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# Immune System Balance After Disease and Stress

Presented by:

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- ▶ Judi Woolger, MD, FACP
- ▶ Kevin Spelman, Ph.D.

Wednesday, May 20, 2020

7:00 P.M. - 9:00 P.M. (EST)

Session 2

# Agenda

1. Lecture
  2. Q&A
  3. Non-CE Product Discussion
  4. Post-Lecture Survey
- 

Special Thanks to: Jessie Phipps, Jason Armada, Kara Brien



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# Learning Objectives

- ▶ Review Cases Involving the Immune System
- ▶ Learn Why Network Pharmacology is important in drug and herbal therapies
- ▶ Review Viruses, Bacteria, Fungus and Parasites
- ▶ Examine pharmacology of various drug therapies
- ▶ Review phytotherapy and herbal therapies and when appropriate



# COVID-19 (Coronavirus Disease 2019)

- Severe Acute Respiratory Syndrome (SARS)
  - “Belt across my chest that burns and severe pain when coughing”
  - Middle East respiratory syndrome (MERS)
- Started in China
  - 80,000 COVID-19 cases have been reported in China at end of 2019
- Droplets: Way to transmit



# Symptoms

- **GI symptoms**

- Pain
- Diarrhea

- **Fever**

- 100-104

- **Respiratory Symptoms**

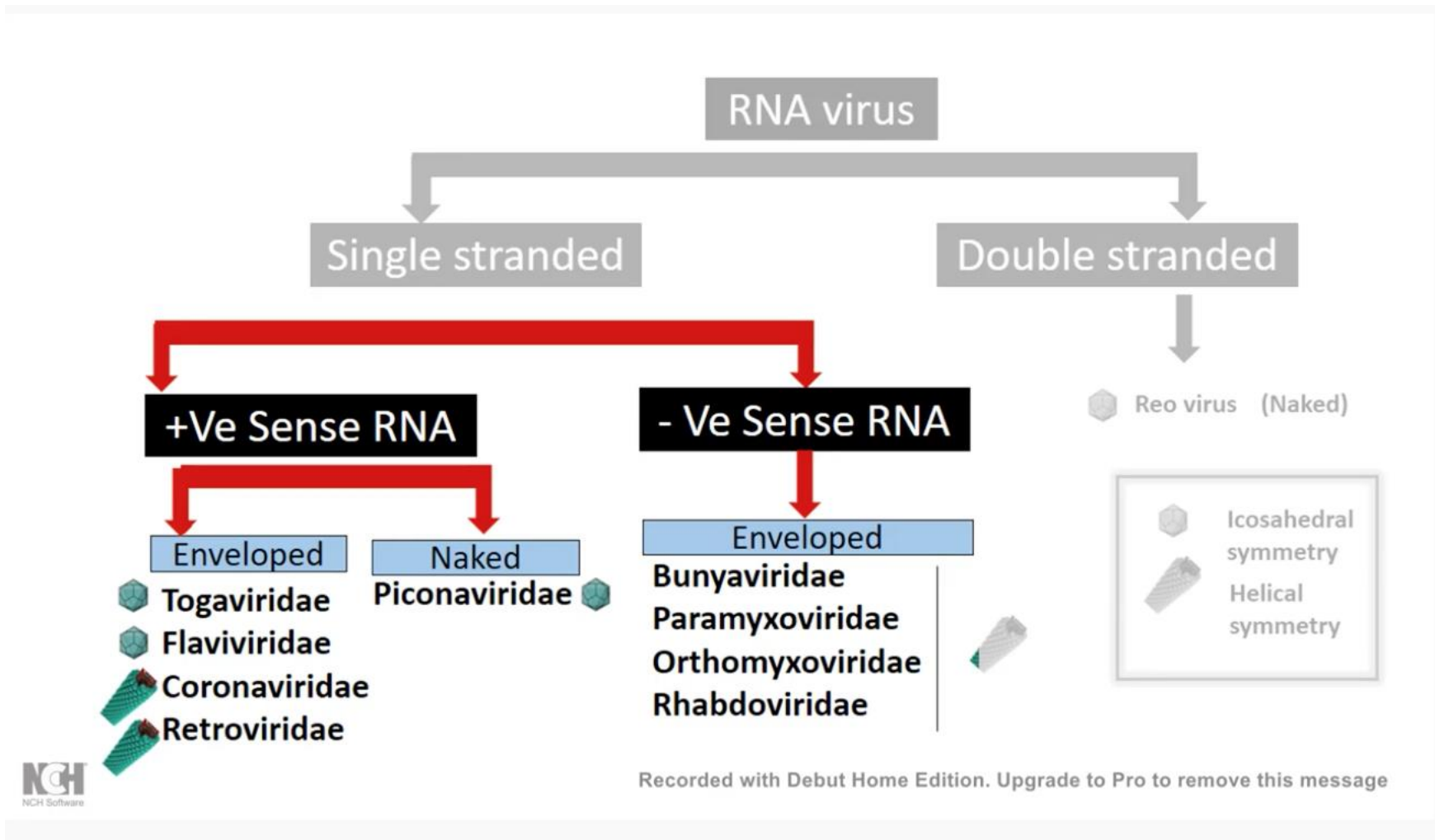
- Burning
  - Pain
  - Coughing
  - Secretions
- 



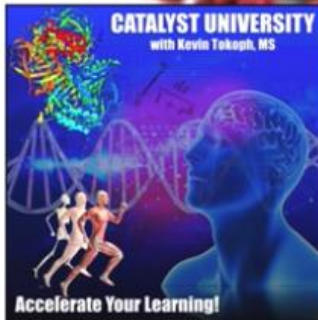
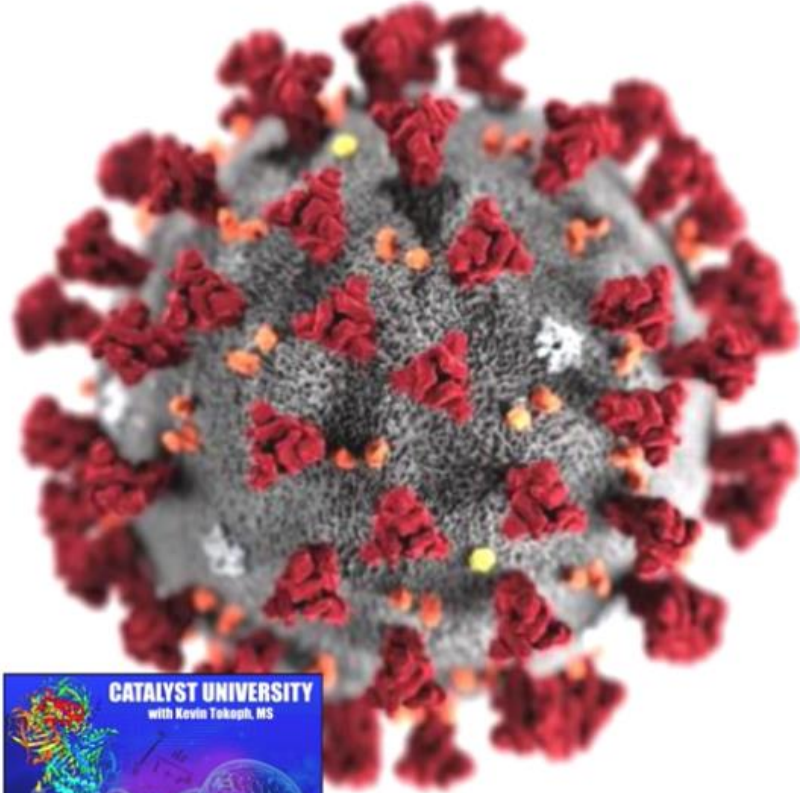
# Viruses

- Strictly dependent on cellular metabolic processes
  - Possess only limited intrinsic enzyme systems and building blocks that may serve as specific targets for a drug.
  - Antiviral drug should not only display considerable specificity in its antiviral action, but should also irreversibly block viral synthesis in order to stop cell suicide due to the viral infection and restore normal cell synthesis (Vanden Berghe et al., 1986).
  - In addition to this inhibition, the antiviral agent must have a broad spectrum of activity, favorable pharmacodynamic properties, and not be immunosuppressive.
  - In the ideal situation, the antiviral drug checks the infection while the immune system prepares to destroy the last virus particles (Munro et al., 1987).
    - This point is critical for those immune-compromised by illness (AIDS, cancer) or drug therapy (transplants, cancer). A frequent cause of death in these instances is from viral infections, so that adjuvant antiviral chemotherapy is vital in these circumstances





# Coronavirus Disease 2019 (COVID-19)

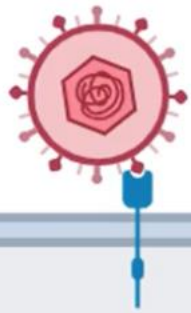


- **Coronaviruses** | Large, enveloped RNA viruses that cause severe acute respiratory syndrome (SARS) with a large RNA genome.
- Coronavirus replication entails:
  - [1] ribosome frameshifting during genome translation
  - [2] synthesis of both genomic and multiple subgenomic RNA species
- The hallmark of coronavirus transcription is the production of multiple **subgenomic mRNAs** that contain sequences corresponding to both ends of the genome.
- Coronavirus RNA **genome size** ~ 30,000 nucleotides
  - Nonstructural proteins that have a critical role in viral RNA synthesis
  - Nonstructural proteins that are nonessential for virus replication
  - RNA synthesis proteins | nonstructural protein 2 (nsp2) and nucleocapsid protein (N) (structural)





**Attachment:** This is the first step in viral replication. Surface proteins of the virus interact with specific receptors on the target cell surface



**+Ve sense RNA virus**

**Host cell**

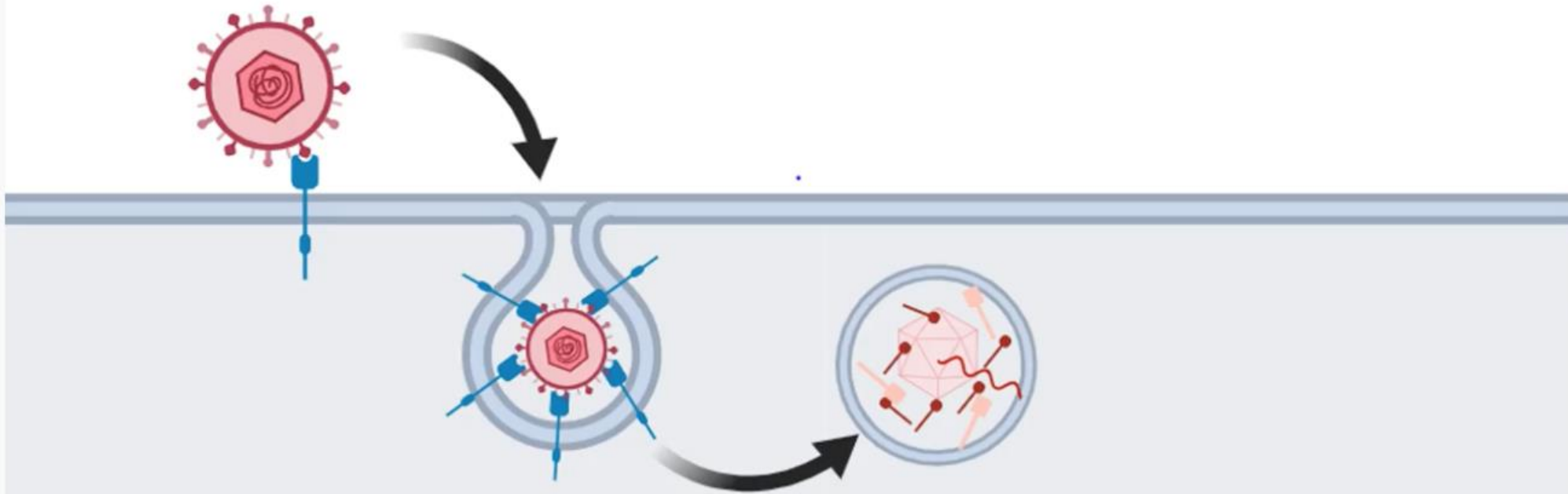


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# Penetration:



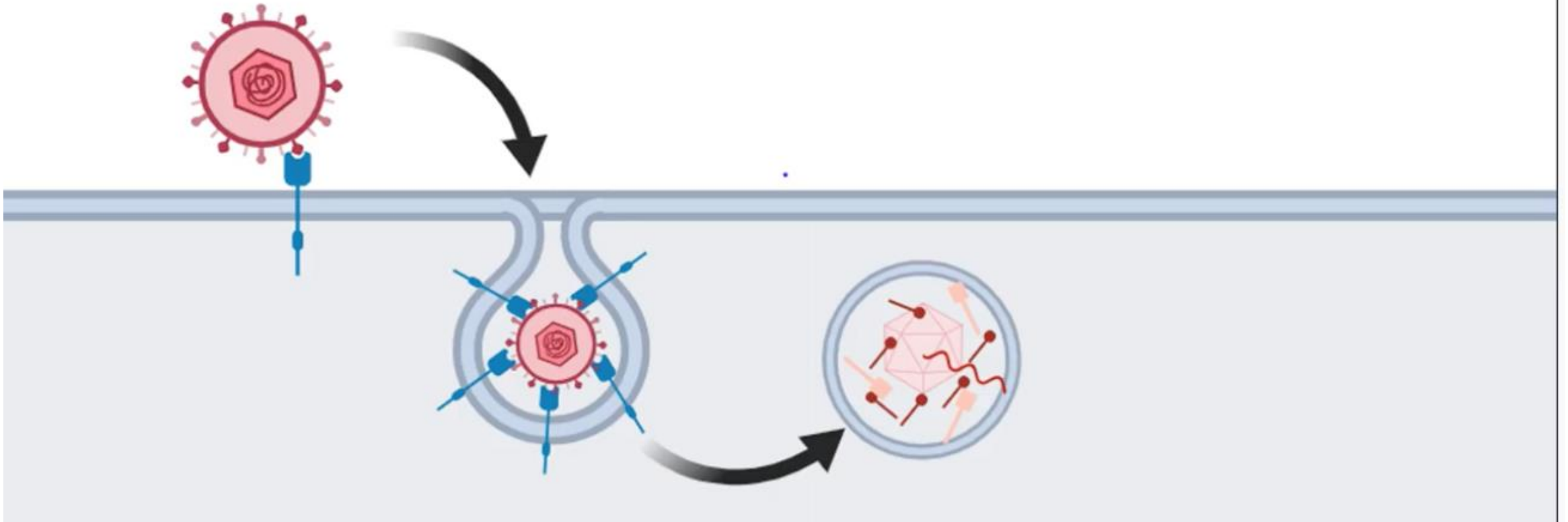
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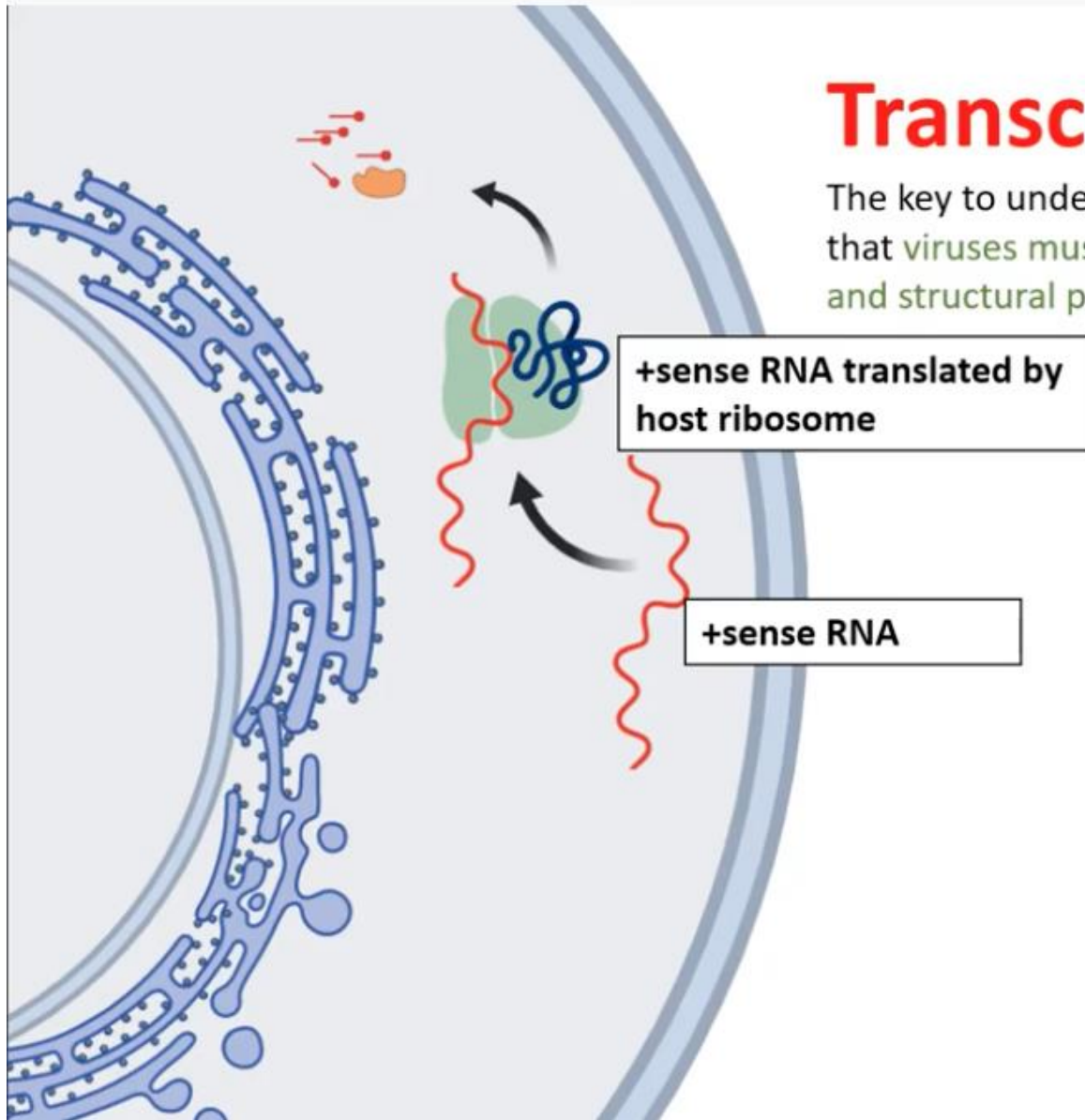
# Penetration:

Enveloped viruses (e.g., HIV, influenza virus) penetrate cells through fusion of the viral envelope with the host cell membrane.

