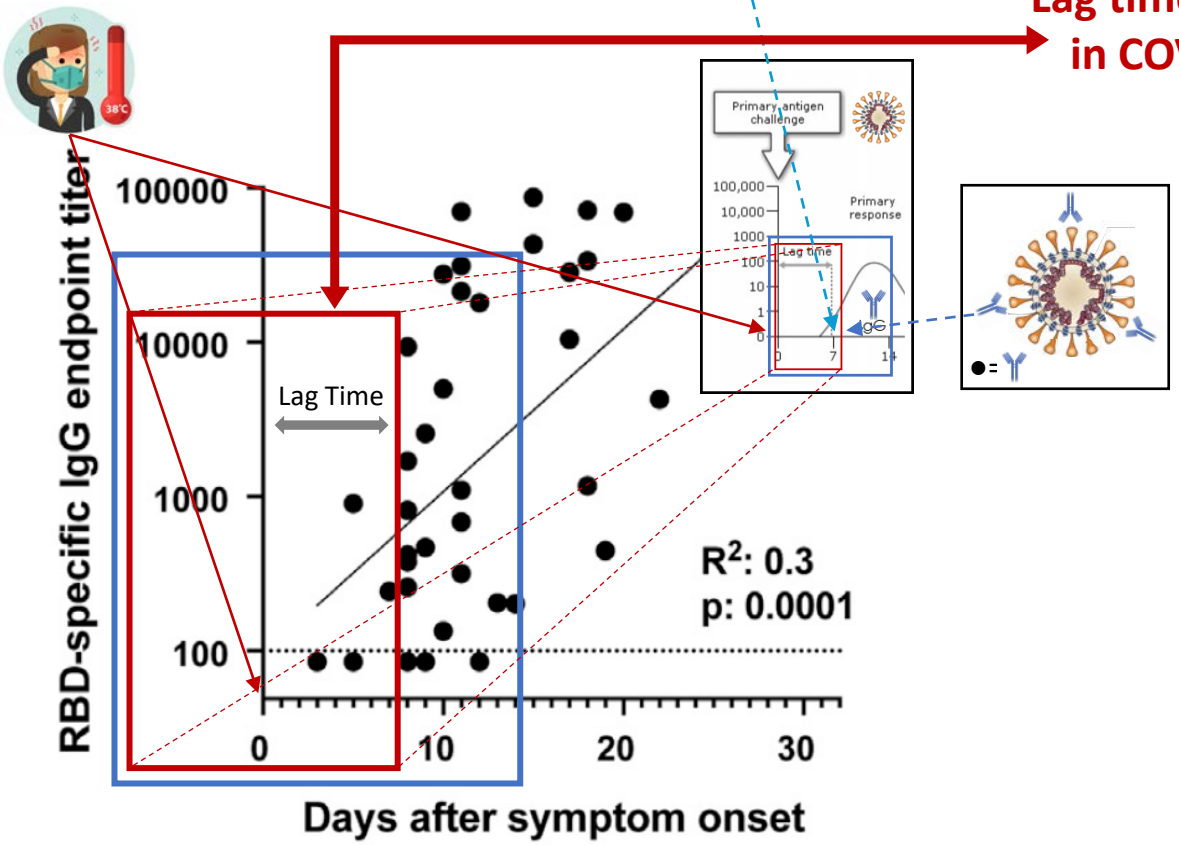
He X., et al; Nature Medicine 26 672-675 (2020)

The lag time (delay) between incubation and antibody response allows rapid virus proliferation, systemic spread and inflammation

RBD neutralizing antibodies were quantitated starting day 7/8 after symptom onset

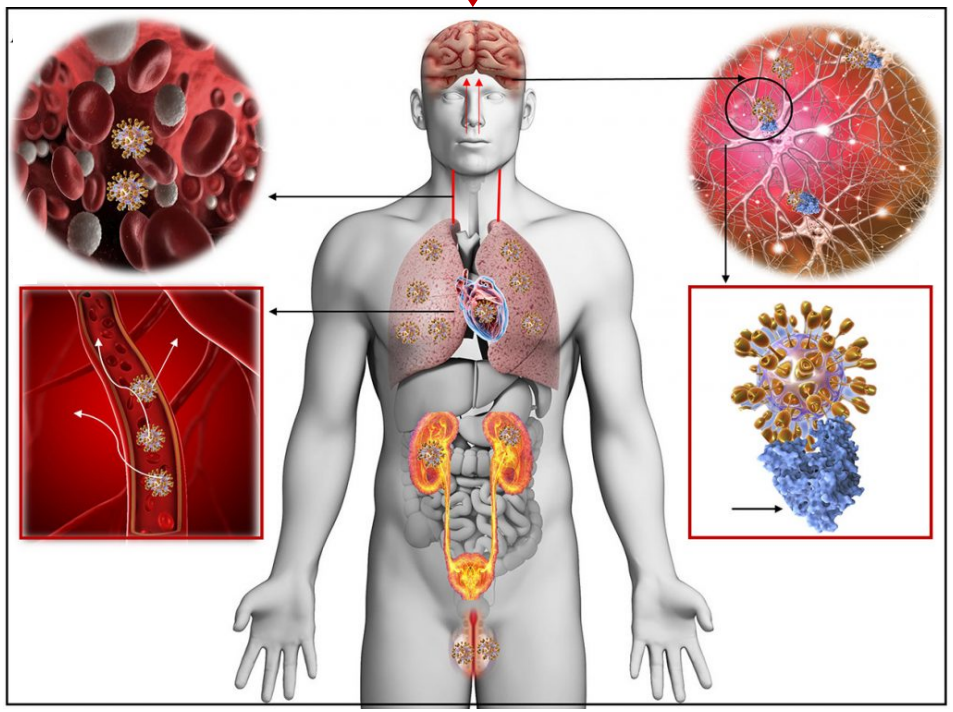
Cell Reports Medicine
June 23, 2020 © 2020 The Author(s).
https://doi.org/10.1016/j.xcrm.2020.100040

IgG (antibodies) specific for SARS Spike(S) protein RBD and capable of neutralizing SARS-CoV-2



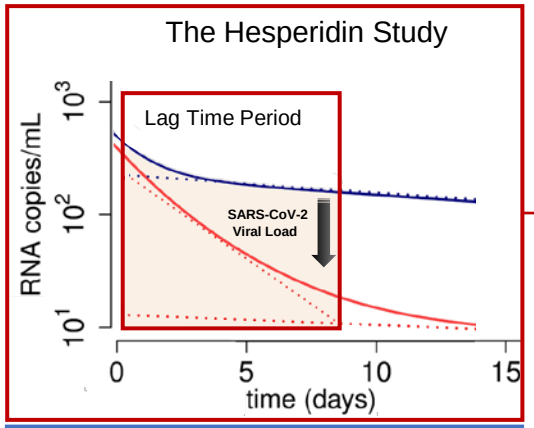
Lag time period (~7 days) in COVID-19 patients

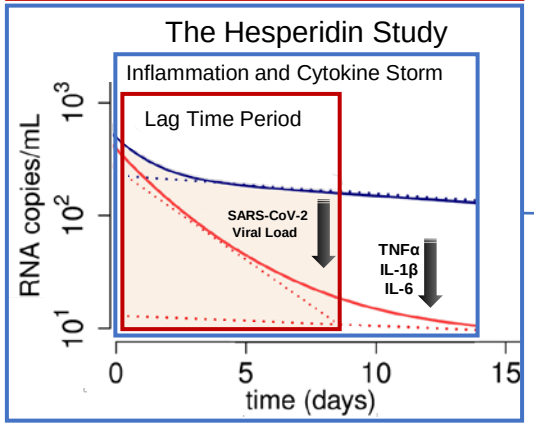
Allows for systemic spread and inflammation

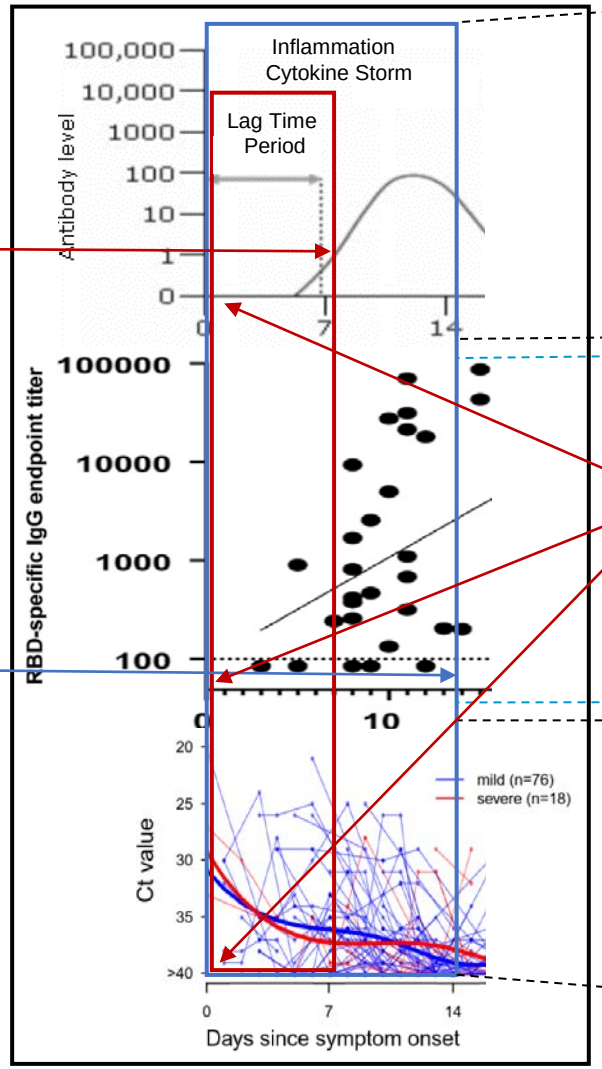


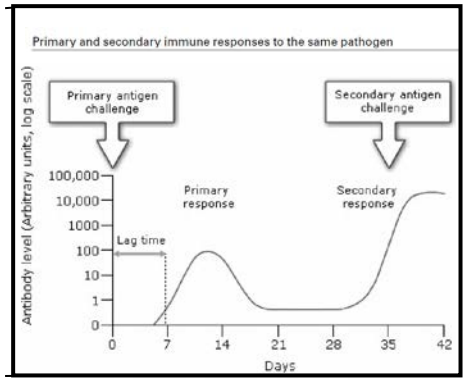
Suthar M.S., et al.; 2020, Cell Reports Medicine 1, 100040
https://multiple-sclerosis-research.org/2020/03/mscovid19-guest-post/

The Hesperidin Study: hesperidin to assist COVID-19 patients in elaborating a prompt response to their viral and inflammation phases



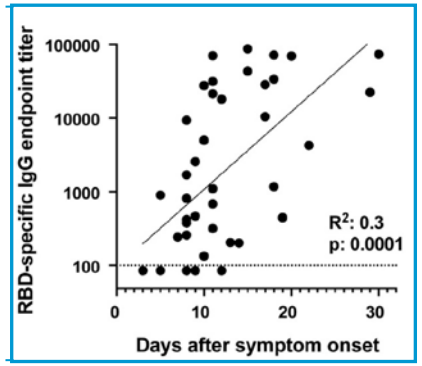




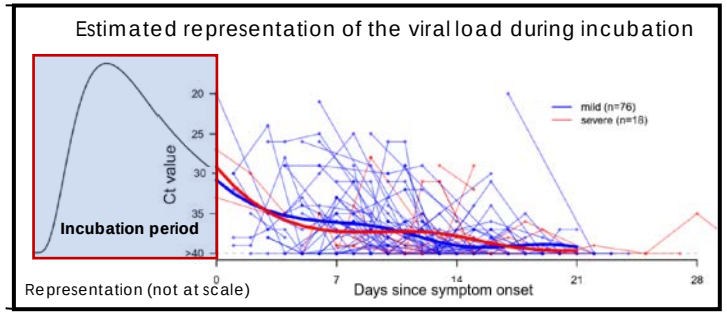


World Health Organization VACCINE SAFETY BASICS

Cell Reports Medicine
IgG (antibodies) specific for SARS Spike(S) protein RBD and capable of neutralizing SARS-CoV-2



Temporal dynamics in viral shedding and transmissibility of COVID-19
NATURE MEDICINE | VOL 26 | MAY 2020 | 672-675 |



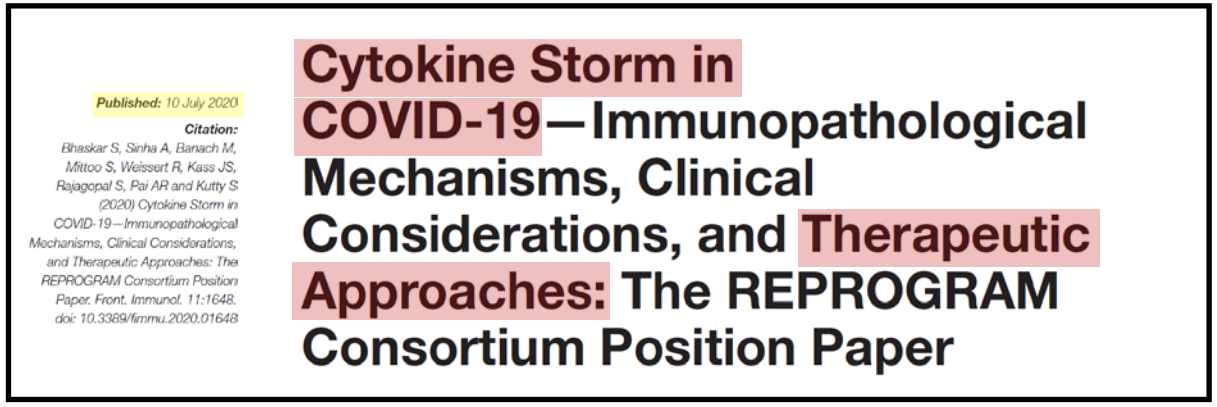
Mort M., et al.; 2013 WHO Vaccine Safety Basics; Learning Manual 207 pages
Suthar M.S., et al.; 2020, Cell Reports Medicine 1, 100040
He X., et al; Nature Medicine 26 672-675 (2020)

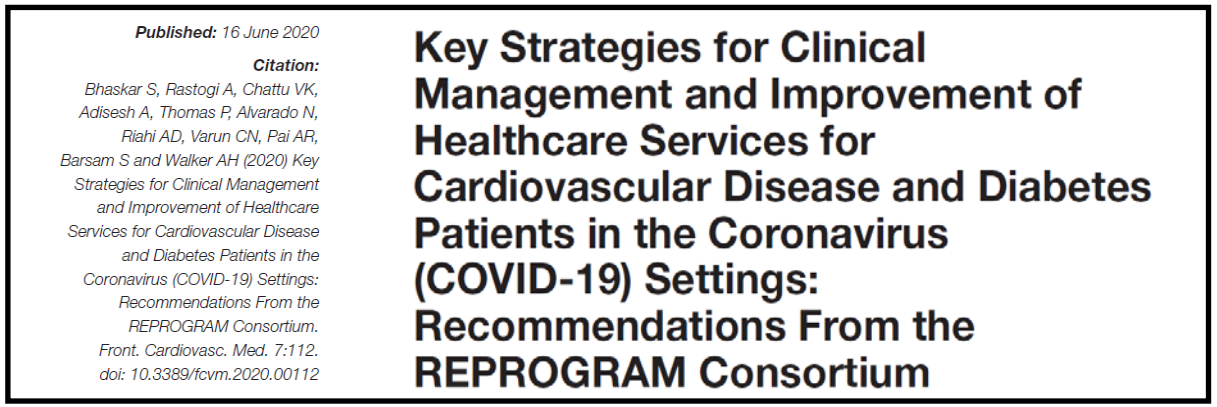
The Hesperidin Study

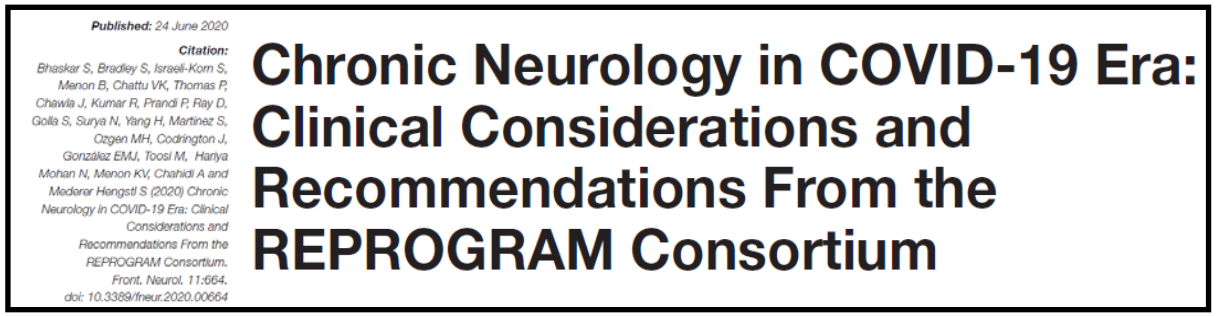
Part III

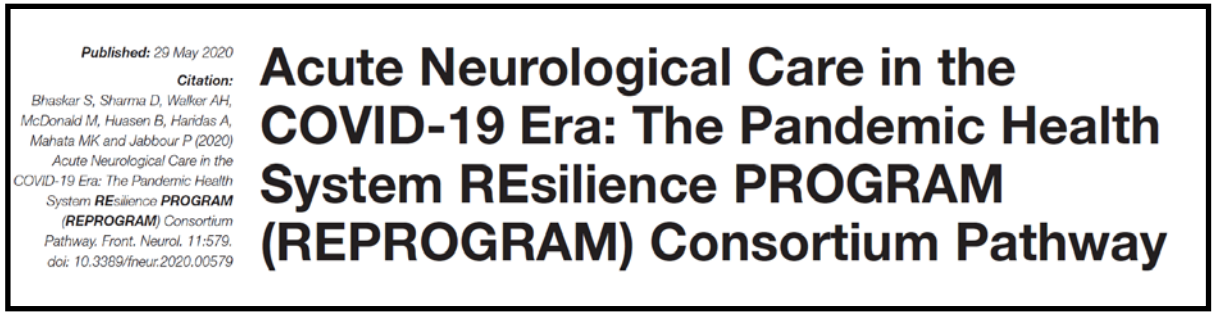
Guidance for the Management of Cytokine Storm in COVID-19 patients from the REPROGRAM Consortium

*†The COVID19 pandemic is causing an unprecedented public health crisis impacting healthcare systems, healthcare workers, and communities. The COVID-19 Pandemic Health System **RE**silience **PROGRAM** (**REPROGRAM**) consortium is an international not-for-profit think-tank for global pandemic preparedness and action*









Bhaskar S., et al; Front. Immunol. 11: 1648 (2020)
Bhaskar S., et al; Front. Cardiovasc. Med. 7:112 (2020)
Bhaskar S., et al; Front. Neurol. 11: 664 (2020)
Bhaskar S., et al; Front. Neurol. 11:579 (2020)

Attempt to decrease the acute inflammation mediators IL-6, IL-1, TNFα, IFN-γ and IL-2

Which inflammation/cytokine storm markers should the therapeutic approaches focus on

The COVID-19 Pandemic Health System REsilience PROGRAM (REPROGRAM) consortium is an international not-for-profit think-tank for global pandemic preparedness and action

Cytokine Storm in COVID-19—Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper

Frontiers in Immunology July 2020 | Volume 11 | Article 1648

Sonu Bhaskar[1,2,3], Akansha Sinha[1,4], Maciej Banach[1,5,6,7], Shikha Mittoo[1,8], Robert Weissert[1,9], Joseph S. Kass[1,10], Santhosh Rajagopal[1,11], Anupama R. Pai[1,12] and Shelby Kutty[1,13,14]*

[1] Pandemic Health System REsilience PROGRAM (REPROGRAM) Consortium, REPROGRAM Immunity Sub-committee†, [2] Department of Neurology & Neurophysiology, Liverpool Hospital and South Western Sydney Local Health District, Sydney, NSW, Australia, [3] Neurovascular Imaging Laboratory & NSW Brain Clot Bank, Ingham Institute for Applied Medical Research, The University of New South Wales, UNSW Medicine, Sydney, NSW, Australia, [4] The University of New South Wales, UNSW Medicine, Sydney, NSW, Australia, [5] Polish Mother's Memorial Hospital Research Institute, Lodz, Poland, [6] Cardiovascular Research Centre, University of Zielona Góra, Zielona Gora, Poland, [7] Department of Hypertension, Medical University of Lodz, Lodz, Poland, [8] Department of Rheumatology, University Health Network and The University of Toronto, Toronto, ON, Canada, [9] Department of Neurology, University of Regensburg, Regensburg, Germany, [10] Department of Neurology, Ben Taub General Hospital and Alzheimer's Disease and Memory Disorders Center, Baylor College of Medicine, Houston, TX, United States, [11] World Health Organisation, Country Office for India, NPSP, Madurai, India, [12] Department of Neuromicrobiology, National Institute of Mental Health and Neurosciences, Bengaluru, India, [13] Department of Pediatric and Congenital Cardiology, Blalock-Taussig-Thomas Heart Center, John Hopkins Hospital, Baltimore, MD, United States, [14] Johns Hopkins Bloomberg School of Public Health, School of Medicine, John Hopkins University, Baltimore, MD, United States

Significance of Cytokine Storm

Hypercytokinemia is an unregulated hyperinflammatory response that results from the systemic spread of a localized inflammatory response to viral or bacterial infection. Elevated cytokine levels result in endothelial dysfunction, vascular damage, and paracrine/metabolic dysregulation, thereby damaging multiple organ systems. Levels of acute-response cytokines (TNF and IL-1β) and chemotactic cytokines (IL-8 and MCP-1) rise early in hypercytokinemia, facilitating a sustained increase in IL-6.

