From Detection to Treatment: Exploring Viral Testing, Reactivation and Therapy

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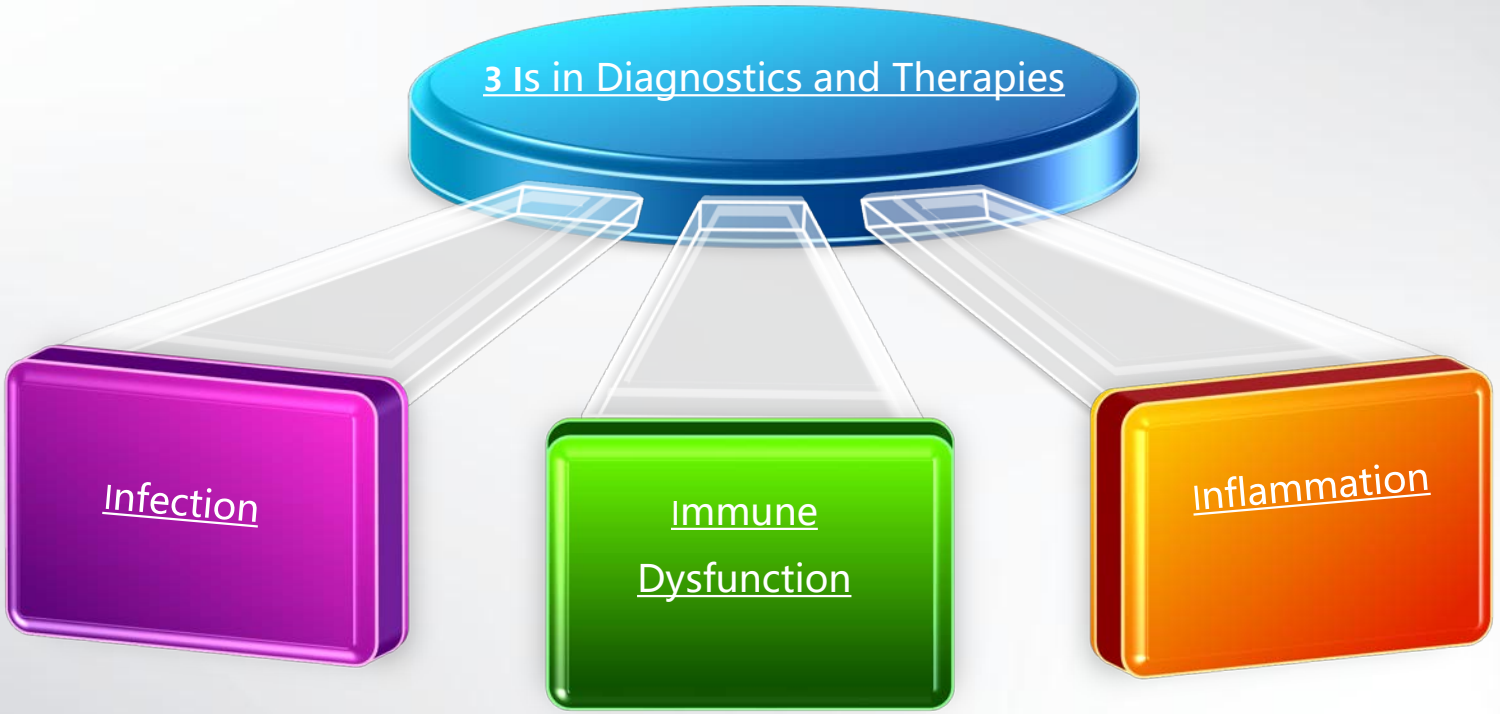
3 I´s in Diagnostics and Therapies



Agenda

- Recent research evidencing huge viral involvement/reactivation in the post-COVID era
- Optimal testing for DNA and RNA viruses
- Therapeutic options for viral infections
  - Infection
  - Inflammation
  - Immune dysfunction and detoxification

Agenda

- **Recent research evidencing huge viral involvement / reactivation in the post-COVID era**
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  - Immune dysfunction and detoxification

The prevalence of herpes infection / reactivation in the COVID era is now fully recognised

First systematic meta-analysis (Banko et al) covering all studies evaluating HHV infection in CV-19 patients

Contents lists available at ScienceDirect

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

Systematic review with meta-analysis of active herpesvirus infections in patients with COVID-19: Old players on the new field

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ABSTRACT

Objectives: Herpesviruses are ubiquitous and after primary infection they establish lifelong latency. The impairment of maintaining latency with short-term or long-term consequences could be triggered by other infection. Therefore, reactivation of herpesviruses in COVID-19 patients represents an emerging issue.

Design and methods: This study provided the first systematic review with meta-analysis of studies that evaluated active human herpesvirus (HHV) infection (defined as the presence of IgM antibodies or HHV-DNA) in COVID-19 patients and included 36 publications collected by searching through PubMed, SCOPUS, and Web of science until November 2022.

Results: The prevalence of active EBV, HHV6, HSV, CMV, HSV1, and VZV infection in COVID-19 population was 41% (95% CI =27%-57%), 3% (95% CI=17%-54%), 28% (95% CI=1%-85%), 25% (95% CI=1%-63%), 22% (95% CI=10%-35%), and 18% (95% CI=4%-34%), respectively. There was a 6 times higher chance for active EBV infection in patients with severe COVID-19 than in non-COVID-19 controls (OR=6.45, 95% CI=1.09-38.13, p=0.040), although there was no difference in the prevalence of all evaluated active herpesvirus infections between COVID-19 patients and non-COVID-19 controls.

Conclusions: Future research of herpesvirus and SARS-CoV-2 coinfections must be prioritized to define: who, when and how to be tested, as well as how to effectively treat HHVs reactivations in acute and long COVID-19 patients.

2023 meta-analysis

"The prevalence of **active EBV** infection in COVID-19 population of **41%** was the highest. A bit lower was the prevalence of **active HHV6** infection of **34%**. In the third place was the prevalence of **active HSV** infection at **28%**, followed by **CMV 25%, VZV 22% …**"

As in the Banko meta-analysis, EBV is the most prominent reactivation: mechanism now also becoming clear

Open Access | Editor's Choice | Article

Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation

by Jeffrey E. Gold [1,*], Ramazan A. Okyay [2], Warren E. Licht [3] and David J. Hurley [4]

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[2] Department of Public Health, Kahramanmaraş Sütçü İmam University, Kahramanmaraş 46040, Turkey
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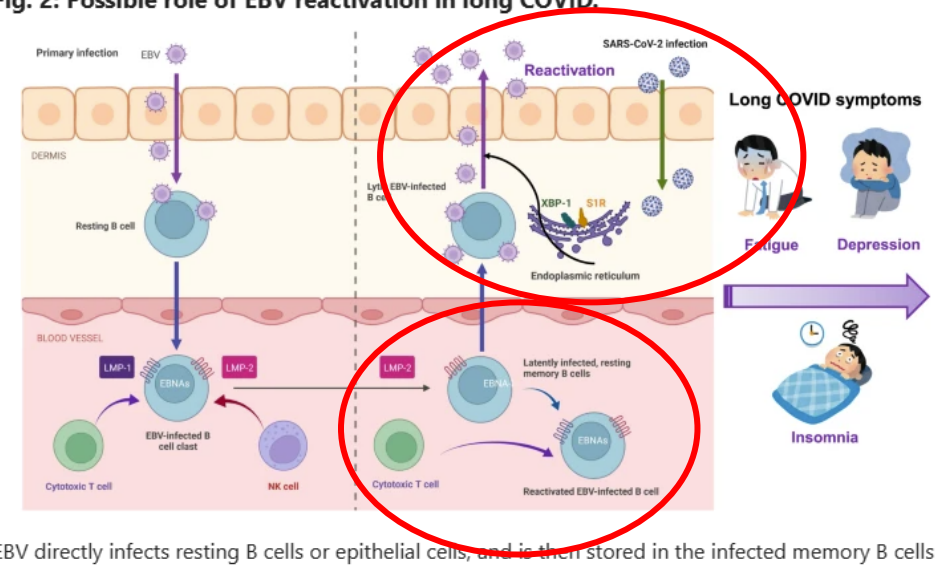
* Author to whom correspondence should be addressed.

Gold study 2021: "We found that **66.7%** (20/30) of **long-term long COVID** subjects versus 10% (2/20) of long-term control subjects were **positive for EBV reactivation**"[1]

Hashimoto et al 2023 **have found the mechanism** by which **EBV** stored in memory B cells and EBNAs can be **reactivated by SARS-CoV-2** infection[2]

Fig. 2: Possible role of EBV reactivation in long COVID.



EBV directly infects resting B cells or epithelial cells, and is then stored in the infected memory B cells of the peripheral blood that express latent membrane protein 2 (LMP-2) and EBV nuclear antigens (EBNAs). After SARS-CoV-2 infection, these B cells can cause EBV reactivation, resulting in severe systemic inflammation. As the interaction of the XBP-1 (X-box binding protein 1) with S1R (sigma-1 receptor) may play a role in EBV reactivation, sigma-1 receptor agonists (e.g., fluvoxamine) may attenuate EBV reactivation, resulting in reduced long COVID symptoms. Part of the figure was designed using resources from Biorender.com and www.irasutoya.com.

Source: 1. Gold JE et al. Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation. Pathogens. 2021 Jun 17;10(6):763; 2. Hashimoto, K. (2023). Detrimental effects of COVID-19 in the brain and therapeutic options for long COVID: The role of Epstein–Barr virus and the gut–brain axis. Molecular Psychiatry. 10.1038/s41380-023-02161-5; 2.

Various phenomena contribute to EBV reactivation in COVID

- **EBV can be reactivated by SARS-CoV-2/COVID[1]**
- **Chronic EBV can be exacerbated by SARS-CoV-2/COVID[2]**
- **EBV, whether dormant or chronic and active, can increase susceptibility to COVID[3]**
- **Immune suppression plays a big role: "**Recent studies suggest the possible interaction between SARS-CoV-2 and EBV. .. One possible mechanism involves a decrease in CD8+ cells which are the primary cells responsible for immunity against EBV infection … A correlation between reduced $CD8^+$ T cells and NK counts, EBV DNA levels and COVID-19 severity was observed."
- **Drugs used in the treatment of COVID promote EBV reactivation[5]:** "Drugs used in the treatment of COVID-19 may also play a major role in altering immune responses by means of regulating intracellular signaling pathways, thus prompting the reactivation process of EBV. The use of high-dose corticosteroids has been stated as a risk factor for herpes virus reactivation"[5]

Source: 1. https://pubmed.ncbi.nlm.nih.gov/34204243/; 2. https://pubmed.ncbi.nlm.nih.gov/35872097/; *3. https://journals.asm.org/doi/pdf/10.1128/JVI.00192-21/; 4. https://pubmed.ncbi.nlm.nih.gov/35505635/; 5. https://pubmed.ncbi.nlm.nih.gov/35505635/*

Increasing correlation of HHV6 - and even HHV7 and HHV8 - with neurological manifestations; CMV also very high

Virology Journal

BMC

Virol J. 2022; 19: 101.
Published online 2022 Jun 8. doi: 10.1186/s12985-022-01828-9

PMCID: PMC9174631
PMID: 35676707

Journal Article

Herpesvirus and neurological manifestations in patients with severe coronavirus disease

Vanessa Cristine de Souza Carneiro,[1,2] Soniza Vieira Alves-Leon,[3,6] Dmitry José de Santana Sarmento,[4] Wagner Luis da Costa Nunes Pimentel Coelho,[2] Otacilio da Cruz Moreira,[1,5] Andreza Lemos Salvio,[6] Carlos Henrique Ferreira Ramos,[6] Carlos Henrique Ferreira Ramos Filho,[6] Carla Augusta Barreto Marques,[6] João Paulo da Costa Gonçalves,[3,6] Luciane Almeida Amado Leon,[2] and Vanessa Salete de Paula[1,7]

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Background

Certain clinical manifestations of coronavirus disease (COVID-19) mimic those associated with human herpesvirus (HHV) infection. In this study, we estimated the prevalence of herpesvirus in patients with COVID-19 and determined if coinfection is associated with poorer outcomes and neurological symptoms.