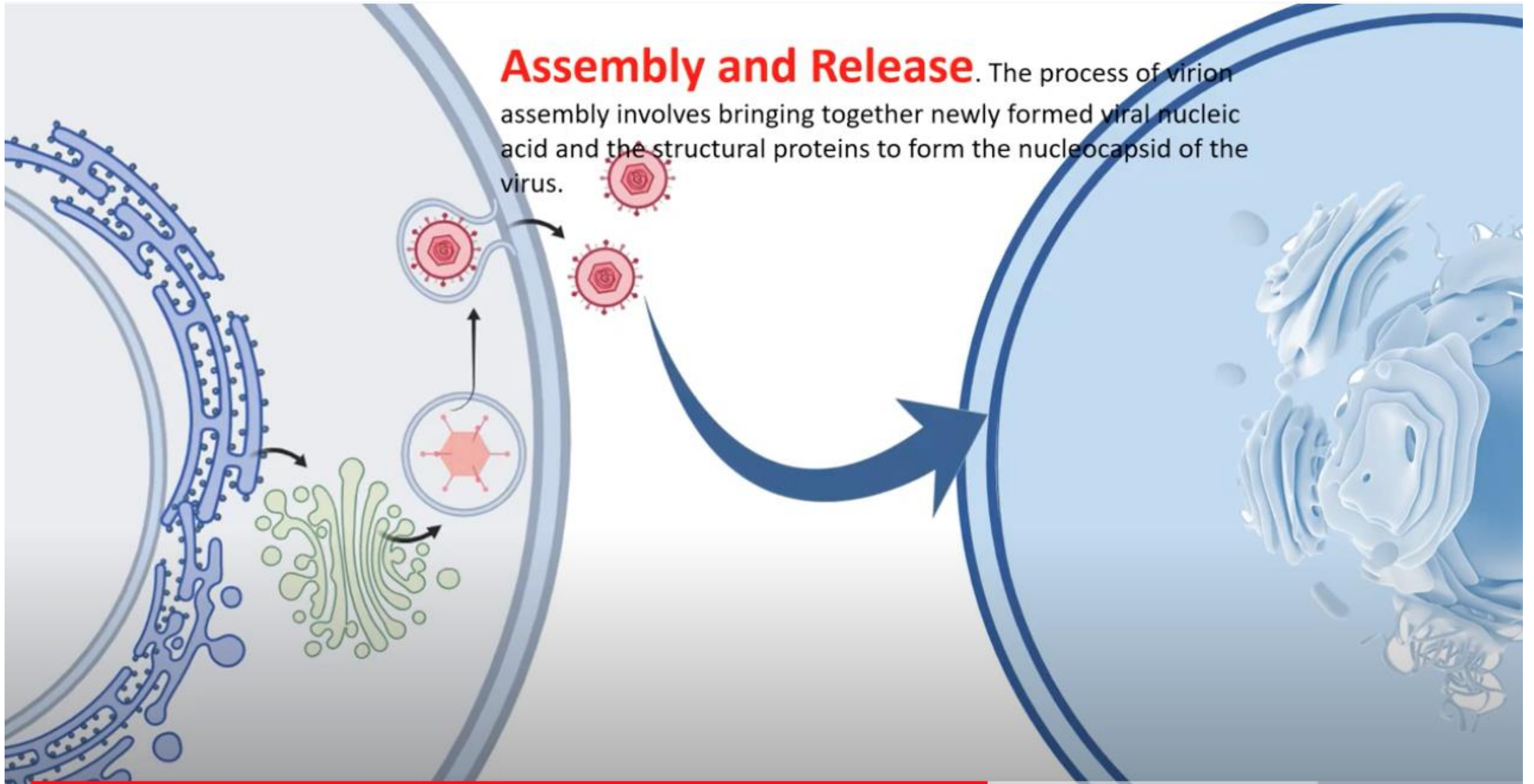


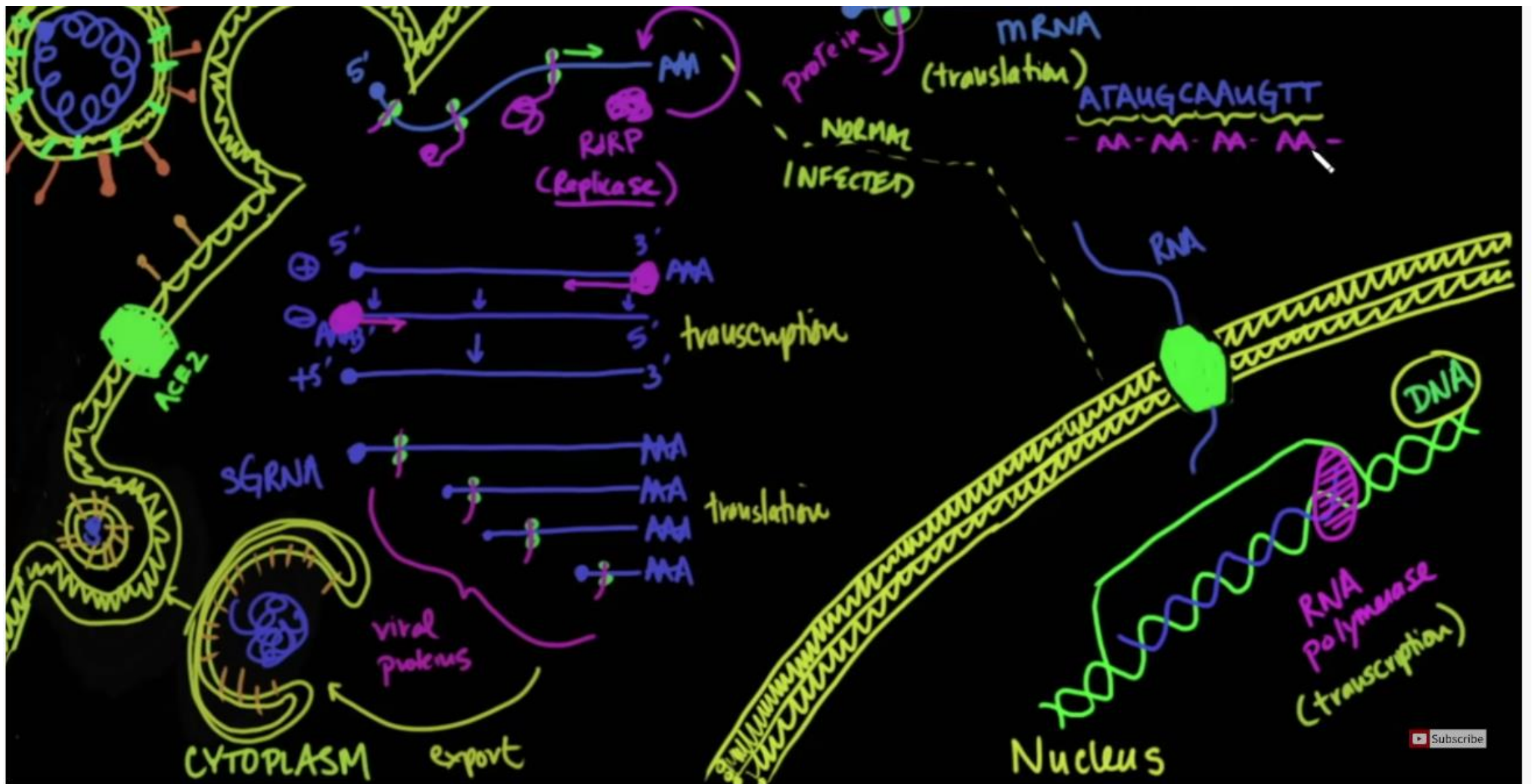
# Transcription and Translation.

The key to understanding the genomic expression of viruses is noting the fact that viruses must use host cellular machinery to replicate and make functional and structural proteins



**Assembly and Release.** The process of virion assembly involves bringing together newly formed viral nucleic acid and the structural proteins to form the nucleocapsid of the virus.





# Zinc in COVID

- ▶ This effect may underlie therapeutic efficiency of chloroquine known to act as zinc ionophore (move ions across lipid membrane)
- ▶ Zn<sup>2+</sup> possesses antiviral activity through inhibition of SARS-CoV RNA polymerase.
- ▶ Indirect evidence also indicates that Zn<sup>2+</sup> may decrease the activity of angiotensin-converting enzyme 2 (ACE2), known to be the receptor for SARS-CoV-2.
- ▶ Improved antiviral immunity by zinc may also occur through up-regulation of interferon  $\alpha$  production and increasing its antiviral activity
- ▶ Zinc possesses anti-inflammatory activity by inhibiting NF- $\kappa$ B signaling and modulation of regulatory T-cell functions that may limit the cytokine storm in COVID-19.
- ▶ Improves improving mucociliary clearance and barrier function of the respiratory epithelium



# Chloroquine Is a Zinc Ionophore

Jing Xue<sup>1,2</sup>, Amanda Moyer<sup>1</sup>, Bing Peng<sup>1,3</sup>, Jinchang Wu<sup>2</sup>, Bethany N. Hannafon<sup>1</sup>, Wei-Qun Ding<sup>1\*</sup>

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## Abstract

Chloroquine is an established antimalarial agent that has been recently tested in clinical trials for its anticancer activity. The favorable effect of chloroquine appears to be due to its ability to sensitize cancerous cells to chemotherapy, radiation therapy, and induce apoptosis. The present study investigated the interaction of zinc ions with chloroquine in a human ovarian cancer cell line (A2780). Chloroquine enhanced zinc uptake by A2780 cells in a concentration-dependent manner, as assayed using a fluorescent zinc probe. This enhancement was attenuated by TPEN, a high affinity metal-binding compound, indicating the specificity of the zinc uptake. Furthermore, addition of copper or iron ions had no effect on chloroquine-induced zinc uptake. Fluorescent microscopic examination of intracellular zinc distribution demonstrated that free zinc ions are more concentrated in the lysosomes after addition of chloroquine, which is consistent with previous reports showing that chloroquine inhibits lysosome function. The combination of chloroquine with zinc enhanced chloroquine's cytotoxicity and induced apoptosis in A2780 cells. Thus chloroquine is a zinc ionophore, a property that may contribute to chloroquine's anticancer activity.

**Citation:** Xue J, Moyer A, Peng B, Wu J, Hannafon BN, et al. (2014) Chloroquine Is a Zinc Ionophore. PLoS ONE 9(10): e109180. doi:10.1371/journal.pone.0109180

**Editor:** Yuan-Soon Ho, Taipei Medical University, Taiwan

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**Data Availability:** The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper.

**Funding:** This work was supported in part by grants from the American Cancer Society (CNE-117557); the Susan G. Komen for the Cure Foundation (KG081083);



i·on·o·phore

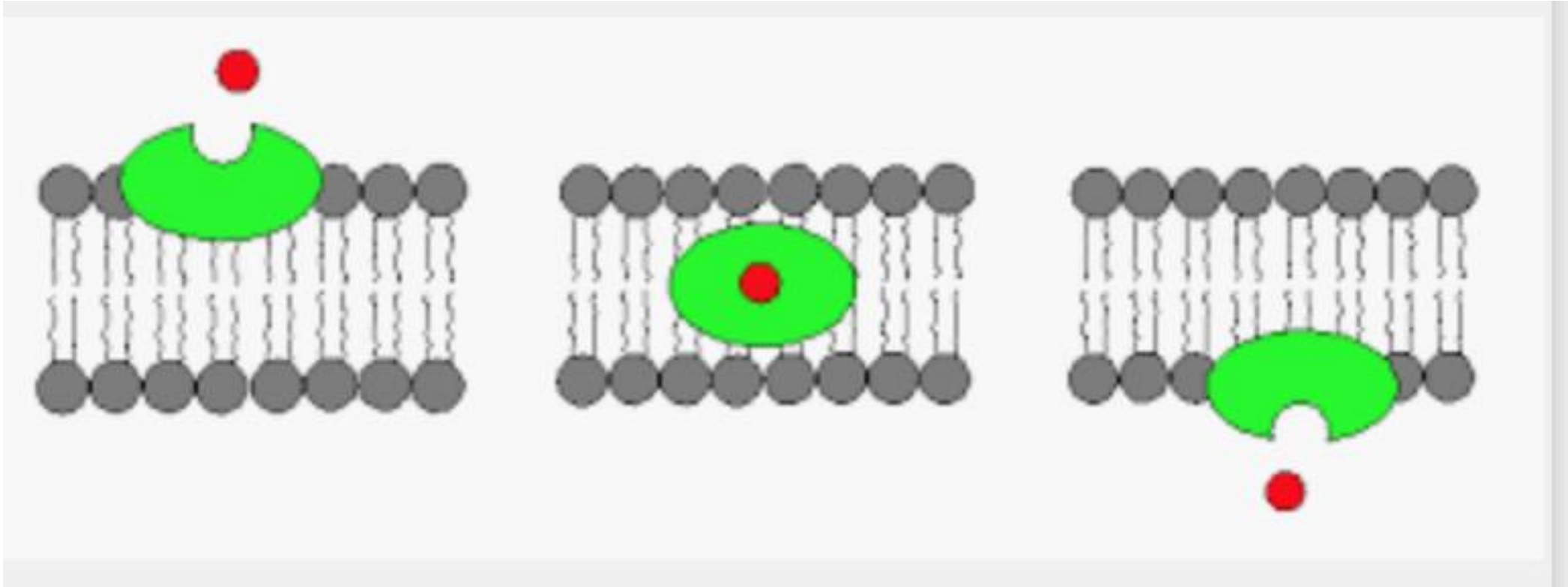
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a substance which is able to transport particular ions across a lipid membrane in a cell.



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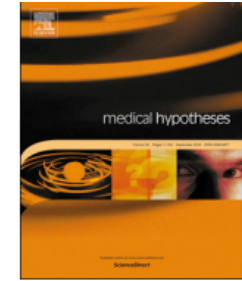




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journal homepage: [www.elsevier.com/locate/mehy](http://www.elsevier.com/locate/mehy)



# Does zinc supplementation enhance the clinical efficacy of chloroquine/hydroxychloroquine to win today's battle against COVID-19?



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### ARTICLE INFO

#### Keywords:

COVID-19  
SARS-CoV-2  
Therapy  
Chloroquine  
Hydroxychloroquine  
Zinc

### ABSTRACT

Currently, drug repurposing is an alternative to novel drug development for the treatment of COVID-19 patients. The antimalarial drug chloroquine (CQ) and its metabolite hydroxychloroquine (HCQ) are currently being tested in several clinical studies as potential candidates to limit SARS-CoV-2-mediated morbidity and mortality. CQ and HCQ (CQ/HCQ) inhibit pH-dependent steps of SARS-CoV-2 replication by increasing pH in intracellular vesicles and interfere with virus particle delivery into host cells. Besides direct antiviral effects, CQ/HCQ specifically target extracellular zinc to intracellular lysosomes where it interferes with RNA-dependent RNA polymerase activity and coronavirus replication. As zinc deficiency frequently occurs in elderly patients and in those with cardiovascular disease, chronic pulmonary disease, or diabetes, we hypothesize that CQ/HCQ plus zinc sup-

# Chloroquine

- ▶ Comes from the bark of the Cinchona Tree (like Quinine)
- ▶ Spectrum of Activity
  - Asexual erythrocytic forms of *Plasmodium malariae*, *Plasmodium ovale*, *Plasmodium vivax*, many strains of *Plasmodium falciparum*, and *Entamoeba histolytica*
- ▶ Clinical Uses
  - Labeled Indications
    - Malaria (Does not allow the parasite to enter RBC where it needed to feed)
    - Extra-intestinal amebiasis
  - Off-Label Indications
    - Discoid lupus erythematosus
    - Rheumatoid arthritis
    - Coronavirus disease 2019 (COVID-19)
      - Seems to be effective in limiting the replication of the virus causing COVID-19, SARS-CoV-2, in vitro



# Chloroquine

## *Mechanism of Action*

### ▶ *Antimalarial*

- *Binds to and inhibits DNA and RNA polymerase*
- *Interferes with parasite's metabolism and utilization of hemoglobin*
- *Inhibits the effects of prostaglandin*
- *Raises the internal pH of parasites which inhibits their growth*

### ▶ *Antiviral*

- *Not fully understood*
- *May alter the cell membrane surface's pH and therefore inhibit viral fusion*
- *May inhibit glycosylation of viral proteins*

### ▶ *Anti-Inflammatory*

- *Not fully understood*
- *May antagonize histamine and serotonin*
- *Inhibits the effects of prostaglandins*
- *May inhibit chemotaxis of polymorphonuclear leukocytes, macrophages, and eosinophils*



# Azithromycin and Hydroxychloroquine

- ▶ Azithromycin is thought to have antiviral and anti-inflammatory activity and may work synergistically with other antiviral treatments.
- ▶ In *in vitro* laboratory studies azithromycin has demonstrated antiviral activity against Zika virus and against rhinoviruses, which cause the common cold.
- ▶ **What is the current clinical evidence for using azithromycin to treat COVID-19?**
  - 20 patients with COVID-19 in France.
  - Patients were treated with hydroxychloroquine (Plaquenil) alone or in combination with azithromycin.
  - Viral loads were significantly reduced in patients receiving hydroxychloroquine compared with those who did not receive the treatment.
  - Patients taking hydroxychloroquine also appeared to clear the virus from their system more quickly.
  - Virus elimination was even more efficient in the 6 patients in the trial who received both azithromycin and hydroxychloroquine.



[Am J Respir Crit Care Med.](#) 1998 Mar;157(3 Pt 1):853-7.

## Therapeutic effect of erythromycin on influenza virus-induced lung injury in mice.

[Sato K<sup>1</sup>](#), [Suga M](#), [Akaike T](#), [Fujii S](#), [Muranaka H](#), [Doi T](#), [Maeda H](#), [Ando M](#).

### + Author information

#### Abstract

Erythromycin (EM) is an antibiotic with potent antiinflammatory effects that is used for treating chronic lower respiratory tract infections. It has been shown that free radicals, such as the superoxide anion and nitric oxide (NO), are pathogenic molecules in viral disease. Much attention has been given to a critical role of NO in the pathologic events of various inflammatory diseases. In the present study, we evaluated the effects of EM on influenza-virus-induced pneumonia in mice infected with a lethal dose of influenza virus A/Kumamoto/Y5/67 (H2N2). The administration of EM at a dose of 3.3 mg/kg/d (intraperitoneally, from Days 1 to 6 after infection), significantly improved the survival rate of mice infected with influenza virus, and the survival rate of the virus-infected mice at Day 20 after infection increased in a dose-dependent fashion with EM administered to the animals, from 14% among controls to 42% among animals given EM at 1.0 mg/kg/d and 57% among those given EM at 3.3 mg/kg/d. The induction of interferon-gamma (IFN-gamma) in the mouse lung was inhibited by EM treatment on Day 6 after infection. Simultaneously, the number of inflammatory cells recovered in lung lavage fluid 6 d after virus infection was significantly reduced by the treatment with EM. The EM treatment resulted in a dose-dependent decrease in the level of nitrite/nitrate (metabolites of NO) in the serum and the NO synthase (NOS)-inducing potential in the lungs of the virus-infected mice. These results indicate that EM may have substantial therapeutic value for various acute inflammatory disorders such as influenza-virus-induced pneumonia, by inhibiting inflammatory-cell responses and suppressing NO overproduction in the lung.



Vit C



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## Intravenous vitamin C for reduction of cytokines storm in acute respiratory distress syndrome



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### ARTICLE INFO

#### Keywords:

Vitamin C  
Severe acute respiratory syndrome coronavirus  
Antiviral agents  
Covid19  
Cytokines

### ABSTRACT

The recent outbreak of Covid19 has required urgent treatments for numerous patients. No suitable vaccines or antivirals are available for Covid19. The efficiency against Covid19 of WHO therapies of choice, that are two antivirals developed for other pathologies, is controversial. Therefore, alternative approaches are required. Intravenous (IV) Vitamin C (Vit-C) has emerged as one of the other alternatives for this purpose. Here we review the effects of IV Vit-C on the immune system response, the antiviral properties of IV Vit-C, and finally the antioxidant properties of IV Vit-C to specifically address the cytokines' storm characteristic of the Acute Respiratory Distress Syndrome (ARDS) that occur in the later cycle of the Covid19 infectious disease.

### 1. Introduction

The recent outbreak of Covid19 has required urgent treatments for numerous patients. The Covid19 originated in Wuhan, China has spread to other continents and has caused significant harm to the public. Fig. 1 represents a transmission electron microscope image of Covid19 along with a 3D structure of coronavirus. No suitable vaccines or antiviral drugs exist against Covid19. At the time of writing (15 March 2020),

efficacy of these processes for Covid19 is controversial. Therefore, alternative approaches are urgently needed.