Targeting Interleukins

Interleukin-6 (IL-6) plays a key role in cytokine storm (102).

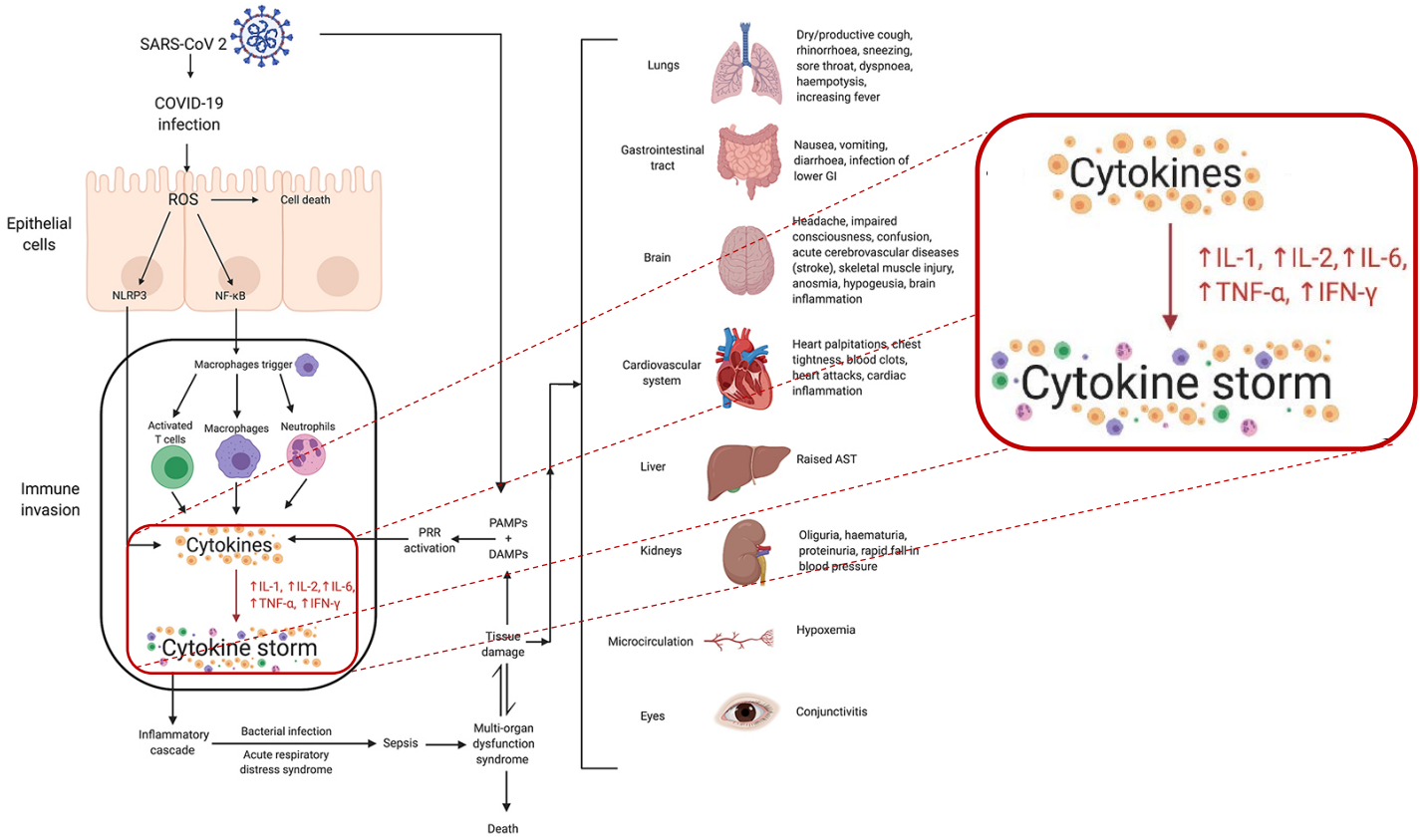


FIGURE 1 | Mechanisms of SARS-CoV-2 associated cytokine storm and associated damages. Infection with SARS-CoV 2 can stimulate a hyperinflammatory immune response wherein epithelial-cell-mediated production of reactive oxygen species (ROS) can cause cell death. ROS can also stimulate the synthesis of NLRP3 and NF-κB which contribute to increased cytokine levels, and thus, the cytokine storm. This essentially causes immune invasion which can lead to clinically relevant conditions such as ARDS, sepsis, MODS and potentially even death. The organs affected as a result of MODS, and their associated symptoms, have been shown. Lower gastrointestinal (GI) is rich in ACE2 receptors and hence at higher risk of infection due to COVID-19. Twenty percent of COVID-19 patients have diarrhea as symptoms. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; ROS, reactive oxygen species; NLRP3, (NOD)-like receptor protein 3 inflammasome; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; PRR, pattern recognition receptors; AST, aspartate aminotransferase; MODS, multiple organ dysfunction syndrome.

Bhaskar S., et al; Front. Immunol. 11: 1648 (2020)

Understanding the crosstalk between the immune system and CNS system cytokine networks

The COVID-19 Pandemic Health System REsilience PROGRAM (REPROGRAM) consortium is an international not-for-profit think-tank for global pandemic preparedness and action

Cytokine Storm in COVID-19—Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper

Frontiers in Immunology July 2020 | Volume 11 | Article 1648

Sonu Bhaskar[1,2,3], Akansha Sinha[1,4], Maciej Banach[1,5,6,7], Shikha Mittoo[1,8], Robert Weissert[1,9], Joseph S. Kass[1,10], Santhosh Rajagopal[1,11], Anupama R. Pai[1,12] and Shelby Kutty[1,13,14]*

[1] Pandemic Health System REsilience PROGRAM (REPROGRAM) Consortium, REPROGRAM Immunity Sub-committee†, [2] Department of Neurology & Neurophysiology, Liverpool Hospital and South Western Sydney Local Health District, Sydney, NSW, Australia, [3] Neurovascular Imaging Laboratory & NSW Brain Clot Bank, Ingham Institute for Applied Medical Research, The University of New South Wales, UNSW Medicine, Sydney, NSW, Australia, [4] The University of New South Wales, UNSW Medicine, Sydney, NSW, Australia, [5] Polish Mother's Memorial Hospital Research Institute, Lodz, Poland, [6] Cardiovascular Research Centre, University of Zielona Góra, Zielona Gora, Poland, [7] Department of Hypertension, Medical University of Lodz, Lodz, Poland, [8] Department of Rheumatology, University Health Network and The University of Toronto, Toronto, ON, Canada, [9] Department of Neurology, University of Regensburg, Regensburg, Germany, [10] Department of Neurology, Ben Taub General Hospital and Alzheimer's Disease and Memory Disorders Center, Baylor College of Medicine, Houston, TX, United States, [11] World Health Organisation, Country Office for India, NPSP, Madurai, India, [12] Department of Neuromicrobiology, National Institute of Mental Health and Neurosciences, Bengaluru, India, [13] Department of Pediatric and Congenital Cardiology, Blalock-Taussig-Thomas Heart Center, John Hopkins Hospital, Baltimore, MD, United States, [14] Johns Hopkins Bloomberg School of Public Health, School of Medicine, John Hopkins University, Baltimore, MD, United States*

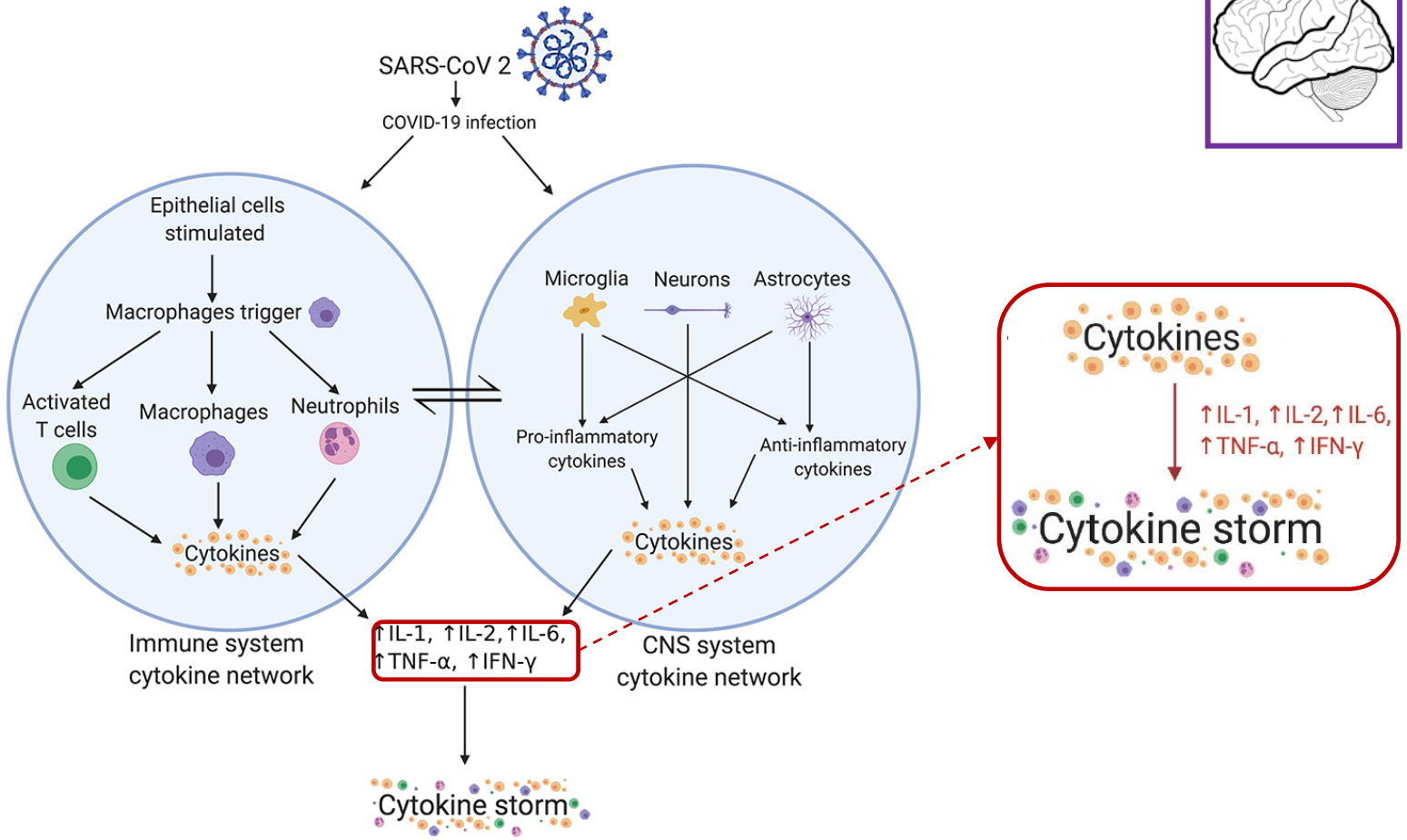


FIGURE 2 | Crosstalk between immune system and CNS system cytokine networks.

Bhaskar S., et al; Front. Immunol. 11: 1648 (2020)

Attempt to decrease levels of reactive oxygen species (ROS), inflammasome and NFκB

While increasing levels of superoxide dismutase and other ROS scavenging enzymes

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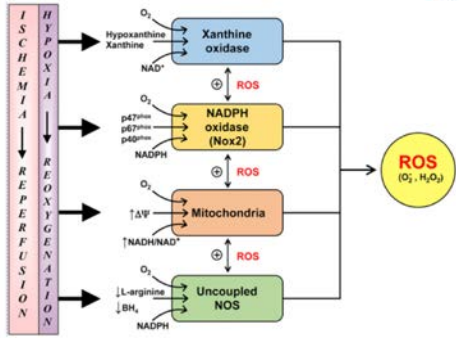
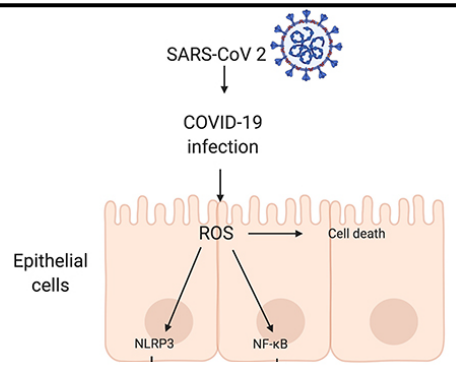


Redox Biology 6 (2015) 524-551



Cytokine production becomes rapidly dysregulated, damaging healthy cells typically first in the lungs but potentially spreading to other organs including the kidneys, heart, blood vessels, and brain. The cascade of cytokine storm-associated damage begins with disruption of the epithelial barrier in the lungs. Activation of NOD, LRR-, and pyrin domain-containing protein 3 (NLRP-3) inflammasome and the relative blunted response of histone deacetylase 2 on nuclear factor kappa betta (NFκB) complex has been suggested to be associated with cytokine storms.

Redox Biology 6 (2015) 524–551

Reperfusion injury and reactive oxygen species: The evolution of a concept

D. Neil Granger[a,*], Peter R. Kvietys[b]

3. Reactive oxygen species contribute to reperfusion injury

The early ROS scavenging studies employed native superoxide distmutase (SOD)

ROS scavenging enzymes, such as SOD, catalase, and glutathione peroxidase, have also provided results that are consistent with a role for ROS as mediators of I/R injury in different organs [64–68].

Bhaskar S., et al; Front. Immunol. 11: 1648 (2020)
Granger D.N., et al.; Redox Biology 6 (2015) 524–551

Reduce the phosphorylation of p38, JNK, IκB to reduce inflammasome driven inflammation process

While increasing levels PPAR to decrease production of pro-inflammatory cytokines

Activation of Toll-Like Receptors and Inflammasome Complexes in the Diabetic Cardiomyopathy-Associated Inflammation

J. Fuentes-Antrás,[1] A. M. Ioan,[1] J. Tuñón,[1] J. Egido,[1,2] and Ó. Lorenzo[1,2]

International Journal of Endocrinology
Volume 2014, Article ID 847827, 10 pages

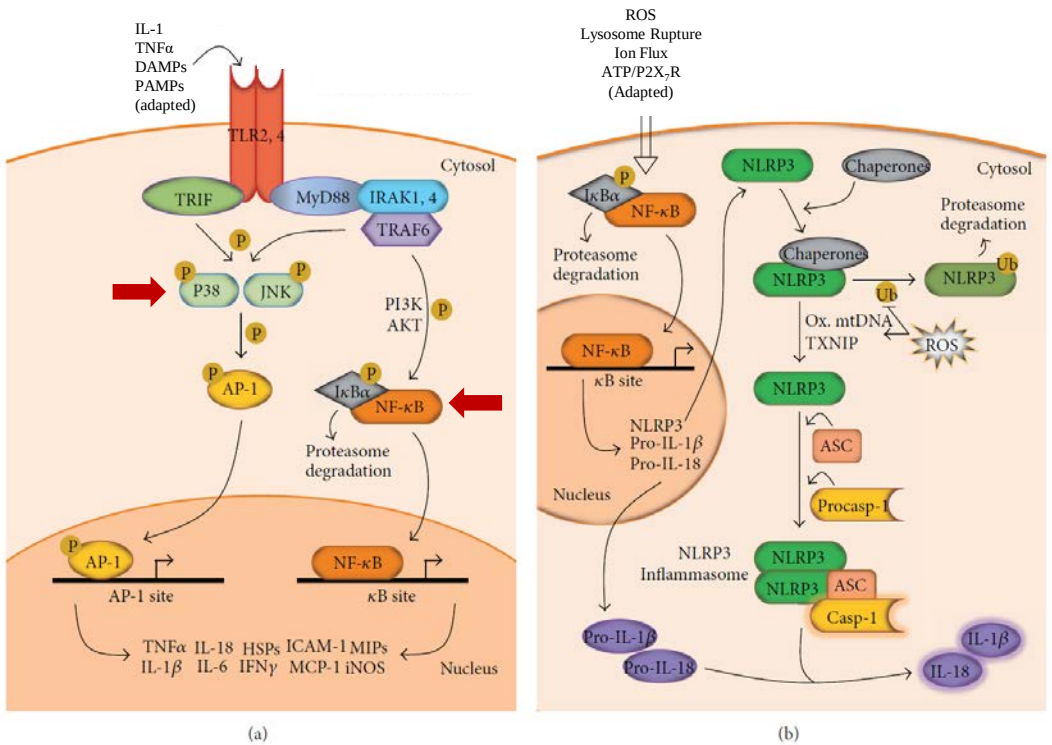


FIGURE 1: TLRs and NLRP3 inflammasome activation in the proinflammatory myocardium. (a) Activation of TLR2 and TLR4, (b) and NLRP3 inflammasome complexes in cardiomyocytes.

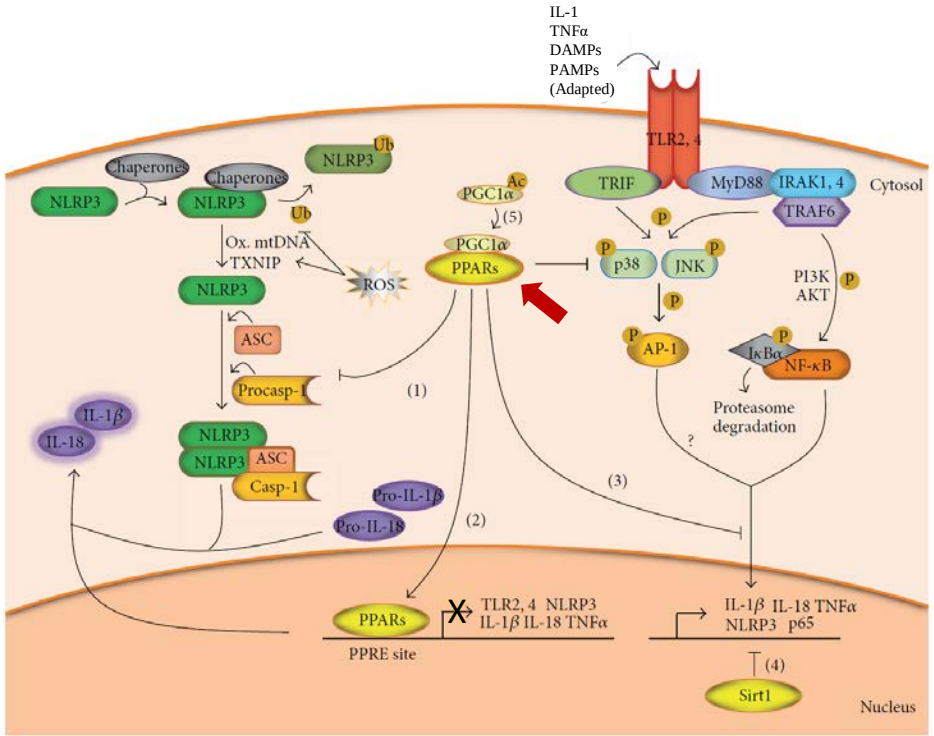


FIGURE 2: Crosstalk between TLRs, NLRP3 inflammasomes and dysregulated metabolic factors in DCM. PPARs and Sirt1 may control NLRP3 inflammasome and TLR pathways by interfering with the inflammasome assembly (1), proinflammatory gene overexpression (2), and NF-κB signaling (3-4). In addition, Sirt1 could mediate PPARs activation by PGC1α deacetylation (5).