2022 study in Virology:

"With respect to the prevalence of herpesviruses, **79.2% (42/53) of the patients tested positive for at least one herpesvirus.** Of the 42 patients, **75.0%** showed **coinfection with two or more** viral subtypes. The **most prevalent herpes viruses were HHV-6 (47.2%), CMV (43.4%), HHV-7 (39.6%), and HHV-8 (17%).**"

Source: Carneiro VCS, Alves-Leon SV, Sarmento DJS, Coelho WLDCNP, Moreira ODC, Salvio AL, Ramos CHF, Ramos Filho CHF, Marques CAB, da Costa Gonçalves JP, Leon LAA, de Paula VS. Herpesvirus and neurological manifestations in patients with severe coronavirus disease. Virol J. 2022 Jun 8;19(1):101

Cytomegalo-Virus influences the coagulation system

Review Article

Effects of human cytomegalovirus infection on the coagulation system

Alessandro Squizzato, Victor E. A. Gerdes, Harry R. Büller
Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

Summary
Pathophysiological mechanisms of acute vascular thrombosis are not fully understood. It has been suggested that different infectious pathogens are responsible agents of thrombotic disorders. The infection hypothesis is supported by an increasing number of reports on the interaction between acute infection and coagulation. Cytomegalovirus (CMV) is supposed to play an important role in apparently unprovoked thrombosis. We reviewed all human *in vitro* and *in vivo* studies on the influence of human CMV infection on the coagulation system, as well as all case reports of acute thrombosis during acute human CMV infection. In the published literature there is mounting evidence that human CMV may play a role i
finitive conclusions, however, cann
vitro studies are convincing and offe

Keywords
Infection / bacterial, viral, hypercoagulability, inflammatory mediators, endothelial cells

Thromb Haemost 2005; 93: 403-

„More proof that CMV can be the reason for thrombosis“

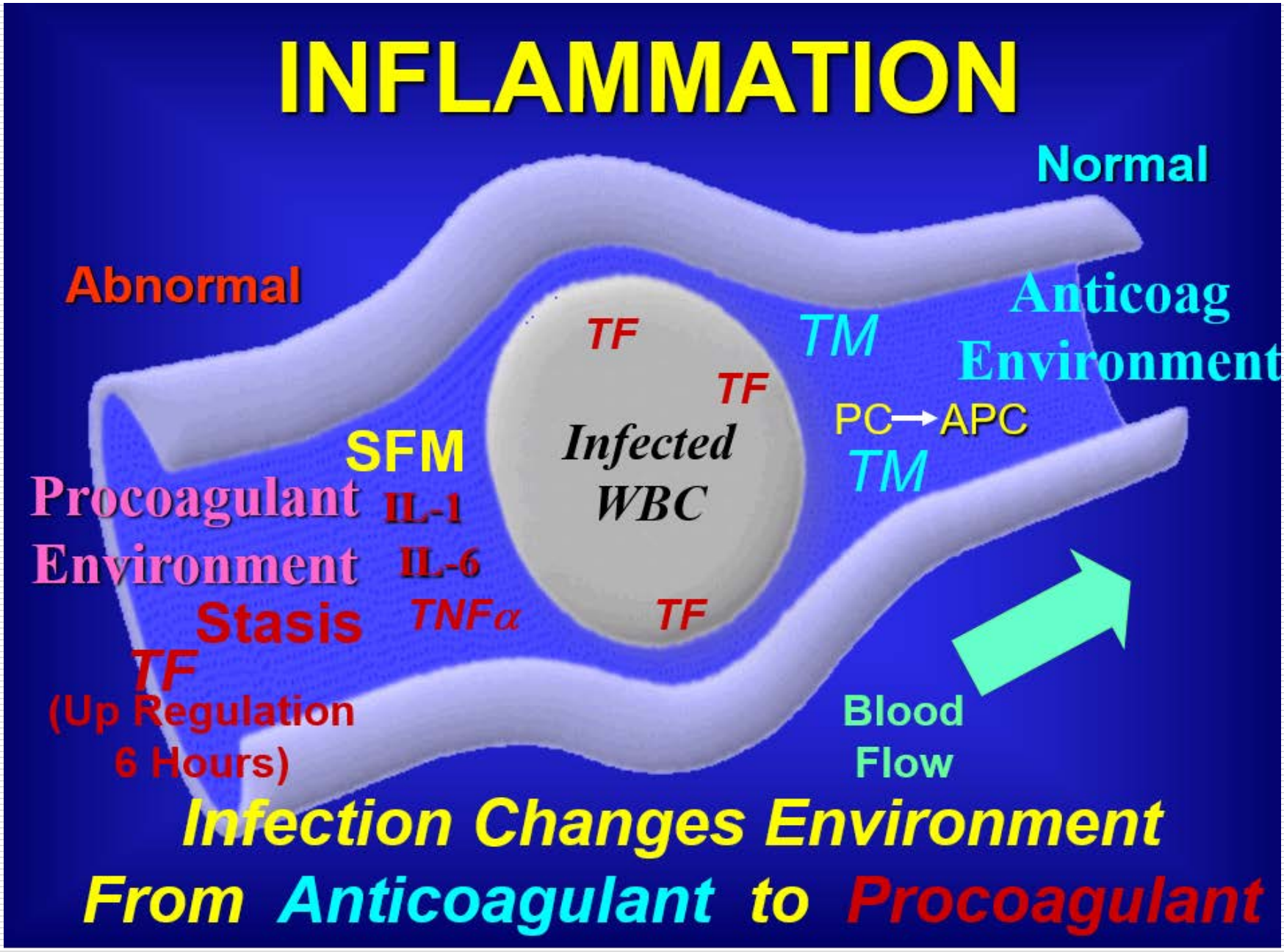
Introduction

Acute vascular thrombosis represents a major socioeconomic challenge for its heavy burden on mortality and morbidity. Acute vascular thrombosis also represents a scientific challenge since

CMV: relevant biological and clinical features

CMV, or Human Herpes Virus 5, is a double-stranded enveloped

Source: Squizzato A, Gerdes VEA, Büller HR. Effects of human cytomegalovirus infection on the coagulation system. Thromb Haemost. 2005;93:403–410;



Source: David Berg Coagulation 202 Proteins and Coagulation Pathways, from The Role of Hypercoagulation and Biofilms in Chronic Illness Conference (2011)

Association of HHV-6 and HHV-7 in M.E. has long been known, as well as Parvovirus B19 …

Adv Virol. 2012; 2012: 205085.
Published online 2012 Aug 13. doi: 10.1155/2012/205085
PMCID: PMC3426163
PMID: 22927850

Journal Article

Association of Active Human Herpesvirus-6, -7 and Parvovirus B19 Infection with Clinical Outcomes in Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Svetlana Chapenko, [1] Angelika Krumina, [2,*] Inara Logina, [3] Santa Rasa, [1] Maksims Chistjakovs, [1] Alina Sultanova, [1] Ludmila Viksna, [2] and Modra Murovska [1]

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Abstract Go to: ▸

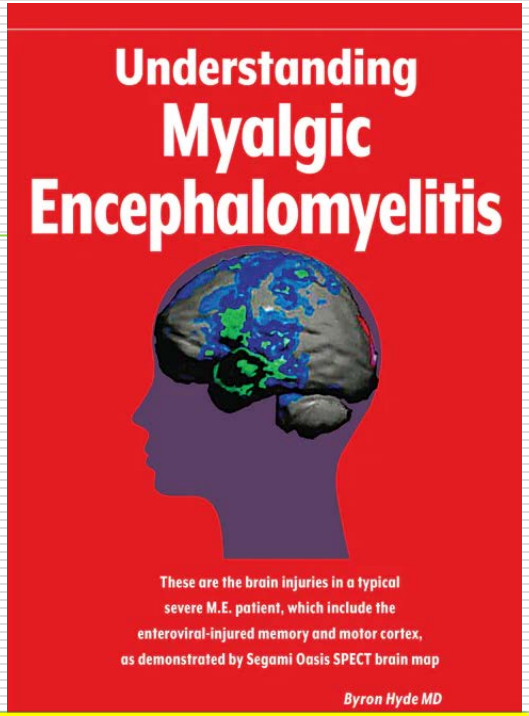
Frequency of active human herpesvirus-6, -7 (HHV-6, HHV-7) and parvovirus B19 (B19) infection/coinfection and its association with clinical course of ME/CFS was evaluated. 108 ME/CFS patients and 90 practically healthy persons were enrolled in the study. Viral genomic sequences were detected by PCR, virus-specific antibodies and cytokine levels—by ELISA, HHV-6 variants—by restriction analysis. Active viral infection including concurrent infection was found in 64.8% (70/108) of patients and in 13.3% (12/90) of practically healthy persons. Increase in peripheral blood leukocyte DNA HHV-6 load as well as in proinflammatory cytokines' levels was detected in patients during active viral infection. Definite relationship was observed between active betaherpesvirus infection and subfebrility, lymphadenopathy and malaise after exertion, and between active B19 infection and multijoint pain. Neuropsychological disturbances were detected in all patients. The manifestation of symptoms was of more frequent occurrence in patients with concurrent infection. The high rate of active HHV-6, HHV-7 and B19 infection/coinfection with the simultaneous increase in plasma proinflammatory cytokines' level as well as the association between active viral infection and distinctive types of clinical symptoms shows necessity of simultaneous study of these viral infections for identification of possible subsets of ME/CFS.

"HHV-6 and HHV-7 are lymphotropic, neurotropic, and immunomodulating viruses … primary infection is followed by lifelong persistency. Reactivation of viruses can provoke the development of abnormalities involving the immune system and nervous system and probably may trigger ME/CFS"

"**The high rate of active HHV-6, HHV-7 and B19 infection/coinfection** with the simultaneous increase in plasma proinflammatory cytokines' level as well as the association between active viral infection and distinctive types of clinical symptoms **shows the necessity of simultaneous study of these viral infections for identification of possible subsets of ME/CFS.**"

Source: Chapenko S, Krumina A, Logina I, Rasa S, Chistjakovs M, Sultanova A, Viksna L, Murovska M. Association of active human herpesvirus-6, -7 and parvovirus b19 infection with clinical outcomes in patients with myalgic encephalomyelitis/chronic fatigue syndrome. Adv Virol. 2012;2012:205085.

“Prior to the SARS-CoV-2 pandemic, the ability of RNA viruses to persist in tissues for long periods was largely ignored” [1]



PLOS PATHOGENS

PEARLS

The viral origin of myalgic encephalomyelitis/ chronic fatigue syndrome

Maureen R. Hanson*

Department of Molecular Biology and Genetics, Cornell University, Ithaca, New York, United States of America

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ME/CFS is a disabling and often severe disease, so-far incurable, that has long been associated with discrete outbreaks and sporadic incidents of viral-like illness. First, a word about the controversial name. The designation “Myalgic Encephalomyelitis” (abbreviated ME) originated following an outbreak at London’s Royal Free Hospital in 1955. More than 200 members of the hospital staff became disabled [1]. Melvin Ramsay, MD, eventually published important case descriptions in *Lancet* [2]. He coined “ME” based on predominant symptoms of muscle pain (myalgia) and effects on the brain (encephalo), spinal cord (myel), and inflammation (itis). For 32 years, “ME” was deemed acceptable until, in 1987, the Centers for Disease Control (CDC) convened an extramural committee to change the name. CDC did so in response to a series of outbreaks of a similar, if not identical, illness in the United States, introducing “chronic fatigue syndrome” in 1988 [3].

Because the CDC name trivializes the serious nature of the disease, the patient community and many medical professionals prefer ME, which continues to be widely used in the United Kingdom and Europe. In 2015, a US Institute of Medicine (IOM) committee recommended yet another name, Systemic Exertion Intolerance Disease [4], which has been largely ignored. Should inflammation of the brain and spinal cord be definitively shown with modern methods, the name Myalgic Encephalomyelitis will finally be vindicated. The compromise name ME/CFS is now used most frequently and will be used here despite its faults. [1]

Citation: Hanson MR (2023) The viral origin of myalgic encephalomyelitis/chronic fatigue syndrome. PLoS Pathog 19(8): e1011523. https://doi.org/10.1371/journal.ppat.1011523