In China, the death rate was peaked at 3% a few weeks ago but is now declined to 0.7 %. Good results are obtained using Interferon Alpha 2B (IFNrec) without any combination with Kaletra. The use of Intravenous (IV) Vitamin C (Vit-C) has shown promise in this area in China. The IV Vit-C (or Ascorbic acid) protocols are mentioned in [clinicaltrials.gov](http://clinicaltrials.gov), for Covid19 and other pathologies. Shanghai now

- ▶ Vitamin C is a antioxidant
  - High doses it causes oxidation
- ▶ Co-factor in Enzymes
- ▶ Major player in Collagen Production
- ▶ In shock treatment the use of IV Vitamin C, Thiamine and Hydrocortisone has been very successful
- ▶ Chemotaxis is improved by Vit-C  
The neutrophil phagocytic activity and oxidative death are enhanced
- ▶ Lymphocyte proliferation was also accelerated





NUTRITION

✓ Evidence Based

# Can Vitamin C Protect You from COVID-19?



Written by [SaVanna Shoemaker, MS, RDN, LD](#) on April 2, 2020



[Vitamin C & immunity](#) | [Vitamin C & COVID-19](#) | [Recommendation](#)

Bottom line

## An important note

No supplement will cure or prevent disease.

With the 2019 coronavirus COVID-19 pandemic, it's especially important to understand that no supplement, diet, or other lifestyle modification other than physical distancing, also known as social distancing, and proper hygiene practices can protect you from COVID-19.

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[Nutrients](#). 2019 Apr; 11(4): 708.

PMCID: PMC6521194

Published online 2019 Mar 27. doi: [10.3390/nu11040708](https://doi.org/10.3390/nu11040708)

PMID: [30934660](https://pubmed.ncbi.nlm.nih.gov/30934660/)

# Vitamin C Can Shorten the Length of Stay in the ICU: A Meta-Analysis

[Harri Hemilä](#)<sup>1,\*</sup> and [Elizabeth Chalker](#)<sup>2</sup>

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See letter "[Vitamin C for Cardiac Surgery Patients: Several Errors in a Published Meta-Analysis](#). Comment on "[Effects of Vitamin C on Organ Function in Cardiac Surgery](#)."

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**Meta-analysis** = an epidemiological study designed to systematically assess the results of previous research to derive conclusions about that body of research.

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mortality rate was 29.8% (p=0.03). In a disease process with an estimated mortality rate of 40%, this difference is huge. In addition, this comes with no adverse side effects noted for any of the patients receiving vitamin C. To many pure statisticians, this difference, while significant, is lessened because mortality was not the primary outcome the study was designed to address.

Another question that arises with this secondary finding is if vitamin C had such an impact on mortality, why were changes not seen in the primary outcomes, especially the mSOFA scores. With regards to mSOFA, [EMCrit has a fantastic summary](#) discussing the impact of survivorship bias. Basically, in this study when a patient expired they were removed from the study, which selectively removes the sickest patients, especially in the control group which had a higher mortality rate. Thus, of the larger number that survived in the vitamin C group makes the intervention group look sicker on average.

With regard to the biomarkers, this study was meant to be a continuation of the prior phase 1 study, which had shown improvements in CRP and thrombomodulin biomarkers. The patients enrolled in this study were very sick; nearly 60% were requiring pressor support and about 40% received steroids by the time the study had started. The key difference between these studies (the first that found a statistically significant difference in these markers and this one) may have been the point in the disease course when the vitamin C had started. Some reviewers of this article have postulated that the disease course may have been too advanced to see a significant difference in the primary outcomes as the body's inflammatory response was already in full swing when vitamin C was started.

### EM TAKE-AWAYS

Despite no difference in the primary outcomes, **this study is showing a significant mortality benefit with using vitamin C in ARDS due to sepsis**, with no adverse side effects. As one of the first RCTs, this study is adding significantly to the ongoing debate of the impact of vitamin C in sepsis.

#### Related Articles

Critical Care ALERT! Apneic Oxygenation in RSI

Yanika Wolfe, MD 12/04/2017

Critical Care ALERT! Apneic Oxygenation in RSI A 57-year-old male presents to the emergency department for shortness of breath. He became more hypoxic despite applying NIPPV. You decided to proceed w

Introducing the ALTO Alternatives to Opioids Program

Katrina D'Amore DO, MPH David Traficante, DO Alexis M. LaPietra, DO, FACEP 08/01/2016

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# Immune-enhancing Role of Vitamin C and Zinc and Effect on Clinical Conditions

- ▶ Vitamin C concentrations in the plasma and leukocytes rapidly decline during infections and stress.
  - ▶ Responsible for antimicrobial and natural killer cell activities, lymphocyte proliferation, chemotaxis, and delayed-type hypersensitivity. Vitamin C contributes to maintaining the redox integrity of cells and thereby protects them against reactive oxygen species generated during the respiratory burst and in the inflammatory response.
  - ▶ Zinc undernutrition or deficiency was shown to impair cellular mediators of innate immunity such as phagocytosis, natural killer cell activity, and the generation of oxidative burst.



# Remdesivir

- ▶ Remdesivir is a broad spectrum antiviral medication that is specifically being tested as a treatment for COVID-19
- ▶ Remdesivir was originally developed to treat hepatitis C and later tested against Ebola and Marburg viruses but unfortunately were found ineffective against all of these viral infections
- ▶ However, recent studies have shown Remdesivir has antiviral activity against several RNA viruses, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) coronaviruses
- ▶ Mechanism of Action
  - Remdesivir is an adenosine nucleotide prodrug that is metabolized to the pharmacologically active nucleoside triphosphate metabolite after distribution into cells (FDA 2020)
  - Remdesivir triphosphate acts as an adenosine triphosphate analog and competes for incorporation into RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, resulting in delayed chain termination during viral RNA replication (FDA 2020)
  - Therefore Remdesivir is being classified as a direct acting antiviral agent that inhibits RNA-dependent RNA-polymerase by working as a delayed chain terminator, preventing viral



# Remdesivir

## NIH Clinical Trial Shows Remdesivir Accelerates Recovery from Advanced COVID-19

April 29, 2020

Hospitalized patients with advanced COVID-19 and lung involvement who received remdesivir recovered faster than similar patients who received placebo, according to a preliminary data analysis from a randomized, controlled trial involving 1063 patients, which began on February 21. The trial (known as the [Adaptive COVID-19 Treatment Trial](#), or ACTT), sponsored by the [National Institute of Allergy and Infectious Diseases \(NIAID\)](#), part of the National Institutes of Health, is the first clinical trial launched in the United States to evaluate an experimental treatment for COVID-19.

An independent data and safety monitoring board (DSMB) overseeing the trial met on April 27 to review data and shared their interim analysis with the study team. Based upon their review of the data, they noted that remdesivir was better than placebo from the perspective of the primary endpoint, time to recovery, a metric often used in influenza trials. Recovery in this study was defined as being well enough for hospital discharge or returning to normal activity level.

Preliminary results indicate that patients who received remdesivir had a 31% faster time to recovery than those who received placebo ( $p < 0.001$ ). Specifically, the median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group ( $p = 0.059$ ).

- ▶ Study conducted by the National Institutes of Health (NIH) suggests that treatment with Remdesivir helps reduce the recovery time in seriously ill patients with COVID-19 from 15 days to 11 days



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N Engl J Med. 2020 Apr 10. doi: 10.1056/NEJMoa2007016. [Epub ahead of print]

### Compassionate Use of Remdesivir for Patients with Severe Covid-19.

Grein J<sup>1</sup>, Ohmagari N<sup>1</sup>, Shin D<sup>1</sup>, Diaz G<sup>1</sup>, Asperges E<sup>1</sup>, Castagna A<sup>1</sup>, Feldt T<sup>1</sup>, Green G<sup>1</sup>, Green ML<sup>1</sup>, Lescure FX<sup>1</sup>, Nicastri E<sup>1</sup>, Oda R<sup>1</sup>, Yo K<sup>1</sup>, Quiros-Roldan E<sup>1</sup>, Studemeister A<sup>1</sup>, Redinski J<sup>1</sup>, Ahmed S<sup>1</sup>, Bernett J<sup>1</sup>, Chelliah D<sup>1</sup>, Chen D<sup>1</sup>, Chihara S<sup>1</sup>, Cohen SH<sup>1</sup>, Cunningham J<sup>1</sup>, D'Arminio Monforte A<sup>1</sup>, Ismail S<sup>1</sup>, Kato H<sup>1</sup>, Lapadula G<sup>1</sup>, L'Her E<sup>1</sup>, Maeno T<sup>1</sup>, Majumder S<sup>1</sup>, Massari M<sup>1</sup>, Mora-Rillo M<sup>1</sup>, Mutoh Y<sup>1</sup>, Nguyen D<sup>1</sup>, Verweij E<sup>1</sup>, Zoufaly A<sup>1</sup>, Osinusi AO<sup>1</sup>, DeZure A<sup>1</sup>, Zhao Y<sup>1</sup>, Zhong L<sup>1</sup>, Chokkalingam A<sup>1</sup>, Elboudwarej E<sup>1</sup>, Telep L<sup>1</sup>, Timbs L<sup>1</sup>, Henne I<sup>1</sup>, Sellers S<sup>1</sup>, Cao H<sup>1</sup>, Tan SK<sup>1</sup>, Winterbourne L<sup>1</sup>, Desai P<sup>1</sup>, Mera R<sup>1</sup>, Gaggar A<sup>1</sup>, Myers RP<sup>1</sup>, Brainard DM<sup>1</sup>, Childs R<sup>1</sup>, Flanigan T<sup>1</sup>.

#### Author information

#### Abstract

**BACKGROUND:** Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown in vitro activity against SARS-CoV-2.

**METHODS:** We provided remdesivir on a compassionate-use basis to patients hospitalized with Covid-19, the illness caused by infection with SARS-CoV-2. Patients were those with confirmed SARS-CoV-2 infection who had an oxygen saturation of 94% or less while they were breathing ambient air or who were receiving oxygen support. Patients received a 10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. This report is based on data from patients who received remdesivir during the period from January 25, 2020, through March 7, 2020, and have clinical data for at least 1 subsequent day.

**RESULTS:** Of the 61 patients who received at least one dose of remdesivir, data from 8 could not be analyzed (including 7 patients with no post-treatment data and 1 with a dosing error). Of the 53 patients whose data were analyzed, 22 were in the United States, 22 in Europe or Canada, and 9 in Japan. At baseline, 30 patients (57%) were receiving mechanical ventilation and 4 (8%) were receiving extracorporeal membrane oxygenation. During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged, and 7 patients (13%) died; mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation.

**CONCLUSIONS:** In this cohort of patients hospitalized for severe Covid-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy. (Funded by Gilead Sciences.)

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- ▶ Study published in the New England Journal of Medicine claims that clinical improvements were observed in 36 out of 53 patients (68%) hospitalized for severe COVID-19 treated with Remdesivir



## 2. PHARMACY IN ANCIENT BABYLONIA

Babylon, jewel of ancient Mesopotamia, often called the cradle of civilization, provides the earliest known record of practice of the art of the apothecary. Practitioners of healing of this era (about 2600 B.C.) were priest, pharmacist and physician, all in one. Medical texts on clay tablets record first the symptoms of illness, the prescription and directions for compounding, then an invocation to the gods. Ancient Babylonian methods find counterpart in today's modern pharmaceutical, medical, and spiritual care of the sick.



# Fatty acid and sweet wormwood on road to clinical trials for COVID-19



15 Apr 2020 --- Eicosapentaenoic acid free fatty acid (EPA-FFA) and extract from *Artemisia annua* (also known as sweet wormwood) are being investigated in the fight against COVID-19. EPAspire, the drug candidate of KD Pharma and its partner, SLA Pharma, is soon entering clinical trials as a promising candidate to treat patients with symptoms of the novel coronavirus infection. Meanwhile, ArtemiLife is collaborating with the Max Planck Institute of Colloids and Interfaces to test *Artemisia annua* plant extract and artemisinin (an anti-malarial drug) derivatives in laboratory cell studies.



"EPAspire is the free fatty acid form of EPA delivered to the gut by gastro-resistant capsules. Based on the speed of progression in COVID-19 patients, our researchers believe a rapid absorption of the EPA is necessary. The pharmacokinetic studies show that the product is readily and rapidly absorbed by providing EPA as a free fatty acid in its most native molecular form and bypassing the stomach," Adam Ismail, Chief Strategy Officer at KD Pharma Group, tells ***NutritionInsight***.

He adds that while it is not clear how consumption of EPA in other forms in a trial would differ from EPAspire, the company believes that rapid uptake of EPA should be the goal in an acute care environment like this. EPAspire is a novel oral formulation of highly purified EPA-FFA in gastro-resistant capsules, which are delivered to the gut at optimal pH allowing maximal absorption.

"This unique preparation has potential – not only to modify the COVID-19 disease process by reducing harmful, excess inflammatory responses – but also to do so without suppressing the immune response to the virus. This is vital to seroconversion giving the patient ongoing protection against continued viral challenge," says Oscar Groot, KD Pharma's Chief Executive Officer.





“Guinea-Bissau’s president says he will test the unproven coronavirus treatment on members of his government. Children in Madagascar are being given bottles of the concoction as they restart school after the loosening of a lockdown. And a Pennsylvania-based company is taking preorders for tea and coffee mixtures containing the substance.”

# The challenge with African countries promoting traditional cures for Covid-19 without research

Yaoundé, Cameroon · May 6, 2020



By Daniel Ekonde



Madagascar's President Andry Rajoelina tries Covid-Organics at a launch ceremony in Antananarivo on 20 April. Several other African leaders have expressed an interest in the unproven treatment. RIJASOLO/AFP VIA GETTY IMAGES

## Unproven herbal remedy against COVID-19 could fuel drug-resistant malaria, scientists warn

By Linda Nordling | May. 6, 2020, 4:00 PM

Science's COVID-19 reporting is supported by the Pulitzer Center.

An herbal tonic developed in Madagascar and touted as a cure for COVID-19 could fuel drug-resistant malaria in Africa, scientists warn. Several African countries have said they are placing orders for the brew, whose efficacy has yet to be shown.

Branded Covid-Organics, the therapy was developed by the Malagasy



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# Artemisia and COVID-19

- *Artemisia annua* is being considered as a possible treatment for COVID-19<sup>15</sup>
- Crude extract of *Artemisia annua* is known to be active against SARS-CoV and may also be curative for SARS-CoV-2<sup>16</sup>



The screenshot shows the WHO Africa website. At the top left is the WHO logo and 'World Health Organization REGIONAL OFFICE FOR Africa'. To the right is a search bar. Below is a navigation bar with 'Home', 'Health topics', 'Countries', 'Newsroom', and 'About us'. The main headline reads 'WHO supports scientifically-proven traditional medicine' with a date of '04 May 2020'. The text below states: 'Brazzaville – The World Health Organization (WHO) welcomes innovations around the world including repurposing drugs, traditional medicines and developing new therapies in the search for potential treatments for COVID-19. WHO recognizes that traditional, complementary and alternative medicine has many benefits and Africa has a long history of traditional medicine and practitioners that play an important role in providing care to populations. Medicinal plants such as Artemisia annua are being considered as possible treatments for COVID-19 and should be tested for efficacy and adverse side effects. Africans deserve to use medicines tested to the same standards as people in the rest of the world. Even if therapies are derived from traditional practice and natural, establishing their efficacy and safety through rigorous clinical trials is critical.' To the right of the text is a small image of a person and a caption 'Click image to enlarge'. Below the image is a call to action: 'For Additional information or to Request Interviews, Please contact:'.



# IMPORTANT

- ▶ Diligent hand washing, particularly after touching surfaces in public. Use of hand sanitizer that contains at least 60 percent alcohol is a reasonable alternative if the hands are not visibly dirty.
- ▶ Respiratory hygiene (eg, covering the cough or sneeze).
- ▶ Avoiding touching the face (in particular eyes, nose, and mouth).
- ▶ Avoiding crowds (particularly in poorly ventilated spaces) if possible and avoiding close contact with ill individuals.
- ▶ Cleaning and disinfecting objects and surfaces that are frequently touched. The CDC has issued [guidance](#) on disinfection in the home setting; a list of EPA-registered products can be found [here](#).
- ▶ In particular, older adults and individuals with chronic medical conditions should be encouraged to



# MICROBIOLOGY REVIEW

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Bacteria

---

Viruses

---

Parasites

---

Fungus

---

Undigested Proteins

---

Toxins

---

**Foreign Invaders**



# VIRUS

- ▶ A cellular inert protein particles made of DNA or RNA with or without a lipid envelop
- ▶ Benign or deadly
- ▶ Infect every life form: plants, animals and bacteria
- ▶ Variations in surface antigenic structure, host cell receptors and lifecycles



# Viruses

Strictly dependent on cellular metabolic processes

- ▶ Possess only limited intrinsic enzyme systems and building blocks that may serve as specific targets for a drug
- ▶ Antiviral drug should not only display considerable specificity in its antiviral action but should also irreversibly block viral synthesis in order to stop cell suicide due to the viral infection and restore normal cell synthesis (Vanden Berghe et al., 1986).
- ▶ In addition to this inhibition, the antiviral agent must have a broad spectrum of activity, favorable pharmacodynamic properties, and not be immunosuppressive.
- ▶ In the ideal situation, the antiviral drug checks the infection while the immune system prepares to destroy the last virus particles (Munro et al., 1987).
  - This point is critical for those immune-compromised by illness (AIDS, cancer) or drug therapy (transplants, cancer). A frequent cause of death in these instances is from viral infections, so that adjuvant antiviral chemotherapy is vital in these circumstances



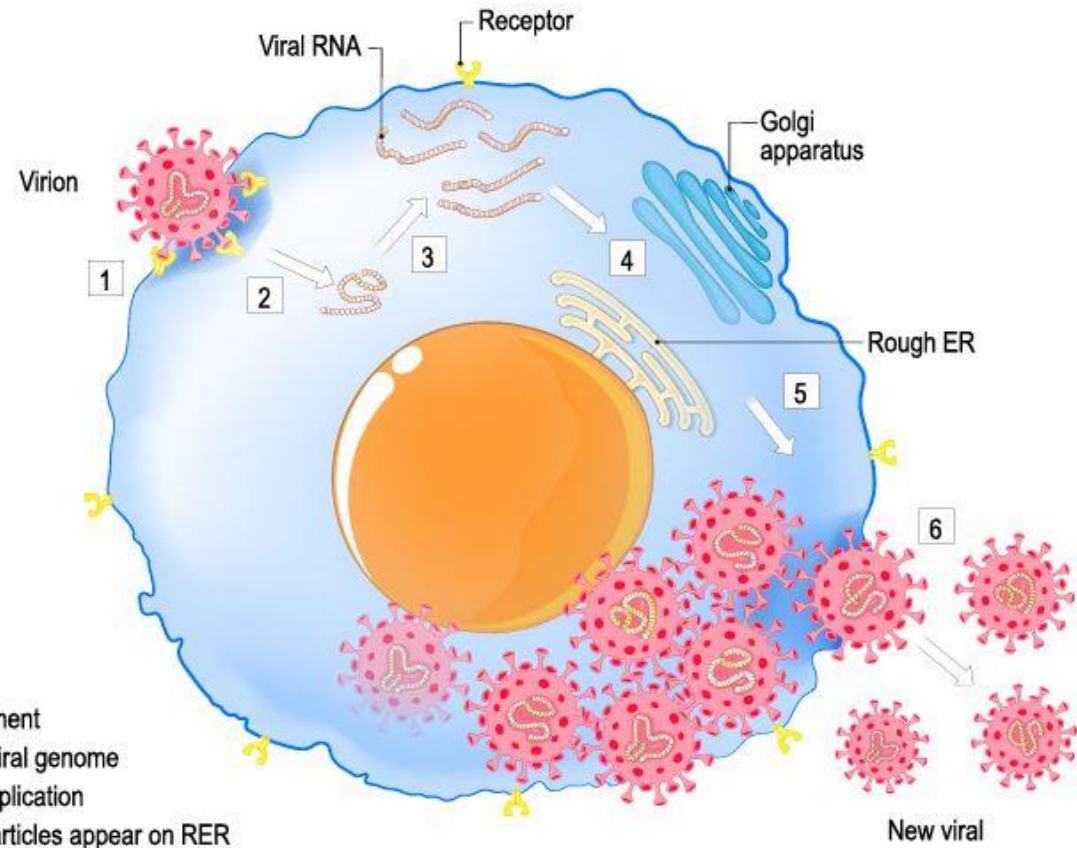
# VIRION

- ▶ Virion is the infectious particle of RNA or DNA which is designed to transmit the viral nucleic acid genome to its hosts or host cells
- ▶ A virion is not the same as a virus
- ▶ Needs to enter cell for infection