Fuentes-Antrás J., et al.; International Journal of Endocrinology Vol 2014, 10 pages

Elevated Inflammasome markers MIP-2 (CXCL2) and KC (CXCL1) are observed in acute lung injury model

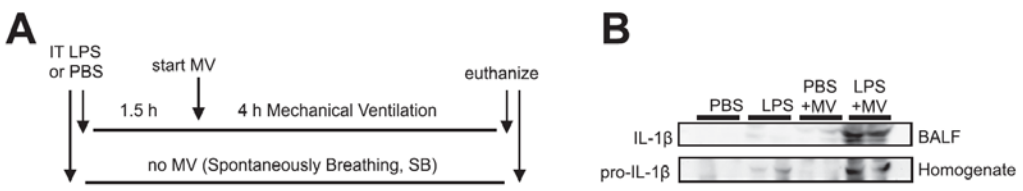
Am J Respir Cell Mol Biol Vol 50, Iss 2, pp 270–280, Feb 2014

The NLRP3 Inflammasome Is Required for the Development of Hypoxemia in LPS/Mechanical Ventilation Acute Lung Injury

Heather D. Jones[1,3], Timothy R. Crother[2,3], Romer A. Gonzalez-Villalobos[4], Madhulika Jupelli[2,3], Shuang Chen[2,3], Jargalsaikhan Dagvadorj[2,3], Moshe Arditi[2,3], and Kenichi Shimada[2,3]

IL-1β is a potent proinflammatory cytokine that is implicated in the pathogenesis of acute respiratory distress syndrome. We hypothesized that LPS and mechanical ventilation (MV) together could lead to IL-1β secretion and the development of acute lung injury (ALI), and that this process would be dependent on caspase-1 and the nucleotide binding domain and leucine-rich repeat (NLR) pyrin domain containing 3 (NLRP3) inflammasome activation.

MV causes alveolar macrophage apoptosis, a key step in the activation of NLRP3 inflammasome and production of IL-1β.



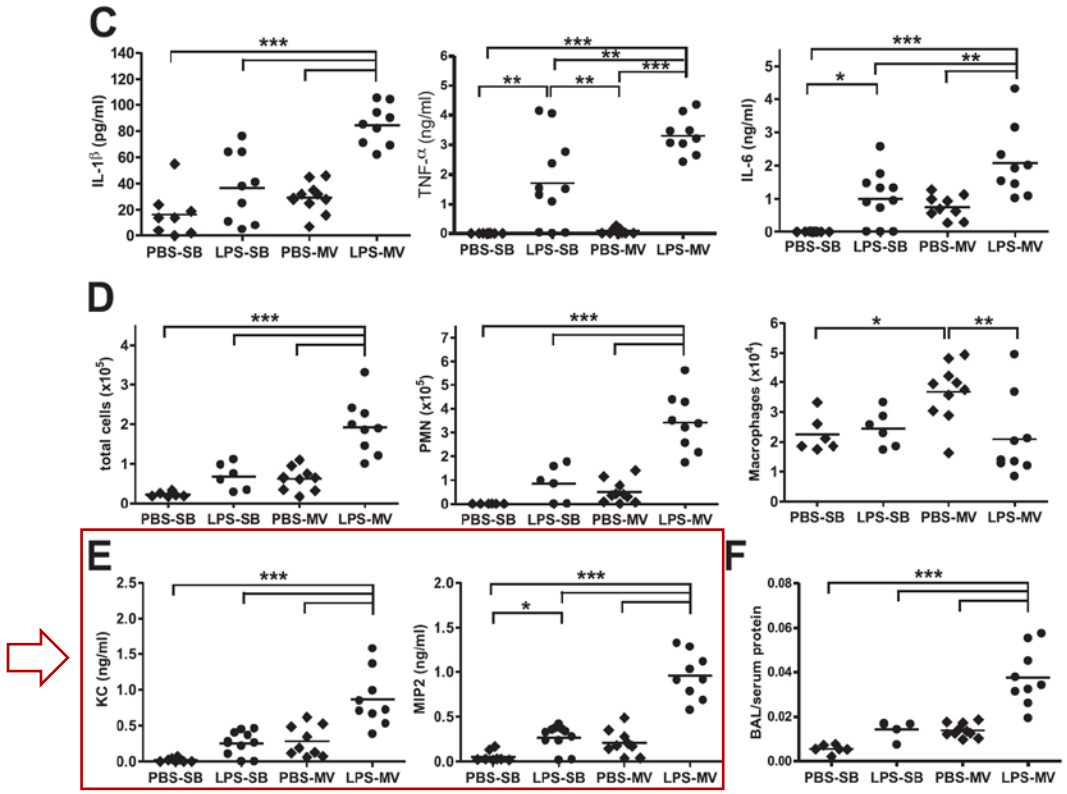
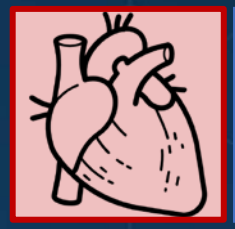


Figure 1. LPS plus mechanical ventilation (MV) increase IL-1β secretion in acute lung injury (ALI). (*A*) A total of 200 ng/g body weight (intratracheal) LPS or PBS was administered to mice. After 90 minutes, some mice were allowed to continue breathing spontaneously (SB, spontaneous breathing; PBS-SB and LPS-SB) and others were anesthetized and placed on MV with tidal volumes of 20 ml/kg and zero positive end-expiratory pressure (PEEP) for 4 hours (PBS-MV and LPS-MV). (*B*) Bronchoalveolar lavage (BAL) fluid (BALF) and lung homogenate were assayed for mature IL-1β and pro–IL-1β proteins, respectively, by immunoblot ($n = 2$ mice/condition). BALF was assayed for: (*C*) IL-1β, TNF-α, and IL-6 concentrations; (*D*) total cells, neutrophils, and macrophages; and (*E*) chemokines, keratinocyte-derived chemokine (KC) and macrophage inflammatory protein 2 (MIP2). (*F*) Serum and BAL protein concentrations were measured for determination of BAL/serum protein ratios ($n = 8$–10/group). Data are representative of three separate experiments. $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$. PMN, polymorphonuclear cells.

The consortium suggests an ensemble of pharmaceutical products to address cytokine storm in COVID-19



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Frontiers in Immunology July 2020 | Volume 11 | Article 1648

Sonu Bhaskar[1,2,3], Akansha Sinha[1,4], Maciej Banach[1,5,6,7], Shikha Mittoo[1,8], Robert Weissert[1,9], Joseph S. Kass[1,10], Santhosh Rajagopal[1,11], Anupama R. Pai[1,12] and Shelby Kutty[1,13,14]*

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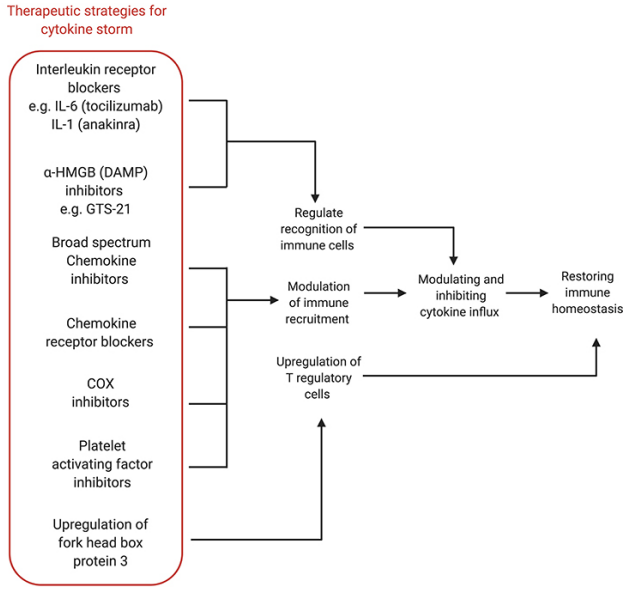

FIGURE 3 | Various therapeutic strategies for targeting cytokine storm.

TABLE 2 | Various immunomodulatory strategies targeting cytokine storm in COVID-19 patients.

Strategies or agents	Studies and indications
Cyclooxygenase (COX) inhibitors	The use of COX inhibitors in COVID-19 has not been evaluated. It should be used on a case-by-case basis.
Corticosteroids	The use of high-dose corticosteroids is not recommended in cases of COVID-19.
Anti-tumor necrosis factor (TNFa) therapy	Anti-TNFa is widely used for several autoimmune diseases. Its use in COVID-19 should be explored.
Intravenous immunoglobulin (IVIg) therapy	Due to its lack of side effects, IVIg may be beneficial in COVID-19 patients especially in settings of cytokine storm or hyperinflammatory state and septic shock.
Angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin-II-receptor-antagonists (ARBs)	The use of ACEI/ARB is associated with lower mortality in COVID-19 in-patients.
Tranilast	An anti-allergic drug which inhibits NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) which plays an important role in the pathogenesis of COVID-19.
Statin	*In-silico* evidence on efficacy of statins as SARS-CoV-2 Mpro inhibitors
Chloroquine/Hydroxychloroquine	Strong anti-inflammatory activity may be of use in targeting cytokine storm.
Peroxisome proliferator-activated receptor (PPAR) agonists	PPAR agonists increase the production of anti-inflammatory cytokines and thus, may be beneficial in COVID-19 patients. PPAR-γ agonists are often used in treatment of type 2 diabetes.
5′ adenosine monophosphate-activated protein kinase (AMPK) activators	AMPK activators such as metformin have direct anti-inflammatory effects. Could have benefit in reducing cytokine storm in COVID-19 infected patients.
Macrolide	The antiviral effects of macrolide may benefit COVID-19 patients.
Arbidol	Arbidol is an antiviral that has been shown to prevent COVID-19 infection.
OX40 (CD134)	There are several limitations in the therapeutic use of OX40.
Antioxidants	Antioxidants, such as vitamin C, have anti-inflammatory effects when administered intravenously.
Suppressor of cytokine signaling (SOCS)	SOCS is involved in regulating antiviral immunity.
Extracorporeal therapy	Extracorporeal therapy is a proposed mechanism to remove cytokines in septic patients
Pyrrolidinedithiocarbamate (PDTC) ammonium	Inhibits IκB phosphorylation and thus blocks NF-κB translocation to the nucleus and reduces the expression of downstream cytokines.
Diacerein	An inhibitor of IL-1B—an acute response cytokine which appears in hypercytokinemia.

Bhaskar S., et al; Front. Immunol. 11: 1648 (2020)

The consortium suggests targeting cytokine storm via the JAK-STAT pathway…and its crosstalk to other pathways

Attempt to decrease levels of MCP-1, GM-CSF and STAT-3 (ICAM-1)

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Targets for Hesperidin in COVID-19

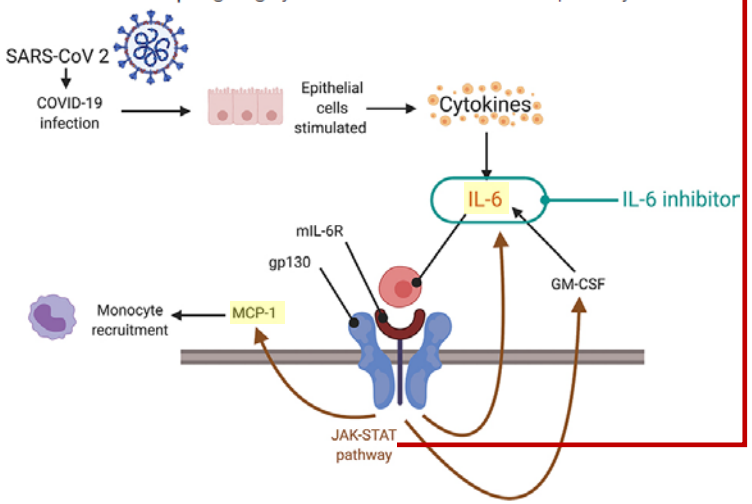
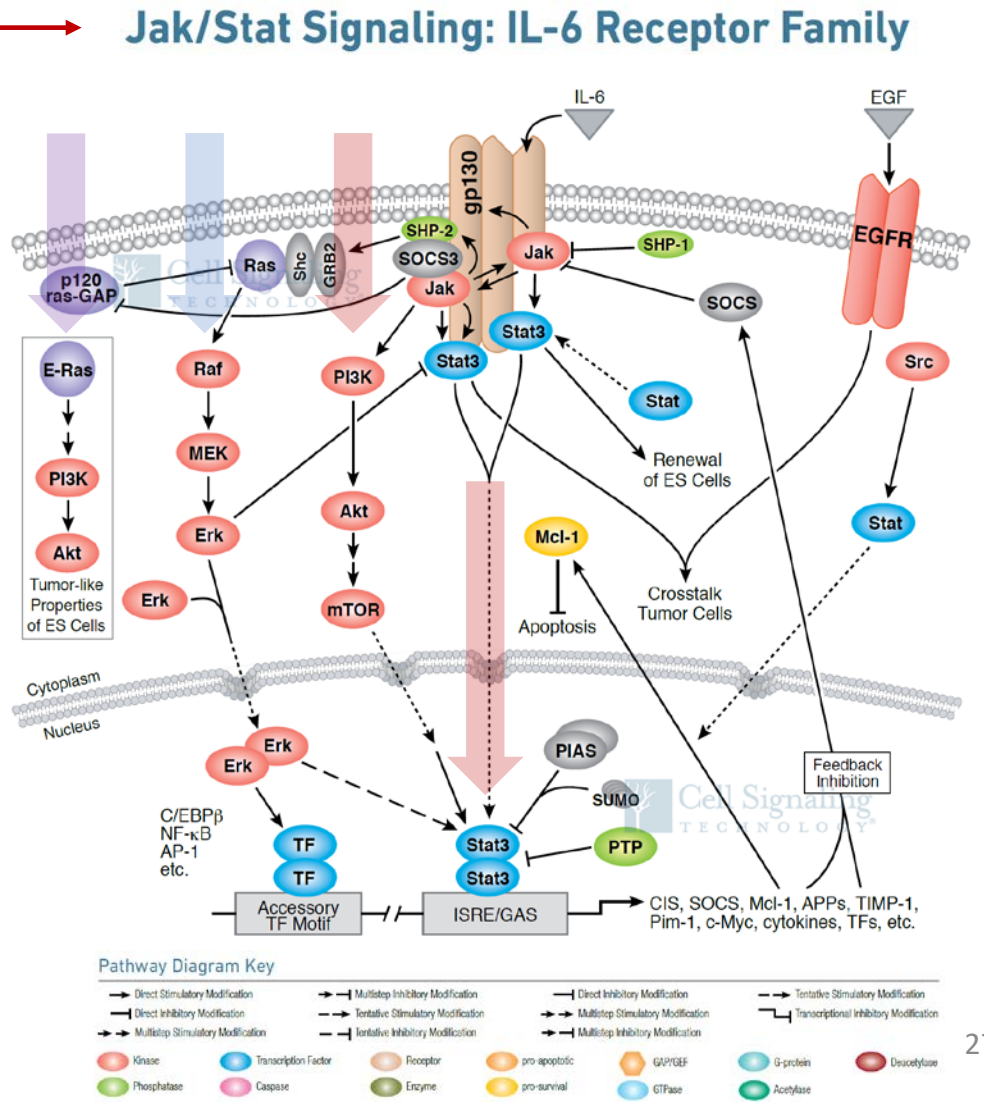


FIGURE 4 | Targeting cytokine storm via the JAK-STAT pathway.

Cardiovascular Research (2014) 102, 281–289

STAT3, a key regulator of cell-to-cell communication in the heart

For example, a JAK3/STAT3-mediated up-regulation of adhesion molecules in the endothelium is mediated by TNF-α as shown in endotoxemic mice, which displayed an increase in phosphorylated STAT3 levels in the heart and subsequent up-regulation of ICAM-1 expression in the arteriolar and capillary endothelium after LPS injection.[14] In cardiomyocytes, IL-6 enhances the expression of ICAM-1 via activation of STAT3.[105] Elevated levels of adhesion molecules at the cell membrane promote migration of inflammatory cells into the tissue and activation at the site of infection or injury.



Bhaskar S., et al; Front. Immunol. 11: 1648 (2020)
Haghikia A., et al.; Cardiovascular Research (2014) 102, 281–289
Cell Signaling Technology Jak/Stat signaling pathway: IL-6 Receptor family

The REPROGRAM therapeutic approaches for cytokine storm is based on data obtained from COVID-19 patients

Cytokine level differences between healthy, non-ICU and ICU on admission

Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China

Lancet 2020; 395: 497–506

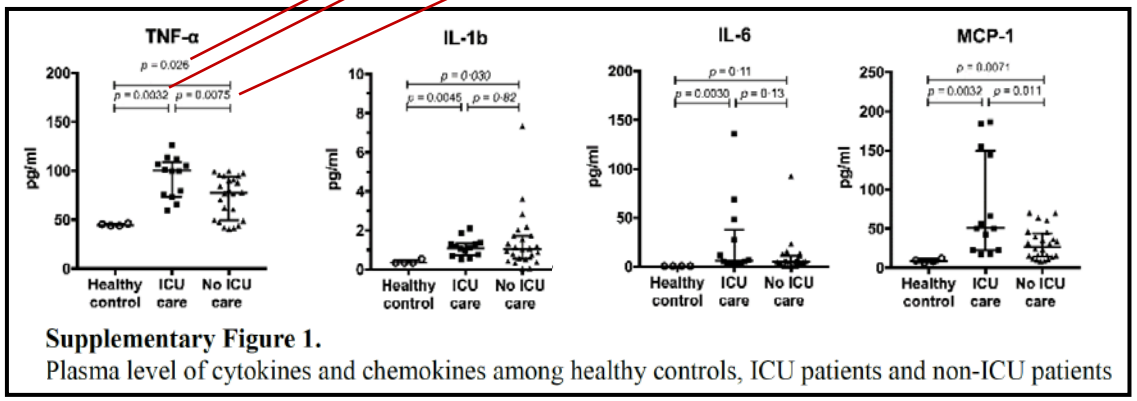
Results

By Jan 2, 2020, 41 admitted hospital patients were identified as laboratory-confirmed 2019-nCoV infection in Wuhan.

Of the 41 patients, 13 (32%) were admitted to the ICU because they required high-flow nasal cannula or higher-level oxygen support measures to correct hypoxaemia.

Initial plasma IL1B, IL1RA, IL7, IL8, IL9, IL10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNFα, and VEGF concentrations were higher in both ICU patients and non-ICU patients than in healthy adults (appendix pp 6–7). Plasma levels of IL5, IL12p70, adults and patients infected with 2019-nCoV. Further comparison between ICU and non-ICU patients showed that plasma concentrations of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα were higher in ICU patients than non-ICU patients.