Editor: Wendy Maury, University of Iowa, UNITED STATES

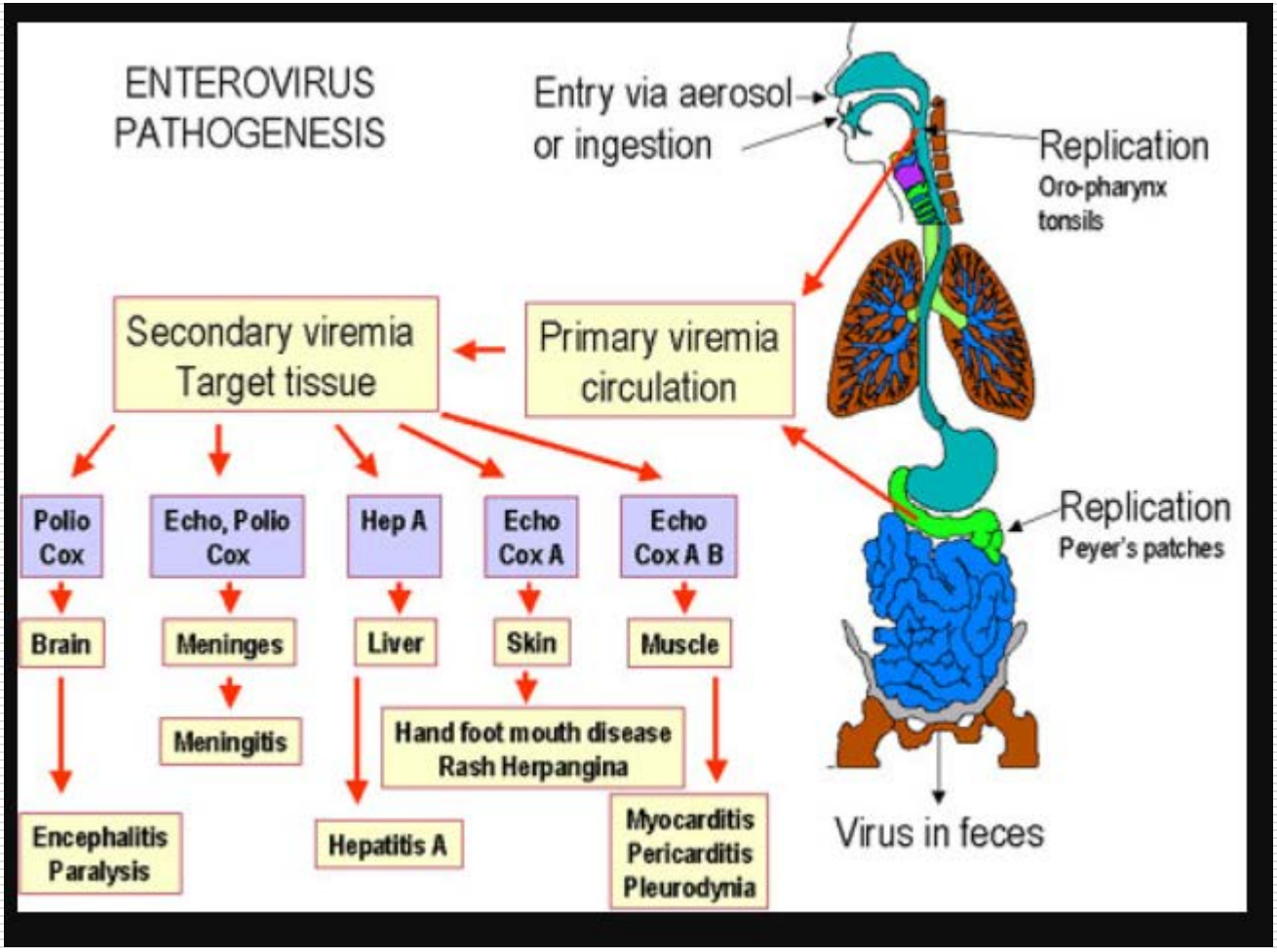
Published: August 17, 2023

Public Library of Science (PLOS) August 2023

PLOS Pathogens article: “Ignoring **the abundant evidence for enteroviral (EV) involvement in ME/CFS has slowed research** into the possible dire but hidden consequences of EV infections, including persistence in virus reservoirs. … **recognizing that EVs are prime candidates for causing ME/CFS** suggests how critical it is to pursue a relevant inquiry into this diverse virus family. Do **hidden reservoirs harbor these viruses? Have they induced autoimmunity** through molecular mimicry?”[1]

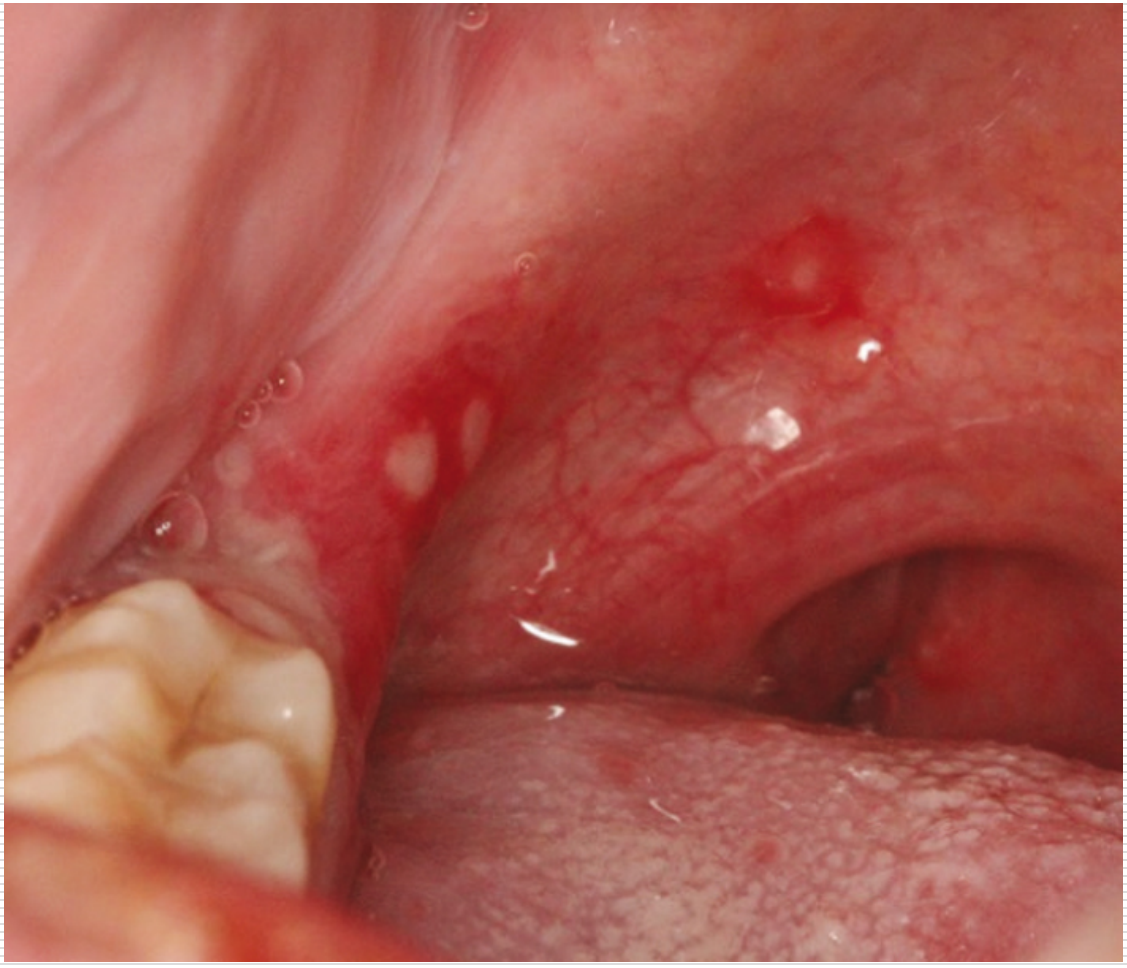
Source: 1. Hanson MR. The viral origin of myalgic encephalomyelitis/chronic fatigue syndrome. PLoS Pathog. 2023 Aug 17;19(8):e1011523.

Pathogenesis of enteroviruses



Source: http://www.microbiologybook.org/virol/picorna.htm

Enterovirus:
Coxsackie may cause Herpangina



Can cause Herpangina: small and symmetrical ulcers of herpangina on the soft palate and retromolar pad, also sometimes simply called ulcers, or aphthous ulcers

Source: ***https://www.uptodate.com/contents/image?imageKey=PEDS%2F127342***

Enterovirus:
Coxsackie Virus A & B

Virus: Coxsackie Virus (obligate intracellular), belongs to the Picornaviridae/enterovirus family (also includes Polio); it is a single-stranded RNA virus divided into group A and group B

Transmission: Contagious, can easily spread from person to person: faecal-oral contamination, droplets of fluid from sneezes/coughs, body fluids, utensils, toys, diaper-changing table

Symptoms: Gastrointestinal (from "entero"), intestinal permeability Group A: Herpangina, AHC (acute hemorrhagic conjunctivitis, HFM (hand-foot-and-mouth disease); Group B: Myocarditis, pericarditis, pleurodynia, hepatitis; Group A and B: fever, rashes, sore throat, diarrhoea, cough, fatigue, conjunctivitis, loss of appetite, headache, night sweats, aseptic meningitis

Complications: CNS disease similar to poliomyelitis, systemic neonatal disease, insulin-dependent diabetes mellitus, Group A: generalized myositis with flaccid paralysis, Group B: focal muscle injury, degeneration of neuronal tissue with spastic paralysis

Enterovirus:
Coxsackie Virus A & B

Complications:

ME (Myalgic Encephalomyelitis) / Mitochondropathies,

Colitis / Leaky Gut, Food intolerances, Histamine Intolerances

Also very neurotropic –attracted to the CNS

Dr. Amy Proal's exciting Polybio Research Foundation is making vital headway in the field of pathogen persistence

REVIEW article

Front. Microbiol., 23 June 2021

Sec. Virology

Volume 12 - 2021 | https://doi.org/10.3389/fmicb.2021.698169

Long COVID or Post-acute Sequelae of COVID-19 (PASC): An Overview of Biological Factors That May Contribute to Persistent Symptoms

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[2] Division of Neurotherapeutics, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

nature immunology

Review article https://doi.org/10.1038/s41590-023-01601-2

SARS-CoV-2 reservoir in post-acute sequelae of COVID-19 (PASC)

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Check for updates

Amy D. Proal, Michael B. VanElzakker, Soo Aleman, Katie Bach, Brittany P. Boribong, Marcus Buggert, Sara Cherry, Daniel S. Chertow, Helen E. Davies, Christopher L. Dupont, Steven G. Deeks, William Elmer, E. Wesley Ely, Alessio Fasano, Marcelo Freire, Linda N. Geng, Diane E. Griffin, Timothy J. Henrich, Akiko Iwasaki, David Izquierdo-Garcia, Michela Locci, Saurabh Mehandru, Mark M. Painter, Michael J. Peluso, Etheresia Pretorius, David A. Price, David Putrino, Richard H. Scheuermann, Gene S. Tan, Rudolph E. Tanzi, Henry F. VanBrocklin, Lael M. Yonker & E. John Wherry

1

Every well-studied pathogen is connected to a chronic syndrome in a portion of infected patients

RNA viruses:
SARS-CoV-2
SARS
Enterovirus
Ebola
Zika
Dengue
Measles
Influenza

DNA viruses:
Epstein Barr
Human Herpes Virus 6/7
Parvovirus 19

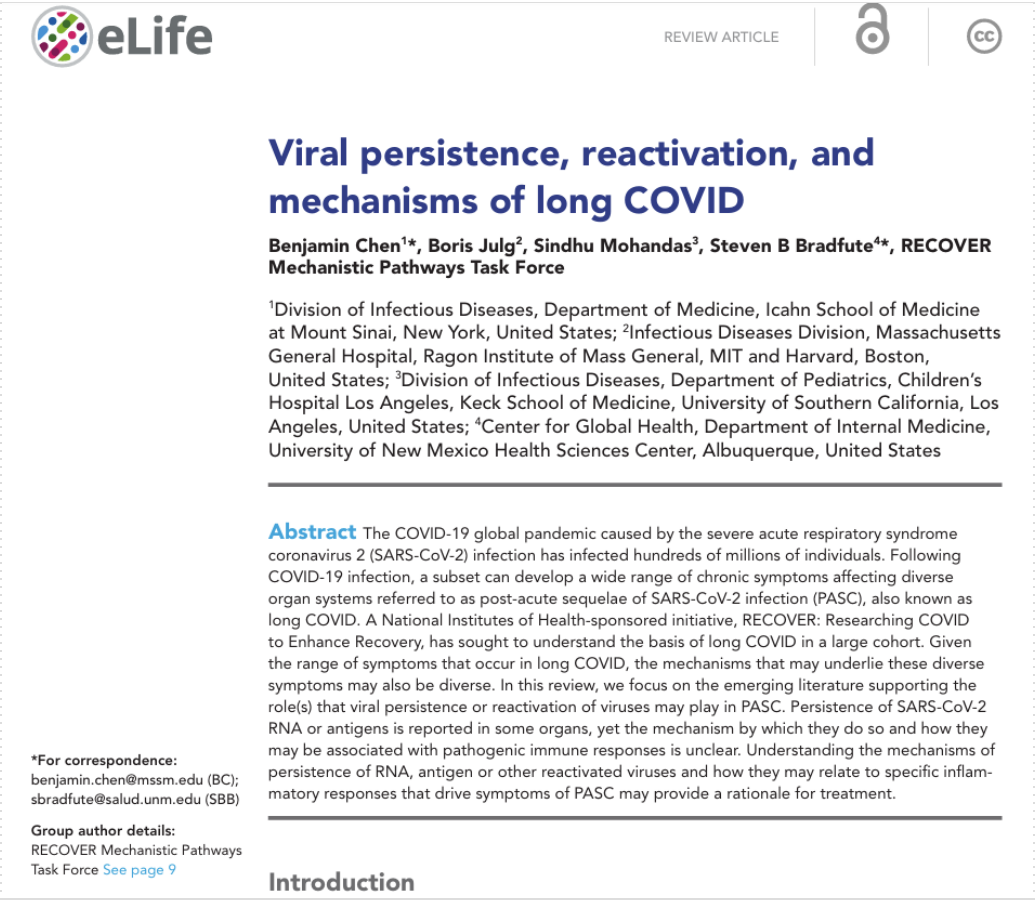
Bacteria:
Borrelia
Bartonella
Babesia
Coxiella burnetti (Q fever)
Brucella