# Virus replication



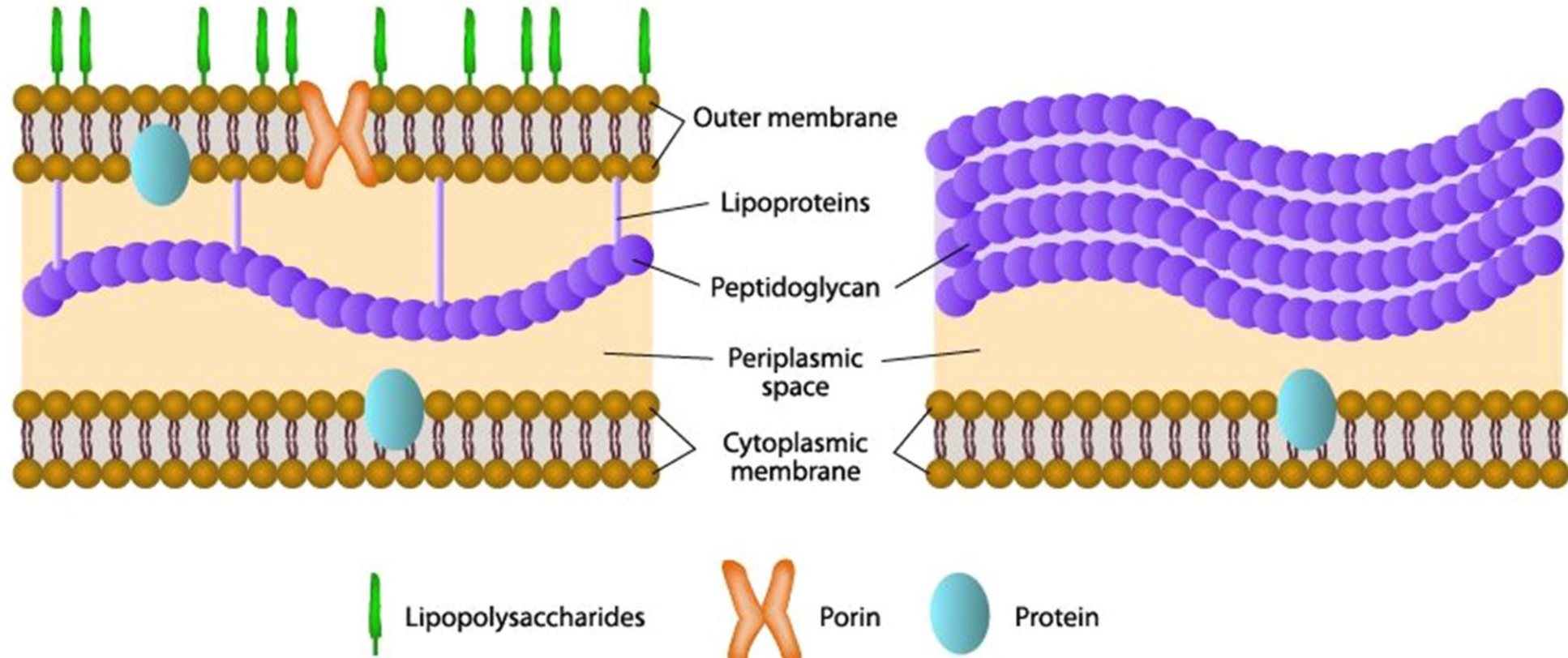
# Bacteria

- ▶ **Unicellular organism without membrane but nucleus and mitochondria are in the cytoplasm**
  - Bacteria needed in soil to make vitamins and remove wastes
    - One of the first life forms
    - All sorts of shapes
    - Gm+/Gm-
- ▶ **Needed to make B12**
- ▶ **Many diseases**
  - Gm- Thought of as more dangerous because antigens on surface are hidden
    - Capsule or slime hides antigens



# GRAM-NEGATIVE

# GRAM-POSITIVE



# Bacteriophage

- ▶ A bacteria that has been infected by a virus
- ▶ They are used to treat bacterial diseases
- ▶ Reproduce by either the lysogenic or lytic life cycles
  - The lysogenic: The virus injects its genes into the bacterium and the viral genes are inserted into the bacterial chromosome
  - The lytic cycle: The virus kills the bacteria when newly replicated viruses break open or lyse the host cell



# Mycoplasma

- ▶ Saprophytic or parasitic organisms
- ▶ Smallest living organism
- ▶ Bacteria, but thought of as “fungus/mold” like
- ▶ Lacks a cell wall around membrane
  - Makes more difficult to treat
  - Beta-lactams do not work
- ▶ Treatment with the “mycins” /macrolides first choice (Clindamycin)
  - Resistance to azithromycin
  - Followed by the fluroquinolones



# Fungus and Yeast

- ▶ **Eukaryotic organisms(cells have a nucleus enclosed within membranes)**
  - Yeasts, molds, and mushrooms
  - Chitin in their cell walls
  - Secrete digestive enzymes into their environment for food to grow



# Fungal Infections

- ▶ **Candidiasis Aspergillosis. ...**
- ▶ **Coccidioidomycosis (Valley Fever) ...**
- ▶ **Histoplasmosis. ...**
- ▶ **Blastomycosis. ...**
- ▶ **Pneumocystis pneumonia.**



# Helminths

- ▶ **Tapeworms**
  - Used for weight loss
- ▶ **Roundworms**
- ▶ **Flukes**
- ▶ **Have been used in medical treatments**
  - Blood suckers
- ▶ **Decrease of parasitic worms have been linked to possible diseases**
  - Parasitic worms needed for a healthy immune system
  - Increase allergies
  - Auto-immune “may be able to damp down the immune system
  - Increased eosinophils and macrophages
  - Glucose control





# An Overview of Various Treatments



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# Macrolides

## Azithromycin, Clarithromycin, Erythromycin

### ► Mechanisms of Action

- Antibacterial
  - Inhibits bacterial protein biosynthesis
  - Time-dependent, bacteriostatic agent
- Immunomodulation
  - Anti-inflammatory properties via suppression of neutrophil granulocyte proliferation, lymphocyte activity, and obstructive secretions in airways

### ► Clinical Uses

- Community acquired pneumonia
- Otitis media
- Mycobacterium avium complex
- Acute exacerbations of chronic obstructive pulmonary disease
- Streptococcal pharyngitis
- Helicobacter pylori eradication (Clarithromycin)



# Macrolides

## Azithromycin, Clarithromycin, Erythromycin

### ► Spectrum of Activity

- Gram Positive Bacteria
  - *Streptococcus pneumoniae*
- Gram Negative Bacteria
  - *Shigella*, *Haemophilus influenzae*, *Salmonella*, *Helicobacter pylori* (Clarithromycin)
- Atypical Bacteria
  - *Chlamydia trachomatis*, *Legionella pneumophila*, *Mycobacterium avium* complex

### ► Possible Therapeutic Use in Viral Infections?

- Studies have demonstrated that the high mortality rate due to respiratory viruses can be attributed to an overactive inflammatory response
- Macrolides have been shown to downregulate the inflammatory cascade via several mechanisms, attenuate excessive cytokine production in viral infections, and also augment interferons
- However, the anti-inflammatory effects of macrolides require very high doses to be compared with other anti-inflammatory drugs like corticosteroids, which calls into question the realistic application of macrolides being used as an anti-inflammatory agent for this purpose. Therefore, further studies are needed.



- ▶ Azithromycin has been shown to induce anti-rhinoviral effects in patients with chronic obstructive pulmonary disease
- ▶ In un-infected COPD cells
  - Azithromycin increases expression of IFN $\beta$  and IFN $\lambda$ 1 and RIG-I like helicases
- ▶ In COPD infected cells
  - Azithromycin augmented RV16-induced expression of interferons and RIG-I like helicases
- ▶ Another study showed that azithromycin has anti-rhinoviral activity in bronchial epithelial cells significantly increased rhinovirus 1B and 16-induced interferons as well as interferon-stimulated gene mRNA expression and protein production
- ▶ These effects were shown to decrease viral load by reducing rhinoviral replication and release



## Azithromycin induces anti-viral effects in cultured bronchial epithelial cells from COPD patients

Mandy Menzel,<sup>1</sup> Hamid Akbarshahi,<sup>1</sup> Leif Bjermer,<sup>2</sup> and Lena Uller<sup>a,1</sup>

▶ Author information ▶ Article notes ▶ Copyright and License information [Disclaimer](#)

This article has been [cited by](#) other articles in PMC.

### Associated Data

▶ [Supplementary Materials](#)

### Abstract

Go to:

Rhinovirus infection is a major cause of chronic obstructive pulmonary disease (COPD) exacerbations and may contribute to the development into severe stages of COPD. The macrolide antibiotic azithromycin may exert anti-viral actions and has been reported to reduce exacerbations in COPD. However, little is known about its anti-viral actions on bronchial epithelial cells at clinically relevant concentrations. Primary bronchial epithelial cells from COPD donors and healthy individuals were treated continuously with azithromycin starting 24 h before infection with rhinovirus RV16. Expression of interferons, RIG-I like helicases, pro-inflammatory cytokines and viral load were analysed. Azithromycin transiently increased expression of IFN $\beta$  and IFN $\lambda$ 1 and RIG-I like helicases in un-infected COPD cells. Further, azithromycin augmented RV16-induced expression of interferons and RIG-I like helicases in COPD cells but not in healthy epithelial cells. Azithromycin also decreased viral load. However, it only modestly altered RV16-induced pro-inflammatory cytokine expression. Adding budesonide did not reduce interferon-inducing effects of azithromycin. Possibly by inducing expression of RIG-I like helicases, azithromycin increased rhinovirus-induced expression of interferons in COPD but not in healthy bronchial epithelium. These effects would reduce bronchial viral load, supporting azithromycin's emerging role in prevention of exacerbations of COPD.

# Tetracyclines

## Doxycycline, Minocycline, Tetracycline

### ► Mechanisms of Action

- Protein synthesis inhibitors
  - Inhibit translation in several ways via binding to the 30S ribosomal subunit
- Time-dependent, bacteriostatic agent
- Inhibit matrix metalloproteinases
  - Doesn't add to antibiotic effects, but has led to research for the treatment of different types of neoplasms, acne and rosacea

### ► Clinical Uses

- Skin and soft tissue infections
- Respiratory tract infections
- Urinary tract infections
- Ophthalmic infections
- Sexually transmitted infections
- Acne



# Tetracyclines

## Doxycycline, Minocycline, Tetracycline

### ► Spectrum of Activity

- Gram Positive Bacteria
  - Staph. aureus (MRSA), Streptococcus pneumoniae, Listeria monocytogenes, Enterococci
- Gram Negative Bacteria
  - Haemophilus influenzae, Moraxella catarrhalis, Vibrio species
- Atypical Bacteria
  - Treponema pallidum (Syphilis), Rickettsia rickettsia (Rocky Mountain Spotted Fever), Borrelia burgdorferi (Lyme disease), Plasmodium species (Malaria), Helicobacter pylori
- Anaerobes
  - Clostridium species (Not difficile)

### ► Possible Therapeutic Use in Viral Infections?

- Minocycline is a 2<sup>nd</sup> generation semi-synthetic derivative of tetracycline and has some clinical activity beyond its antibacterial properties, such as anti-inflammatory, anti-oxidant, anti-apoptotic and immunomodulatory effects
- Prior studies have shown some benefit of Minocycline in some viral infections *in vitro* and in animal studies, however *in vivo* studies have failed to show benefit
- Therefore, further studies are needed



# Penicillins

## ▶ Natural Penicillins

- Penicillin G, Penicillin VK, Benzathine

## ▶ Anti-Staphylococcal Penicillins

- Oxacillin, Nafcillin, Dicloxacillin

## ▶ Mechanism of Action

- Beta-Lactam Antibiotic
  - Inhibits peptidoglycan cross link formation in the bacteria and therefore inhibits cell wall synthesis causing the bacterial cells to die
  - Time-dependent bactericidal agent

## ▶ Overcoming Drug Resistance

- Beta-lactam antibiotics have been widely used for many years causing many bacteria to develop resistance by synthesizing a beta-lactamase, which is an enzyme that destroys the beta-lactam ring in the antibiotic's chemical structure, rendering them ineffective

- Therefore, certain beta-lactams are administered with beta-lactamase inhibitors such as clavulanic acid, sulbactam, tazobactam, avibactam, and vaborbactam which help inhibit enzymatic degradation of the beta lactam ring

## ▶ Aminopenicillins

- Ampicillin/Sulbactam, Amoxicillin/Clavulanate

## ▶ Anti-Pseudomonal Penicillins

- Piperacillin/Tazobactam



# Penicillins

## ▶ Clinical Use of Natural Penicillins

- Syphilis, Gas Gangrene due to clostridium species, Necrotizing fasciitis due to streptococcus pyogenes

## ▶ Clinical Use of Anti-Staphylococcal Penicillins

- Methicillin Susceptible Staphylococcus Aureus (MSSA), skin and soft tissue infections that are known to be susceptible due to very narrow spectrum of activity

## ▶ Clinical Use of Aminopenicillins combined with Beta Lactamase Inhibitors

- Streptococcal pharyngitis (strep throat), otitis media, respiratory tract infections including community acquired pneumonia, skin and soft tissue infections

## ▶ Clinical Use of Anti-Pseudomonal Penicillins combined with Beta Lactamase Inhibitors

- Urinary tract infections, pyelonephritis, pneumonia (hospital, community, and ventilator acquired) intra abdominal infections, skin and soft tissue infections





# Aminoglycosides

## Gentamicin, Tobramycin, Amikacin

### ▶ Mechanism of Action

- Protein synthesis inhibitor
  - Inhibits protein synthesis by binding to to the cytosolic membrane associated bacterial ribosome
- Concentration-dependent bactericidal agent

### ▶ Clinical Uses

- Urinary tract infections
- Inhalation products could be used for ventilator acquired pneumonia and hospital acquired pneumonia
- Due to nephrotoxicity, these agents are generally avoided as first line agents and only used to treat serious infections which are susceptible



# Aminoglycosides

## Gentamicin, Tobramycin, Amikacin

### ► Spectrum of activity

- Gram Positive Bacteria (Not used as monotherapy)
  - Enterococcus species, Streptococcus agalactiae, Listeria monocytogenes
- Gram Negative Bacteria
  - Serratia, Pseudomonas, Acinetobacter, Citrobacter, Enterobacter, Morganella (SPACE-M)
- Atypical Bacteria
  - Some mycobacteria, including the bacteria that cause tuberculosis

### ► Possible Therapeutic Use in Viral Infections?

- A study has shown that when aminoglycoside antibiotics are applied topically, they unexpectedly had the ability of granting broad antiviral resistance to the host *in vivo* and was independent of the host's microbiota
- Topical administration of aminoglycosides induced a significant alteration of the hosts gene expression, increasing the expression of antiviral interferon-stimulated genes, which resulted in protection against RNA and DNA viruses



# Sulfamethoxazole/Trimethoprim (Bactrim)

## ► Mechanism of Action

- Sulfamethoxazole and Trimethoprim work in sequential blockade of bacterial tetrahydrofolic acid synthesis
  - Sulfamethoxazole is a structural analog of para-aminobenzoic acid, and therefore competes with para-aminobenzoic acid to inhibit the synthesis of dihydrofolic acid, a precursor step to form tetrahydrofolic acid
  - Trimethoprim also inhibits the formation of tetrahydrofolic acid by binding to and inhibiting the required enzyme dihydrofolate reductase
- Bacteriostatic agent that is primarily time-dependent, however it is concentration dependent against gram positive bacteria

## ► Clinical Uses

- Urinary tract infections
- Acute otitis media
- Acute bacterial skin and skin structure infections
- Pneumocystis pneumonia (PCP) treatment and prophylaxis



# Sulfamethoxazole/Trimethoprim (Bactrim)

## Spectrum of Activity

### ▶ Gram Positive Bacteria

- Staphylococcus aureus (MSSA & MRSA), Streptococcus pneumoniae, Listeria monocytogenes, Nocardia species

### ▶ Gram Negative Bacteria

- Stenotrophomonas maltophilia, Enterobacteriaceae, Haemophilus influenzae, Moraxella catarrhalis, Providencia species

### ▶ Atypical Bacteria

- Pneumocystis jiroveci (PCP), Legionella pneumophila



# Antiviral Medications

## ▶ Most target one virus

- Viral resistance
- Many rapidly mutate

## ▶ Instead of killing target, like antibiotics they block replication

- Attachment to a host cell
- Release of viral genes and possibly enzymes into the host cell
- Replication of viral components using host-cell machinery
- Assembly of viral components into complete viral particles
- Release of viral particles to infect new host cells



# Viricide

- ▶ Kill virus
- ▶ Able to deactivate or kill particle
- ▶ Many essential oils
  - Tea tree
  - Eucalyptus



# Drug Treatments for Fungus

- ▶ **Amphotericin B**(Amphotericin B binds with ergosterol so that important ions leak out
  - Antifungal therapy for invasive and serious mycoses
- ▶ **Azole Antifungals** (Azoles block the synthesis of ergosterol, an important component of the fungal cell membrane)
  - Most fungal infections
- ▶ **Echinocandins** (water-soluble lipopeptides that inhibit glucan synthase)
  - IV Only
  - Very strong against candida and *Aspergillus*.
- ▶ **Flucytosine** (a nucleic acid analog)
  - Always used with another antifungal, usually amphotericin B
  - Resistance high used with other medications
  - Cryptococcosis



## Potential of essential oils for protection of grains contaminated by aflatoxin produced by *Aspergillus flavus*.

Esper RH<sup>1</sup>, González E<sup>1</sup>, Marques MO<sup>2</sup>, Felicio RC<sup>3</sup>, Felicio JD<sup>1</sup>.

### ⊕ Author information

#### Abstract

Aflatoxin B1 (AFB1) is a highly toxic and carcinogenic metabolite produced by *Aspergillus* species on food and agricultural commodities. Inhibitory effects of essential oils of *Ageratum conyzoides* (mentrasto) and *Origanum vulgare* (oregano) on the mycelial growth and aflatoxin B1 production by *Aspergillus flavus* have been studied previously in culture medium. The aim of this study was to evaluate aflatoxin B1 production by *Aspergillus flavus* in real food systems (corn and soybean) treated with *Ageratum conyzoides* (mentrasto) and *Origanum vulgare* (oregano) essential oils. Samples with 60 g of the grains were treated with different volumes of essential oils, 200, 100, 50, and 10  $\mu$ L for oregano and 50, 30, 15, and 10  $\mu$ L for mentrasto. Fungal growth was evaluated by disk diffusion method. Aflatoxin B1 production was evaluated inoculating suspensions of *A. flavus* containing  $1.3 \times 10^5$  spores/mL in 60 g of grains (corn and soybeans) after adjusting the water activity at 0.94. Aflatoxin was quantified by photodensitometry. Fungal growth and aflatoxin production were inhibited by essential oils, but the mentrasto oil was more effective in soybeans than that of oregano. On the other hand, in corn samples, the oregano essential oil was more effective than that of mentrasto. Chemical compositions of the essential oils were also investigated. The GC/MS oils analysis showed that the main component of mentrasto essential oil is precocene I and of the main component of oregano essential oil is 4-terpineol. The results indicate that both essential oils can become an alternative for the control of aflatoxins in corn and soybeans.