The REPROGRAM Consortium Position Paper		Lancet 2020; 395: 497-506 p value		
	Preferred Regulation	Healthy Control	ICU Care	Non-ICU Care
Interleukin-6 (Il-6)	↓	0.11		
		0.0030		0.13
Interleukin-ILβ (IL-1β)	↓	0.030		
		0.0045		0.82
Tumor Necrosis Factor-α (TNFα)	↓	0.026		
		0.0032		0.0075
Reactive Oxygen Species (ROS)	↓			
Peroxisome Proliferator-Activated Receptors — PPAR Agonist	↑			
Nuclear Factor of kappa light polypeptide gene enhancer in B-cells Inhibitor — IκB	↓			
Nuclear Factor kappa-light-chain-enhancer of activated B cells — NFκ-B	↓			
Superoxyde Dismutase (SOD)	↑			
Monocyte Chemoattractant Protein-1 — MCP-1	↓	0.007		
		0.0032		0.011
Signal Transducer and Activator of Transcription 3 (STAT3) — Intercellular Adhesion Molecule 1 — ICAM-1	↓			
Macrophage Inflammatory Protein 2 — (MIP-2/CXCL2)	↓			
Keratinocyte Chemo-Attractant (KC/CXCL1)	↓			
Mitogen Activated Protein Kinase P38 (p38)	↓			
c-Jun N-terminal kinases (JNK)	↓			



Supplementary Figure 1.
Plasma level of cytokines and chemokines among healthy controls, ICU patients and non-ICU patients

Huang C. et al.; Lancet 2020; 395: 497-506

	All patients (n=41)	ICU care (n=13)	No ICU care (n=28)	p value
Duration from illness onset to first admission	7·0 (4·0–8·0)	7·0 (4·0–8·0)	7·0 (4·0–8·5)	0·87
Oxygen support	..	..	..	<0·0001
Nasal cannula	27 (66%)	1 (8%)	26 (93%)	..
Non-invasive ventilation or high-flow nasal cannula	10 (24%)	8 (62%)	2 (7%)	..
Invasive mechanical ventilation	2 (5%)	2 (15%)	0	..
Invasive mechanical ventilation and ECMO	2 (5%)	2 (15%)	0	..
Prognosis	..	..	..	0·014
Hospitalisation	7 (17%)	1 (8%)	6 (21%)	..
Discharge	28 (68%)	7 (54%)	21 (75%)	..
Death	6 (15%)	5 (38%)	1 (4%)	..

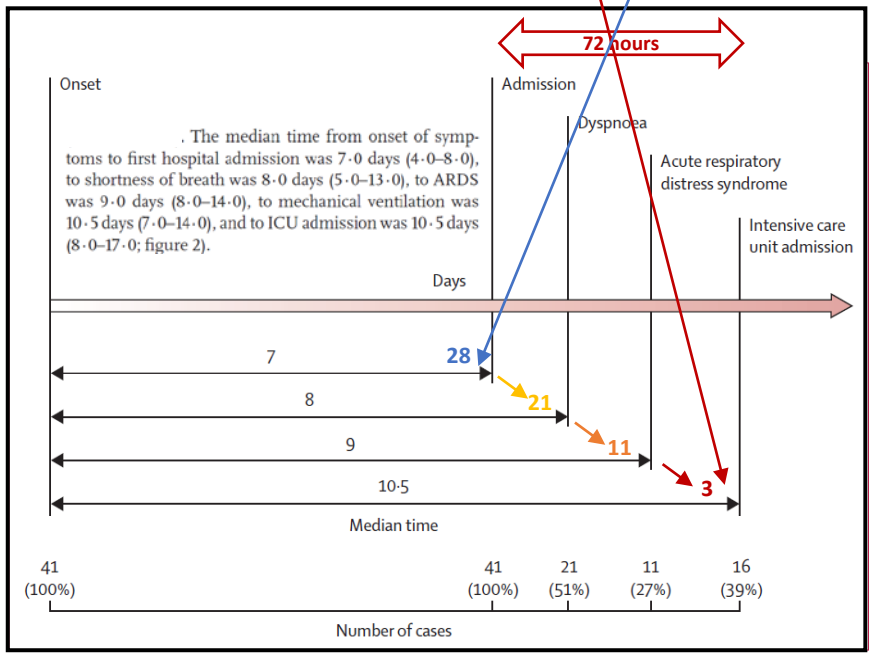
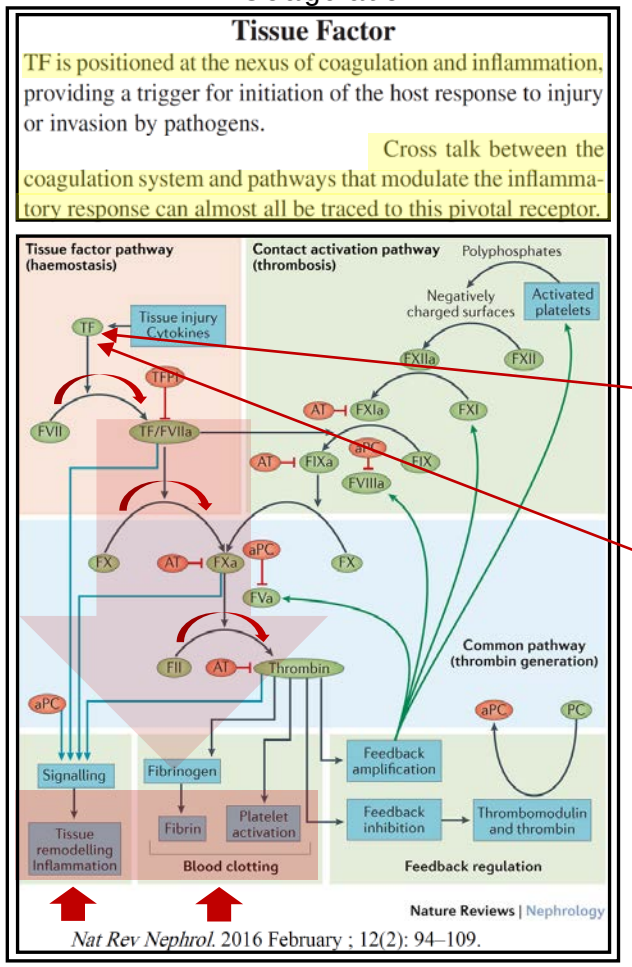


Figure 2: Timeline of 2019-nCoV cases after onset of illness

Coagulation and inflammatory pathways do not exist “in silos” hence, inflammation mediators plays a role in coagulation

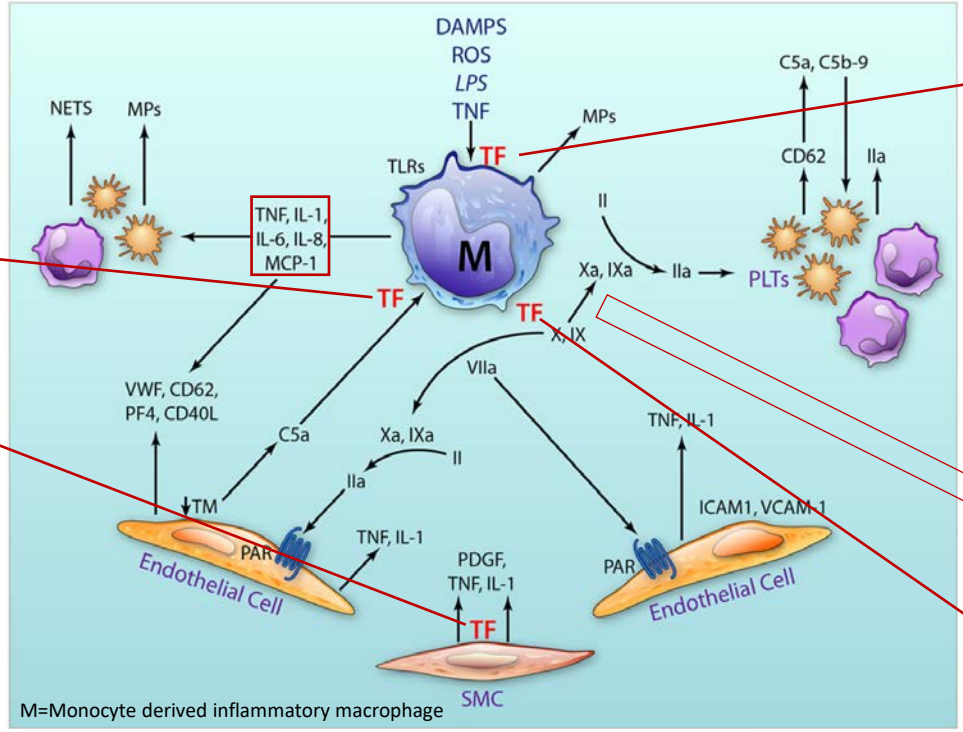
Crosstalk pathways between coagulation and inflammation

Coagulation



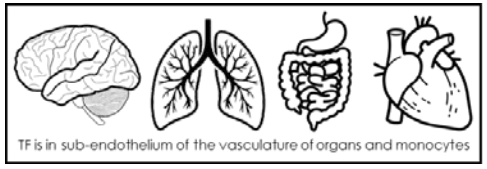
Cross Talk Pathways Between Coagulation and Inflammation

Circ Res. 2016;118:1392-1408.

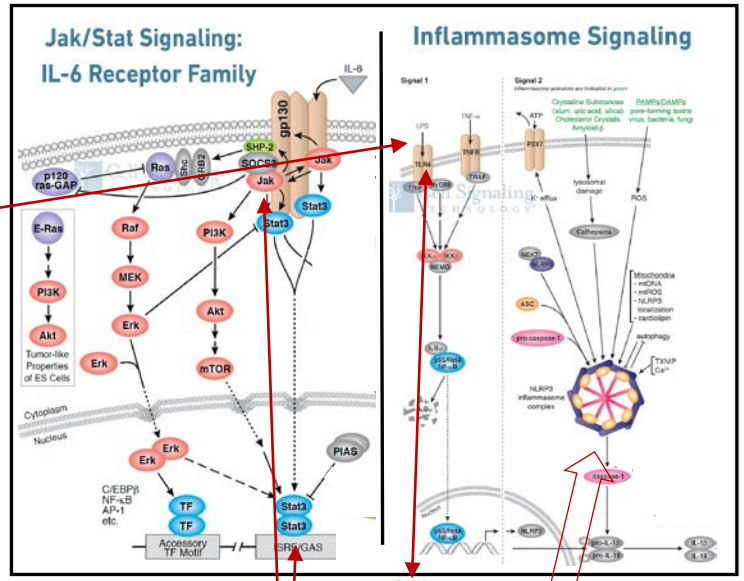


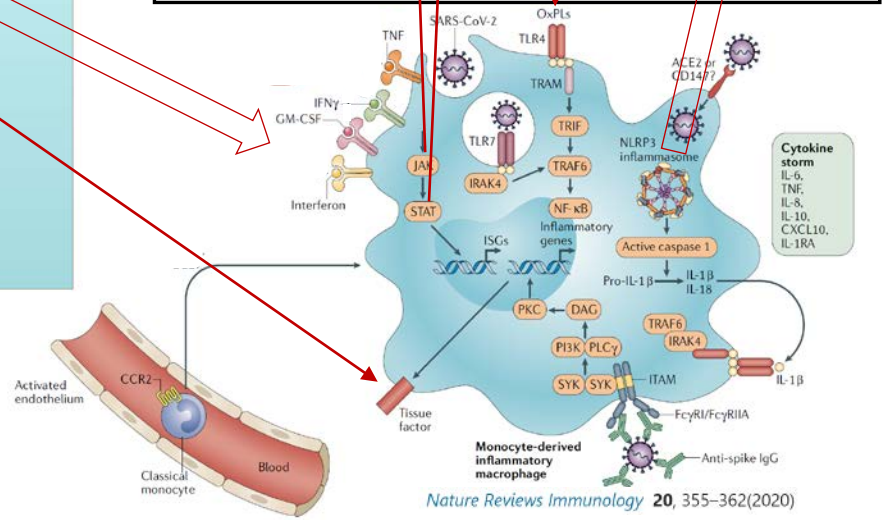
M=Monocyte derived inflammatory macrophage

Central role of tissue factor (TF) in the interplay between coagulation and inflammation.



Inflammation





Madhusudhan T., et al.; Nat Rev Nephrol. 2016 February ; 12(2): 94–109.
Foley J.H., et al.; Circ Res. 2016;118:1392-1408
Merad M., et al.;Nature Reviews Immunology volume 20, pages355–362(2020)
Cell Signaling Technology Imflammasome signaling
Cell Signaling Technology Jak/Stat signaling pathway: IL-6 Receptor family

Hesperidin to address cytokine storm in COVID-19 finds support in the scientific literature

PubMed identified >80 papers related to the benefit of Hesperidin in inflammation

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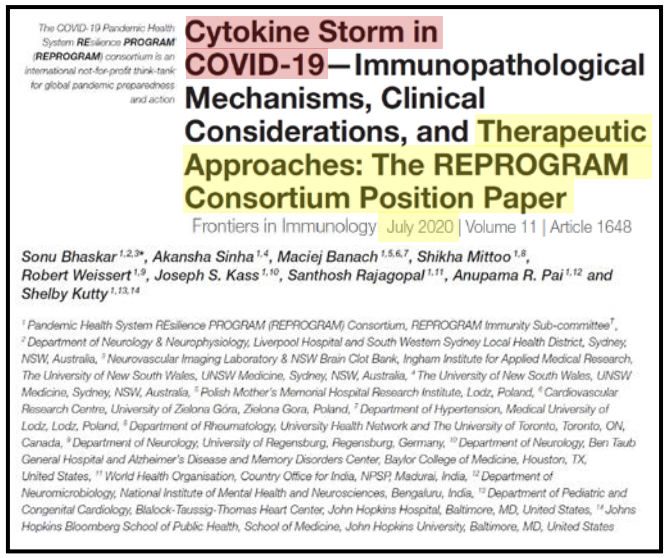
Modulate inflammation and cytokine storm



The COVID-19 Pandemic Health System REsilience PROGRAM (REPROGRAM) consortium is an international not-for-profit think-tank for global pandemic preparedness and action

Cytokine Storm in COVID-19—Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper

Frontiers in Immunology July 2020 | Volume 11 | Article 1648

Sonu Bhaskar[1,2,3*], Akansha Sinha[1,4], Maciej Banach[1,5,6,7], Shikha Mittoo[1,8], Robert Weissert[1,9], Joseph S. Kass[1,10], Santhosh Rajagopal[1,11], Anupama R. Pai[1,12] and Shelby Kutty[1,13,14]

[1] Pandemic Health System REsilience PROGRAM (REPROGRAM) Consortium, REPROGRAM Immunity Sub-committee[7], [2] Department of Neurology & Neurophysiology, Liverpool Hospital and South Western Sydney Local Health District, Sydney, NSW, Australia, [3] Neurovascular Imaging Laboratory & NSW Brain Clot Bank, Ingham Institute for Applied Medical Research, The University of New South Wales, UNSW Medicine, Sydney, NSW, Australia, [4] The University of New South Wales, UNSW Medicine, Sydney, NSW, Australia, [5] Polish Mother's Memorial Hospital Research Institute, Lodz, Poland, [6] Cardiovascular Research Centre, University of Zielona Góra, Zielona Gora, Poland, [7] Department of Hypertension, Medical University of Lodz, Lodz, Poland, [8] Department of Rheumatology, University Health Network and The University of Toronto, Toronto, ON, Canada, [9] Department of Neurology, University of Regensburg, Regensburg, Germany, [10] Department of Neurology, Ben Taub General Hospital and Alzheimer's Disease and Memory Disorders Center, Baylor College of Medicine, Houston, TX, United States, [11] World Health Organisation, Country Office for India, NPSP, Madurai, India, [12] Department of Neuromicrobiology, National Institute of Mental Health and Neurosciences, Bengaluru, India, [13] Department of Pediatric and Congenital Cardiology, Blalock-Taussig-Thomas Heart Center, John Hopkins Hospital, Baltimore, MD, United States, [14] Johns Hopkins Bloomberg School of Public Health, School of Medicine, John Hopkins University, Baltimore, MD, United States

The REPROGRAM Consortium Position Paper		The Hesperidin Study: Hesperidin for 14 day		
Inflammatory Mediators	Preferred Regulation			
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Nuclear Factor kappa-light-chain-enhancer of activated B cells NFκ-B	↓			
Superoxyde Dismutase (SOD)	↑			
Monocyte Chemoattractant Protein-1 MCP-1	↓			
Signal Transducer and Activator of Transcription 3 (STAT3) Intercellular Adhesion Molecule 1 ICAM-1	↓			
Macrophage Inflammatory Protein 2 (MIP-2/CXCL2)	↓			
Keratinocyte Chemo-Attractant (KC/CXCL1)	↓			
Mitogen Activated Protein Kinase P38 (p38)	↓			
c-Jun N-terminal kinases (JNK)	↓			

Jak/Stat Signaling: IL-6 Receptor Family

Bhaskar S., et al; Front. Immunol. 11: 1648 (2020)

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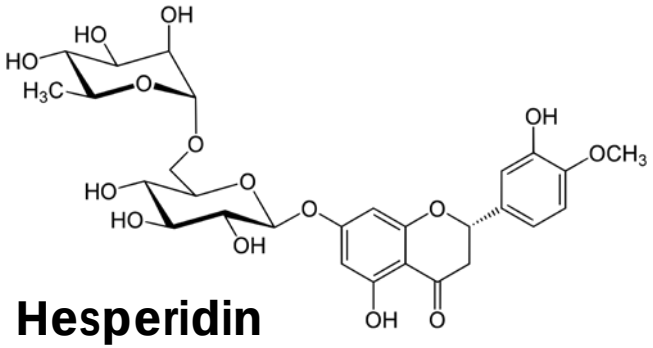
The Hesperidin Study

Part III

Hesperidin to Modulate Inflammatory Mediators, Cytokine Storm and Potential Neurological and Cardiopulmonary Injuries



Hesperidin

To reduce SARS-CoV-2 viral load and cytokine storm for 14 days

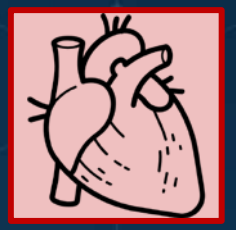
M Health Fairview Experts Turn To ECMO Treatment To Save 38-Year-Old Father And Triathlete From COVID-19

HEALTH
University of Minnesota

https://www.mhealth.org/childrens/blog/2020/april-2020/m-health-fairview-experts-turn-to-ecmo-to-save-covid-19-patient

Hesperidin modulated the inflammatory mediators in an acute myocardial infarct model and decreased the infarct size

Decreased cytokines IL-6, TNFα, IL-Iβ, chemokine MCP-1, ICAM (STAT3) and increased both PPAR and SOD



MOLECULAR MEDICINE REPORTS 17: 1261-1268, 2018

Preventive effect of hesperidin modulates inflammatory responses and antioxidant status following acute myocardial infarction through the expression of PPAR-γ and Bcl-2 in model mice

CHUNYING MENG[1], ZEHENG GUO[2], DAGANG LI[1], HANWEI LI[1], JIANBIN HE[1], DINGGUO WEN[1] and BIN LUO[1]

AMI is a pathological process accompanied by an inflammatory response. Inflammatory cytokines are important in ventricular remodeling following myocardial infarction (5). At the early stage of infarction, the local inflammatory reaction is prominent and, with high levels of inflammatory cell infiltration, inflammatory cells and inflammatory cytokine can adversely affect cell-transplant therapy (6).