Retroviruses:
HIV

"… the study of SARS-CoV-2 reservoir and related biological factors in PASC may inform the identification of disease mechanisms, biomarkers and therapeutics for other **chronic conditions increasingly tied to persistent viral infection.** These diseases include **myalgic encephalomyelitis/chronic fatigue syndrome[111], Alzheimer's disease[99], and autoimmune diseases such as multiple sclerosis[89,112] and systemic lupus erythematosus[113].**" 1

Source: https://www.youtube.com/watch?v=b9k-sI9P8QI

Important to still check for SARS-CoV-2 (IgA): it can persist – not yet known for how long



eLife

REVIEW ARTICLE

Viral persistence, reactivation, and mechanisms of long COVID

Benjamin Chen[1]*, Boris Julg[2], Sindhu Mohandas[3], Steven B Bradfute[4]*, RECOVER Mechanistic Pathways Task Force

[1]Division of Infectious Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, United States; [2]Infectious Diseases Division, Massachusetts General Hospital, Ragon Institute of Mass General, MIT and Harvard, Boston, United States; [3]Division of Infectious Diseases, Department of Pediatrics, Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, United States; [4]Center for Global Health, Department of Internal Medicine, University of New Mexico Health Sciences Center, Albuquerque, United States

Abstract The COVID-19 global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has infected hundreds of millions of individuals. Following COVID-19 infection, a subset can develop a wide range of chronic symptoms affecting diverse organ systems referred to as post-acute sequelae of SARS-CoV-2 infection (PASC), also known as long COVID. A National Institutes of Health-sponsored initiative, RECOVER: Researching COVID to Enhance Recovery, has sought to understand the basis of long COVID in a large cohort. Given the range of symptoms that occur in long COVID, the mechanisms that may underlie these diverse symptoms may also be diverse. In this review, we focus on the emerging literature supporting the role(s) that viral persistence or reactivation of viruses may play in PASC. Persistence of SARS-CoV-2 RNA or antigens is reported in some organs, yet the mechanism by which they do so and how they may be associated with pathogenic immune responses is unclear. Understanding the mechanisms of persistence of RNA, antigen or other reactivated viruses and how they may relate to specific inflammatory responses that drive symptoms of PASC may provide a rationale for treatment.

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Group author details: RECOVER Mechanistic Pathways Task Force See page 9

Introduction

"In peripheral blood monocytes, persistence of S1 antigen has been detected by antibody and mass spectrometry .. in some cases up to 15 months post infection[1]*. .. Viral RNA has been detected in patients with persistent symptoms after COVID-19 in the blood, stool, and urine (Tejerina et al., 2022). Using ultrasensitive ELISA, **60% of individuals with PASC** had detectable plasma Spike antigen** (Swank et al., 2023)."[2]

* Only because the study wasn't continued for longer

**PASC = Post-acute sequelae of Covid-19

Source: 1. Patterson BK et al. Persistence of SARS CoV-2 S1 Protein in CD16+ Monocytes in Post-Acute Sequelae of COVID-19 (PASC) up to 15 Months Post-Infection. Front Immunol. 2022 Jan 10;12:746021. 2. Chen, B et al. RECOVER Mechanistic Pathways Task Force (2023) Viral persistence, reactivation, and mechanisms of long COVID eLife 12:e86015.

Shocking conclusion of some researchers from large-scale studies: "Long COVID does not seem to be self-resolving"

Long Covid and Impaired Cognition — More Evidence and More Work to Do

Ziyad Al-Aly, M.D., and Clifford J. Rosen, M.D.

Article Figures/Media Metrics

10 References

February 29, 2024
N Engl J Med 2024; 390:858-860
DOI: 10.1056/NEJMe2400189

During the early stages of the Covid-19 pandemic, reports emerged that persons who had been infected with SARS-CoV-2 were having lingering health problems. Such long-term issues were collectively referred to as "long Covid" and were reported to affect nearly every organ system.[1] The cardinal features of long Covid include fatigue, dysautonomia (or postural orthostatic tachycardia syndrome), postexertional malaise, and cognitive difficulties that are colloquially referred to as "brain fog."

Several large studies then emerged documenting the presence of neurologic sequelae — including cognition and memory problems — in the postacute phase of SARS-CoV-2 infection.[2,3] A recent analysis of the U.S. Current Population Survey showed that after the start of the Covid-19 pandemic, an additional one million U.S. residents of working age reported having "'serious difficulty' remembering, concentrating, or making decisions" than at any time in the preceding 15 years.[4] Whether these changes are attributable solely to long Covid is unclear, but that report represents a change in the cognitive health of U.S. residents from prepandemic levels.

Study of 800,000 adults from a larger community sample of over 3 million people in the Real-Time Assessment of Community Transmission (REACT) of SARS-CoV-2 transmission **in England** …

… "As compared with uninfected participants (control), **cognitive deficit — commensurate with a 3-point loss in IQ** — was evident even in participants who had had mild Covid-19 with resolved symptoms."

Possible mechanism?: "Studies involving humans and mouse organoids showed that SARS-CoV-2 infection induces fusion of neurons, which compromises neuronal activity."

"Long Covid does not seem to be self-resolving, in the sense of spontaneous recovery or recovery in the absence of a cure or a treatment that's been validated."
Lead author Dr. Ziyad Al-Aly, Clinical Epidemiologist at Washington University in St. Louis

Source: *Al-Aly Z, Rosen CJ. Long Covid and Impaired Cognition - More Evidence and More Work to Do. N Engl J Med. 2024 Feb 29;390(9):858-860*

Agenda

- Recent research evidencing huge viral involvement/reactivation in the post-COVID era
- **Optimal testing for DNA and RNA viruses**
- Therapeutic options for viral infections
  - Infection
  - Inflammation
  - Immune dysfunction and detoxification

Serology (B cells) used commonly, especially by national health services, for testing: the downsides

In chronic disease, IgG may be there, but will be discounted as "past"; IgM probably will not be (dissipates weeks/few months post infection)

ENDOCRINOLOGY

Cytomegalovirus Ab(IgG)	183.0	AU/ml
	<6.0 AU/mL is considered non-reactive	
	>=6.0 AU/mL is considered reactive	
Cytomegalovirus Ab(IgM)	Negative	
Comment	Result suggestive of previous CMV infection.	

IMMUNOLOGY

Epstein-Barr virus screen			
EBNA IgG antibody	* 36	U/ml	(< 5 U/ml Negative)
EBV Early Ag ab.(IgG)	<5	U/ml	(<10 U/ml Negative)
EBV VCA ab.(IgM)	<10	U/ml	(<20 U/ml Negative)
Comment	Results suggestive of past (latent) EBV infection.		

"IgG is produced in a delayed response to an infection and can be retained in the body for a long time …. Detection of IgG usually indicates a prior infection or vaccination."

The tragedy: As a result, patients worldwide fall between the cracks

Source: http://www.microbiologybook.org/mayer/Ab%20formation2000.htm

IgA antibodies very helpful as they indicate active infection along the mucosal membranes: can be used for HSV1/2, VZV, Coxsackie and Echovirus, and SARS-CoV-2

VZV IgG-/IgA-/IgM-antibodies

4 VZV IgG antibodies (ELISA) positive
4643,8 IE/l

<80 IE/l negative
>80 - < 110 IE/l weak
>110 IE/l positive

4 VZV IgA antibodies (ELISA) positive
1,287 Ratio

Ratio < 0,8 = negative
Ratio 0,8 - 1,1 = weak
Ratio >= 1,1 = positive

4 VZV IgM antibodies (ELISA) negative
0,306 Ratio

Ratio < 0,8 = negative
Ratio 0,8 - 1,1 = weak
Ratio >= 1,1 = positive

Analysis		Result Units	Reference Range	Chart
Coxsackie IgG-/IgA-antibodies				
4 Coxsackie-IgG Typ A7 (IFT)	+	1:100	< 1:100	[..... *>
4 Coxsackie-IgG Typ B1 (IFT)	+	1:1000	< 1:100	[..... *>
4 Coxsackie-IgA Typ A7 (IFT)	+	1:100	< 1:10	[..... *>
4 Coxsackie-IgA Typ B1 (IFT)	+	1:10	< 1:10	[..... *>

The specific positive Coxsackie-Virus Type A7/B1-IgG-/IgA-antibodies indicate current humoral immune responses against Coxsackie-Virus Type A7 and Coxsackie-Virus Type B1 (recent infection with Coxsackie-Virus Type A7/B1?).

Analysis		Result Units	Reference Range	Chart
7 ECHO IgG-antibodies (IFT)	+	1:1000	< 1:100	[..... *>
7 ECHO IgA-antibodies (IFT)	+	1:10	< 1:10	[..... *>

The specific positive ECHO-virus IgG/IgA-antibodies indicate current humoral immune responses against ECHO-virus (recent infection with ECHO-virus?).

Analysis	Result Units	Reference Range
SARS-CoV2 virus IgG/IgA Ab		
3 SARS CoV2 IgG-Ab	**positive** ! **5,021 Ratio**	**negative**
Ratio < 0,8	= negative	
Ratio 0,8 - 1,1	= weak	
Ratio >= 1,1	= positive	
3 SARS CoV2 IgA-Ab	**positive** ! **1,140 Ratio**	**negative**
Ratio < 0,8	= negative	
Ratio 0,8 - 1,1	= weak	
Ratio >= 1,1	= positive	

The other arm of the immune system, the cellular response using T-cells, is a specialty of ArminLabs

Using T-cells to show a cellular response against antigens is much more sensitive, and is more likely to **indicate active infection (in contrast to IgG antibodies, which can remain for months or years long after an infection is gone, and IgM a/bs, which generally do not persist very long)**. EliSpot (enzyme-linked immunosorbent spot) technology has long been used in Germany to do exactly this: it quantifies T-cells that secrete signature proteins (such as a given cytokine) against a specific antigen. The Borrelia EliSpot evaluates the number of spot-forming units using a stimulation index (SI) based on IGRA (Interferon Gamma Release Assay).

Humana Press; 3rd ed. 2018 edition (14 July 2018)

New “Springer Protocols“ book (2024) with a chapter on EliSpots

Book | © 2024

Chapter 6

Adaptive Immune Response Investigation in Lyme Borreliosis

Mihail Pruteanu, Armin Schwarzbach, and Markus Berger

Abstract

To diagnose Lyme Borreliosis, it is advised to use an enzyme-linked immunosorbent test to check for serum antibodies specific for Lyme and all tests with positive or ambiguous enzyme-linked immunosorbent assay (ELISA) results being confirmed by immunoblot. This method of measuring the humoral immunity in human fluids (e.g., by ELISA) has provided robust and reproducible results for decades and similar assays have been validated for monitoring of B cell immunity. These immunological tests that detect antibodies to *Borrelia burgdorferi* are useful in the diagnosis of Borreliosis on a routine basis. The variety of different *Borrelia* species and their different geographic distributions are the main reasons why standards and recommendations are not identical across all geographic regions of the world. In contrast to humoral immunity, the T cell reaction or cellular immunity to the *Borrelia* infection has not been well elucidated, but over time with more studies a novel T cell-based assay (EliSpot) has been developed and validated for the sensitive detection of antigen-specific T cell responses to *B. burgdorferi*. The EliSpot Lyme assay can be used to study the T cell response elicited by *Borrelia* infections, which bridges the gap between the ability to detect humoral immunity and cellular immunity in Lyme disease. In addition, detecting cellular immunity may be a helpful laboratory diagnostic test for Lyme disease, especially for seronegative Lyme patients. Since serodiagnostic methods of the *Borrelia* infection frequently provide false positive and negative results, this T cell-based diagnostic test (cellular assay) may help in confirming a Lyme diagnosis. Many clinical laboratories are convinced that the cellular assay is superior to the Western Blot assay in terms of sensitivity for detecting the underlying *Borrelia* infection. Research also suggests that there is a dissociation between the magnitude of the humoral and the T cell-mediated cellular immune responses in the *Borrelia* infection. Lastly, the data implies that the EliSpot Lyme assay may be helpful to identify *Borrelia* infected individuals when the serology-based diagnostic fails to do so. Here in this chapter the pairing of humoral and cellular immunity is employed to evaluate the adaptive response in patients.

The Elispot technique reflects the current T-cellular activity of bacteria and viruses

“The EliSpot Lyme assay can be used to study the T cell response elicited by Borrelia infections, which bridges the gap between the ability to detect humoral immunity and cellular immunity in Lyme disease. **Many clinical laboratories are convinced that the cellular assay is superior to the Western Blot assay in terms of sensitivity for detecting the underlying Borrelia infection..** Research also suggests that there is a dissociation between the magnitude of the humoral and the T cell-mediated cellular immune responses in the Borrelia infection.”