**KEYWORDS:** *Ageratum conyzoides*; *Origanum vulgare*; corn; essential oil; mycotoxins; soybeans



# Differences in Types of Medical Models

- ▶ **Allopathic Medicine:** Make disease diagnosis to label symptom groups and use pharmaceuticals to “treat” disease
  - Evidence-based medicine
- ▶ **Functional Medicine:** Uses Phytochemistry, Biochemistry, Physiology, Genomics
  - Uses “Science Based”
  - Uses more ortho-molecular supplements
- ▶ **Natural/Traditional Medicine:** Uses herbs, plants and animal natural products to support the body to cure disease itself
  - Believes only body can heal itself
  - Symptoms are imbalances
  - Must address whole person
  - Most diseases from G.I. dysfunction
    - Hippocrates



# What is Herbal Medicine

- ▶ It is the study of plants, animal tissues, insect products, sea products, minerals and other natural substances found in nature
- ▶ Not looking for the “one thing” that is causing an effect
  - This is like looking for the one thing that makes humans walk
  - It is a symphony of many magical instruments: Not the one that you think has the melody
  - Not a simplistic of an approach because plants have more genes than human



# Plants are Multi-faceted

- ▶ **Drugs and most vitamins: pure chemicals derived from plant and animal structures**
- ▶ **Drugs more potent, may not work as well be cause of their “single target”**
- ▶ **Whole Foods and Herbs: chemicals in a complex chemical matrix**
  - Chemical complexity advantage
  - More difficult to research because too many complexities
  - IS THE SUM greater than an INDIVIDUAL PART
    - Many studies find better bioavailability(1)
    - Studies show toxic effects from the “one thing”
    - May not work as better



# Pharmacology of Herbs

- ▶ **Phytochemistry**: The chemical nature and classification of archetypal plant constituents.
- ▶ **Pharmacognosy**: Is the study of the definition, description and phytochemistry of natural drugs (typically medicinal plants or preparations derived from them)
- ▶ **Plants have Primary and Secondary Metabolites**
  - Primary metabolites are what sustains the life of the plant: Chlorophyll, proteins, CHO's and Lipids
  - Secondary metabolites: “Chemical Pharmacy” Designed to protect the life of the plant
    - This is where they find new pharmaceuticals
- ▶ **Plants have more genes as a human**
  - Rice (45,500) genes (1,2)
  - The human genome (20,000-25,000) (3)



# Ethnopharmacology

Type of medicine that studies how different cultures view disease, beliefs, practices and how they treat or prevent it

- ▶ Ethnomedicines are a vast repository of structural diversities and extensive bioactivities that can serve as a huge source of potential antiviral drugs
- ▶ A significant number of medicinal plants from Ayurveda and the traditional Chinese system of medicine serve as potential remedies to decrease the severity of illness caused by viruses



# Evolutionary Medicine :Complex Systems of the Human

- ▶ Genome: The study of structure, function, evolution, mapping, and editing as it pertains to DNA and genes
- ▶ **Metabolomics** is the study of chemical processes involving metabolites, the small-molecule intermediates and products of metabolism
- ▶ Proteomics: Study of proteins
- ▶ Epigenomics: Study of modifications made to gene expression
- ▶ Science is going in the direction of whole food and plant-based



# Trophorestorative

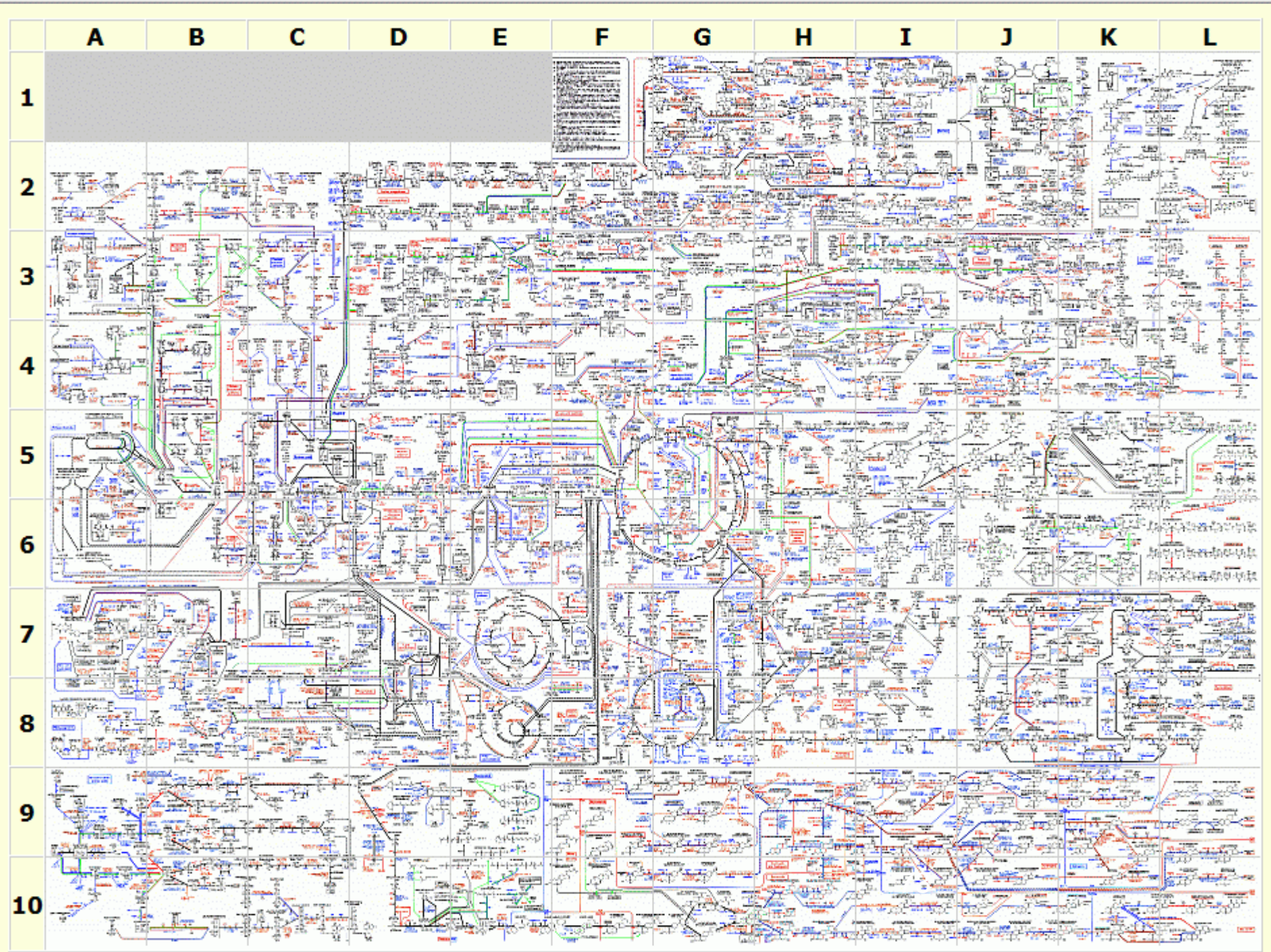
Trophorestorative is an herb, food or other substance that acts as a nutritive restorative for the body, usually with a strong affinity for an organ or organ system and corrects deficiency and weakness not simply through temporary stimulation but through the vital nourishment of that organ or organ system.

# Network Pharmacology's and its Influence on Herbal Medicine



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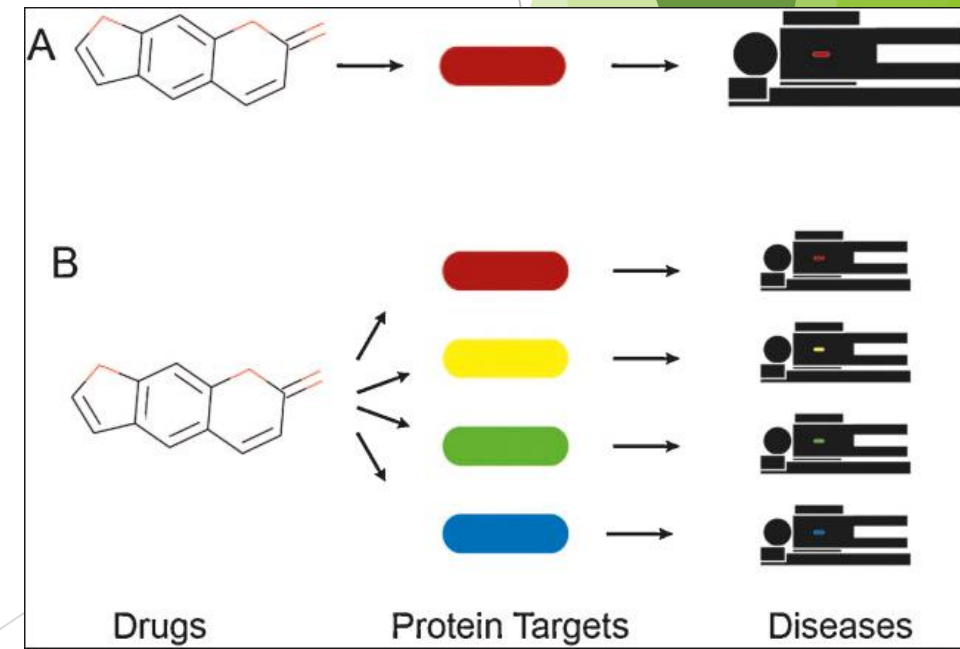
# Network Pharmacology

- ▶ Based on advances in chemical biology and network science, **network pharmacology** is a distinctive new approach to drug discovery.
- ▶ Network analysis most critical in any disease, and then chemical biology to identify molecules capable of targeting that set of proteins.
- ▶ By addressing the true complexity of disease ... Network pharmacology has the potential to provide new treatments for complex diseases where conventional approaches have failed to deliver satisfactory therapies



# Networks

- ▶ Network analysis most critical in any disease, and then chemical biology to identify molecules capable of targeting that set of proteins.
- ▶ Pharmaceutical models based on simplistic models
- ▶ “One Disease - One Drug” has dominated for decades
- ▶ Pharmaceutical companies target single receptor or single enzyme



# Multiple Genes Affect Multiple Networks

- ▶ **Nature is not simple**
- ▶ **Complex adaptive systems**
- ▶ **Genes themselves also on networks**
- ▶ **Multiple models of activity**
  - Network-network interactions
- ▶ **Clinicians use remedies with multiple targets**
  - Especially in Chemotherapy
  - “Network Pharmacology”



# Dynamic New System

There has been an explosion in our knowledge of the pathways and mechanisms by which the immune system can influence the brain and behavior. Pro-inflammatory cytokines can access the central nervous system and interact with a cytokine network in the brain to influence virtually every aspect of brain function relevant to behavior including neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, and neurocircuits that regulate mood, motor activity, motivation, anxiety and alarm.





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# Partial Perturbation

- ▶ Nature is not simple
- ▶ Partial perturbation effect on targets has better outcomes
- ▶ Herbal medicine does not have one target
- ▶ There are multiple active chemicals in plants
- ▶ Herbs have ensemble properties and concomitant compounds
- ▶ Herbs are “Adaptogenic”
  - More genes and chromosomes = More opportunities to adapt



# Simulation Experiments

- ▶ *E.coli* and *Cerevisiae* transcriptional regulatory network models used
- ▶ Various attack strategies:
  - Single target attack (A)
  - Partial inactivation of given node:
    - half of the interactions were removed (B1)
    - all interactions were attenuated (B2)
  - Distributed knockout: inactivation of interactions between nodes (C1)
  - Distributed attenuation (C2)





# Findings of study

## Various attack strategies:

- ▶ Partial weakening of small number (3-5) nodes can have greater impact than complete elimination of single selected node
- ▶ Certain drugs with multiple targets or drug combinations might have better chance to affect complex equilibrium of whole system than single target drugs
- ▶ Broad specificity compounds or multi-target drug therapies may be more effective than individual high-affinity, high-specificity ones



# Chronic Fatigue Syndrome

The concurrent occurrence of four or more of the following symptoms:

- ▶ Substantial impairment in short-term memory or concentration;
- ▶ Sore throat;
- ▶ Tender lymph nodes;
- ▶ Muscle pain;
- ▶ Multi-joint pain without swelling or redness;
- ▶ Headaches of a new type, pattern, or severity;
- ▶ Unrefreshing sleep; and
- ▶ Post-exertional malaise lasting more than 24 hours.

These symptoms must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue.



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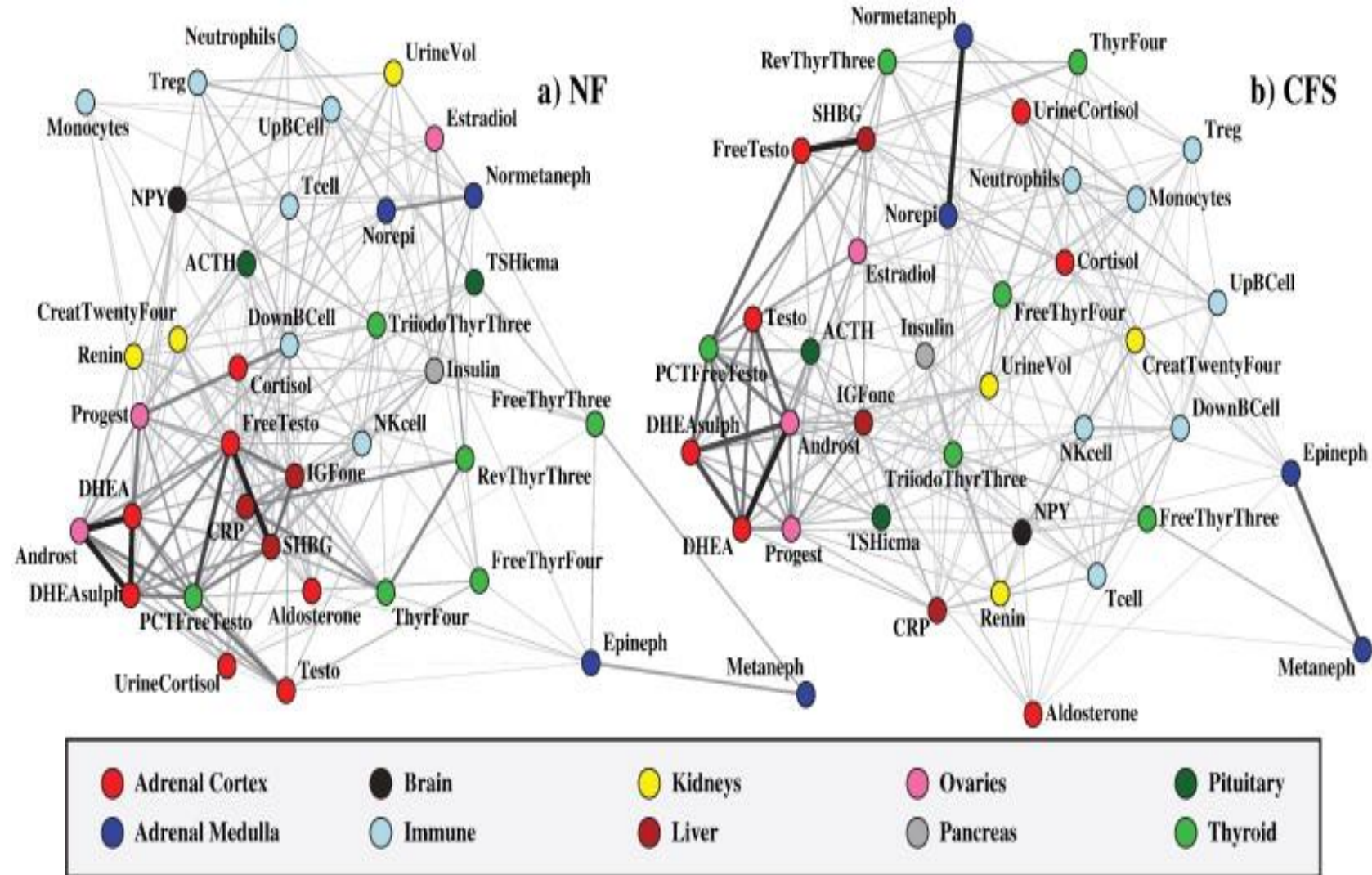
Source: The CDC (Fukuda 1994) Definition for Chronic Fatigue Syndrome Guidelines for the Evaluation and Study of CFS: Fukuda (1994) Definition for Chronic Fatigue Syndrome (CFS)





# Chronic Fatigue Syndrome

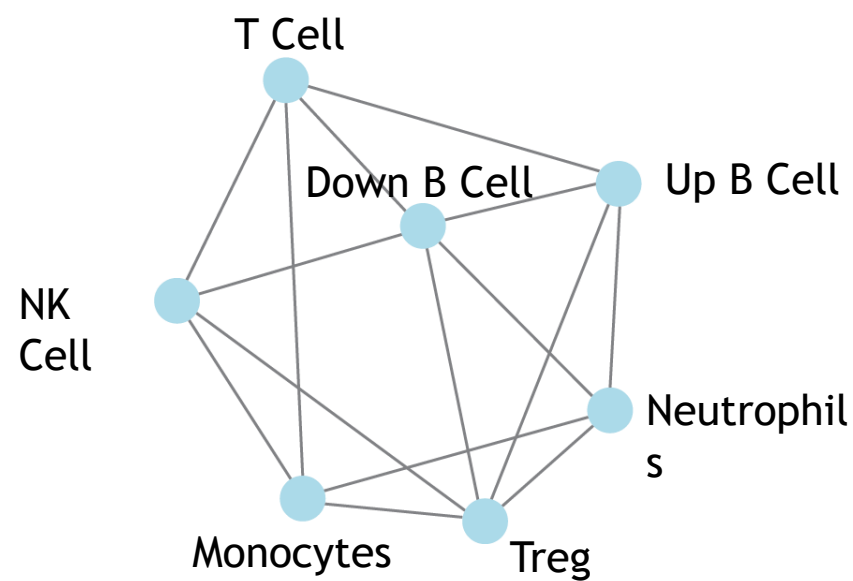
- ▶ 80% women
- ▶ Most are 40-50 years old
- ▶ More likely to have been trauma and abuse as children
- ▶ May have autoimmune conditions
- ▶ Fibromyalgia with at least 11 tender points



CFS and NF networks are visibly different in topology. Spring-electrical embedding of mutual information networks mapping the interactions between 30 neuroendocrine measures and 7 immune cell gene sets constructed using within-group variation in 37 non-fatigued control subjects (a) and 39 CFS patients (b). All edge weights are significant at  $p \leq 0.001$ .



## B) CFS



## A) NF

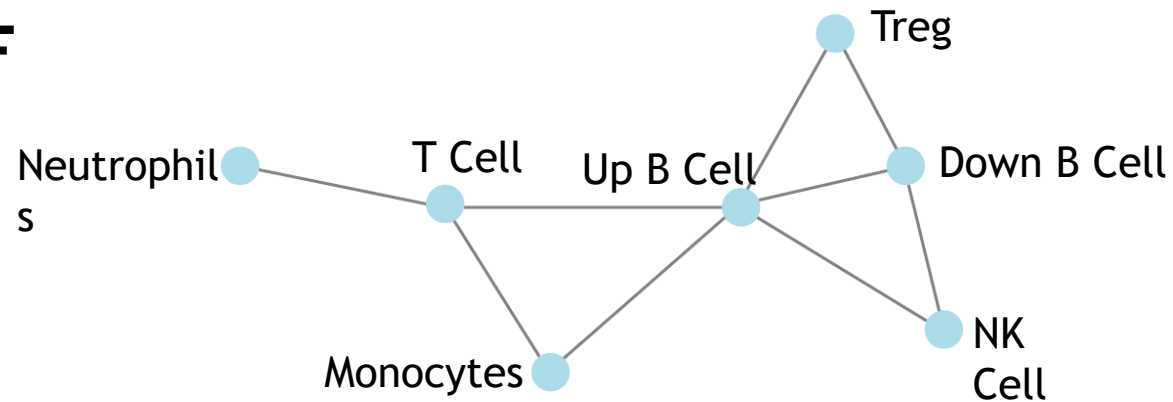


Fig. 5. Chronic inflammatory immune sub-network emerges in CFS. Mutual information sub-networks constructed for the non-fatigued (NF) (a) and CFS (b) subject groups showing co-expression patterns among the immune functional nodes only. Graph size is significantly increased in the case of the CFS immune sub-network in relation to the emergence of immune co-expression pattern absent in the NF group and characteristic of chronic inflammation.