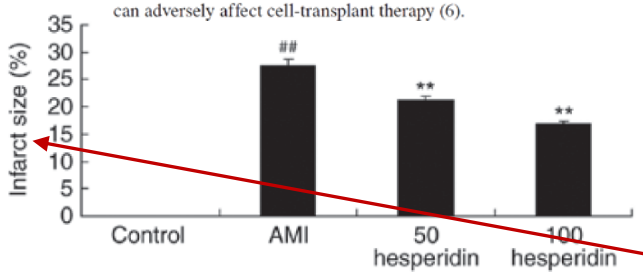
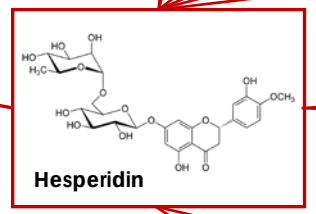
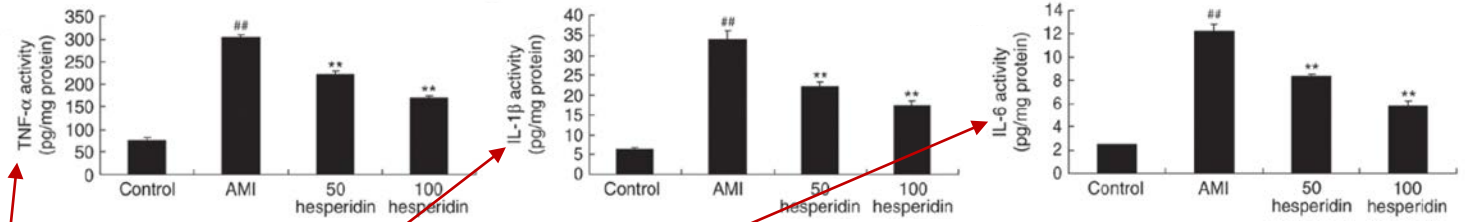
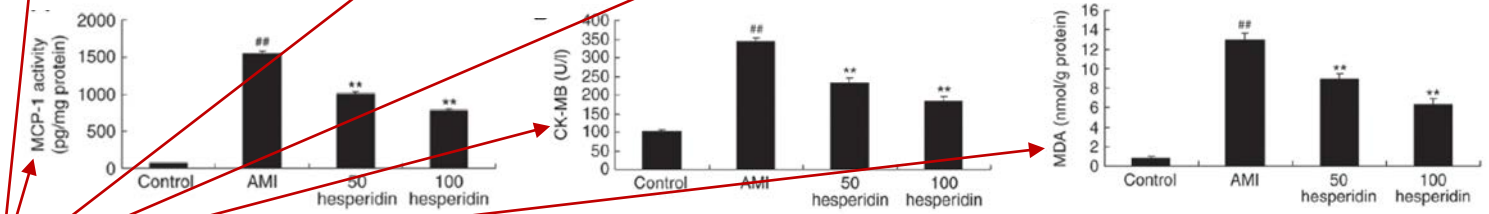
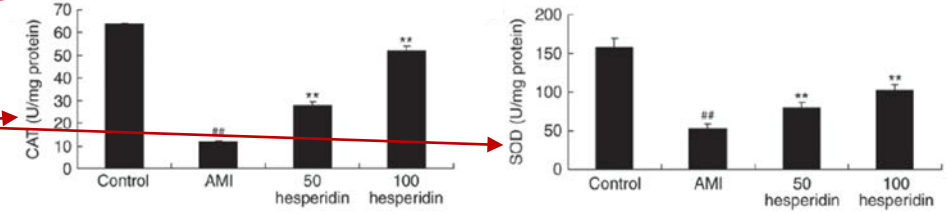


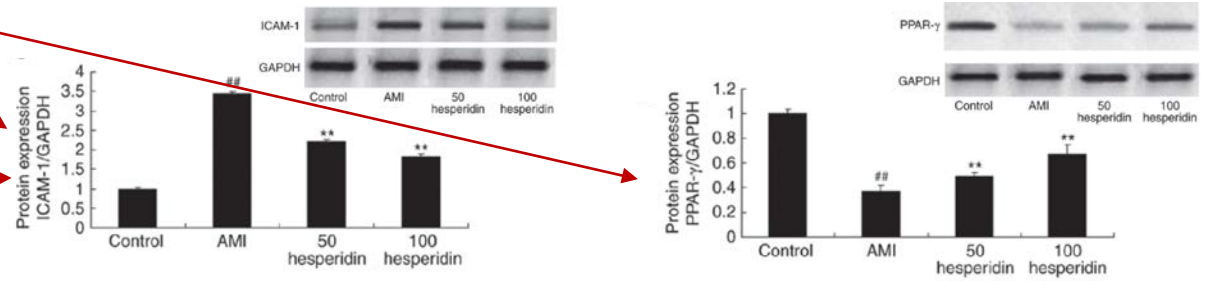
Figure 2. Preventive effect of hesperidin on infarct size in AMI mice. ##P<0.01, compared with the control group; **P<0.01, compared with AMI model mice group. AMI, acute myocardial infarction; Control, control group; 50 hesperidin, 50 mg/kg hesperidin-treated group; 100 hesperidin, 100 mg/kg hesperidin-treated group.











The AMI Model: Anesthesia was performed by inhalation of 1.0-2.0% isoflurane gas. A left thoracotomy was performed to expose the heart, and myocardial infarction was induced and ligated using an 8-0 silk suture at the left anterior descending coronary artery. Following closure of the chest wall, the mice were extubated. The mice were administered orally or hesperidin for 2 weeks. Following treatment, the animals were sacrificed under 1.0-2.0% isoflurane gas. The body weights and heart weights were recorded and were stored at -80°C until analysis.

Cardiovascular Research (2014) **102**, 281–289

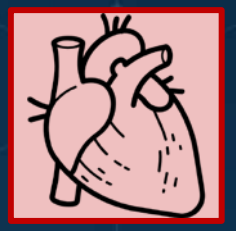
STAT3, a key regulator of cell-to-cell communication in the heart

For example, a JAK3/STAT3-mediated up-regulation of adhesion molecules in the endothelium is mediated by TNF-α as shown in endotoxemic mice, which displayed an increase in phosphorylated STAT3 levels in the heart and subsequent up-regulation of ICAM-1 expression in the arteriolar and capillary endothelium after LPS injection.[14] In cardiomyocytes, IL-6 enhances the expression of ICAM-1 via activation of STAT3.

Meng C., et al.; molecular medicine reports 17: 1261-1268 2018
Haghikia A., et al.; Cardiovascular Research (2014) 102, 281–289

Hesperidin reduced cardiac troponin I (cTnI) and protected against myocardial I/R injury via the PI3K/AKT/mTOR pathway

Univariable cTnI odds ratio were 80:1(level >28) in risk factors associated with COVID-19 in-hospital death



INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE 42: 1917-1924, 2018

Inhibition of autophagy via activation of PI3K/Akt/mTOR pathway contributes to the protection of hesperidin against myocardial ischemia/reperfusion injury

XUEFEI LI[1-3], XIAORONG HU[1-3], JICHUN WANG[1-3], WEIPAN XU[4], CHUNFENG YI[5], RUISONG MA[1-3] and HONG JIANG[1-3]

[1]Department of Cardiology, Renmin Hospital of Wuhan University; [2]Cardiovascular Research Institute of Wuhan University; [3]Hubei Key Laboratory of Cardiology, Wuhan, Hubei 430060; [4]Department of Cardiology, Huangshi Center Hospital, Affiliated Hospital of Hubei Polytechnic University, Huangshi, Hubei 435000; [5]Department of Cardiology, Wuhan No. 1 Hospital, Wuhan, Hubei 430060, P.R. China

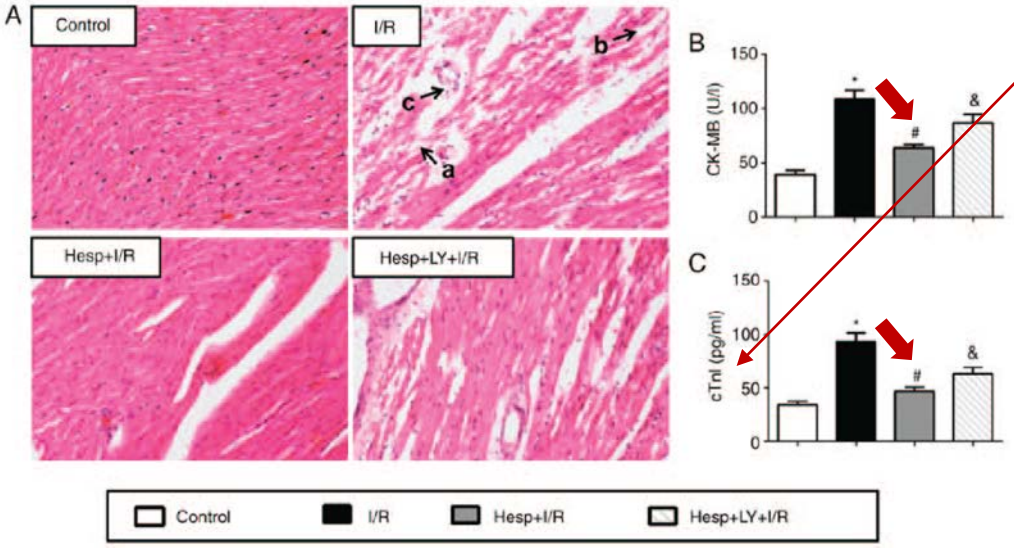
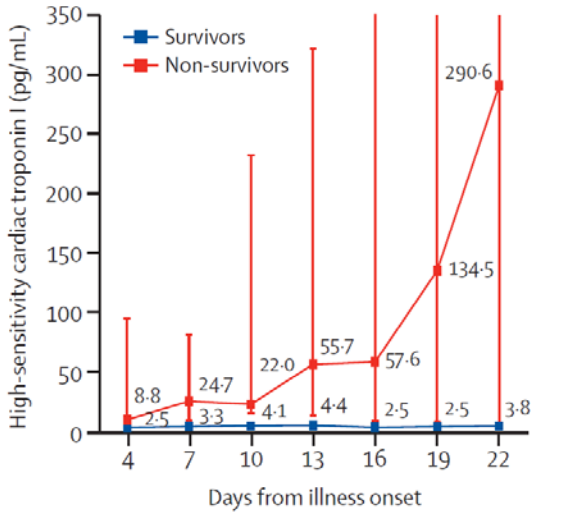


Figure 3. Effect of hesperidin on cardiac injury induced by I/R. (A) Representative images from hematoxylin and eosin staining (x200 magnification) indicating histopathological changes in the myocardium: a, ruptured myocardial fiber; b, edema in between myocardial fibers; c, recruited inflammatory cells. (B) Serum level of CK-MB (n=6). (C) Serum level of cTnI (n=6). *P<0.05 vs. Control group; #P<0.05 vs. I/R group; &P<0.05 vs. Hesp+I/R group. CK-MB, creatine kinase-MB; cTnI, cardiac troponin I; Hesp, hesperidin; I/R, ischemia/reperfusion; LY, LY294002.

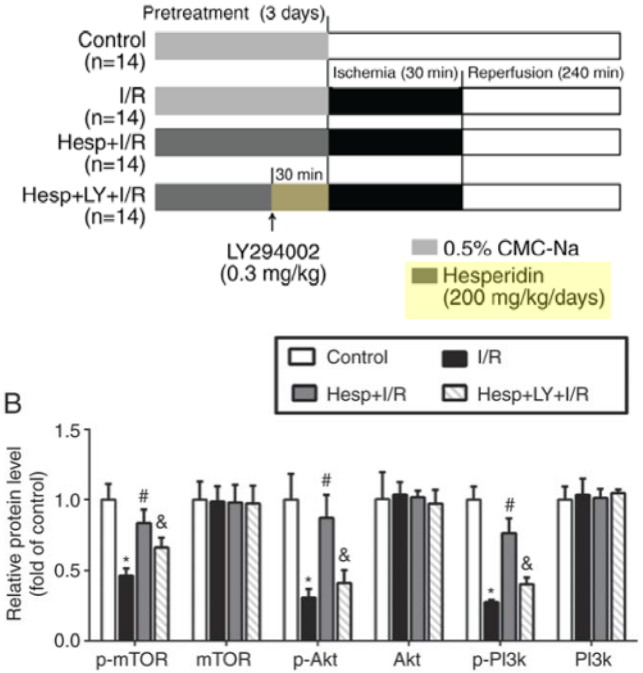
Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study *Lancet* 2020; 395: 1054–62



	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Laboratory findings				
High-sensitivity cardiac troponin I, pg/mL				
≤28	1 (ref)	..	..	..
>28	80·07 (10·34–620·36)	<0·0001	..	..

OR=odds ratio. SOFA=Sequential Organ Failure Assessment. qSOFA=Quick SOFA. ALT=alanine aminotransferase. IL-6=interleukin-6. *Per 1 unit increase.

Table 3: Risk factors associated with in-hospital death



The present study aimed to investigate whether hesperidin inhibited I/R-induced excessive myocardial autophagy through activating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway. Male adult rats were pretreated with hesperidin for a total of 3 days prior to ischemia in the absence or presence of LY294002, a PI3K inhibitor, and then subjected to ischemia for 30 min followed by reperfusion for 4 h. Myocardial infarct size was measured by Evans blue/triphenyltetrazolium chloride staining. Hematoxylin and eosin staining was used for observing the histological changes in the heart, and the serum levels of creatine kinase-MB (CK-MB) and cardiac troponin I (cTnI) were measured by enzyme-linked immunosorbent assay.

Li X., et al.; International journal of molecular medicine 42: 1917-1924, 2018
Zhou F. et al.; Lancet 2020; 395 :1054-1062

Hesperidin to address cytokine storm in COVID-19 finds in the scientific literature

PubMed identified >80 papers related to the benefit of hesperidin in inflammation

The Hesperidin Study: Mechanism 2

Modulate inflammation and cytokine storm

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Cytokine Storm in COVID-19—Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper

Frontiers in Immunology July 2020 | Volume 11 | Article 1648

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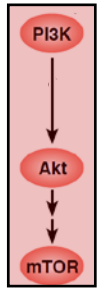
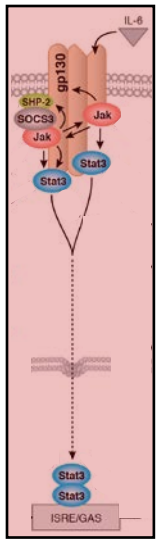
Peroxisome Proliferator-Activated Receptors PPAR Agonist	↑	✓		
Nuclear Factor of kappa light polypeptide gene enhancer in B-cells inhibitor IκB	↓			
Nuclear Factor kappa-light-chain-enhancer of activated B cells NFκ-B	↓			
Superoxyde Dismutase (SOD)	↑	✓		
Monocyte Chemoattractant Protein-1 MCP-1	↓	✓		
Signal Transducer and Activator of Transcription 3 (STAT3) Intercellular Adhesion Molecule 1 ICAM-1	↓	✓		
Macrophage Inflammatory Protein 2 (MIP-2/CXCL2)	↓			
Keratinocyte Chemo-Attractant (KC/CXCL1)	↓			
Mitogen Activated Protein Kinase P38 (p38)	↓			
c-Jun N-terminal kinases (JNK)	↓			
Cardiac Troponin I (cTnI)	↓	✓		

Jak/Stat Signaling: IL-6 Receptor Family





Bhaskar S., et al; Front. Immunol. 11: 1648 (2020)
Cell Signaling Technology Jak/Stat signaling pathway: IL-6 Receptor family

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Hesperidin modulated the inflammatory mediators in an acute lung injury model and dose dependently decreased NFκB

Decreased cytokines IL-6, TNFα, IL-Iβ, chemokine MIP-2, NF-κB and increased PPAR

European Journal of Pharmacology 769 (2015) 333–341

Hesperetin attenuates ventilator-induced acute lung injury through inhibition of NF-κB-mediated inflammation

Hongzhong Ma [a,*], Xiaoli Feng [b], Suchun Ding [a]

Treatment with hesperetin dramatically improved the histology of lung tissue, and reduced the wet/dry ratio, myeloperoxidase activity, protein concentration, and production of tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β, and MIP-2 in the bronchoalveolar lavage fluid of rats with ventilator-induced acute lung injury. Additionally, our study indicated that this protective effect of hesperetin results from its ability to increase the expression of peroxisome proliferator-activated receptor (PPAR)-γ and inhibit the activation of the nuclear factor (NF)-κB pathway. These results suggest that hesperetin may be a potential novel therapeutic candidate for protection against ventilator-induced acute lung injury.

2.2. Experimental design

Rats were randomly divided into six groups: the lung-protective ventilation group (the healthy control) ($n=20$, LV group); injurious ventilation group or ventilator-induced ALI group ($n=20$, HV group); vehicle-treated ALI group ($n=20$, HV+vehicle group); Hsp (10 mg/kg)-treated ALI group ($n=20$, HV+Hsp (10 mg) group); Hsp (20 mg/kg)-treated ALI group ($n=20$, HV+Hsp (20 mg) group); and Hsp (40 mg/kg)-treated ALI group ($n=20$, HV+Hsp (40 mg) group). Rats were killed at the indicated time points after receiving their treatment for the induced ALI.

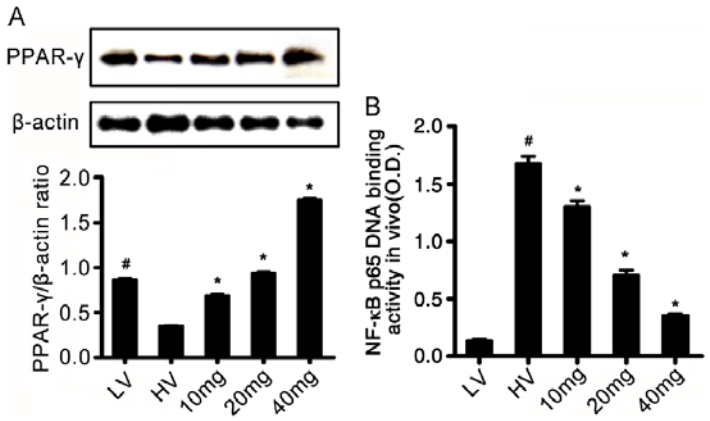


Fig. 7. Effect of Hsp on PPARγ expression and DNA binding activity of NF-κB p65 in infiltrated inflammatory cells.

In Vivo

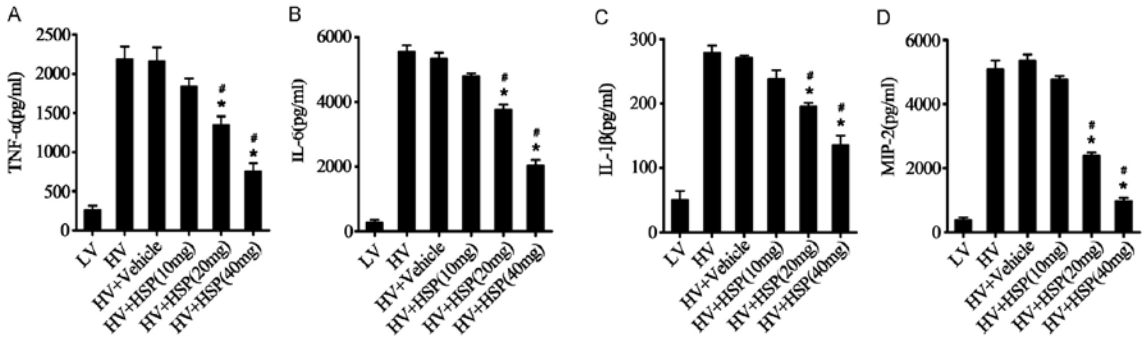


Fig. 3. Effect of Hsp on the production of inflammatory cytokines in the BALF of ventilator-induced ALI rats. (A) The concentration of TNF-α in the BALF of rats with the indicated treatment was monitored using an ELISA. (B) The concentration of IL-6 in the BALF of rats with the indicated treatment was monitored using an ELISA. (C) The concentration of IL-1β in the BALF of rats with the indicated treatment was monitored using an ELISA. (D) The concentration of MIP-2 in the BALF of rats with the indicated treatment was monitored using an ELISA. Results are expressed as the mean ± S.E.M. from the 20 rats in each group. *$P<0.05$ compared with the HV group; #$P<0.05$ compared with the HV+vehicle group.

In Vitro

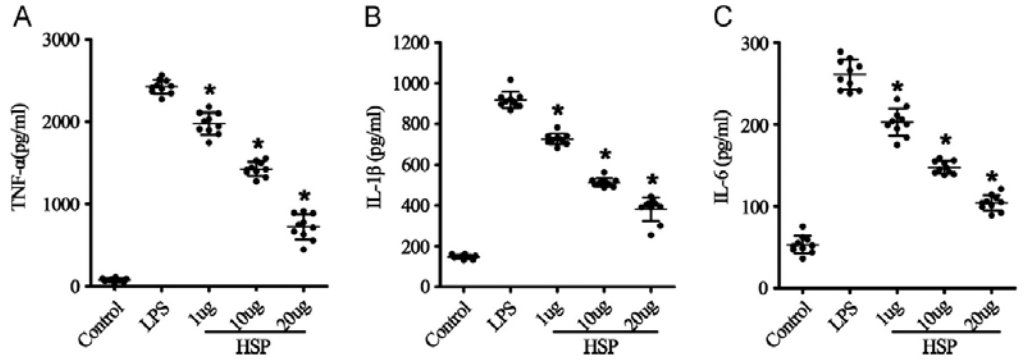


Fig. 6. Effect of Hsp on the expression of TNF-α, IL-1β, and IL-6 *in vitro*. One h before LPS (1 μg/ml) administration, different concentrations of Hsp (1, 10, or 20 μg/ml) were added to the cultures of alveolar macrophages. The secretion of TNF-α (A), IL-1β (B), and IL-6 (C) in the culture supernatants was determined using an ELISA. Results are expressed as the mean ± S.E.M. from the 10 rats in each group. *$P<0.05$ compared with the LPS treated.