Epstein Barr Virus EliSpot results: high stimulation index often seen post COVID, backed up by 1000s of laboratory tests

EBV EliSpot (lytic+latent)

1 EBV EliSpot (lytic)	**!**	**657 SI**	
0-1 = negative			
2-3 = weak positive			
> 3 = positive			
1 EBV EliSpot (latent)	**!**	**65 SI**	
0-1 = negative			
2-3 = weak positive			
> 3 = positive			

← Viral latency suppresses the immune system – also a valuable finding

The result of the EliSpot test indicates current celluar activity against Epstein-Barr-Virus (EBV).

Explanation of EBV antigens:
EBV-lytic antigen: sign for replication of infectious EBV virions
EBV-latent antigen: sign for EBV latency with no production of infectious EBV virions

Source: Arminlabs laboratory results

ArminLabs Long-/Post-COVID Checklist

Post-Covid Checklist

arminlabs

Name, first name ..... Date (DD/MM/YYYY) .....

	Your current and former symptoms Please click on the boxes next to the symptoms that you suffer from	X
1	Stomach ache, gut problems	
2	Anaemia	
3	Diarhoea intermittent, intestinal crampings/pain	
4	Fever or feverish feeling	X
5	Lack of concentration, memory loss, forgetfulness	X
6	Encephalitis/Inflammation of the brain	
7	Yellowish colour of the skin/eyes	
8	Painful joints or swollen joints	
9	General aches and pains, tendon problems	X
10	Flu-like symptoms	X
11	Rash(es), striae, exanthema	
12	Small red/purple spots of the skin	
13	Heart problems, disturbed cardiac rhythm	X
14	Cough, expectoration, "air-hunger"	X
15	Headache, dizziness	
16	Impaired liver function/ liver laboratory values	
17	Pneumonia, bronchitis	
18	Swollen lymph nodes	X
19	Enlargement of the spleen	
20	Fatigue / exhaustion, intermittent or chronic CFS	X
21	Muscle pain, muscle weakness	X
22	Shivering, chill	
23	Blurred, foggy, cloudy, flickering, double vision	
24	Nausea, vomiting	
25	Dark urine	
26	Itching or pain when urinating	
27	Tingling, numbness, "burning" sensations	X
28	Neck pain, neck stiffness	

Below you'll find the number of the symptoms for each of the infections that we test for and the ranking, in which order you should test for them

Ranking of the infections	No. of symptoms	Rank
Chlamydia pneumoniae	10	1
Mycoplasma pneumoniae	10	1
Yersinia	4	7
Campylobacter	5	6
HSV 1/2	8	3
EBV	9	2
CMV	9	2
VZV	6	5
HHV 6	7	4
Parvovirus	7	4
Coxsackie-Virus	10	1
Echovirus	7	4

We pinpoint the cause

ArminLabs Post-COVID Viral Reactivation Panel

arminlabs

ACADEMY of NUTRITIONAL MEDICINE

Post-COVID Reactivated Infection Panels

PATIENT INFORMATION		BARCODE (Lab use only)		ORDERING DR/PRACTITIONER INFORMATION	
Patient FIRST NAME:				Dr. / Practitioner name:	
Patient SURNAME:				Clinic:	
DATE OF BIRTH (DD/MM/YYYY):				Street Address:	
SEX (please circle): nonbinary male female		Time of Blood Draw:		Postcode:	City:
Street Address:		Date (DD/MM):		County:	Country:
Postcode:	City:	Material/Quantity	☐ CPDA (yellow)	Tel no:	
County:	Country:		☐ Serum (orange)	Email:	
Tel no:		AONM HELPLINE:			
Email:		+44 (0) 3331 210 305			

Basic: Post-COVID Viral Reactivation Panel			
☐	EBV EliSpot, t-cell test, lytic only	CPDA	£323
	CMV EliSpot, t-cell test, lytic only	CPDA	
	VZV IgG/IgM/IgA antibodies	Serum	
	Coxsackie A7 & B1 IgG/IgA antibodies	Serum	

New ArminLabs Viral Checklist

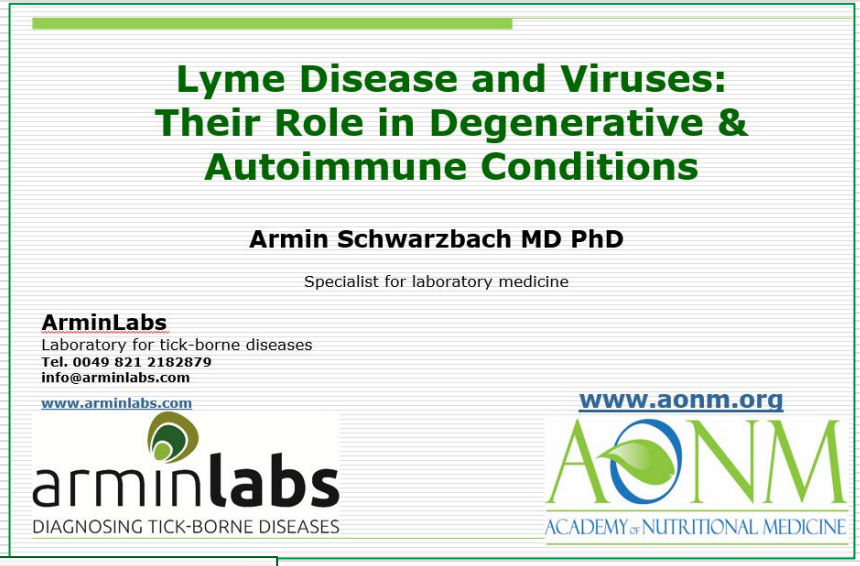
Viral Infections Checklist

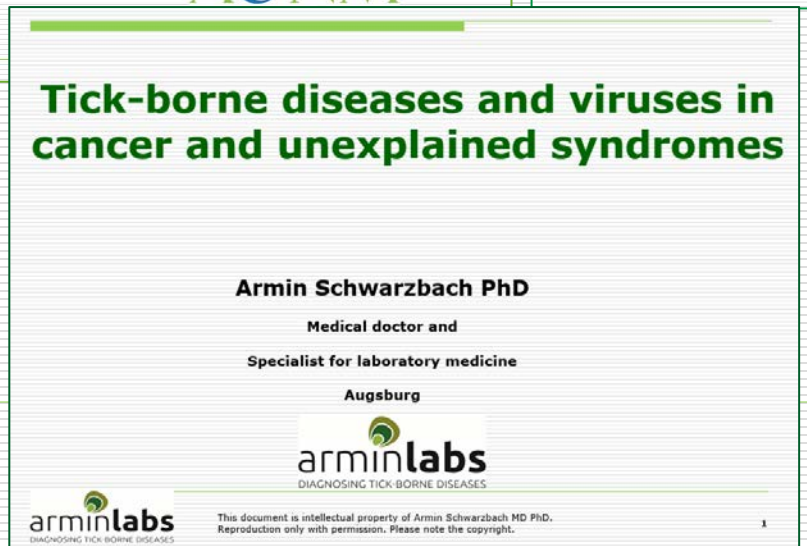
Name, first name ..... Date of birth .....

▶	Current and past symptoms Please mark with a cross	X	Score points (filled by physician/naturopath)	Ranking
1	Previous or recent tick bites		EBV :	
2	Flu-like infection, usually in the summer months, fever		HSV 1/2 :	
3	Growing debility, headaches and aching limbs		CMV :	
4	Intermittent tiredness/exhaustion or chronic fatigue		VZV :	
5	Abdominal discomfort, intestinal cramps/pain, jaundice		TBE Virus :	
6	Alternating of diarrhea and constipation, vomiting		Parvovirus B19:	
7	Previous or current redness, painful blisters		Coxackievirus A7/B1:	
8	Skin symptoms, itchy rash		Echovirus:	
9	Memory and concentration disorders, forgetfulness		HHV6 :	
10	Pain in the back of the head and neck area		HHV7 :	
11	Heart issues, arrhythmia, myocarditis		HHV8 :	
12	Night sweats, respiratory diseases			
13	Numbness of the arms and legs, muscle pain			
14	Paresthesia and pain on touch			

Links to more detailed ArminLabs virus presentations on the AONM website …

https://aonm.org/viruses-and-testing/





Agenda

- Recent research evidencing huge viral involvement/reactivation in the post-COVID era
- Optimal testing for DNA and RNA viruses
- **Therapeutic options for viral infections**
  - **Infection**
  - Inflammation
  - Immune dysfunction and detoxification

Uncaria tomentosa – Samento: well-studied antibacterial and also antiviral properties

Samento is a pentacyclic chemotype of Cat's Claw [Uncaria tomentosa] that does not contain tetracyclic oxindole alkaloids, with reported antibacterial and also antiviral properties

"Uncaria tomentosa hydroethanolic extracts have demonstrated a significant in vitro inhibitory effect on the replication of herpes simplex virus type 1, and the inhibition of viral attachment in the host cells was characterized as the main mechanism of its antiviral activity." [3]

Samento stimulates the production of white blood cells, which play a role in fighting against pathogens that cause infections. It is also described as having analgesic capabilities, which may benefit bone health and improve symptoms of conditions such as osteoarthritis.

Sources: https://www.samento.com.ec/sciencelib/sammain.html; https://www.samento.com.ec/sciencelib/4sam/getarmedjan04.html; 3. Yepes-Pérez AF, Herrera-Calderon O, Quintero-Saumeth J. Uncaria tomentosa (cat's claw): a promising herbal medicine against SARS-CoV-2/ACE-2 junction and SARS-CoV-2 spike protein based on molecular modeling. J Biomol Struct Dyn. 2022 Mar;40(5):2227-2243

Otoba parvifolia – Banderol: broad-spectrum antimicrobial

Banderol is an extract produced from the bark of the Banderilla (Otoba species) tree from the Amazon basin. It is a broad-spectrum antimicrobial that is very effective against Borrelia burgdorferi and its common co-infections. Some microbes treated by Banderol include: Anaerobic and many Aerobic rods and cocci, some Aspergillus, Babesia, Bartonella, Borrelia, some Candida, and Chlamydia.

Interestingly, it also has antiviral properties: it is effective against Cytomegalovirus, some Encephalitis viruses, some Hepatitis viruses, and Human Papilloma Virus.

It is also able to address Mycoplasma, many Protozoal parasites, and Rickettsia (including Coxiella and Ehrlichia).

Some conditions that respond well to Banderol are acute and chronic prostatitis, acute and many chronic respiratory tract infections, acute and chronic sinusitis, asthma, atherosclerotic disease, cellulitis, psoriasis, thrush, and many urinary tract and vaginal infections.

Sources: Shor SM, Schweig SK. The Use of Natural Bioactive Nutraceuticals in the Management of Tick-Borne Illnesses. Microorganisms. 2023 Jul 5;11(7):1759. Weiss J. Herb¯Drug Interaction Potential of Anti-Borreliae Effective Extracts from Uncaria tomentosa (Samento) and Otoba parvifolia (Banderol) Assessed In Vitro. Molecules. 2018 Dec 31;24(1):137.

Crecopia strigosa – Takuna: Remarkable antiviral properties

Takuna is an extract produced from the bark of Cecropia strigosa, a tree that is found throughout South America. It has recently been found to have very powerful antiviral properties as well as some other general antimicrobial properties.

Practitioners using the product have found that Takuna given every hour usually resolves influenzas in just a few hours. In some cases, the symptoms are resolved in as little as one hour.

Takuna can be used to fight colds, flu, viral hepatitis, shingles, cytomegalovirus, Epstein-barr virus, acute and chronic viral encephalitis, and meningitis. Robust studies have also shown its effectiveness against Herpes types 1 and 2.