# Strategy with Immune Building using Natural, Functional and Integrative Strategies

## G.I. Tract is Priority

- ▶ Well fed with phytonutrients, CHO's, proteins and FA
- ▶ Immune system
  - pH
  - Probiotica
  - Prebiotics
  - SIgA
    - Strong Barrier
    - Connected to stress, adrenal
  - Taking out the trash



# Strategy with Immune Building using Natural, Functional and Integrative Strategies

- ▶ **Blood**
- ▶ **Bones**
- ▶ **Organ systems need nutrition and exercise**
  - Lymphatics
  - Thymus
  - Spleen
  - Bones



# Biofilms

- ▶ Consortium of Bacteria
- ▶ Polymer Matrix
  - Polysaccharide
  - Protein
  - DNA
- ▶ Resistant to Antibiotics
- ▶ Resistant to Phagocytosis
- ▶ Communicate through quorum sensing

*“The National Institutes of Health (NIH) revealed that among all microbial and chronic infections, 65% and 80%, respectively, are associated with biofilm formation.”*



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Journal of the Chinese Medical  
Association

Volume 81, Issue 1, January 2018, Pages 7-11

open access



Review Article

## Bacterial biofilm and associated infections

Muhsin Jamal <sup>a</sup>  , Wisal Ahmad <sup>a</sup>, Saadia Andleeb <sup>c</sup>, Fazal Jalil <sup>b</sup>,  
Muhammad Imran <sup>e</sup>, Muhammad Asif Nawaz <sup>d</sup>, Tahir Hussain <sup>a</sup>, Muhammad Ali  
<sup>d</sup>, Muhammad Rafiq <sup>a</sup>, Muhammad Atif Kamil <sup>b</sup>

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<https://doi.org/10.1016/j.jcma.2017.07.012>

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### Abstract

Microscopic entities, microorganisms that drastically affect human health need to be thoroughly investigated. A biofilm is an architectural colony of microorganisms, within a matrix of extracellular polymeric substance that they produce. Biofilm contains microbial cells adherent to one-another and to a static surface (living or non-living). Bacterial biofilms are usually pathogenic in nature and can cause nosocomial infections. The National Institutes of Health (NIH) revealed that among all microbial and chronic infections, 65% and 80%, respectively, are associated with biofilm formation. The process of biofilm formation consists of many steps, starting with attachment to a



# Biofilm Throughout the G.I.



ELSEVIER

International Journal of Food Microbiology

Volume 195, 16 February 2015, Pages 30-39



## Cinnamon bark oil and its components inhibit biofilm formation and toxin production

Yong-Guy Kim <sup>a, 1</sup>, Jin-Hyung Lee <sup>a, 1</sup>, Soon-Il Kim <sup>b</sup>, Kwang-Hyun Baek <sup>c</sup>, Jintae Lee <sup>a</sup>  

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<https://doi.org/10.1016/j.ijfoodmicro.2014.11.028>

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### Highlights

- The antibiofilm effects of 83 essential oils were examined.
- Cinnamon bark oil and its components inhibited biofilm formation of *P. aeruginosa* and *E. coli* O157:H7.
- Eugenol inhibited biofilm formation of *E. coli* O157:H7.
- Eugenol inhibited toxin production and hemolytic activity of *P. aeruginosa*.
- An antibiofilm polymer coating was fabricated.



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# Fungus Biofilms

*“Candida albicans is the most adept at forming biofilms and is the principal nosocomial fungal pathogen based on its high rates of mortality, which are often associated with the biofilm lifestyle.”*



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International Journal of Antimicrobial Agents

Volume 43, Issue 2, February 2014, Pages 114-120



Review

## Strength in numbers: antifungal strategies against fungal biofilms

Gordon Ramage <sup>a</sup>  , Shaun N. Robertson <sup>a, b</sup>, Craig Williams <sup>b</sup>

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<https://doi.org/10.1016/j.ijantimicag.2013.10.023>

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### Abstract

Pathogenic fungi have the capacity to form tenacious biofilm structures that are notoriously unresponsive to antifungal therapies. Fungal biofilms are ubiquitous, located all over the human host, including the oral cavity, respiratory tract, gastrointestinal tract, urinary tract, wounds and upon biomedical devices. This latter category represents one of the greatest hurdles in clinical management, where the presence of inert substrates such as a catheter provides a reservoir for fungal biofilm development. Here, *Candida albicans* is the most adept at forming biofilms and is the principal nosocomial fungal pathogen based on its high rates of mortality, which are often associated with the biofilm lifestyle. This review will summarise some of the key fungal biofilm-forming organisms and their clinical significance and will discuss current and novel strategies to manage these hard-to-treat infections based on in vitro and in vivo studies.

# Natural Antibiotics

## ANTIBACTERIAL

Golden Seal/Berberine herbs

Citrus seed extract

Oregon grape root

Garlic

Red Thyme Oil

Oregano Oil

Caprylic acid

Uva ursi

## ANTIFUNGALS

Golden Seal/Berberine herbs

Citrus seed extract

Black walnut hull

Garlic

Red Thyme Oil

Oregano Oil

Caprylic acid

Uva ursi



- ▶ **5-hydroxy-1,4-naphthoquinone (Black Walnut)**
- ▶ **Alliin (Garlic)**
- ▶ **Arbutin (Arctosphylos uva ursi)**
- ▶ **Artemesinin (Artemesia sp.)**
- ▶ **Berberine (Goldenseal, uva ursi, berberine sulf.)**
- ▶ **Caprylic acid (Fatty Acid; octanoic from coconut)**
- ▶ **Carvacrol (Oregano)**
- ▶ **Oleuropein (Olive Leaf)**
- ▶ **Quinic Acid (Cat's Claw)**
- ▶ **Thymol (Thyme, Myrrh)**
- ▶ **Undecylenic acid (Castor oil)**



# Antiviral Herbs

- ▶ Olive Leaf Extract
- ▶ Elderberry
- ▶ Licorice
- ▶ Astragalus
- ▶ Andrographis
- ▶ Oregano Oil
- ▶ Essential Oils



# GARLIC

- ▶ **Antibacterial, antifungal, antiparasitic, antiviral**
  - Allyl sulfur compounds - allicin and ajoene
- ▶ **Immune modulating**
  - Enhances macrophage and lymphocyte proliferation rate
  - Enhances natural killer (NK) cell production and activity



# Licorice

## ▶ Antibacterial

- Constituents such as glabridin, glabrol, and 3-hydroxyglabrol posses this activity

## ▶ Antiviral

- Preliminary evidence suggests that the constituent glycyrrhizin may inhibit the growth of the coronavirus, which is associated with severe acute respiratory syndrome (SARS)

## ▶ Stimulates immune cells

- Increased CD69 expression on CD4 and CD8 T cells



# Protective Effect of Licorice

## ► Liver Protective and Increase cortisol

- Kimura, M., T. Moro, et al. (2008). *"In vivo glycyrrhizin accelerates liver regeneration and rapidly lowers serum transaminase activities in 70% partially hepatectomized rats."* Eur J Pharmacol **579**(1-3): 357-64.
- Lee, C. H., S. W. Park, et al. (2007). *"Protective mechanism of glycyrrhizin on acute liver injury induced by carbon tetrachloride in mice."* Biol Pharm Bull **30**(10): 1898-904.
- Veldt, B. J., B. E. Hansen, et al. (2006). *"Long-term clinical outcome and effect of glycyrrhizin in 1093 chronic hepatitis C patients with non-response or relapse to interferon."* Scand J Gastroenterol **41**(9): 1087-94.





# Golden Seal

- ▶ **Antimicrobial**
  - H.pylori symptoms
  - Lower GI problems
- ▶ **Cholagogue**
- ▶ **Anti-inflammatory**
- ▶ **Trophorestorative for mucus membrane**
- ▶ **\*\*\*\*OXYTOCIC \*\*\*\***

# Elderberry

- ▶ **Directly blocks and neutralizes the activity of viral glycoproteins**
  - Viruses can no longer attach to the cell membrane or enter the cell
  - Cannot replicate
- ▶ **A higher level of inhibition was achieved when viruses were pre-treated with elderberry juice before being exposed to the cells**
  - Mild inhibitory effect at the early stages of the influenza virus cycle.
- ▶ **There is no antiviral activity when cells were pre-treated with elderberry before an infection**



# Elderberry

- ▶ Indirectly working to increase the expression of cytokines such as interleukin IL-6, IL-8 and tumor necrosis factor
- ▶ IL-6 responds to infections and tissue injuries, contributes to host defense through the stimulation of acute phase response
  - Strictly controlled but can be dysregulation constant IL-6 plays a pathological effect on chronic inflammation
- ▶ IL-8 calls in neutrophils, granulocytes, to infection and stimulates phagocytosis
- ▶ TNF activates inflammatory cytokines



# Astragalus

## Mechanism of Action

### ▶ Immunomodulating

- Promotes B-cell proliferation, antibody production and enhances cytotoxic T lymphocyte activity
- Shown to potentiate both thymus and spleen function, and to augment both humoral and cell-mediated immunity

### ▶ Antioxidant

- Increases superoxide dismutase and decreases lipid peroxide activity

### ▶ Anti-inflammatory

- Reduces IL-1 $\beta$  induced production of proinflammatory cytokines IL-6 and TNF- $\alpha$

### ▶ Antitumorigenic

- Modulates various cancer signaling pathways



A close-up photograph of Astragalus flowers, showing several clusters of small, light purple to pink blossoms on green stems. The background is a soft-focus field of similar flowers.

# Astragalus

## Clinical Uses

- ▶ Reduce side effects of chemotherapy
- ▶ Diabetes
- ▶ Chronic hepatitis
- ▶ Chronic fatigue syndrome
- ▶ Immune booster
- ▶ Inflammation
- ▶ Vaginal infections
- ▶ Chronic kidney disease
- ▶ Lung cancer

# Artemisia (Wormwood)

- ▶ Flavonoids in extracts contain antiviral, antibacterial, antifungal, anti-cancer, antioxidant, and anti-inflammatory properties<sup>13</sup>
- ▶ Contains sitosterol and stigmasterol - Sterols that exhibit viral inhibitory activity<sup>14</sup>
- ▶ Contains santonin - an anthelmintic compound

## Molecules

Multidisciplinary Digital Publishing Institute (MDPI)

### Romanian Wormwood (*Artemisia absinthium* L.): Physicochemical and Nutraceutical Screening

Elena-Alina Moacă, Ioana Zinuca Pavel, [...], and  
Cristina-Adriana Dehelean

[Additional article information](#)

#### Associated Data

- ▶ [Supplementary Materials](#)

## Abstract

*Artemisia* species are used worldwide for their antioxidant, antimicrobial and anti-inflammatory properties. This research was designed to investigate the phytochemical profile of two ethanolic extracts obtained from leaves and stems of *A. absinthium* L. as well as the biological potential (antioxidant activity, cytotoxic, anti-migratory and anti-inflammatory properties). Both plant materials showed quite similar thermogravimetric, FT-IR phenolic profile (high chlorogenic acid) with mild antioxidant capacity [ascorbic acid (0.02–0.1) > leaves (0.1–2.0) > stem (0.1–2.0)]. Alcoholic extracts from these plant materials showed a cytotoxic effect against A375 (melanoma) and MCF7 (breast adenocarcinoma) and affected less the non-malignant HaCaT cells (human



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Artemisia Herba-Alba. Natural Medicines Comprehensive Database. Natural Medicines [database online]. Stockton, CA: Therapeutic Research Facility; Updated: May 10, 2019. Accessed: May 18, 2020.

<https://naturalmedicines.therapeuticresearch.com/search.aspx?q=Artemisia>

# Nutrients for Immune

Vitamin D

Zinc

Vitamin C

Vitamin A

Calcium

Vitamin E

Selenium

B (Thiamine)

# Treatments

## Vitamins

- ▶ **Natural “food based” vs. synthetic**
  - synthetic means two things:
    - - manmade
    - - occurs nowhere in nature
- ▶ **Ascorbic acid is not vitamin C. Alpha tocopherol is not vitamin E. Retinoic acid is not vitamin A.**
- ▶ **Vitamins are not individual molecular compounds.**
- ▶ **Vitamins are biological complexes**





# Antiviral and immune modulating mechanisms of vitamin D

- ▶ Induction of LL-37 to inhibit viral replication<sup>1</sup>
- ▶ Induction of human beta defensin 2 which degrades membranes<sup>1</sup>
- ▶ Induction of cathelicidin, antimicrobial peptide that is able to bind endotoxins and directly kill pathogens<sup>2</sup>
- ▶ Vitamin D receptor is expressed on all immune cells (B Cells, T Cells, Antigen Presenting Cells) and is crucial for modulating the innate and adaptive immune responses<sup>3</sup>

## Inflammation & allergy drug targets

Author Manuscript

HHS Public Access

### The Role of Vitamin D in Prevention and Treatment of Infection

Cameron F. Gunville, Peter M. Mourani, and Adit A. Ginde

[Additional article information](#)

#### Abstract

Vitamin D is well known for its classic role in the maintenance of bone mineral density. However, vitamin D also has an important “non-classic” influence on the body’s immune system by modulating the innate and

adaptive immune system, influencing the production of important endogenous antimicrobial peptides such as cathelicidin, and regulating the inflammatory cascade. Multiple epidemiological studies in adults and children have demonstrated that vitamin D deficiency is associated with increased risk and greater severity of infection, particularly of the respiratory tract. Although the exact mechanisms by which vitamin D may improve immune responses to infection continue to be evaluated, vitamin D supplementation trials of prevention and adjunct therapy for infection are underway. Given its influence on the immune system and inflammatory cascade, vitamin D may have an important future role in the prevention and treatment of infection.

**Keywords:** Antimicrobial, cathelicidin, immune system,



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# Vitamin D deficiency

- ▶ Age-related micronutrient deficiencies as well as the nutrition status of the individual play a role in determining functionality of the immune system<sup>4</sup>
- ▶ Vitamin D supplementation has shown to be protective against acute respiratory infections when taken before the onset of infection and the risk of viral infections and inflammation-related pneumonia can be reduced<sup>4</sup>
- ▶ Optimal vit D levels between 50-70 nmol/L reduce the risk of developing microbial infection<sup>5,6</sup>






# Vitamin D and COVID-19

- ▶ Although it has been demonstrated in studies that high dose vitamin D is not a sufficient treatment for COVID-19, the incidence of mortality is correlated with Vit D deficiency<sup>7</sup>
- ▶ Mortality from COVID-19 has been associated with increased age and chronic conditions, both of which are also associated with decreased vit D<sup>5</sup>
- ▶ Vitamin D levels of individuals are lowest in the winter months when we aren't receiving much sunlight. This is also when the outbreak of COVID-19 began<sup>5</sup>



Review

## Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths

William B. Grant <sup>1,\*</sup>, Henry Lahore <sup>2</sup>, Sharon L. McDonnell <sup>3</sup>, Carole A. Baggerly <sup>3</sup>,  
Christine B. French <sup>3</sup>, Jennifer L. Aliano <sup>3</sup> and Harjit P. Bhattoa <sup>4</sup>

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<sup>3</sup> GrassrootsHealth, Encinitas, CA 92024, USA; Sharon@grassrootshealth.org (S.L.M.); carole@grassrootshealth.org (C.A.B.); Christine@grassrootshealth.org (C.B.F.); jen@grassrootshealth.org (J.L.A.)

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\* Correspondence: wbgrant@infionline.net; Tel.: +1-415-409-1980

Received: 12 March 2020; Accepted: 31 March 2020; Published: 2 April 2020



**Abstract:** The world is in the grip of the COVID-19 pandemic. Public health measures that can reduce the risk of infection and death in addition to quarantines are desperately needed. This article reviews the roles of vitamin D in reducing the risk of respiratory tract infections, knowledge about the epidemiology of influenza and COVID-19, and how vitamin D supplementation might be a useful measure to reduce risk. Through several mechanisms, vitamin D can reduce risk of infections. Those mechanisms include inducing cathelicidins and defensins that can lower viral replication rates and reducing concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increasing concentrations of anti-inflammatory cytokines. Several observational studies and clinical trials reported that vitamin D supplementation reduced the risk of influenza, whereas others did not. Evidence supporting the role

# Too Much Vitamin D May Also Be A Cause For Concern

- ▶ Anorexia, weight loss, polyuria, and heart arrhythmias are symptoms of toxicity<sup>8</sup>
- ▶ More severe symptoms are due to the elevation in blood levels of calcium
  - Vascular and tissue calcification, with subsequent damage to the heart and blood vessels, causing a stroke or coronary disease<sup>6,8</sup>
  - Damage to the kidneys, causing stones<sup>8</sup>
- ▶ Intake of greater than 10,000 IU/day and blood levels of 125-150 nmol/L should be **avoided**<sup>8</sup>



# Calcium and the Immune Response

- ▶ Calcium has a crucial role in the development of the immune response.
- ▶ An elevation in calcium is often associated with the activation of immune system cells.
- ▶ A calcium flash is the first step of the immune response for healing
- ▶  $\text{Ca}^{2+}$  signaling has a role in many immune system cells including: T cells, B cells, natural killer (NK) cells, macrophages and mast cells.
  - Intracellular calcium is crucial for various short term and long-term function of these immune system cells



# Calcium Lets T Cells Use Sugar to Multiply & Fight Infection



**A** calcium signal controls whether immune cells can use the nutrients needed to fuel their multiplication into a cellular army designed to fight invading viruses. This is the finding of a study in human cells and mice led by researchers at NYU School of Medicine and [published online](#) October 10 in *Immunity*.

The study results concern the precise and massive immune counterattack by T cells in response to viral infection. When this type of white blood cell is turned on by an invader, it divides and multiplies into an army of clones primed specifically to attack that invader.