Ma H., et al.; european journal of pharmacology 769 (2015) 333-341

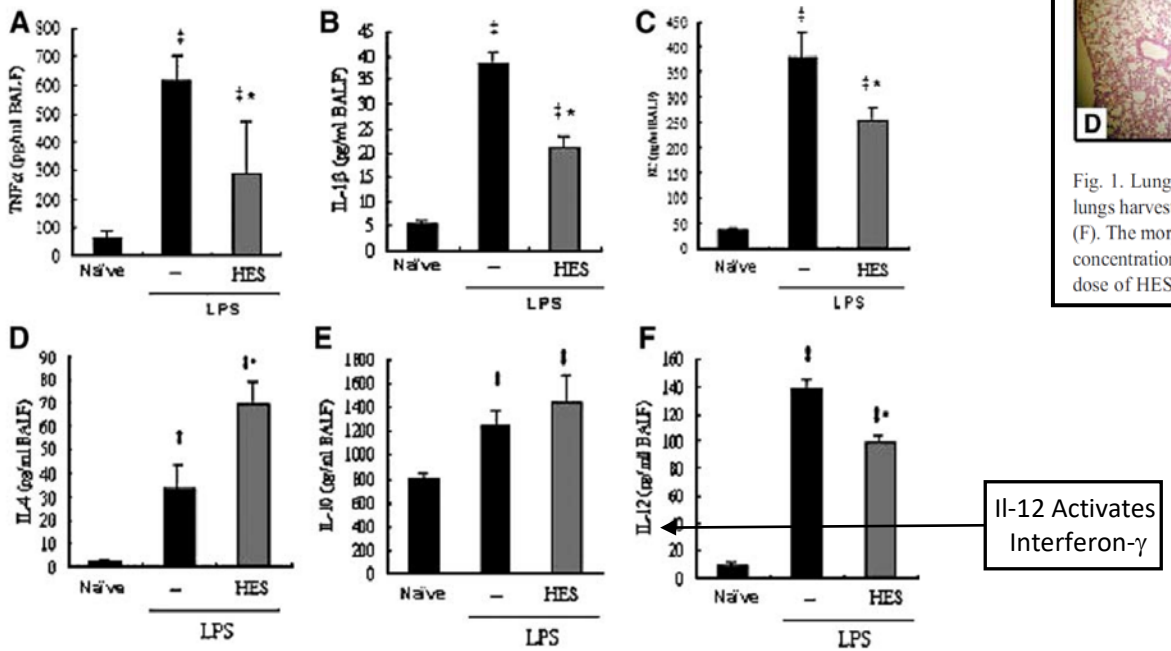
Hesperidin modulated the inflammatory mediators in an acute lung injury model and dose dependently decreased IL-12 (activates INFγ)

Decreased the chemokine KC and phosphorylation of p38, JNK and IκB

Life Sciences 80 (2007) 1821–1831

The immunomodulation of endotoxin-induced acute lung injury by hesperidin *in vivo* and *in vitro*

Chia-Chou Yeh [a,c], Shang-Jyh Kao [d], Chih-Che Lin [a], Shulhn-Der Wang [a], Ching-Ju Liu [a], Shung-Te Kao [b,c,*]



Il-12 Activates Interferon-γ

Fig. 3. Concentrations of proinflammatory cytokine? chemokine, and anti-inflammatory cytokine in BALF. Cytokines were measured in the BALF and lung tissue obtained 24 h after intratracheal instillation of LPS or naïve. Mice receiving LPS were treated with HES. And the concentration of TNF-α (A), IL-1β (B), KC (C), IL-4 (D), IL-10 (E), and IL-12 (F) was detected by ELISA.

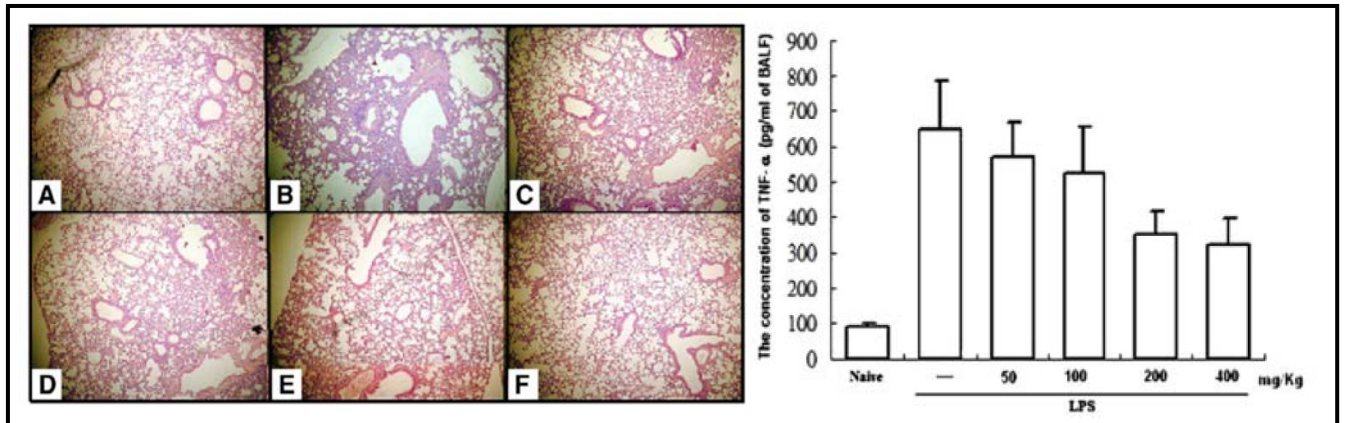
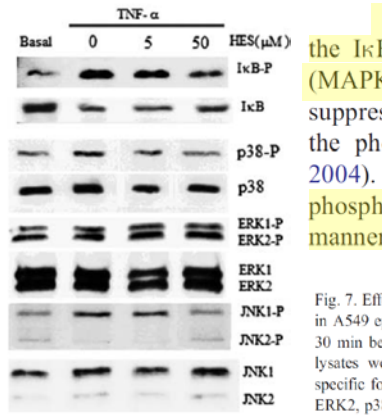


Fig. 1. Lung morphology and TNF-α concentration in BALF after mice challenged with lipopolysaccharide (LPS) or HES. Representative histological sections of lungs harvested 24 h naïve (A), after the intratracheal instillation of LPS-treated mice (B), 50 mg/kg HES (C), 100 mg/kg HES (D), 200 mg/kg HES (E) or 400 mg/kg (F). The morphologic alterations induced by LPS were reduced by HES treatment. Pictures are representative of $n=6$ mice/treatment group. Magnification ×100. The concentration of TNF-α was measured in the BALF (G) obtained 24 h after intratracheal instillation of LPS or none and mice receiving LPS were treated with different dose of HES.



NF-κB and AP-1 binding activity were controlled by the IκB pathway and the mitogen-activated protein kinase (MAPK) pathway. It has been demonstrated that flavonoids suppressed NF-κB and AP-1 binding activity by inhibiting the phosphorylation of IκB, p38, and JNK (Chen et al., 2004). Our study demonstrated that HES inhibited the phosphorylation of IκB, p38, and JNK in dose-dependent manner.

Fig. 7. Effect of HES on TNF-α-induced IκB, ERK1/2, p38, or JNK activation in A549 epithelial cells. In A, cells were pretreated with 5 or 50 μM HES for 30 min before incubation with 40 ng/ml TNF-α for 30 min, then whole cell lysates were prepared and subjected to Western blotting using antibodies specific for the phosphorylated form of IκB, ERK1/2, p38, JNK, or for IκB, ERK2, p38, or JNK as described under Materials and methods.

Yeh C-C., et al.; Life Sciences 80 (2007) 1821-1831

Hesperidin modulated the inflammasome mediators in a sepsis-induced lung injury model and dose dependently decreased ROS

Decreased inflammasome cytokines IL-6, TNFα, IL-Iβ and increased the oxygenation index

Protective Effect of Hesperidin Against Sepsis-Induced Lung Injury by Inducing the Heat-Stable Protein 70 (Hsp70)/Toll-Like Receptor 4 (TLR4)/ Myeloid Differentiation Primary Response 88 (MyD88) Pathway

© Med Sci Monit, 2019; 25: 107-114

Lung injury was induced by sepsis in all animals, in which sepsis was produced by cecal ligation and puncture (CLP). Animals were treated with hesperidin 10 and 20 mg/kg i.v. 30 min after the surgery. Oxygenation index and lung injury score were determined and levels of pro-inflammatory mediators and markers of oxidative stress were also estimated in the lung tissues. Moreover, expression of caspase-3, B-cell lymphoma (Bcl-2), Toll-like receptor 4 (TLR4), heat-stable protein 70 (Hsp70) and myeloid differentiation primary response 88 (MyD88) protein was estimated by Western blot assay and immunofluorescence assay.

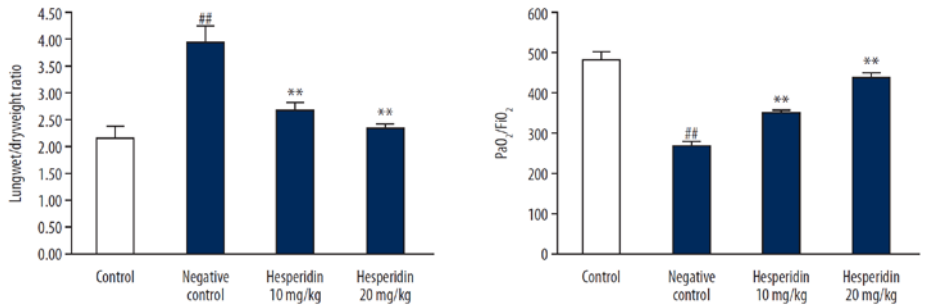


Figure 1. Effect of hesperidin on oxygenation index and wet/dry weight ratio of lung in CLP-induced lung injury mice. Mean ±SEM (n=6). ## p<0.01 than control group. ** p<0.01 than negative control group.

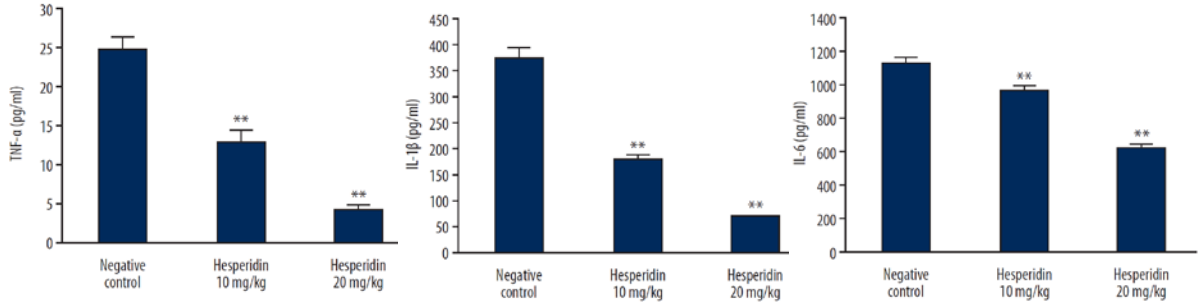


Figure 3. Effect of hesperidin on the level of pro-inflammatory mediator in the lung tissue of CLP-induced lung injury mice. Mean ±SEM (n=6). ** p<0.01 than negative control group.

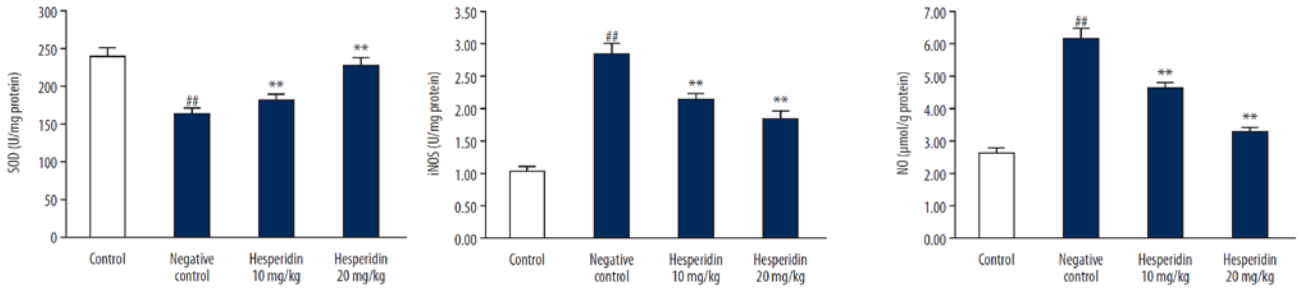


Figure 4. Effect of hesperidin on markers of oxidative stress in lung tissue of CLP-induced lung injury mice. Mean ±SEM (n=6). ## p<0.01 than control group; * p<0.05, ** p<0.01 than negative control group.

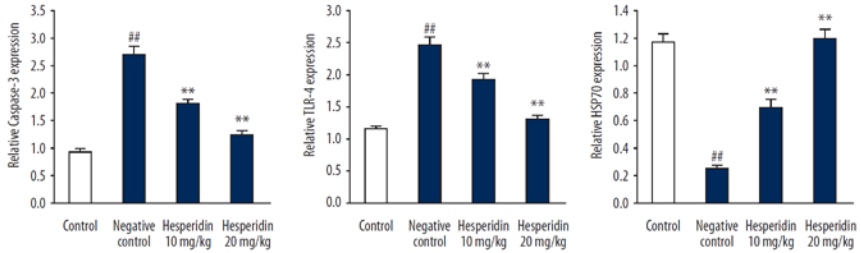


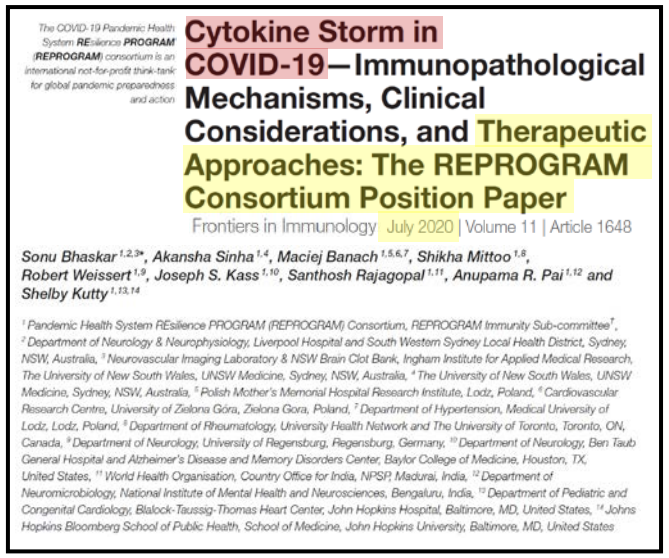
Figure 5. Effect of hesperidin on the expression of Bcl-2, caspase-3, TLR-4, and HSP70 protein in the lung tissue of CLP-induced lung injury mice. Mean ±SEM (n=6). ## p<0.01 than control group; ** p<0.01 than negative control group.

Hesperidin to address cytokine storm in COVID-19 finds support in the scientific literature (7 papers/ 3 organs)

PubMed identified >80 papers related to the benefit of Hesperidin in inflammation

The Hesperidin Study: Mechanism 2

Modulate inflammation and cytokine storm



The COVID-19 Pandemic Health System REsilience PROGRAM (REPROGRAM) consortium is an international not-for-profit think-tank for global pandemic preparedness and action

Cytokine Storm in COVID-19—Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper

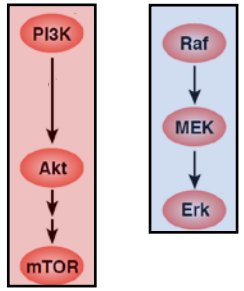
Frontiers in Immunology July 2020 | Volume 11 | Article 1648

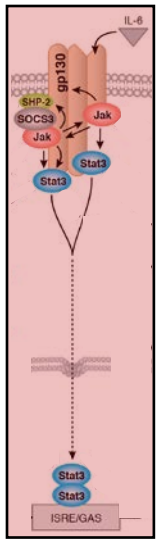
Sonu Bhaskar[1,2,3*], Akansha Sinha[1,4], Maciej Banach[1,5,6,7], Shikha Mittoo[1,8], Robert Weissert[1,9], Joseph S. Kass[1,10], Santhosh Rajagopal[1,11], Anupama R. Pai[1,12] and Shelby Kutty[1,13,14]

[1] Pandemic Health System REsilience PROGRAM (REPROGRAM) Consortium, REPROGRAM Immunity Sub-committee[7], [2] Department of Neurology & Neurophysiology, Liverpool Hospital and South Western Sydney Local Health District, Sydney, NSW, Australia, [3] Neurovascular Imaging Laboratory & NSW Brain Clot Bank, Ingham Institute for Applied Medical Research, The University of New South Wales, UNSW Medicine, Sydney, NSW, Australia, [4] The University of New South Wales, UNSW Medicine, Sydney, NSW, Australia, [5] Polish Mother's Memorial Hospital Research Institute, Lodz, Poland, [6] Cardiovascular Research Centre, University of Zielona Góra, Zielona Gora, Poland, [7] Department of Hypertension, Medical University of Lodz, Lodz, Poland, [8] Department of Rheumatology, University Health Network and The University of Toronto, Toronto, ON, Canada, [9] Department of Neurology, University of Regensburg, Regensburg, Germany, [10] Department of Neurology, Ben Taub General Hospital and Alzheimer's Disease and Memory Disorders Center, Baylor College of Medicine, Houston, TX, United States, [11] World Health Organisation, Country Office for India, NPSP, Madurai, India, [12] Department of Neuromicrobiology, National Institute of Mental Health and Neurosciences, Bengaluru, India, [13] Department of Pediatric and Congenital Cardiology, Blalock-Taussig-Thomas Heart Center, John Hopkins Hospital, Baltimore, MD, United States, [14] Johns Hopkins Bloomberg School of Public Health, School of Medicine, John Hopkins University, Baltimore, MD, United States

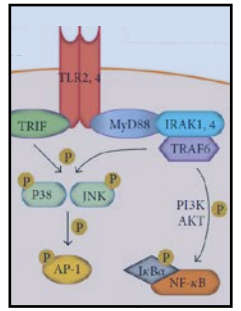
The REPROGRAM Consortium Position Paper			The Hesperidin Study: Hesperidin for 14 day		
Inflammatory Mediators		Preferred Regulation			
Interleukin-6 (Il-6)		↓	✓	✓	
Interleukin-ILβ (IL-1β)		↓	✓	✓	
Tumor Necrosis Factor-α (TNFα)		↓	✓	✓	
Reactive Oxygen Species (ROS)		↓		✓	
Peroxisome Proliferator-Activated Receptors	PPAR Agonist	↑	✓	✓	
Nuclear Factor of kappa light polypeptide gene enhancer in B-cells inhibitor	IκB	↓		✓	
Nuclear Factor kappa-light-chain-enhancer of activated B cells	NFκ-B	↓		✓	
Superoxyde Dismutase (SOD)		↑	✓	✓	
Monocyte Chemoattractant Protein-1	MCP-1	↓	✓		
Signal Transducer and Activator of Transcription 3 (STAT3)	Intercellular Adhesion Molecule 1 ICAM-1	↓	✓		
Macrophage Inflammatory Protein 2	(MIP-2/CXCL2)	↓		✓	
Keratinocyte Chemo-Attractant (KC/CXCL1)		↓		✓	
Mitogen Activated Protein Kinase P38 (p38)		↓		✓	
c-Jun N-terminal kinases (JNK)		↓		✓	
Cardiac Troponin I (cTnI)		↓	✓		

Jak/Stat Signaling: IL-6 Receptor Family





Inflammasome Complexes



Int J Endocrinol. 2014: 847827

Bhaskar S., et al; Front. Immunol. 11: 1648 (2020)

Cell Signaling Technology Jak/Stat signaling pathway: IL-6 Receptor family

Fuentes-Antrás J., et al.; International Journal of Endocrinology Vol 2014,10 pages

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Hesperidin decreased neuronal apoptosis and cognitive impairment through the PI3/Akt/PTEN and NFκB signaling pathways

Levels of cytokines IL-6, TNFα, IL-Iβ and phosphorylation of NFκB and IκB were decreased

The Effects of Hesperidin on Neuronal Apoptosis and Cognitive Impairment in the Sevoflurane Anesthetized Rat are Mediated Through the PI3/Akt/PTEN and Nuclear Factor-κB (NF-κB) Signaling Pathways

Med Sci Monit, 2020; 26: e920522
DOI: 10.12659/MSM.920522

Neonatal rat study groups

Sixty neonatal rats, weighing between 16–21 gm, were randomized into five groups. Group I (n=12) was the control group of non-anesthetized rats without treatment with hesperidin (HPD). Group II (n=12) included the sevoflurane anesthetized rats not treated with HPD. Group III (n=12) included the sevoflurane anesthetized rats treated with an oral dose of 25 mg/kg/day (HPD25). Group IV (n=12) included the sevoflurane anesthetized rats treated with an oral dose of 50 mg/kg/day (HPD50). Group V (n=12) included the sevoflurane anesthetized rats treated with an oral dose of 100 mg/kg/day (HPD100).