"These data showed that the MeOH(AMB) **fraction has an antiviral activity against HHV types 1 and 2.** The C-glycosylflavonoids are the major constituents of this fraction, which suggests that they could be one of the compounds responsible for the detected anti-herpes activity."[1]

Source: 1. Silva IT, Costa GM, Stoco PH et al (2010) In vitro antiherpes effects of C-glycosylflavoid-enriched fraction of Cecropia glaziovii Seth. Letters in Applied Microbiology 51:143-148

Houttuynia – virucial effects studied in Norovirus, HSV-1, influenza and others

molecules

MDPI

Article

Antiviral Effects of *Houttuynia cordata* Polysaccharide Extract on Murine Norovirus-1 (MNV-1)—A Human Norovirus Surrogate

Dongqing Cheng [1,2,†], Liang Sun [1,†], Songyan Zou [2], Jiang Chen [1], Haiyan Mao [1], Yanjun Zhang [1], Ningbo Liao [1,3,*] and Ronghua Zhang [1,2,*]

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Received: 4 March 2019; Accepted: 9 May 2019; Published: 13 May 2019

check for updates

Abstract: *Houttuynia cordata* is an herbal plant rich in polysaccharides and with several pharmacological activities. Human noroviruses (HuNoVs) are the most common cause of foodborne viral gastroenteritis throughout the world. In this study, *H. cordata* polysaccharide (HP), with a molecular weight of ~43 kDa, was purified from *H. cordata* water extract (HWE). The polysaccharide HP was composed predominantly of galacturonic acid, galactose, glucose, and xylose in a molar ratio of 1.56:1.49:1.26:1.11. Methylation and NMR analyses revealed that HP was a pectin-like acidic polysaccharide mainly consisting of α-1,4-linked Gal*p*A, β-1,4-linked Gal*p*, β-1,4-linked Glc*p*, and β-1,4-linked Xyl*p* residues. To evaluate the antiviral activity of *H. cordata* extracts, we compared the anti-norovirus potential of HP with HWE and ethanol extract (HEE) from *H. cordata* by plaque assay (plaque forming units (PFU)/mL) for murine norovirus-1 (MNV-1), a surrogate of HuNoVs. Viruses at high (8.09 log10 PFU/mL) or low (4.38 log10 PFU/mL) counts were mixed with 100, 250, and 500 μg/mL of HP, HWE or HEE and incubated for 30 min at room

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Immunomodulatory and anti-SARS activities of *Houttuynia cordata*

Kit-Man Lau[a,1], Kin-Ming Lee[a,1], Chi-Man Koon[a,1], Crystal Sao-Fong Cheung[b], Ching-Po Lau[a], Hei-Ming Ho[b], Mavis Yuk-Ha Lee[a], Shannon Wing-Ngor Au[b], Christopher Hon-Ki Cheng[b], Clara Bik-San Lau[c], Stephen Kwok-Wing Tsui[b], David Chi-Cheong Wan[b], Mary Miu-Yee Waye[b], Kam-Bo Wong[b], Chun-Kwok Wong[d], Christopher Wai-Kei Lam[d], Ping-Chung Leung[a], Kwok-Pui Fung[a,b,*]

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ABSTRACT

Background: Severe acute respiratory syndrome (SARS) is a life-threatening form of pneumonia caused by SARS coronavirus (SARS-CoV). From late 2002 to mid 2003, it infected more than 8000 people worldwide, of which a majority of cases were found in China. Owing to the absence of definitive therapeutic Western medicines, *Houttuynia cordata* Thunb. (Saururaceae) (HC) was shortlisted by Chinese scientists to tackle SARS problem as it is conventionally used to treat pneumonia.
Aim of the study: The present study aimed to explore the SARS-preventing mechanisms of HC in the immunological and anti-viral aspects.
Results: Results showed that HC water extract could stimulate the proliferation of mouse splenic lymphocytes significantly and dose-dependently. By flow cytometry, it was revealed that HC increased the proportion of $CD4^+$ and $CD8^+$ T cells. Moreover, it caused a significant increase in the secretion of IL-2 and IL-10 by mouse splenic lymphocytes. In the anti-viral aspect, HC exhibited significant inhibitory effects on SARS-CoV 3C-like protease ($3CL^{pro}$) and RNA-dependent RNA polymerase (RdRp). On the other hand, oral acute toxicity test demonstrated that HC was non-toxic to laboratory animals following oral administration at 16 g/kg.
Conclusion: The results of this study provided scientific data to support the efficient and safe use of HC to combat SARS.

1. Introduction

1997). Recently, several studies also provided scientific data to sup-

Source: Cheng D et al Antiviral Effects of Houttuynia cordata Polysaccharide Extract on Murine Norovirus-1 (MNV-1)-A Human Norovirus Surrogate. Molecules. 2019 May 13;24(9):1835.; Lau K.-M. et al. Immunomodulatory and anti-SARS activities of Houttuynia Cordata. J. Ethnopharmacol. 2008;118:79–85; Hayashi, K et al. Virucidal effects of the steam distillate from Houttuynia cordata and its components on HSV-1, influenza virus, and HIV. Planta Med. 1995, 61, 237–241.

Cumanda – microbial support with a tradition of hundreds of years

Cumanda is a herbal extract made from the bark of the Campsiandra Angustifolia tree, found in South America. It has been used by indigenous groups in that region for hundreds of years.

Cumanda bark contains anthocyanins, cyanogenic glycosides, heterosides, saponins and tannins. It is known to have many medicinal properties which include:

- Antibacterial
- Antifungal
- Antiviral
- Antiparasitic
- Anti-inflammatory
- Analgesic
- Immune system modulator

Source: Vojdani A, Hebroni F, Raphael Y, Erde J, Raxlen B. Novel Diagnosis of Lyme Disease: Potential for CAM Intervention. Evid Based Complement Alternat Med. 2009 Sep;6(3):283-95; Arthur S. The effectiveness of Samento, Cumada, Burbur and Drl Lee Cowden's protocol in the treatment of chronic lyme disease. Townsend Letter 2007;101–6.

Baicalin – Chinese Skullcap: Numerous antiviral molecular pathways

J Microbiol Biotechnol. 2019 Aug 28;29(8):1230-1239. doi: 10.4014/jmb.1904.04050.

Scutellaria baicalensis Inhibits Coxsackievirus B3–Induced Myocarditis Via AKT and p38 Pathways

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Affiliations + expand

PMID: 31370111 DOI: 10.4014/jmb.1904.04050

Free article

Abstract

Scutellaria baicalensis Georgi has been widely used in China for treatment of various diseases. This study investigated the effect of *Scutellaria baicalensis* Georgi extracts (SBE) against Coxsackievirus B3 (CVB3)-induced myocarditis in vitro and in vivo. In vitro, Hela cells and primary myocardial cells were infected with CVB3 and treated with SBE (50-800 μg/ml) and ribavirin (200 μM) for 48 h and then determined by CCK8 assay. Real-time PCR and western blotting assays were performed. In vivo, a myocarditis model was induced in male BALB/c mice by injecting CVB3 suspension intraperitoneally for three times, followed by treatment with SBE (400 and 200 mg/kg) and ribavirin (100 mg/kg) for 28 days. SBE ameliorated the cytotoxicity of CVB3 in Hela cells, especially at 400 μg/ml (39.93% vs 65.67%, $p < 0.05$) without influencing cell growth and also significantly reduced CVB3 replication in primary myocardial cells. The levels of AKT, ERK, and p38 were increased after CVB3 infection. SBE could downregulate the expressions of AKT and p38. In vivo, the mortality rate from CVB3 reached to 66.67%, while 10.00% and 23.33% of this came after 400 and 200 mg/kg SBE treatment, respectively

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The Second SREE Conference on Engineering Modelling and Simulation (CEMS 2012)

Inhibitory Role of Baicalin on Human Herpes Virus Type 6 in Vitro

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Abstract

To study the inhibitory effect of Baicalin on Human Herpes Virus Type 6, the human T-cell strain of HSB_2 was used to test the anti-HHV6 effect in vitro. The result suggests that Baicalin has evident effect on cytopathic effect (CPE) caused by HHV-6 GS. This result prompts that Baicalin has prophylaxis and therapeutical effect on infection caused by HHV-6.

Keywords: Baicalin; Human Herpes Virus 6; inhibitory role; in vitro.

1. Introduction

Human Herpes Virus 6 (HHV-6), a kind of addicted human lymphocytic double-stranded virus belongs to β-herpesvirus subfamily. HHV-6 was first isolated by Salahuddin[1] from peripheral blood mononuclearcells of AIDS patients and lymphoproliferative disorders. HHV-6 is divided into HHV-6A and HHV-6B according to viral DNA restriction enzyme analysis, nucleotide sequence analysis, the responsivity to monoclonal antibody and the growth in different T lymphocytes culture. The primary

"Baicalin (BA) is a flavonoid compound purified from Scutellaria baicalensis Georgi and has been shown to **possess a potent inhibitory activity against viruses."**[2]

Sources: 1. Li K et al. Antiviral Properties of Baicalin: a Concise Review. Rev Bras Farmacogn. 2021;31(4):408-419; 2. Chu M et al. Role of Baicalin in Anti-Influenza Virus A as a Potent Inducer of IFN-Gamma. Biomed Res Int. 2015;2015:263630; Fu Q et al. Scutellaria baicalensis Inhibits Coxsackievirus B3-Induced Myocarditis Via AKT and p38 Pathways. J Microbiol Biotechnol. 2019 Aug 28;29(8):1230-1239.

Stevia rebaudiana shown to have potent antiviral activity in some studies

Pages 1558-1562 | Received 01 Jul 2018, Accepted 23 Aug 2018, Published online: 22 Dec 2018
Short Communication

Anti-herpes activity of polysaccharide fractions from *Stevia rebaudiana* leaves

Ligia Fernanda Ceole, Mychelle Vianna Pereira Companhoni, Sheila Mara Sanches Lopes, Arildo José Braz de Oliveira, Regina Aparecida Correia Gonçalves, Benedito Prado Dias Filho, ...show all

Cite this article https://doi.org/10.1080/14786419.2018.1516662 Check for updates

Abstract

The antiviral potential of natural polysaccharide compounds has been demonstrated, especially against enveloped viruses and members of the *Herpesviridae* family. Two polysaccharide fractions obtained from *Stevia rebaudiana* (Bertoni) leaves, that were active against Herpes simplex virus type 1 (HSV-1) were studied to investigate their mode of action. Both polysaccharides - SFW (crude faction) and SSFK (homogeneous alkaline fraction) - exerted antiviral effects on the initial stages of HSV-1 infection by inhibiting viral adsorption and penetration. When added after virus internalization, both fractions decreased plaque size. The effect of the fractions was confirmed by investigating viral glycoprotein expression. Based on the mode of action of the polysaccharides demonstrated in the present work and on their selectivity index, the polysaccharides obtained from *S. rebaudiana* could be an alternative treatment of infections caused by HSV-1.

Relat

"… solutions of the dried, purified Stevia extract had marked virustatic and virucidal properties. Until recently, dried Stevia extracts (steviosides) were regarded mainly as sweet eners. The demonstration of antiviral properties of Stevia ex tract makes it attractive for further investigation as a poten tial medicinal agent." [1]

Finally, steviol from Stevia rebaudiana (F: Asteraceae) **shown to have potent antiviral activity** (Peteliuk et al., 2021)

Source: 1. Kedik SA, Yartsev EI, Stanishevskaya IE. Antiviral activity of dried extract of Stevia. Pharm Chem J. 2009;43(4):198-199; Ceole LF, Companhoni MVP, Sanches Lopes SM, de Oliveira AJB, Gonçalves RAC, Dias Filho BP, Nakamura CV, Ueda-Nakamura T. Anti-herpes activity of polysaccharide fractions from Stevia rebaudiana leaves. Nat Prod Res. 2020 Jun;34(11):1558-1562.

Agenda

- Recent research evidencing huge viral involvement/reactivation in the post-COVID era
- Optimal testing for DNA and RNA viruses
- **Therapeutic options for viral infections**
  - Infection
  - **Inflammation**
  - Immune dysfunction and detoxification

Dandelion – Taraxacum officinale

Taraxacum officinale belongs to the Asteraceae/ Compositae family and is native to Europe, though it is widespread throughout the northern hemisphere. Ith has been used for centuries in traditional health practices for comprehensive health support.

Dandelion leaf extract is effective in liver detox and preventing spike protein from entering the cell and binding to the ACE (Angiotensin Converting Enzyme) receptor on the cell membranes. Dandelion leaf may help with comprehensive health maintenance, including liver support, metabolic support, antioxidant support, and healthy inflammatory response support, breakdown of glyphosate, and removal of toxins in the body. Dandelion leaves support endogenous superoxide dismutase (SOD), an enzyme that helps break down potentially harmful oxygen molecules in the body's cells, and glutathione (GSH), which is vital in helping the liver perform its detoxifying functions.