## IN THIS ARTICLE

### OUR EXPERTS

[Stefan Feske, MD](#)

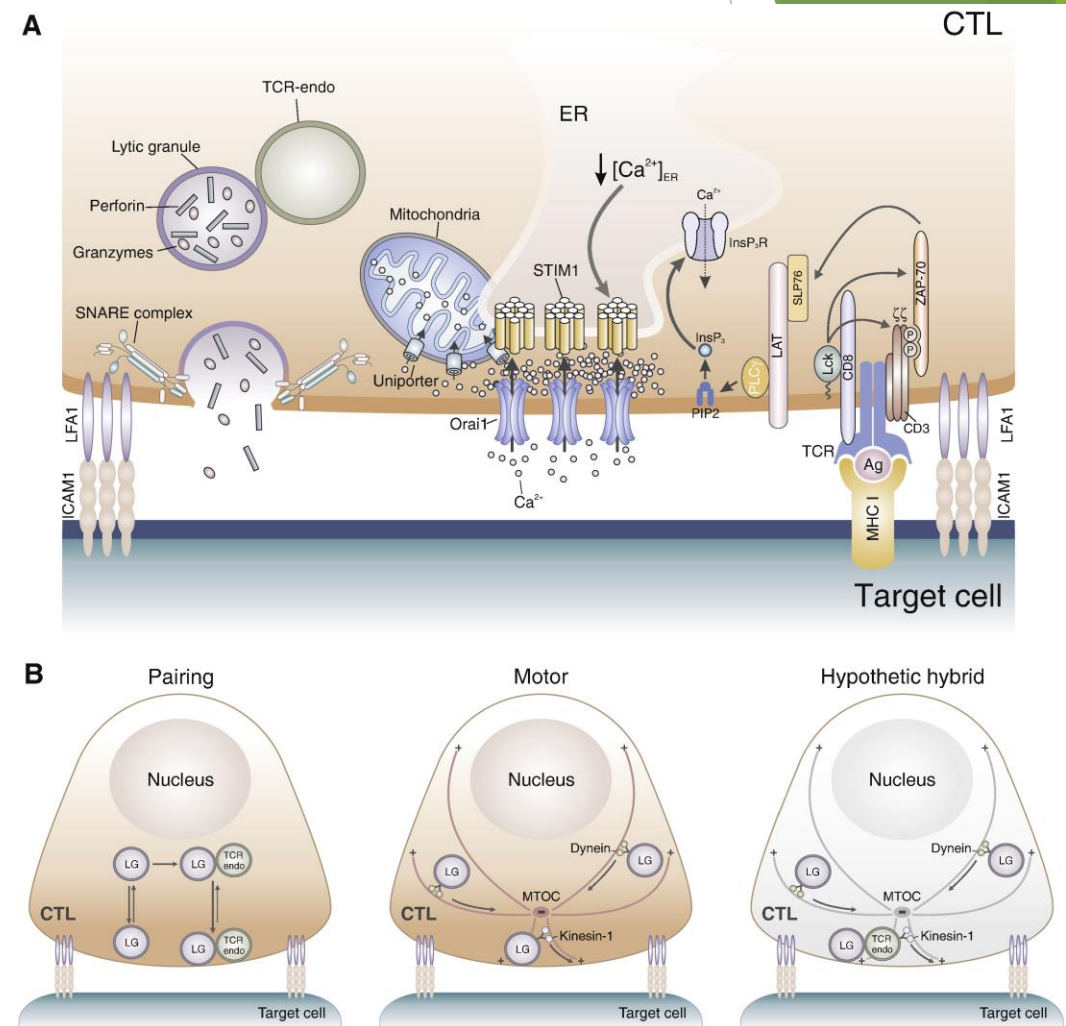
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698-7243.



# Calcium and Cancer

- ▶ Calcium has a role in apoptosis of cancer cells and immune cells
- ▶ Killing cancer cells by cytotoxic T lymphocytes (CTL) and natural killer (NK) cells is  $\text{Ca}^{2+}$  dependent during multiple steps
- ▶ Intracellular  $\text{Ca}^{2+}$  is important for CTL and NK cell function



# Vitamin A

Vitamin A and its metabolites play critical roles in both innate and adaptive immunity

- ▶ Maintain these structural and functional integrity of mucosal cells.
- ▶ Immune cells important in the innate response, including natural killer (NK) cells, macrophages, and neutrophils
- ▶ Proper function of cells that mediate adaptive immunity, such as T and B cells;
- ▶ Necessary for the generation of antibody responses to specific antigens.





# Vitamin C and Immune Function

- ▶ Enhances integrity of skin and epithelial barrier functions<sup>9</sup>
- ▶ Enhances expression of wound healing mediators<sup>9</sup>
- ▶ Improves leukocyte chemotaxis (migration to site of infection)<sup>9</sup>
- ▶ Promotes lymphocyte proliferation and antibody generation<sup>9</sup>
- ▶ Increases T-lymphocyte activity, phagocyte function, and leukocyte mobility
- ▶ Some experts suggest taking vitamin C 200 mg daily to prevent COVID-19 and other respiratory tract infections, or 1-2 grams daily at the onset of symptoms to improve recovery



# Vitamin C

- ▶ Highly effective antioxidant that protects the body's cells against reactive oxygen species (ROS) that are generated by immune cells to kill pathogens.
- ▶ Stimulate both the production and function of leukocytes (white blood cells), especially neutrophils, lymphocytes,
- ▶ Phagocytes and Neutrophils attack foreign bacteria and viruses



# Important Immune Builders

- ▶ Adrenal
- ▶ Thymus
- ▶ Bones
- ▶ Spleen
- ▶ Liver
- ▶ Bile
- ▶ **SLEEP**
- ▶ Echinacea
- ▶ Mushrooms
- ▶ Aloe Vera
- ▶ Whole Food
  - Polysaccharides
  - Vitamins
  - Minerals



# Organotherapy

## Desiccated Spleen

- ▶ Immune modulating
  - Peptide tuftsin stimulates phagocytosis, motility, and immunogenic response of phagocytic cells

Spleen Extract. Natural Medicines Comprehensive Database. Natural Medicines [database online]. Stockton, CA: Therapeutic Research Facility; Updated: Aug. 30, 2019. Accessed: May 18, 2020.

<https://naturalmedicines.therapeuticresearch.com/search.aspx?q=Spleen+extract+>

## Desiccated Thymus

- ▶ Immune modulating
  - Increase T- and B-lymphocyte counts
  - T alpha 1, a compound found in thymus extract, activates natural killer cell-mediated cytotoxicity
  - Thymosin plays a role in the differentiation of T-cell subpopulations
  - Increase neutrophil activity
  - Thymic peptide increased secretion of monocyte chemotactic protein-1 (MCP-1) and IL-8 and enhanced cell-mediated immune reactions

Thymus Extract. Natural Medicines Comprehensive Database. Natural Medicines [database online]. Stockton, CA: Therapeutic Research Facility; Updated: Feb. 15, 2016. Accessed: May 18, 2020. <https://naturalmedicines.therapeuticresearch.com/search.aspx?q=Thymus+extract+>



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# Glandulars

## Whole Glands

- ▶ Only Used short term because of atrophy
- ▶ Contains all factors of the glands
  - Hormones
  - Enzymes
  - Tissue Factors
- ▶ **Thyroid**
- ▶ **Adrenal**
- ▶ **Thymus**
- ▶ **Spleen**



# Protomorphogens

- ▶ Can be used long term
- ▶ Extracts of nucleic acids from cell nucleus
  - RNA (Ribonucleic)
    - messenger, transfer, ribosomal
    - DNA and Protein synthesis
  - DNA (Deoxyribonucleic acid)
    - Contains genetic instructions in development and functioning of all living things
    - Carries the “genes”
    - Held together by sugars and phosphate



# Glandulars: Cytosol Extracts

## Cytosol Extracts

- ▶ From cell cytoplasm which is inside the membrane of the cell
- ▶ The cytoplasm is the site where most cellular activities occur, such as many metabolic pathways like glycolysis and processes such as cell division.
- ▶ Used in more acute cases



# Antiviral and Immune Modulating Effects of Echinacea

- ▶ Contain prebiotic components which interact with the host microbiome to improve health and disease<sup>10</sup>
- ▶ Enhanced phagocytosis by macrophages<sup>10</sup>
- ▶ Increased leukocyte mobility<sup>10</sup>
- ▶ Enhanced production of nitric oxide (an inhibitor of viral replication)<sup>11</sup>
- ▶ Enhanced production of TNF- $\alpha$ <sup>11</sup>
- ▶ Inhibit enveloped viruses; Increase levels and activity of T lymphocytes, neutrophils, and natural killer (NK) cells
- ▶ **Daisy allergy**

- Echinacea. Natural Medicines Comprehensive Database. Natural Medicines [database online]. Stockton, CA: Therapeutic Research Facility; Updated: May 6, 2020. Accessed: May 18, 2020.  
<https://naturalmedicines.therapeuticresearch.com/search.aspx?q=Echinacea&go.x=10&go.y=14&go=submit>





# Mushrooms

- ▶ **Mushrooms with antiviral activity include:**
  - *Ganoderma lucidum* (Lingzhi)
  - *Inonotus hispidus* (shaggy bracket)
  - *Rhodocollybia maculata* (Spotted Toughshank)
  - *Inonotus obliquus* (chaga)
  - *Trametes versicolor* (turkey tail)
  - *Flammulina velutipes* (enokitake)
  - Maitake D-fraction of *Grifola frondosa* (hen-of-the-wood)
- ▶ **Direct inhibition of viral enzymes**
- ▶ **Inhibition of synthesis of viral nucleic acids**
- ▶ **Increased phagocytosis by mammalian cells**

## The Pharmacological Potential of Mushrooms

Ulrike Lindequist, Timo H. J. Niedermeyer, and Wolf-Dieter Jülich

[Additional article information](#)

### Abstract

This review describes pharmacologically active compounds from mushrooms. Compounds and complex substances with antimicrobial, antiviral, antitumor, antiallergic, immunomodulating, anti-inflammatory,



# Immune Modulating Mechanisms of the Maitake Mushroom ("D-fraction" of beta-glucan)

- ▶ Enhancing phagocytosis
- ▶ Increasing natural killer cell cytotoxicity
- ▶ Activation of helper T cells
- ▶ Increased production of Interferon-gamma, interleukin (IL)-12 p70, and IL-18



# Polysaccharides

## Immunomodulatory and Anti-Tumour Polysaccharides From Medicinal Plants

C K Wong <sup>1</sup>, K N Leung, K P Fung, Y M Choy

Affiliations + expand

PMID: 7895893 DOI: [10.1177/030006059402200601](https://doi.org/10.1177/030006059402200601)

### Abstract

Many Chinese medicinal plants have immunomodulatory and anti-tumour activities. Most of the anti-tumour activities of these Chinese herbs are probably due to their immunostimulating polysaccharide components. A general scheme for the isolation and purification of the bioactive polysaccharides from naturally occurring medicinal plants is described. Hot-water extraction followed by various chromatographic methods are usually used to purify the bioactive polysaccharides. The different fractions separated from Chinese medicinal plants show a range of immunomodulatory and anti-tumour activities. The analytical methods used for monosaccharide sequence determination and structural elucidation of the bioactive polysaccharides are described, as are the tests used to evaluate their immunopharmacological activities, both in vitro and in vivo. The purification, characterization and structural elucidation of immunomodulatory polysaccharides from medicinal plants may have important implications in the immunotherapy of cancer and in the treatment of various other diseases.



# Case Study

## 5 y.o. boy with sore throat, runny nose and headache

- ▶ Your respiratory illness might be the flu if you have fever, cough, sore throat, runny or stuffy nose, body aches, headache, chills and fatigue. Some people may have vomiting and diarrhea<sup>[1]</sup>
  - Caused by a pathogen flu virus or possible bacteria like strep throat
- ▶ Dendritic cells display an antigen to present it to the immune system messengers between the innate and the adaptive immune systems
  - An antigen is a part of virus or bacteria which trigger antibodies
- ▶ White blood cells attack (also known as **leukocytes**)
  - Produced in many places: tissues, thymus, spleen, and bone marrow
  - Circulate through lymphatic network and lymph organs
  - Circulate through blood vessel



# Calcium Signaling in Lymphocyte Activation and Disease

- ▶ Calcium signals in cells of the immune system participate in the regulation of cell differentiation, gene transcription and effector functions.
- ▶ Increase in intracellular levels of calcium ions ( $\text{Ca}^{2+}$ ) results from the engagement of immunoreceptors, such as the T-cell receptor, B-cell receptor and Fc receptors, as well as chemokine and co-stimulatory receptors



# Inflammatory Cytokines Important

- ▶ They stimulate the immune system to call in fighter cells to rid the body of viruses, bacteria, and other pathogens
- ▶ Constant stimulation a problem
- ▶ There can be a problem with too many



# Activation of Cells of the Immune System

1. Cells in thymus (T) and bone marrow (B) seed lymphatic organs throughout the body and line epithelial and epidermal tissues where the body meets the outer world.
2. In concert with the cells of the inborn (innate) immunity their defense role starts with a stepwise activation pattern that follows invasion of a microbiological intruder, usually a virus, bacterium, fungus, or a multicellular parasite.
3. Damaged by the intrusion, tissues set an alarm by activating the innate immunity (DCs, NK cells). DCs can translocate to lymph nodes and activate T cells. These in turn help B cells to develop into plasma cells and secrete antibodies specific for intruders' antigens, or go and become effector cells that can activate peripheral tissue cells like macrophages by secreting cytokines, and some of them (CD8 T) can directly kill infected somatic cells.



# Even In 1931 They Recognized the Importance of Stomach Acid

## CLINICAL CONDITIONS ASSOCIATED WITH ACHLORHYDRIA.

*To the Editor of THE LANCET.*

SIR,—In their interesting paper in your last issue Dr. J. F. Wilkinson and Dr. T. H. Oliver say that I regard achlorhydria as a common factor in the production of cancer of the stomach. I have never made such a statement. On the other hand, if they will read my Schorstein Lecture,<sup>1</sup> they will find abundant evidence that chronic gastritis is a common precursor of cancer of the stomach, and that the achlorhydria found in 60 per cent. of cases of the latter is not secondary to the cancer but is a result of the chronic gastritis which preceded it. This is one reason why I regret that Dr. Wilkinson and Dr. Oliver have not distinguished between achylia gastrica and achlorhydria. Achylia is generally due to an inborn error of secretion and is often familial, but it may also be caused by severe gastritis, which has led to destruction of the oxyntic cells of the stomach.

<sup>1</sup> THE LANCET, 1929, ii., 1023.





# H. Pylori

## ▶ WHO: Class 1 Carcinogen

- Infection very high in Russia, China and India

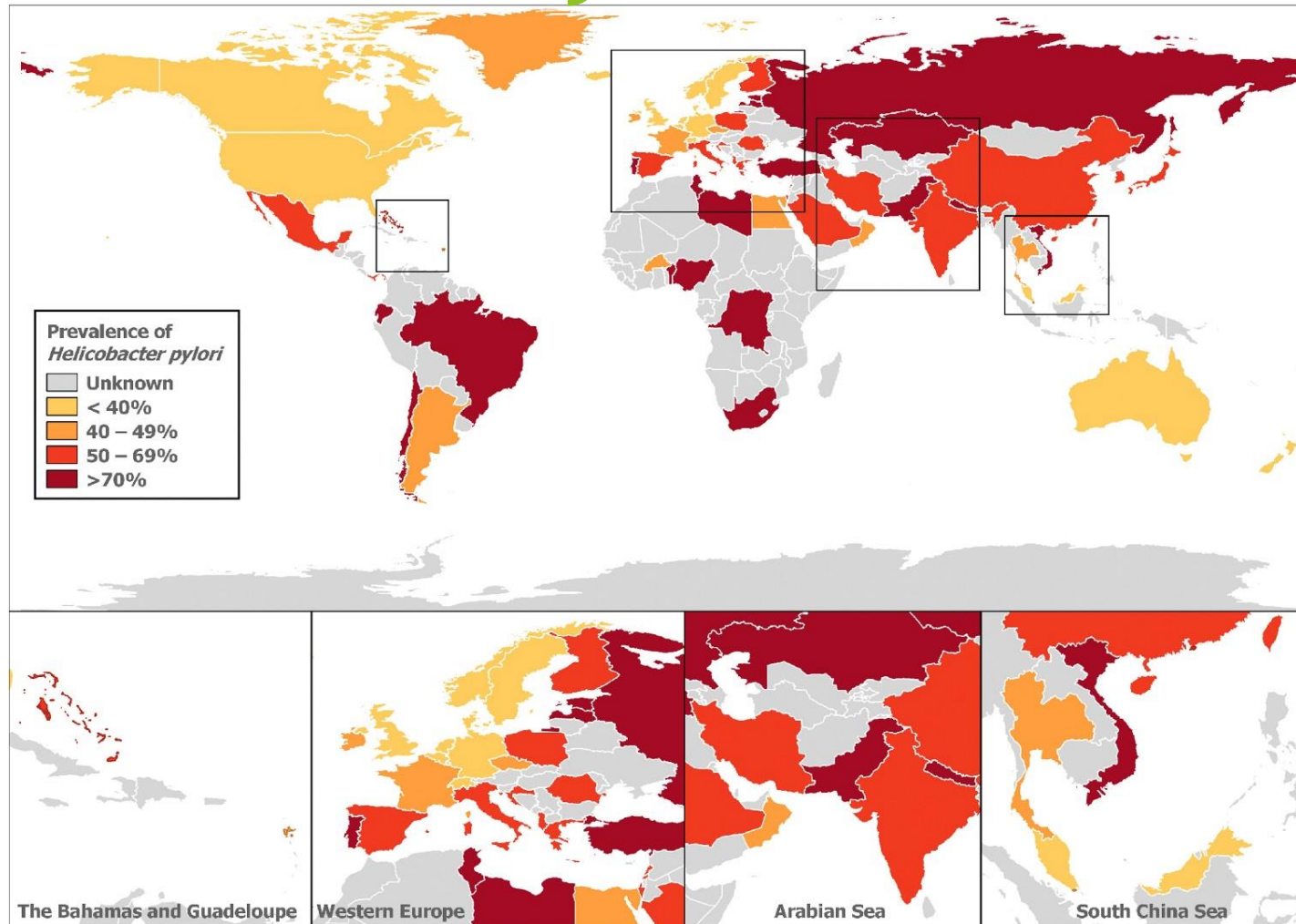
## ▶ Infection leads to acute or chronic inflammation of the gastric mucosa and peptic ulcer disease (PUD)

## ▶ “Tunnels” into the mucus layer covering the gastric epithelium

- Creates a highly immunogenic protein dubbed “CagA” and/or a vacuolization inducing protein dubbed “VacA”
- This can cause atrophy which leads to gastric adenocarcinoma and MALT (mucosa-associated lymphoid tissue) lymphoma



# Prevalence of H. Pylori



## *Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis*

James K.Y. Hooi, Wan Ying Lai, et.al. *Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. Gastroenterology* Volume 153 Issue 2 Pages 420-429 (August 2017) DOI: 10.1053/j.gastro.2017.04.022



INTEGRATIVE  
HEALTH &  
WELLNESS

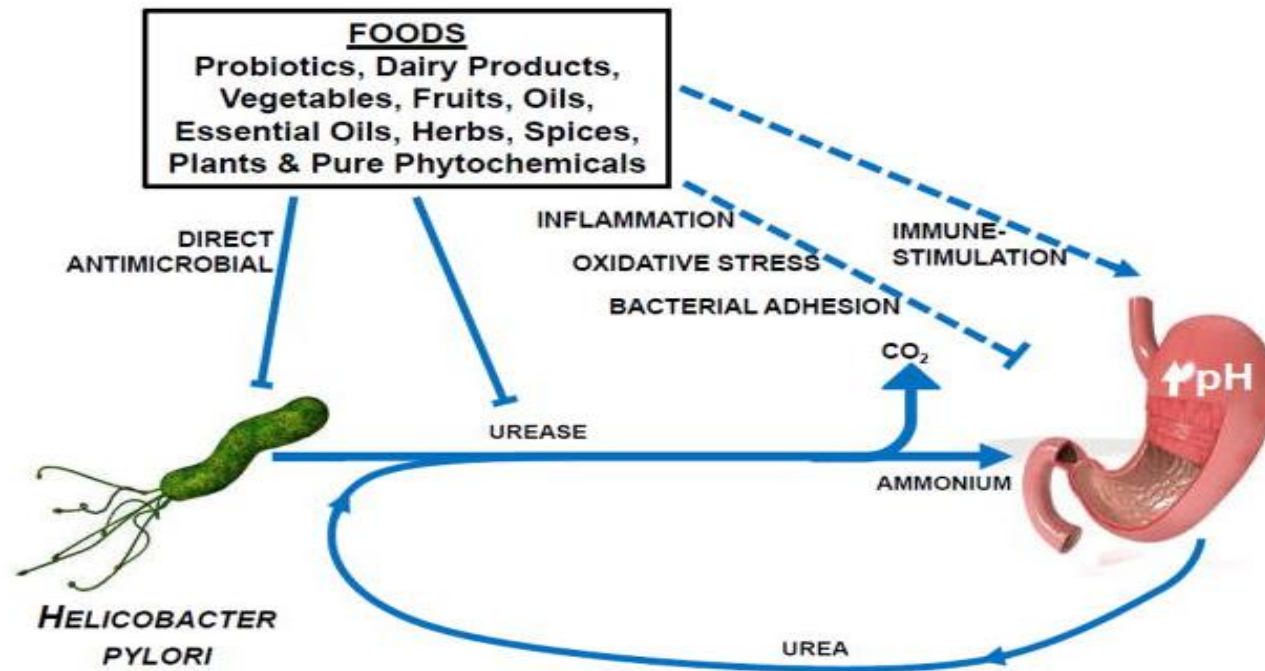
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Figure 1



A large number of foods have been evaluated for their ability to inhibit *Helicobacter pylori*, *in vitro*. Some of these, and other food components reduce colonization of the stomach and the sequelae of colonization, in animal models and small human trials. Primary mechanisms of action are not in all cases focused on the direct antimicrobial effects, but include inhibition of the urease produced by *H. pylori* as a pathogenic factor, anti-inflammatory antioxidant, anti-adhesive, and immune-stimulatory properties of these foods.