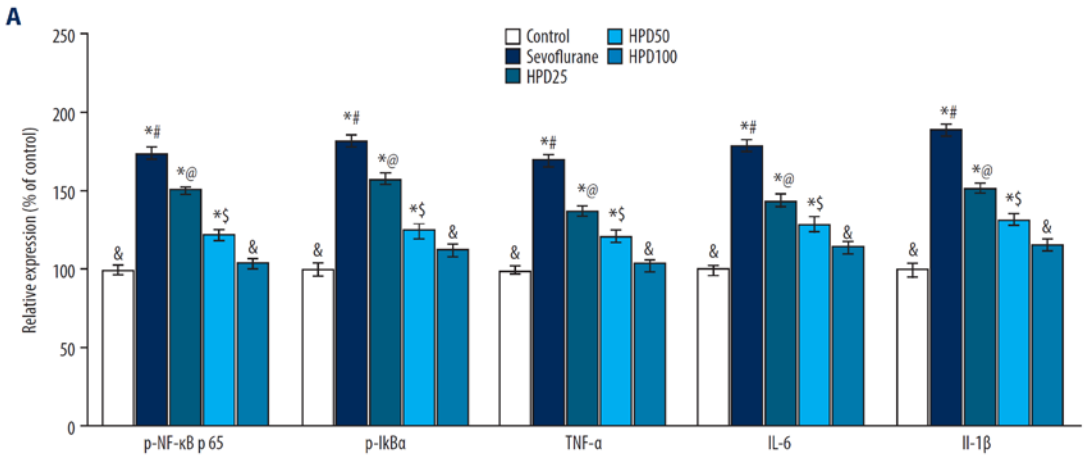

Figure 5. Hesperidin (HPD) treatment modulated the components of the NF-κB pathway in the hippocampus of neonatal rats exposed to sevoflurane anesthesia. (**A, B**) Relative protein expression values shown graphically. Hesperidin treatment resulted in significant inhibition of NF-κB signaling resulting in reduced transcription of cytokines and inflammatory markers and upregulation of anti-apoptotic proteins. Values are represented as the mean±standard deviation (SD) (n=6). The symbol '&' indicates p<0.05 compared with the control group. The symbols '*, #, @, $' indicate intragroup mean values that differ from each other at p<0.05, as calculated by one-way analysis of variance (ANOVA), and then analyzed by Duncan's multiple range test.

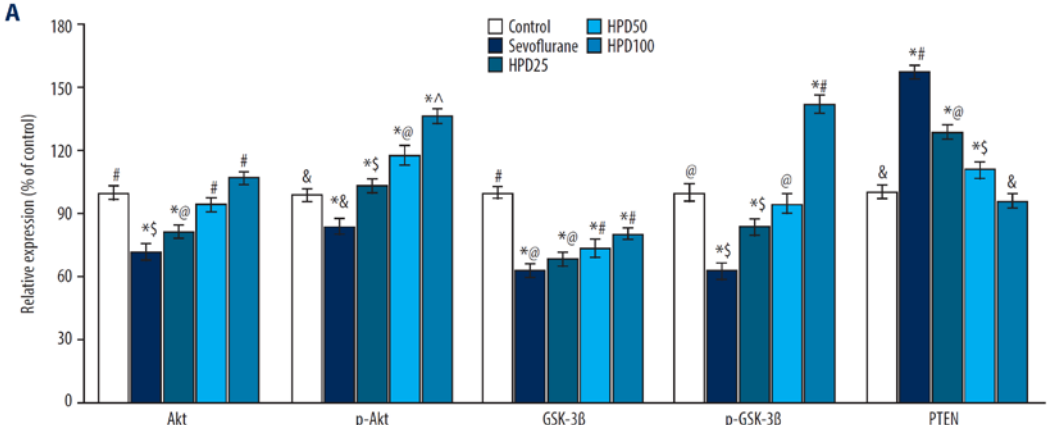

Figure 4. Hesperidin (HPD) treatment modulated the components of the PI3K/Akt signaling pathway in the hippocampus of neonatal rats exposed to sevoflurane anesthesia. (**A**) Graphs of the relative protein expression values show that HPD significantly activated the PI3K/Akt pathway.

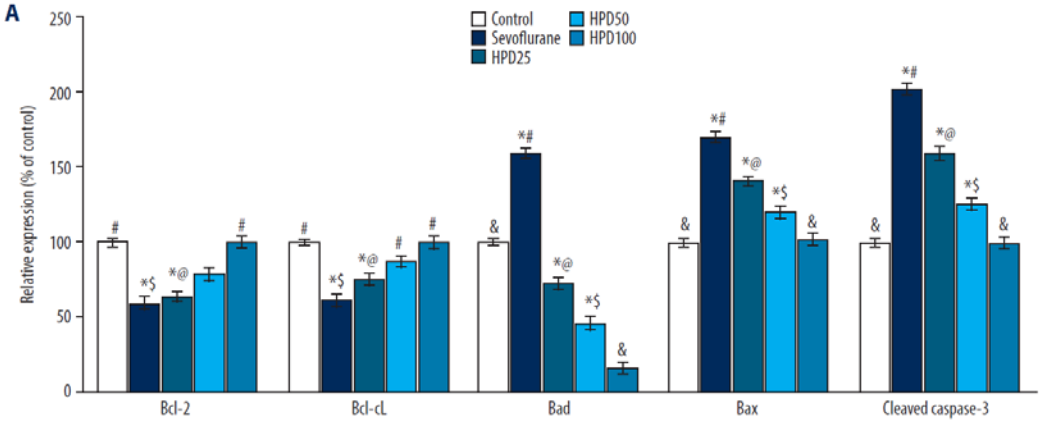

Figure 3. Hesperidin (HPD) treatment reduced the expression levels of apoptotic proteins in the hippocampus of neonatal rats exposed to sevoflurane anesthesia. (**A**) Graphs of the relative protein expression values. HPD treatment significantly increased the expression of Bcl-2 and Bcl-xL protein levels (p<0.05), and significantly reduced the expression of BAX, BAD, and cleaved caspase-3. (**B**) Representative Western blot images of the proteins. Values are represented as the mean±standard deviation

Huang H., et al.; Med Sci Monit, 2020; 26: e920522

Hesperidin provided benefits to the central nervous system (CNS) and neuroinflammation in 19 models

Hesperidin is reported in multiple studies as decreasing key mediators of inflammation

Benefits of hesperidin in central nervous system disorders: a review

Jeongtae Kim[1], Myung-Bok Wie[2], Meejung Ahn[1], Akane Tanaka[3], Hiroshi Matsuda[4], Taekyun Shin[1]

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Review Article
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Anatomy & Cell Biology acb

Hesperidin and neuroinflammation
Anat Cell Biol 2019;52:369-377

Table 1. Bioactivity properties of hesperidin and their underlying mechanisms in animal models

Model	Compound and treatment protocol	Results and underlying mechanism
Normal status		
Swiss albino mice	Hesperidin (10 mg/kg) per B.W., i.p.	Reduction in the phosphorylation state of ERK 1/2, in the cerebral cortex, cerebellum and hippocampus
Swiss albino mice	Hesperidin (0.1, 0.3 and 1 mg/kg, B.W.), i.p.	Decreasing the immobility time in the forced swimming test Kappa-opioid, but not with the δ-opioid, μ-opioid or adenosinergic receptors mediate the antidepressant-like activity of hesperidin
Swiss albino mice	Hesperidin or hesperetin (0.1, 0.3 and 1 mg/kg, B.W.), i.p.	Significantly decreasing in nitrate/nitrite levels in the hippocampus Increasing of BDNF level in the hippocampus Inhibition of L-arginine-nitric oxide-cGMP pathway in hippocampus
Swiss albino mice	Hesperidin (0.3 mg/kg, B.W.), i.p.	Decreasing the immobility time in the tail suspension test and forced swimming time Decreasing the antidepressant-like activity of hesperidin in mice with selective $5HT_{1A}$ receptor antagonist
Learning and memory deficit model		
Wistar rat, AlCl3-induced cognitive impairment	Hesperidin (100 mg/kg, B.W.), orally, 60 days	Prevention of cognitive deficits, biochemical anomaly and apoptosis induced by $AlCl_3$
Wistar rat, $AlCl_3$-induced cognitive impairment	Hesperidin (100 mg/kg, B.W.), orally, 60 days	Reduction of inflammatory markers (GFAP, Iba-1, NF-κB, COX-2, IL-1β, TNF-α, iNOS) and apoptotic markers (cytosolic cytochrome c, caspase-3, -8, and -9) Increasing of phospho-Akt and phospho-GSK3β
Swiss albino mice STZ injection-induced cognitive impairment	Hesperidin (100 and 200 mg/kg, B.W.), orally, 15 days, pretreatment	Prevention of the cognitive impairment Improvement of memory consolidation process as tested by Morris water maze possibly through modulation of AChE activity Inhibition in the overexpression of inflammatory markers, including NF-κB, iNOS, COX-2, and GFAP-positive astrocytes
Sprague-Dawley rat KA-induced neurotoxicity (Seizure model)	Hesperidin (10 or 50 mg/kg, i.p.), pretreatment	Inhibition of glutamate release Protection of CA3 neurons against excitotoxicity induced by KA Inhibition of pro-inflammatory molecules by microglia

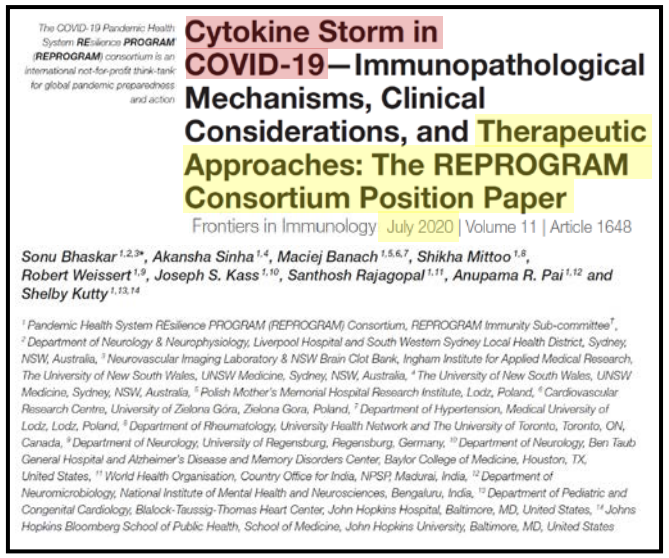
Kim J., et al.; Anat Cell Biol 2019;52:369-377

Hesperidin to address inflammation and cytokine storm in COVID-19 finds support in the scientific literature

PubMed identified >80 papers related to the benefit of Hesperidin in inflammation

The Hesperidin Study: Mechanism 2

Modulate inflammation and cytokine storm



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Cytokine Storm in COVID-19—Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper

Frontiers in Immunology July 2020 | Volume 11 | Article 1648

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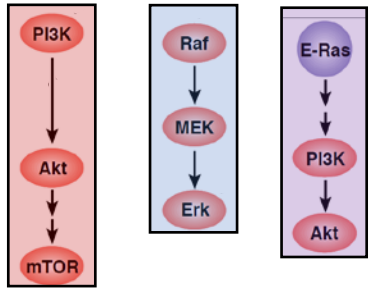
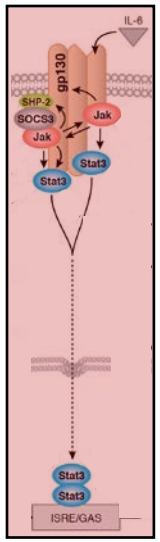
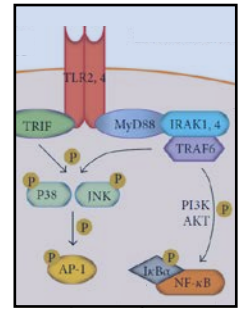
The REPROGRAM Consortium Position Paper			The Hesperidin Study: Hesperidin for 14 day		
Inflammatory Mediators		Preferred Regulation			
Interleukin-6 (Il-6)		↓	✓	✓	✓
Interleukin-ILβ (IL-1β)		↓	✓	✓	✓
Tumor Necrosis Factor-α (TNFα)		↓	✓	✓	✓
Reactive Oxygen Species (ROS)		↓		✓	✓
Peroxisome Proliferator-Activated Receptors	PPAR Agonist	↑	✓	✓	
Nuclear Factor of kappa light polypeptide gene enhancer in B-cells inhibitor	IκB	↓		✓	✓
Nuclear Factor kappa-light-chain-enhancer of activated B cells	NFκ-B	↓		✓	✓
Superoxyde Dismutase (SOD)		↑	✓	✓	
Monocyte Chemoattractant Protein-1	MCP-1	↓	✓		
Signal Transducer and Activator of Transcription 3 (STAT3)	Intercellular Adhesion Molecule 1 ICAM-1	↓	✓		
Macrophage Inflammatory Protein 2	(MIP-2/CXCL2)	↓		✓	
Keratinocyte Chemo-Attractant (KC/CXCL1)		↓		✓	
Mitogen Activated Protein Kinase P38 (p38)		↓		✓	
c-Jun N-terminal kinases (JNK)		↓		✓	
Cardiac Troponin I (cTnI)		↓	✓		

Jak/Stat Signaling: IL-6 Receptor Family





Inflammasome Complexes



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Bhaskar S., et al; Front. Immunol. 11: 1648 (2020)
Cell Signaling Technology Jak/Stat signaling pathway: IL-6 Receptor family
Fuentes-Antrás J., et al.; International Journal of Endocrinology Vol 2014,10 pages

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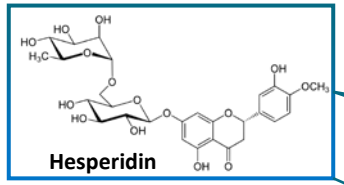
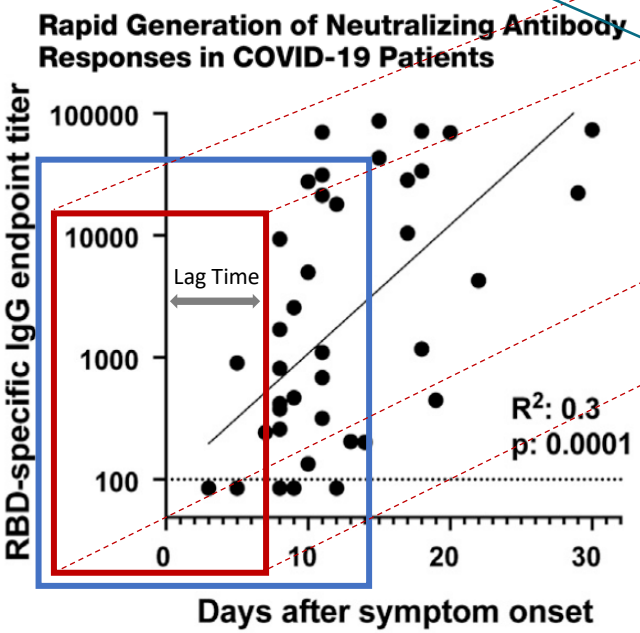
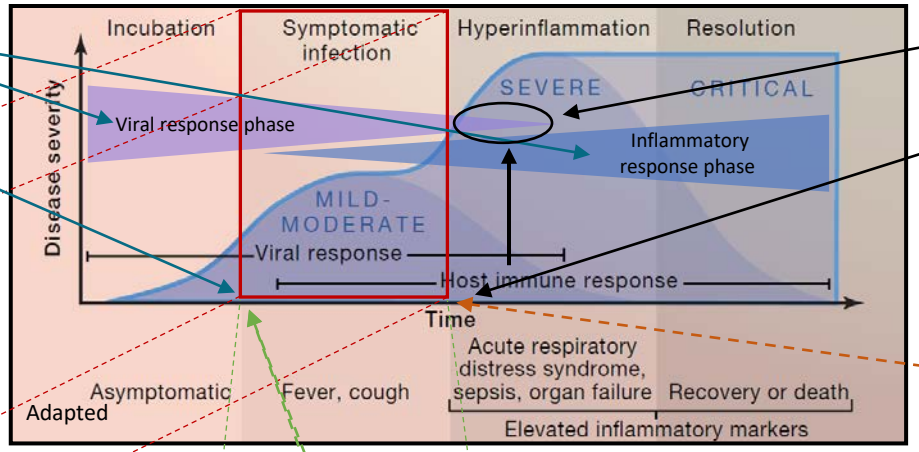
The Hesperidin Study: evaluating the ability of hesperidin to reduce the infection and inflammatory phases in non-hospitalized COVID-19 patients

Evaluate if hesperidin can reduce the requirements for hospitalization

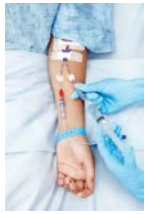




Cell Reports Medicine June 23, 2020 © 2020 The Author(s). https://doi.org/10.1016/j.xcrm.2020.100040



954.e1 Cell 181, May 14,2020

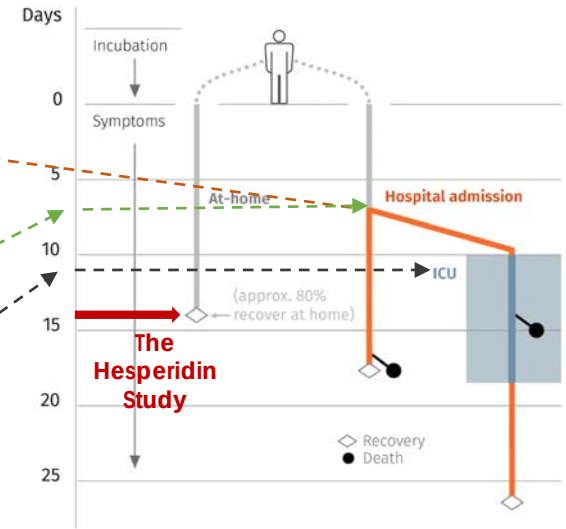


Remdesivir for the Treatment of Covid-19 — Preliminary Report

This article was published on May 22, 2020, at NEJM.OI DOI: 10.1056/NEJMoa2007764

Remdesivir administration ≤ 9th day of onset

Typical progression of COVID-19



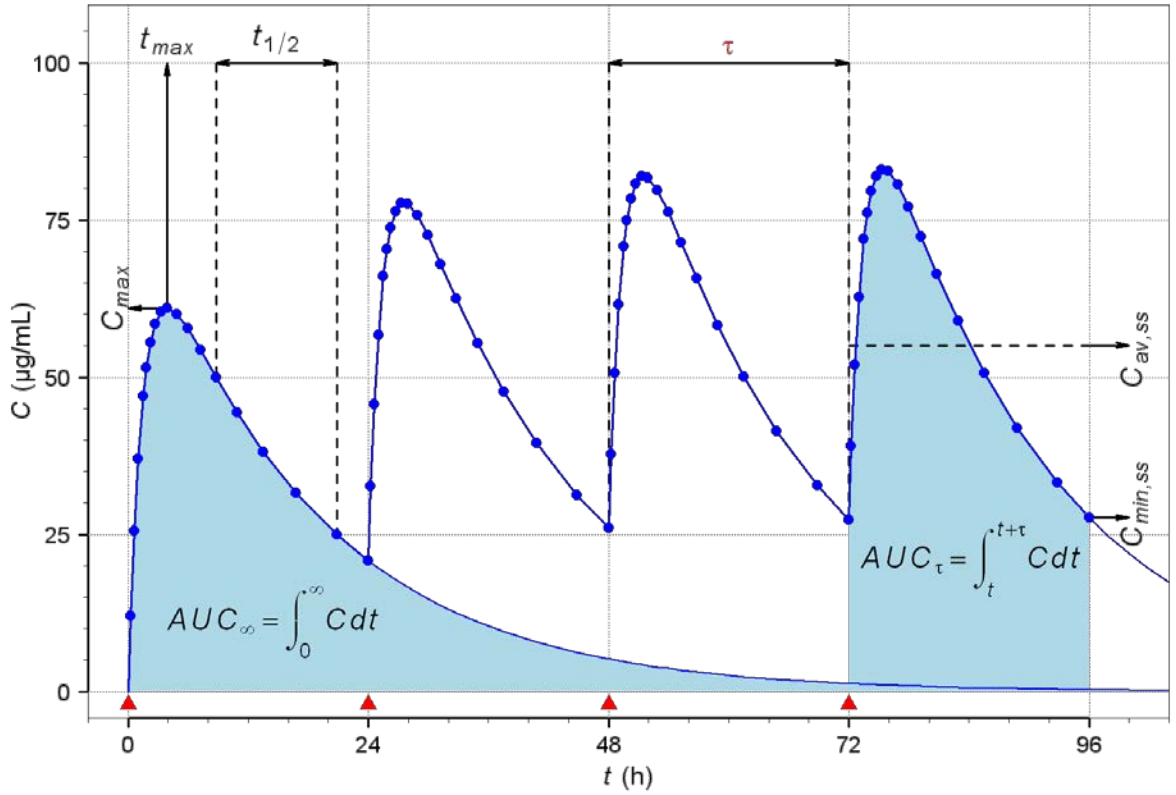
https://www.cbc.ca/news/health/typical-covid-19-progression-1.5546949