ELSEVIER

Journal of Ethnopharmacology
Volume 115, Issue 1, 4 January 2008, Pages 82-88

Anti-inflammatory activity of *Taraxacum officinale*

Hye-Jin Jeon [a], Hyun-Jung Kang [b], Hyun-Joo Jung [a], Young-Sook Kang [a], Chang-Jin Lim [b], Young-Myeong Kim [c d], Eun-Hee Park [a]

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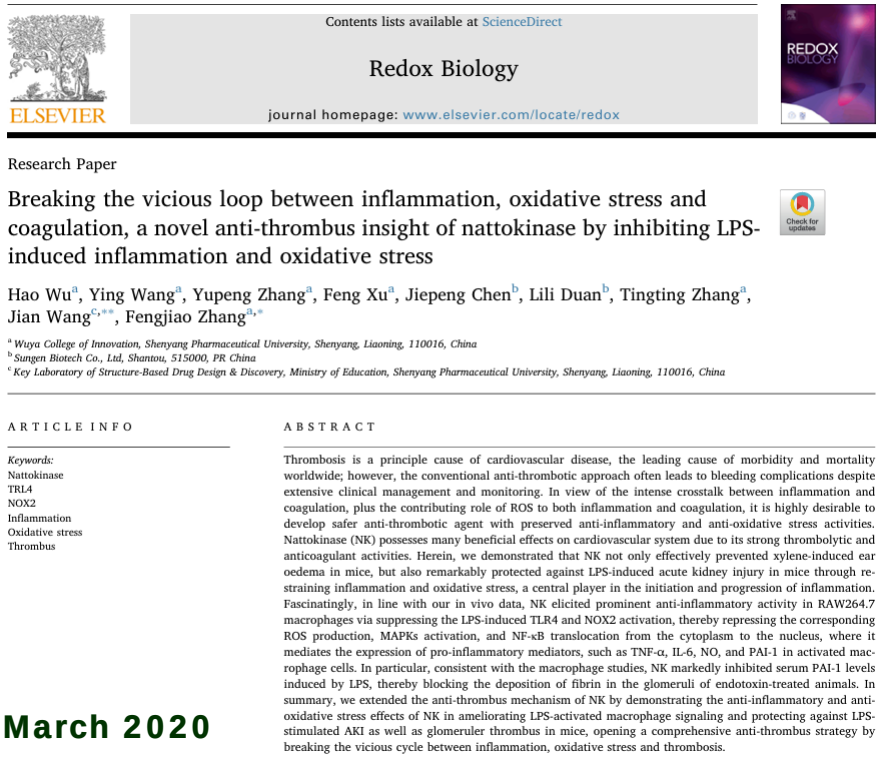
Abstract

Taraxacum officinale has been widely used as a folkloric medicine for the treatment of diverse diseases. The dried plant was extracted with 70% ethanol to generate its ethanol extract (TEE). For some experiments, ethyl acetate (EA), *n*-butanol (BuOH) and aqueous (Aq) fractions were prepared in succession from TEE. TEE showed a scavenging activity in the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay, a diminishing effect on intracellular reactive

Nattokinase – neuroprotective, proteolytic, anti-inflammatory

Nattokinase supports healthy coagulation and cardiovascular health through fibrinolytic support. It helps break down both fibrin and plasmin without affecting the healing response, as it does not inhibit the formation of fibrin from fibrinogen. Nattokinase also helps maintain PAI-1, t-PA, D-dimer, factor VII, factor VIII, and PTT within the normal range

"… data suggested that the neuroprotective effect of NK was due to its proteolytic, anti-inflammatory, and antiapoptotic effects. a study by Ji et al14 showed that the neuroprotective effect of NK was associated with its antiplatelet activity, antiapoptotic effect, its ability to relax vascular smooth muscle, and its protection of endothelial cells through increased fibrinolytic activity and facilitating spontaneous thrombolysis." [1]



Contents lists available at ScienceDirect

Redox Biology

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

Research Paper

Breaking the vicious loop between inflammation, oxidative stress and coagulation, a novel anti-thrombus insight of nattokinase by inhibiting LPS-induced inflammation and oxidative stress

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Thrombus

ABSTRACT

Thrombosis is a principle cause of cardiovascular disease, the leading cause of morbidity and mortality worldwide; however, the conventional anti-thrombotic approach often leads to bleeding complications despite extensive clinical management and monitoring. In view of the intense crosstalk between inflammation and coagulation, plus the contributing role of ROS to both inflammation and coagulation, it is highly desirable to develop safer anti-thrombotic agent with preserved anti-inflammatory and anti-oxidative stress activities. Nattokinase (NK) possesses many beneficial effects on cardiovascular system due to its strong thrombolytic and anticoagulant activities. Herein, we demonstrated that NK not only effectively prevented xylene-induced ear oedema in mice, but also remarkably protected against LPS-induced acute kidney injury in mice through re-straining inflammation and oxidative stress, a central player in the initiation and progression of inflammation. Fascinatingly, in line with our in vivo data, NK elicited prominent anti-inflammatory activity in RAW264.7 macrophages via suppressing the LPS-induced TLR4 and NOX2 activation, thereby repressing the corresponding ROS production, MAPKs activation, and NF-κB translocation from the cytoplasm to the nucleus, where it mediates the expression of pro-inflammatory mediators, such as TNF-α, IL-6, NO, and PAI-1 in activated macrophage cells. In particular, consistent with the macrophage studies, NK markedly inhibited serum PAI-1 levels induced by LPS, thereby blocking the deposition of fibrin in the glomeruli of endotoxin-treated animals. In summary, we extended the anti-thrombus mechanism of NK by demonstrating the anti-inflammatory and anti-oxidative stress effects of NK in ameliorating LPS-activated macrophage signaling and protecting against LPS-stimulated AKI as well as glomeruler thrombus in mice, opening a comprehensive anti-thrombus strategy by breaking the vicious cycle between inflammation, oxidative stress and thrombosis.

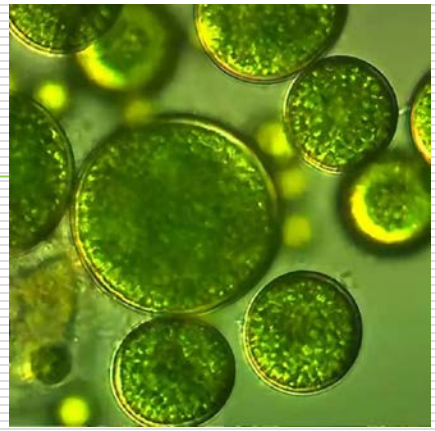
March 2020

Source: 1. Chen H, McGowan EM, Ren N, Lal S, Nassif N, Shad-Kaneez F, Qu X, Lin Y. Nattokinase: A Promising Alternative in Prevention and Treatment of Cardiovascular Diseases. Biomark Insights. 2018 Jul 5;13:1177271918785130; Ji H, Yu L, Liu K, et al. Mechanisms of nattokinase in protection of cerebral ischemia. Eur J Pharmacol. 2014;745:144–151.

Agenda

- Recent research evidencing huge viral involvement/reactivation in the post-COVID era
- Optimal testing for DNA and RNA viruses
- **Therapeutic options for viral infections**
  - Infection
  - Inflammation
  - **Immune dysfunction and detoxification**

Binders to ensure efficient elimination



Examples, may also be combined:

Chlorella vulgaris or pyrenoidosa, a nutrient-dense freshwater algae
Agave inulin: is a prebiotic fiber that also binds certain toxins in the gut
Zeolite is a volcanic clay with copious negatively-charged binding sites to attract positively-charged heavy metals so they can be carried into the toilet
Bentonite clay: is an edible clay that binds various toxins in the bowel
Activated charcoal: binds man-made toxins, biotoxins and even nutrients & pharmaceuticals, so the drugs & nutrients must be re-dosed 2-3 hours after
Aloe Vera: assists in healing leaky gut & improves immunity
Fulvic minerals: help to replace trace minerals that are lost from the body escorting lactic acid out; these minerals push heavy metals off cell receptors
Natural biopolymers from Baby Portobello (Agaricus bisporus): is a hypoallergenic vegetarian binder of mycotoxins

Source: Mastinu A, Kumar A, Maccarinelli G, Bonini SA, Premoli M, Aria F, Gianoncelli A, Memo M. Zeolite Clinoptilolite: Therapeutic Virtues of an Ancient Mineral. Molecules. 2019 Apr 17;24(8):1517.

Burbur and Pinella – the ideal combination to support detoxification

Burbur is produced from Desmodium molliculum, a perennial plant indigenous particularly to South America. It has traditionally been used in aiding detoxification of the liver, kidneys and lymphatic system, as well as to support the immune system.

Pinella is produced from Pimpinella anisum, also a perennial native to South America. Pinella is reported to be very effective in eliminating both man-made and biotoxins from the brain, spinal cord, and peripheral nervous system. Recent studies have shown that anise seeds and essential oil have antioxidant, antibacterial, antifungal, anticonvulsant, anti-inflammatory

Sun et al., *Cogent Biology* (2019), 5: 1673688
https://doi.org/10.1080/23312025.2019.1673688

cogent biology

PLANT SCIENCES | REVIEW ARTICLE

Anise (*Pimpinella anisum L.*), a dominant spice and traditional medicinal herb for both food and medicinal purposes

Wenli Sun[1,2***], Mohamad Hesam Shahrajabian[1,2**] and Qi Cheng[1,2**]

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Reviewing editor:: Sabrina Sabatini, Sapienza University of Rome, Italy ** All authors contributed equally to this work.

Additional information is available at the end of the article

Abstract: Aromatic plants such as anise seed have a long traditional use in both folk and conventional medicine and of course in the pharmaceutical industry. Important compounds found in anise seed include estragol, p-anisaldehyde, anise alcohol, acetophenone, pinene, and limonene, but the most important volatile oil that gives the characteristic sweet, aromatic flavor to seeds is anethole. The recent studies have shown that anise seeds and essential oil have antioxidant, antibacterial, antifungal, anticonvulsant, anti-inflammatory, analgesic, gastro-protective, antidiabetic, and antiviral activities. Other important benefits of anise seeds are stimulant, carminative, expectorant, insecticide, vermifuge, digestive, antispasmodic, antirheumatic, antiseptic, antiepileptic, antihysteric, culinary significance, keeps the heart strong by its importance role to control the blood pressure, one of the best

Sun et al., Cogent Biology (2019)

Source: Olascuaga-Castillo K, Rubio-Guevara S, Valdiviezo-Campos JE, Blanco-Olano C. Desmodium molliculum (Kunth) DC (Fabaceae); ethnobotanical, phytochemical and pharmacological profile of a Peruvian Andean plant. Ethnobot Res Appl. 2020;19:1–13; Shojaii A, Abdollahi Fard M. Review of Pharmacological Properties and Chemical Constituents of Pimpinella anisum. ISRN Pharm. 2012;2012:510795;

Magnesium malate – essential for cardiovascular, muscle, nerve and cellular function

Magnesium is an essential mineral required by every cell in the human body and is important for helping to maintain normal cardiovascular, muscle, nerve, bone and cellular function. Malic acid is preferentially utilised by the cells for energy production in the mitochondria: it is drawn through the cell membrane into the mitochondria. It is vital for activating the terminal complex of the electron transport chain: without it, mitochondrial ATP – our cells' key energy currency - cannot be made.

Integrating malic acid enhances magnesium's antioxidant properties, boosts energy levels, and reduces muscle pain and fatigue. Mg malate is probably the type best absorbed and utilised by the body.

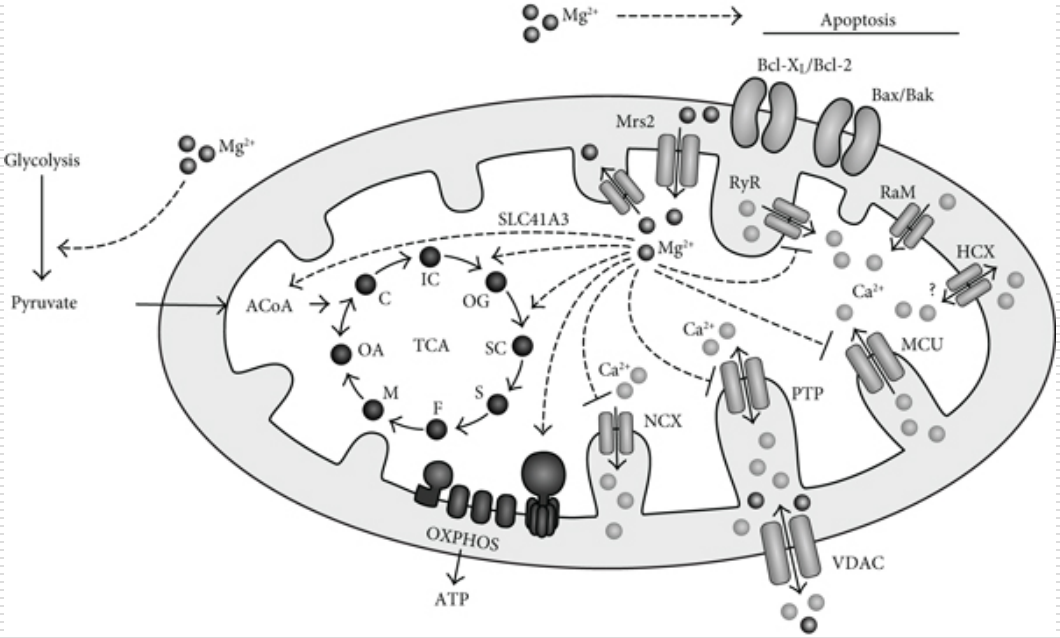


Figure 1: Regulation of mitochondrial functions by Mg^{2+}. Mitochondrial Mg^{2+} activates (----->) three dehydrogenases in the mitochondrial matrix: pyruvate dehydrogenase (conversion of mitochondrial pyruvate to acetyl coenzyme A), isocitrate dehydrogenase (conversion of isocitrate to 2-oxoglutarate), and 2-oxoglutarate dehydrogenase (conversion of 2-oxoglutarate to succinyl coenzyme A). In addition, mitochondrial Mg^{2+} activates F_0/F_1-ATP synthase, which is the terminal complex of mitochondrial oxidative phosphorylation (OXPHOS). This regulatory activity contributes to mitochondrial energy metabolism.[1]

Source: 1. Pilchova I et al. The Involvement of Mg^{2+} in Regulation of Cellular and Mitochondrial Functions. Oxid Med Cell Longev. 2017;2017:6797460. ; R. Yamanaka, S. Tabata, Y. Shindo et al., "Mitochondrial Mg^{2+} homeostasis decides cellular energy metabolism and vulnerability to stress," Scientific Reports, vol. 6, article 30027, 2016

Vitamin C crucial especially when suffering from a viral load

Vitamin C plays a critical role in your body. It is a powerful antioxidant, aids in wound healing, stimulates white blood cell immune activity and helps the body combat colds, flu and other infections, and neutralizes free-radicals. It also supports cardiovascular health and aids in iron absorption.