A...  
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ancer

## Gastric Cancer as Preventable Disease

Massimo Rugge <sup>\*</sup>, <sup>‡</sup>, <sup>ⓧ</sup>, Robert M. Genta <sup>§</sup>, Francesco Di Mario <sup>¶</sup>, Emad M. El-Omar <sup>¶</sup>, Hashem B. El-Serag <sup>#</sup>, Matteo Fassan <sup>\*</sup>, Richard H. Hunt <sup>\*\*</sup>, Ernst J. Kuipers <sup>‡‡</sup>, Peter Malfertheiner <sup>§§</sup>, Kentaro Sugano <sup>¶¶</sup>, David Y. Graham <sup>#</sup>

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<https://doi.org/10.1016/j.cgh.2017.05.023>

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Gastric cancer, 1 of the 5 most common causes of cancer death, is associated with a 5-year overall survival rate less than 30%. A minority of cancers occurs as part of syndromic diseases; more than 90% of adenocarcinomas are considered as the ultimate consequence of a longstanding mucosal inflammation. *Helicobacter pylori* infection is the leading etiology of non–self-limiting gastritis, which may result in atrophy of the gastric mucosa and impaired acid secretion. Gastric atrophy establishes a field of cancerization prone to further molecular and phenotypic changes, possibly resulting in cancer growth. This well-understood natural history provides the clinicopathologic rationale for primary and secondary cancer prevention strategies. A large body of evidence demonstrates that combined primary (*H pylori* eradication) and secondary (mainly endoscopy) prevention efforts may prevent or limit the progression of gastric oncogenesis. This approach, which is tailored to different country-specific gastric cancer incidence, socioeconomic, and cultural factors, requires that the complementary competences of gastroenterologists, oncologists, and pathologists be amalgamated into a common strategy of health policy.



# Case 1: 31 y.o. With Pain and Gas in GI Upon Eating

- ▶ A 31 y.o woman has lost 20 lbs. 5 ft. 4 in. 102 lbs. cannot eat because of pain
- ▶ Had tests to R/O Gastritis
- ▶ For over 5 years she had gone to 5 different medical doctors who did food sensitivity tests
  - First day of food removal good, then it feel bad again.
  - Constipated
- ▶ My recommendation is to go to Gastroenterologist and get h. pylori test
  - “What kind of doctor recommended this?”
  - H. pylori is positive all other tests negative
  - omeprazole, amoxicillin, metronidazole and clarithromycin



# Pharmaceutical Treatments for H. Pylori

- ▶ About 40% of anti-cancer and antimicrobial drugs have roots in herbal medicine 1
- ▶ She called and complained “I am in so much pain from this regimen” Please help!
- ▶ Diet: GAPS
- ▶ Aloe Vera Gel :mucilaginous herb to repair mucus lining
- ▶ Licorice: Adrenal and Kill pylori
- ▶ Garlic Juice
- ▶ Manuka Honey
- ▶ Vitamin D
- ▶ Probiotics/prebiotic



## Anti-*Helicobacter pylori* flavonoids from licorice extract

Toshio Fukai<sup>a,\*</sup>, Ai Marumo<sup>a</sup>, Kiyoshi Kaitou<sup>b</sup>, Toshihisa Kanda<sup>b</sup>,  
Sumio Terada<sup>b</sup>, Taro Nomura<sup>a</sup>

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Received 4 February 2002; accepted 27 March 2002

### Abstract

Licorice is the most used crude drug in Kampo medicines (traditional Chinese medicines modified in Japan). The extract of the medicinal plant is also used as the basis of anti-ulcer medicines for treatment of peptic ulcer. Among the chemical constituents of the plant, glabridin and glabrene (components of *Glycyrrhiza glabra*), licochalcone A (*G. inflata*), licoricidin and licoisoflavone B (*G. uralensis*) exhibited inhibitory activity against the growth of *Helicobacter pylori* *in vitro*. These flavonoids also showed anti-*H. pylori* activity against a clarithromycin (CLAR) and amoxicillin (AMOX)-resistant strain. We also investigated the methanol extract of *G. uralensis*. From the extract, three new isoflavonoids (3-arylcoumarin, pterocarpan, and isoflavan) with a pyran ring, gancaonols A–C, were isolated together with 15 known flavonoids. Among these compounds, vestitol, licoricone, 1-methoxyphaseollidin and gancaonol C exhibited anti-*H. pylori* activity against the CLAR and AMOX-resistant strain as well as four CLAR (AMOX)-sensitive strains. Glycyrin, formononetin, isolicoflavonol, glyasperin D, 6,8-diprenylorobol, gancaonin I, dihydrolicoisoflavone A, and gancaonol B possessed weaker anti-*H. pylori* activity. These compounds may be useful chemopreventive agents for peptic ulcer or gastric cancer in *H. pylori*-infected individuals. © 2002 Elsevier Science Inc. All rights reserved.

**Keywords:** Anti-*Helicobacter pylori*; Flavonoids; Licorice; *Glycyrrhiza*; Gancaonol



Research Article

# Effect of GutGard in the Management of *Helicobacter pylori*: A Randomized Double Blind Placebo Controlled Study

Sreenivasulu Puram,<sup>1</sup> Hyung Chae Suh,<sup>2</sup> Seung Un Kim,<sup>3</sup> Bharathi Bethapudi,<sup>4</sup>  
Joshua Allan Joseph,<sup>4</sup> Amit Agarwal,<sup>4</sup> and Venkateswarlu Kudiganti<sup>5</sup>

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A randomized, double blind placebo controlled study was conducted to evaluate the efficacy of GutGard (root extract of *Glycyrrhiza glabra*) in the management of *Helicobacter pylori* (*H. pylori*) gastric load. Participants diagnosed with *H. pylori* infection were randomly assigned to two groups to orally receive 150 mg of GutGard ( $n = 55$ ) or placebo ( $n = 52$ ) once daily for 60 days. *H. pylori* infection was assessed using <sup>13</sup>C-urea breath test (<sup>13</sup>C-UBT) at days 0, 30, and 60. Stool Antigen test (HpSA) was also performed on days 0, 30, and 60. Repeated measures of analysis of variance (RMANOVA), chi-square, and Fisher's exact probability tests were used to compare the treatment outcomes. A significant interaction effect between group and time ( $P = 0.00$ ) and significant difference in mean Delta Over Baseline (DOB) values between GutGard ( $n = 50$ ) and placebo ( $n = 50$ ) treated groups after intervention period were observed. On day 60, the results of HpSA test were negative in 28 subjects (56%) in GutGard treated group whereas in placebo treated group only 2 subjects (4%) showed negative response; the difference between the groups was statistically significant. On day 60, the results of <sup>13</sup>C-UBT were negative in 24 (48%) in GutGard treated group and the difference between the groups was statistically significant. The findings suggest GutGard is effective in the management of *H. pylori*.







## Anti-*Helicobacter pylori* flavonoids from licorice extract

Toshio Fukai<sup>a,\*</sup>, Ai Marumo<sup>a</sup>, Kiyoshi Kaitou<sup>b</sup>, Toshihisa Kanda<sup>b</sup>,  
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**Keywords:** Anti-*Helicobacter pylori*; Flavonoids; Licorice; *Glycyrrhiza*; Gancaonol



# Licorice Root

## Glycyrrhiza Glabra

### Mechanism of Action

- ▶ Licorice contains an ingredient known as glycyrrhizic acid which contributes to its medicinal benefits and has been the main ingredient of licorice root that has been studied among more than 20 triterpenoids and nearly 300 flavonoids
- ▶ Inhibits type 2 isoenzyme of 11 beta-hydroxysteroid dehydrogenase (11 beta-HSD2) which prevents the inactivation of cortisol
- ▶ Anti-inflammatory
  - May be due to inhibition of prostaglandin  $E_2$
- ▶ Anti-microbial
  - Decreases the expression of key virulence genes
  - Reduces the production of  $\alpha$ -toxin and  $\alpha$ -hemolysin
- ▶ Antiviral
  - Not fully understood
  - May be due to inhibition of viral binding to host cell membranes
  - May inhibit viral replication
  - May interfere with cellular signal transduction



A photograph of several pieces of licorice root sticks, cut into various lengths and thicknesses, resting in a dark wooden bowl. The roots are light brown with a fibrous texture. The bowl is placed on a light-colored, textured surface, possibly burlap. The background is a soft, out-of-focus green.

# Licorice Root

## Glycyrrhiza Glabra

### ► Clinical Uses

- Stomach Ulcers
- Bronchitis
- Sore Throat
- Viral Hepatitis
- Eczema

### ► Spectrum of Activity

- Gram Positive
  - Staphylococcus aureus, Bacillus subtilis, Candida albicans (yeast)
- Gram Negative
  - Escherichia coli, Pseudomonas aeruginosa

# Goldenseal

*Hydrastis canadensis* (goldenseal) is one of a number of plants that contain the alkaloid berberine. Berberine extracts and decoctions have demonstrated significant antimicrobial activity against a variety of organisms.

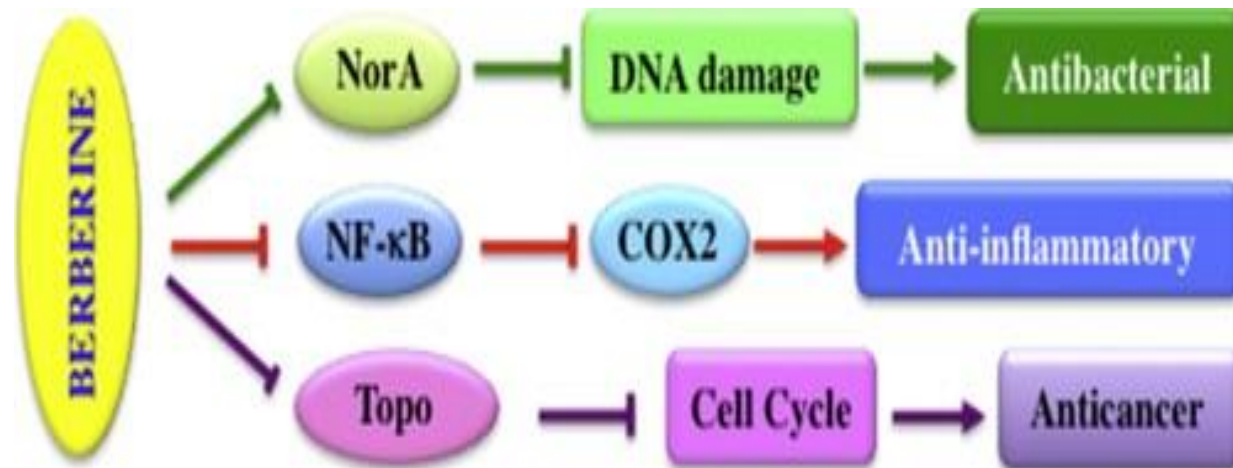
- ▶ used clinically to treat bacterial diarrhea, intestinal parasite infections, and ocular trachoma infection



## Berberine: New perspectives for old remedies

Micol Tillhon, Luis M. Guamán Ortiz, Paolo Lombardi, A. Ivana Scovassi, *Biochemical Pharmacology*, Volume 84, Issue 10, 15 November 2012, Pages 1260-1267

- ▶ Berberine exerts antimicrobial effects being a NorA substrate able of accumulating in bacterial cells and of binding both single- and double-stranded DNA, thus leading to bacterial death by DNA damage. It has a weak activity against Gram-negative bacteria, and is more potent against Gram-positive bacteria, including *Mycobacterium tuberculosis* and MRSA (Methicillin-Resistant *Staphylococcus aureus*), by the MDR pump NorA inhibition. It also exhibits antifungal activity on *Aspergillus*, *Penicillium*, *Candida*, and *Cryptococcus*.



# Oregano Oil

- ▶ Carvacrol and thymol which have anthelmintic, fungicidal, and irritant properties.
- ▶ Oregano oil also has in vitro activity against a variety of common gram positive and gram negative organisms
  - including: *Acinetobacter calcoacetica*, *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella* species, *Serratia marcescens*, *Staphylococcus aureus*, and the yeast *Candida albicans*.
- ▶ The carvacrol and thymol constituents also inhibit bacterial growth, with additive or possibly synergistic activity in oregano oil.
  - Carvacrol has a bacteriocidal effect on *Bacillus cereus*, a common food pathogen, by altering bacterial membrane permeability
- ▶ Oregano oil and carvacrol in vitro has anti-influenza virus activity
- ▶ Oregano oil seems to inhibit the growth intestinal parasites in vivo
- ▶ No resistance shown

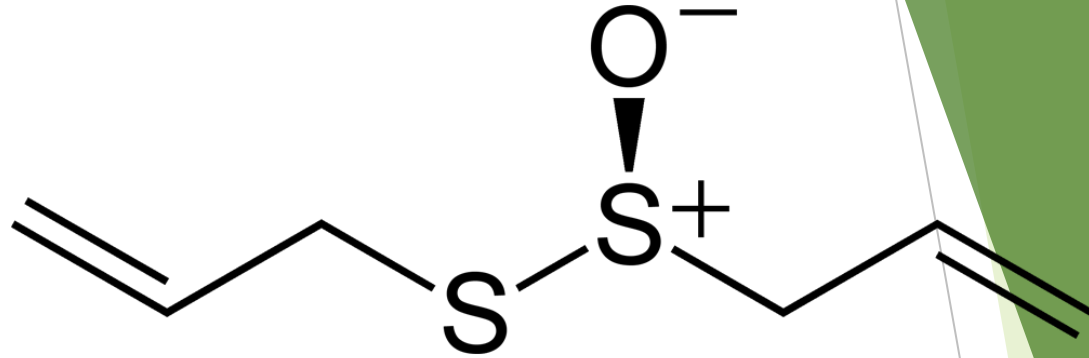


# Garlic

- ▶ **“Immuonutrition” is enhanced by garlic as it is immunostimulant and immunosuppressant.**
  - Enhances total white blood cell (WBC) count
  - Enhances NK cell and lymphokine-activated killer cell
  - Increases the production and release of nitric oxide (NO) and enhanced release of IFN-alpha
    - Inhibits viruses and proliferative diseases
  - Increases lymphocytes and macrophage phagocytosis infiltration of macrophages and lymphocytes;
- ▶ **Stimulates release of IL-2, TNF-alpha, and IFN-γ**  
**Immunomodulatory**
  - IL-2 prevents autoimmune diseases by promoting the differentiation of certain immature T cells into regulatory



# Allicin



- ▶ Most abundant and characteristic sulfur-compound in garlic
- ▶ Shown to exhibit broad-spectrum antimicrobial activity against Gram-positive and -negative bacteria, including multidrug-resistant bacteria
- ▶ Also shown to possess antiviral, anti-fungal and anti-parasitic activity
- ▶ Mechanism of antimicrobial action is initial reduction of glutathione levels followed by induction of protein aggregation and inactivation of crucial enzymes.





## Inhibition of *Helicobacter pylori* by garlic extract (*Allium sativum*)

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Received 16 August 1995; revised 20 November 1995; accepted 21 November 1995

### Abstract

The antibacterial effect of aqueous garlic extract (AGE) was investigated against *Helicobacter pylori*. Sixteen clinical isolates and three reference strains of *H. pylori* were studied. Two different varieties of garlic were used. The concentration of AGE required to inhibit the bacterial growth was between 2–5 mg ml<sup>-1</sup>. The concentration, for both AGE types, to inhibit 90% (MIC<sub>90</sub>) of isolates was 5 mg ml<sup>-1</sup>. The minimum bactericidal concentration (MBC) was usually equal to, or two-fold higher than, minimum inhibitory concentration (MIC). Heat treatment of extracts reduced the inhibitory or bactericidal activity against *H. pylori*; the boiled garlic extract showed a loss of efficacy from two- to four-fold the values of MIC and the MBC obtained with fresh AGE. The antibacterial activity of garlic was also studied after combination with a proton pump-inhibitor (omeprazole) in a ratio of 250:1. A synergistic effect was found in 47% of strains studied; an antagonistic effect was not observed.

**Keywords:** *Helicobacter pylori*; Aqueous garlic extract; Minimum inhibitory concentration; Minimum bactericidal concentration; Omeprazole

### 1. Introduction

The long history of the medicinal use of garlic is well-documented: the properties of garlic against atherosclerosis, coronary thrombosis [1–3], inhibition of platelet aggregation [4] and much information on its antibacterial [5–9], antifungal [10–12] and antiprotozoal [13,14] properties are widely known.

In 1944, Cavallito and Bailey identified diallyl

[9] specified that allicin is an inhibitor of sulphhydryl metabolic enzymes and reported that the antimicrobial properties are due to specific interference with SH-groups.

*Helicobacter pylori* is a fastidious Gram-negative, curved rod which is associated with active chronic gastritis and gastroduodenal ulcer disease and in the development of gastric cancer [17–20]. Although *H. pylori* is sensitive to a large number of antimicrobial



**Carvacrol-rich oregano oil and thymol-rich thyme red oil inhibit  
biofilm formation and the virulence of uropathogenic *Escherichia*  
*coli***

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# Garlic

- ▶ It has antibiotic properties and it acts to restore normal gut flora by acting as a prebiotic
- ▶ Use enteric coated for bowel issues
- ▶ Use regular for h. pylori issues



# 18 y.o. with History of RA

## ▶ History:

- Dx: RA at age 2, Bleeding ulcers age 10; tumor size grapefruit left knee age 15. Age 17 wrists fused

## ▶ Chief Complaints

- Arthritis Pain, esp. Neck/shoulders
- Swollen knees and ankles
- Hormone Problems
- Acne
- Stomach Problems



# Severe and Moderately Severe Symptoms

- ▶ Cold Extremities
- ▶ Chilled often
- ▶ Joint stiffness in a.m.
- ▶ Always hungry
- ▶ Hand and feet get numb easily
- ▶ Poor circulation
- ▶ Stomach Bloating
- ▶ Bowel disorders
- ▶ Depression
- ▶ Allergies
- ▶ Easily fatigued
- ▶ Menstrual problems
- ▶ Acne
- ▶ Vaginal discharge
- ▶ Crying easily
- ▶ Headaches
- ▶ Dizzy and weak



# Recommendations

- ▶ **Diet: GAPS or vegetarian**
- ▶ **Alternate: Gut Complex (oregano oil); golden seal; enteric coated garlic**
- ▶ **Pre and Pro biotics**
- ▶ **Natural Anti inflammatory herbal**
  - Fish oils
  - Turmeric
  - Ginger
  - Boswellia
- ▶ **Hormone saliva test**
  - Adrenal
  - Female



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