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Demographics and clinical characteristics				
Age, years	56·0 (46·0–67·0)	69·0 (63·0–76·0)	52·0 (45·0–58·0)	<0·0001
Sex	..	..	..	0·15
Female	72 (38%)	16 (30%)	56 (41%)	..
Male	119 (62%)	38 (70%)	81 (59%)	..
Time from illness onset to fever, days	1·0 (1·0–1·0)	1·0 (1·0–1·0)	1·0 (1·0–1·0)	0·16
Time from illness onset to cough, days	1·0 (1·0–3·0)	1·0 (1·0–1·0)	1·0 (1·0–4·0)	0·30
Time from illness onset to dyspnoea, days	7·0 (4·0–9·0)	7·0 (4·0–10·0)	7·0 (4·0–9·0)	0·51
Time from illness onset to sepsis, days	9·0 (7·0–13·0)	10·0 (7·0–14·0)	9·0 (7·0–12·0)	0·22
Time from illness onset to ARDS, days	12·0 (8·0–15·0)	12·0 (8·0–15·0)	10·0 (8·0–13·0)	0·65
Time from illness onset to ICU admission, days	12·0 (8·0–15·0)	12·0 (8·0–15·0)	11·5 (8·0–14·0)	0·88

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

www.thelancet.com Published online March 9, 2020

The Hesperidin Study: pharmacokinetic modelling suggests hesperidin (1g/BID) administered fasted could target the potential therapeutic window



The dose chosen is the result of an exhaustive pharmacokinetic analysis in order to obtain what we believe to be a therapeutic window of efficacy

By Alfie↑↓© (Helmut Schütz) - Own work, CC BY 3.0

This Winter at the Montreal Heart Institute:

Hesperidin to concomitantly assist the viral and inflammation response phases to SARS-COV-2 in newly diagnosed COVID-19 patients to prevent hospitalization

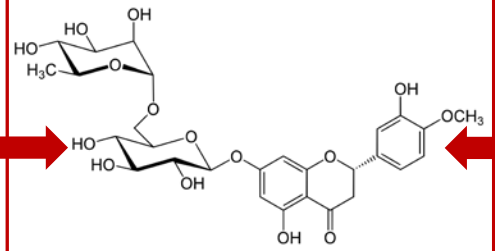
Montreal Heart Institute -The Hesperidin Study trial				
Hesperidin for 14 day to:		♥	🫁	🧠
Interleukin-6 (Il-6)	↓	✓	✓	✓
Interleukin-ILβ (IL-1β)	↓	✓	✓	✓
Tumor Necrosis Factor-α (TNFα)	↓	✓	✓	✓
Reactive Oxygen Species (ROS)	↓		✓	✓
PPAR Agonist	↑	✓	✓	
IκB	↓		✓	✓
NFκ-B	↓		✓	✓
Superoxyde Dismutase (SOD)	↑	✓	✓	
MCP-1	↓	✓		
ICAM-1	↓	✓		
(MIP-2/CXCL2)	↓		✓	
Keratinocyte Chemo-Attractant (KC/CXCL1)	↓		✓	
Mitogen Activated Protein Kinase P38 (p38)	↓		✓	
c-Jun N-terminal kinases (JNK)	↓		✓	
Cardiac Troponin I (cTnI)	↓	✓		
TNFα, IL-6, INFα in H1N1 related infection	↓		✓	
Binding of SARS-COV-2 to ACE2 (Spike (S))	↓	Spike(S) Protein		
Replication of SARS-CoV-2 (3CLpro)	↓	3CLpro/Mpro		

Oberfeld B., et al.; 954 Cell 181, May 14, 2020

MONTREAL HEART INSTITUTE

Hesperidin

To reduce the severity of illness and requirement for hospitalization in COVID-19



For 14 days from the day of onset

NIH U.S. National Library of Medicine

ClinicalTrials.gov

ClinicalTrials.gov Identifier: NCT04715932

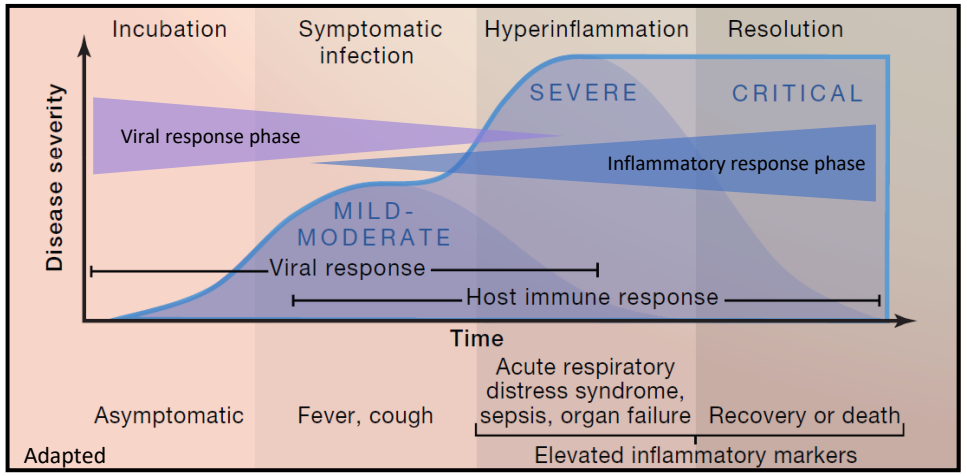
https://www.clinicaltrials.gov/ct2/show/NCT04715932?term=hesperidin&draw=2&rank=2

SnapShot: COVID-19

Blake Oberfeld,[1] Aditya Achanta,[1] Kendall Carpenter,[1] Pamela Chen,[1] Nicole M. Gilette,[1] Pinky Langat,[1] Jordan T. Said,[1] Abigail E. Schiff,[1,2,*] Allen S. Zhou,[1] Amy K. Barczak,[1,2] and Shiv Pillai[1,2]
[1]Harvard Medical School, Boston, MA 02115, USA; [2]Ragon Institute of MGH, MIT, and Harvard,

954.e1 Cell 181, May 14, 2020 DOI https://doi.org/10.1016/j.cell.2020.04.013

Cell



Hesperidin has the potential to cover all 4 phases of COVID-19 progression

…And one more thing…Fall is coming…So is the flu season…

[2020-2021] flu season combined with COVID-19 could be challenging for the American public health care system

CDC Director Warns of COVID-19 and Flu Coinciding Surge in Fall

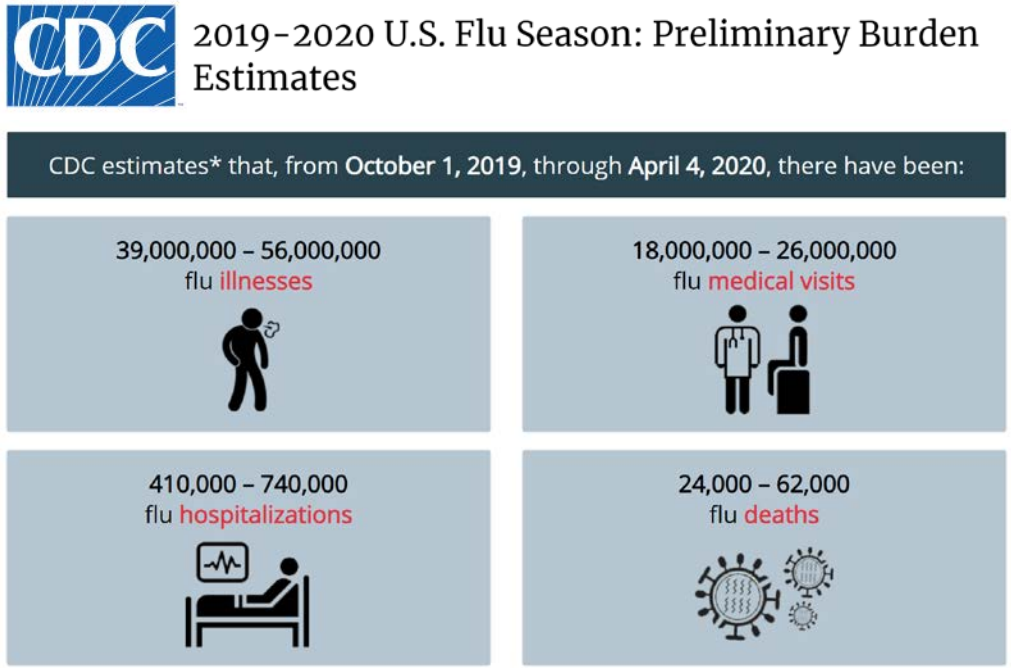
BY SPECTRUM NEWS STAFF | NATIONWIDE
PUBLISHED 8:59 AM ET JUL. 15, 2020

NATIONWIDE – Flu season is approaching, causing grave concerns for America's health care system while the coronavirus pandemic surges on.

Robert Redfield, the director of the Centers for Disease Control and Prevention, expressed his concerns on Tuesday about COVID-19 infections and influenza cases expected in the fall.

"I do think the fall and the winter of 2020 and 2021 are going to be probably one of the most difficult times that we've experienced in American public health," Redfield said during a webinar with the Journal of the American Medical Association.

According to Business Insider, flu season in the U.S. usually arrives in October and then peaks from December to February. An estimated 12,000 to 61,000 Americans die of the flu every year, dependent on the success of vaccines and timing. Flu cases could place more strain on hospitals that are already stretched thin by COVID-19.



https://www.baynews9.com/fl/tampa/news/2020/07/15/cdc-director-warns-of-covid-19-and-flu-coinciding-surge-in-fall
https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm

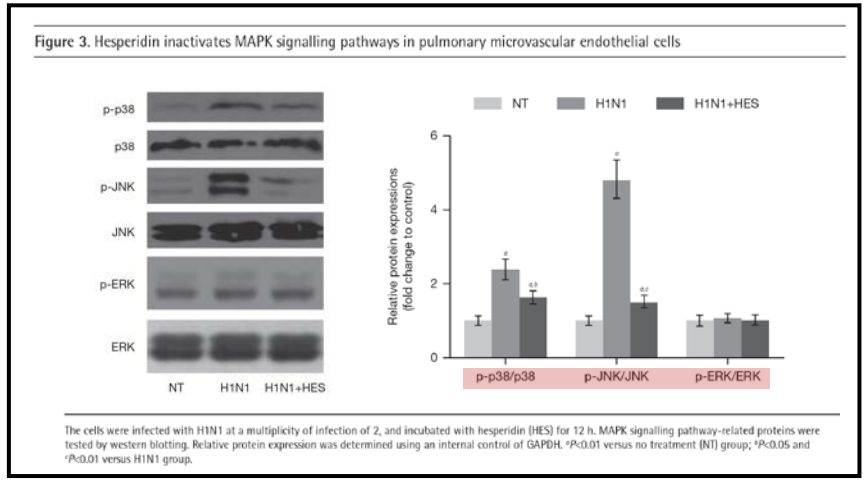
Hesperidin decreased TNFα, IL-6, INFα, macrophages recruitment and reversed decreased pulmonary function in a H1N1 induced lung injury model

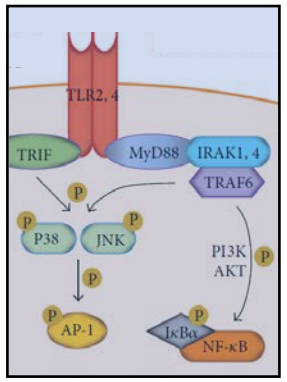
Also reduced the phosphorylation of inflammasome markers p38 and JNK

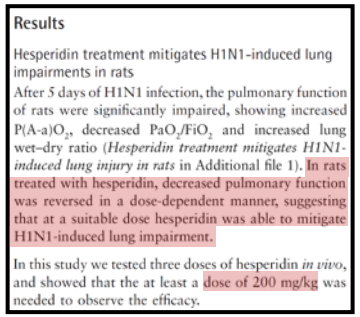
Antiviral Therapy 2018; **23**:611–615

Hesperidin attenuates influenza A virus (H1N1) induced lung injury in rats through its anti-inflammatory effect

Zhen Ding[1,2], Gengyun Sun[1], Zhongming Zhu[1]*






Results

Hesperidin treatment mitigates H1N1-induced lung impairments in rats

After 5 days of H1N1 infection, the pulmonary function of rats were significantly impaired, showing increased $P(A\text{-}a)O_2$, decreased PaO_2/FiO_2 and increased lung wet–dry ratio (*Hesperidin treatment mitigates H1N1-induced lung injury in rats* in Additional file 1). In rats treated with hesperidin, decreased pulmonary function was reversed in a dose-dependent manner, suggesting that at a suitable dose hesperidin was able to mitigate H1N1-induced lung impairment.

In this study we tested three doses of hesperidin *in vivo*, and showed that the at least a dose of 200 mg/kg was needed to observe the efficacy.

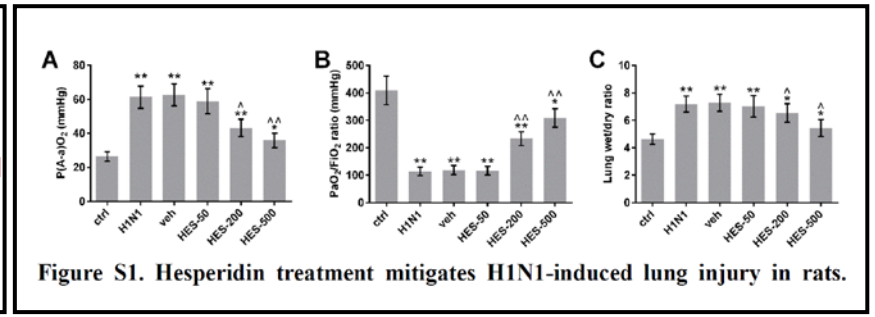


Figure S1. Hesperidin treatment mitigates H1N1-induced lung injury in rats.

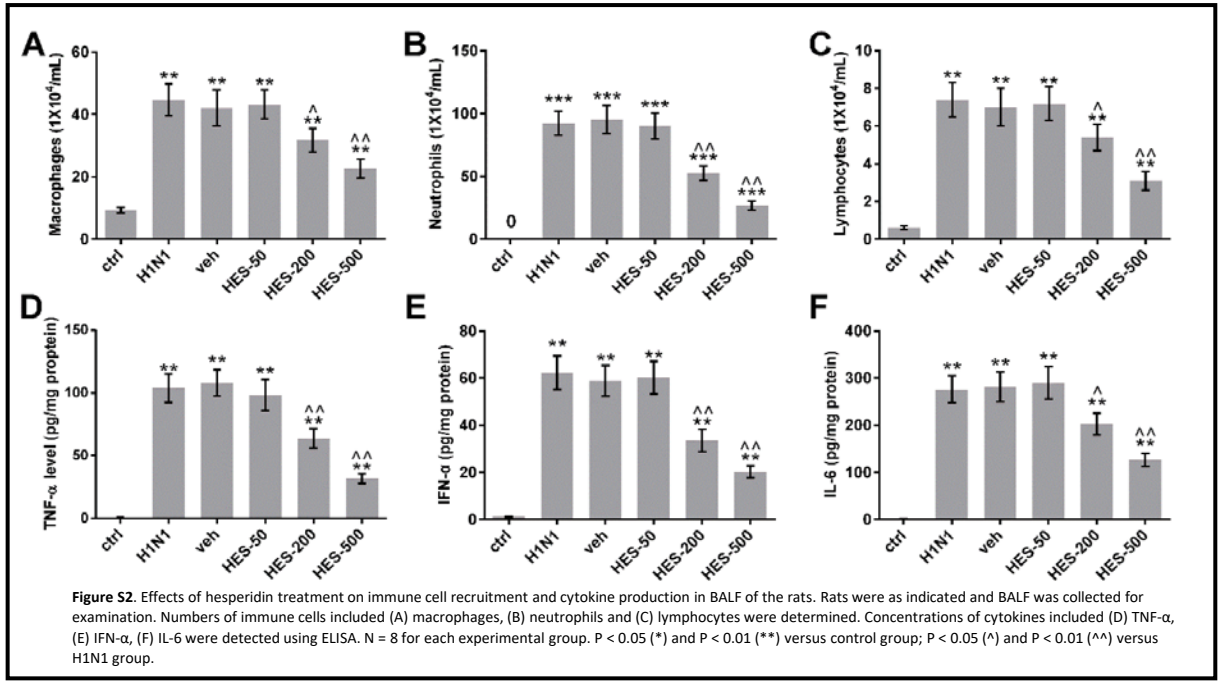


Figure S2. Effects of hesperidin treatment on immune cell recruitment and cytokine production in BALF of the rats. Rats were as indicated and BALF was collected for examination. Numbers of immune cells included (A) macrophages, (B) neutrophils and (C) lymphocytes were determined. Concentrations of cytokines included (D) TNF-α, (E) IFN-α, (F) IL-6 were detected using ELISA. N = 8 for each experimental group. P < 0.05 (*) and P < 0.01 (**) versus control group; P < 0.05 (^) and P < 0.01 (^^) versus H1N1 group.

Ding Z., et al.; antiviral therapy 2018; 23: 611-615

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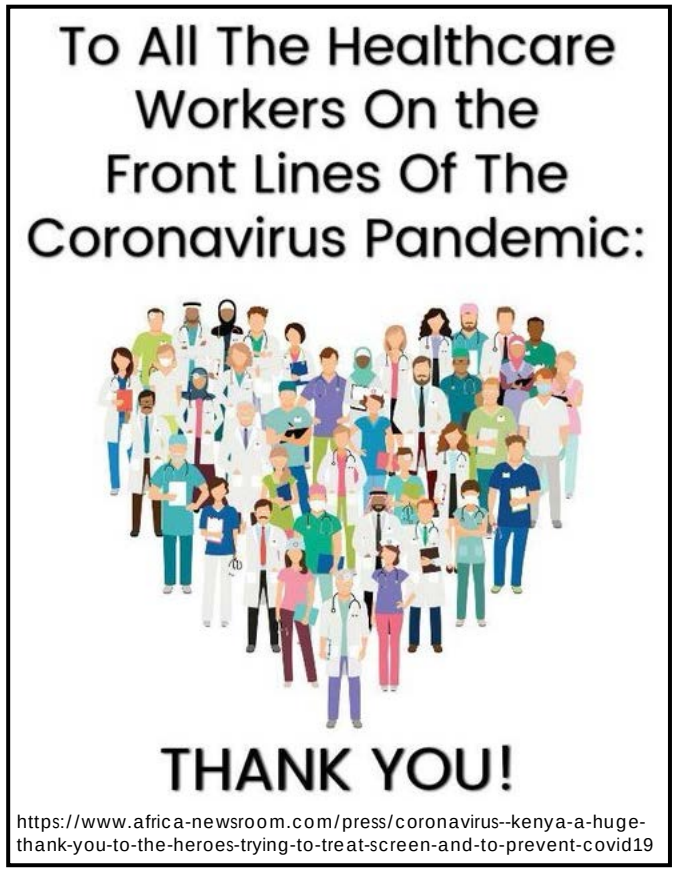

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	g	Fever mask temperature iStock order number 2064994595	https://www.istockphoto.com/purchase/checkout?fastcheckoutasset=1218066849
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