- Vitamin C deficiency is not uncommon when undergoing emotional stress or higher levels of physical stress such as burns, surgery, or other trauma. It is very beneficial when dealing with other ailments such as allergies and infections.

NB We lack the ability to synthesise endogenous Vitamin C, along with only bats, guinea pigs and other anthropoid primates

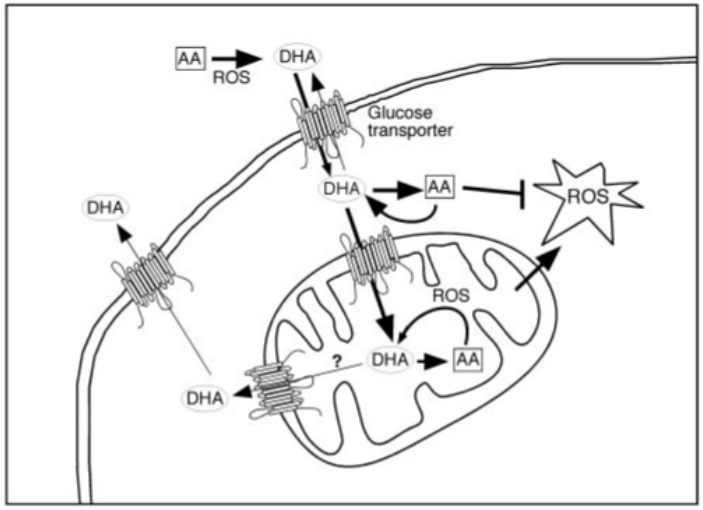
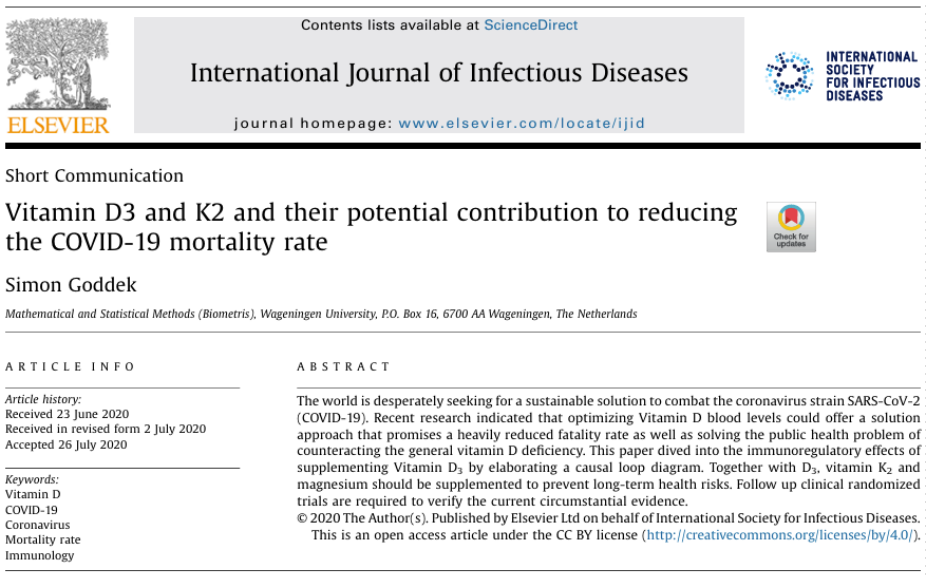


Figure 6. Schematic illustration of vitamin C uptake and recycling in the cell. Vitamin C in its oxidized form, DHA, is transported into mitochondria via facilitative glucose transporter 1 and reduced to mitochondrial AA. Mitochondrial AA quenches ROS, protects the mitochondrial genome, and inhibits mitochondrial membrane depolarization. The mechanisms involved in the uptake, trapping, and recycling of vitamin C in mitochondria appear to recapitulate the metabolism of AA in the cytosolic compartment.

Source: KC S, Cárcamo JM, Golde DW. Vitamin C enters mitochondria via facilitative glucose transporter 1 (Glut1) and confers mitochondrial protection against oxidative injury. FASEB J. 2005 Oct;19(12):1657-67.

D3 and K2-MK7: More effective as a duo

Vitamins D3 & K2 support a healthy immune system, joints, muscle, and blood pressure management. They improve the immune response by upregulating both T and B cells, giving resistance to respiratory tract infections. A broader immune modulatory effect both in the innate and adaptive immune system benefits patients with immune disorders such as Crohn's, IBS, and UC. They have been shown to lower the risk of neurological diseases, and have anti-inflammatory properties by decreasing the expression of inflammatory cytokines.



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International Journal of Infectious Diseases

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

Short Communication

Vitamin D3 and K2 and their potential contribution to reducing the COVID-19 mortality rate

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ABSTRACT

The world is desperately seeking for a sustainable solution to combat the coronavirus strain SARS-CoV-2 (COVID-19). Recent research indicated that optimizing Vitamin D blood levels could offer a solution approach that promises a heavily reduced fatality rate as well as solving the public health problem of counteracting the general vitamin D deficiency. This paper dived into the immunoregulatory effects of supplementing Vitamin D_3 by elaborating a causal loop diagram. Together with D_3, vitamin K_2 and magnesium should be supplemented to prevent long-term health risks. Follow up clinical randomized trials are required to verify the current circumstantial evidence.

The MK7 form of K2 is fat-soluble and gives longer bioavailability in the blood and better support to osteoblasts in the bone matrix. Vitamin K2 reduces the risk of Type II diabetes and helps to reverse insulin resistance with higher insulin sensitivity. It also improves energy levels by aiding ATP production.

Together, vitamins D3 and K2 – MK7 more effectively help maintain good bone marrow density and cardiovascular health. Vitamin D3 helps code for 2000 genes, some of them detoxification enzymes.

Source: Goddek S. Vitamin D3 and K2 and their potential contribution to reducing the COVID-19 mortality rate. Int J Infect Dis. 2020 Oct;99:286-290.; DeLuca HF. The metabolism and functions of vitamin D. Adv Exp Med Biol. 1986;196:361-75.

Zinc a key player in your antiviral armoury

Zinc is a cofactor in 300 different enzymes (and about 20 detox enzymes).

Bisglycinate zinc has superior bioavailability, offers excellent tissue retention, and is gentle on the system. The oral bioavailability of zinc bisglycinate chelate was compared in two clinical research trials to zinc gluconate, a commonly used chelate form in zinc supplements. The first trial, a randomized crossover trial, showed that a single dose of zinc bisglycinate had a significantly higher bioavailability than zinc gluconate. A subsequent double-blind, placebo-controlled trial revealed that a 60 mg daily dose of zinc bisglycinate significantly increased plasma zinc.

Was seen to be particularly effective when combined with quercetin for combating SARS-CoV-2

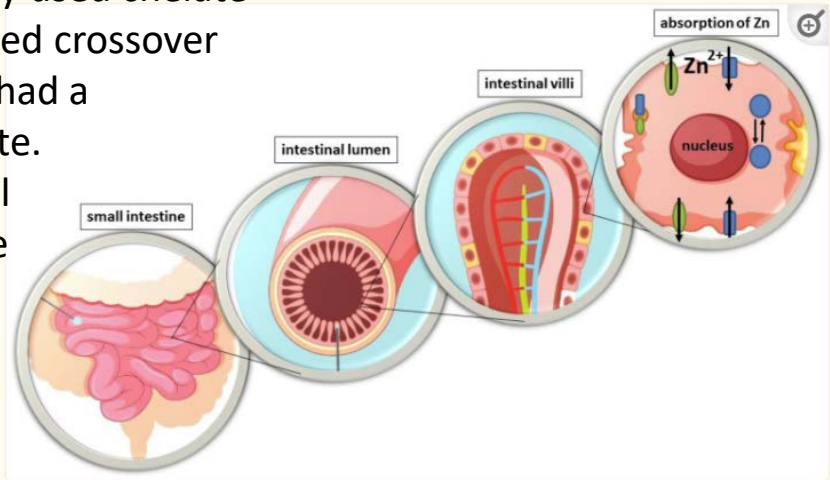
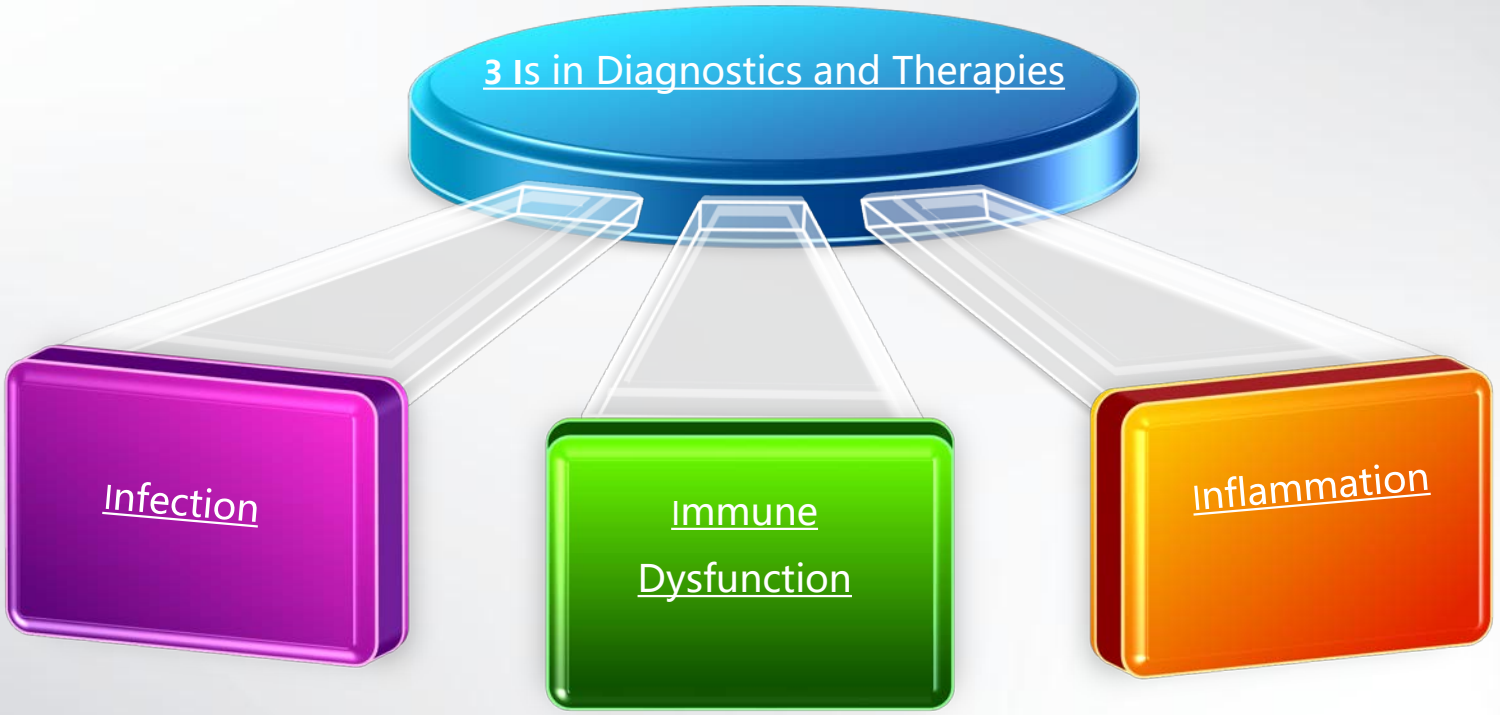


Figure 1

Zinc absorption in the intestinal tract [5].

Source: Ośko J, Pierlejewska W, Grembecka M. Comparison of the Potential Relative Bioaccessibility of Zinc Supplements-In Vitro Studies. Nutrients. 2023 Jun 20;15(12):2813.

3 I´s in Diagnostics and Therapies



Thank you very much!
Q&A / Discussion

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