BENEFITS & EFFICACY OF VIUSID IN SARS-CoV-2 / COVID-19

WWW.CATALYSIS.ES

VIUSID

Glycyrrhizic acid

ANTIOXIDANT

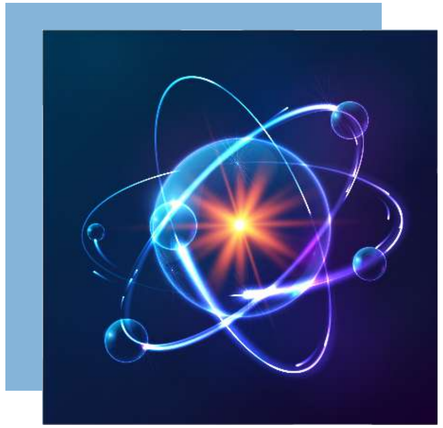
ANTIVIRAL

IMMUNOMODULATOR

HEPATOPROTECTOR

WWW.CATALYSIS.ES

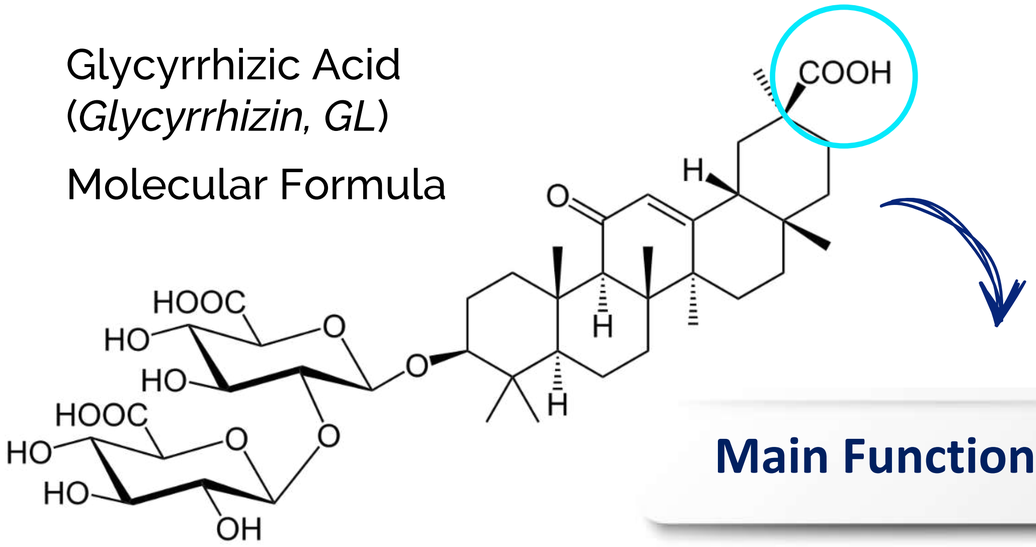
Active components



Potentiated by Molecular Activation Technology

Glycyrrhizic Acid
(*Glycyrrhizin, GL*)

Molecular Formula



Main Functional A

ANTIVIRAL

Glycyrrhizic Acid
Glucosamine
Malic Acid

ANTIOXIDANTS

Ascorbic Acid
Malic Acid
Zinc
L-Arginine

ANTIANEMIC AGENTS

Folic Acid
Cyanocobalamine
Pyridoxine

IMMUNO-MODULADOR

L-Arginine
Glucosamine
Glycyrrhizic Acid
Zinc

BIOCATALYTICS

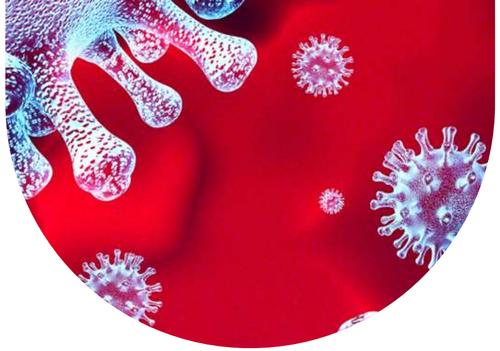
Zinc
Calcium
Pentatotenic

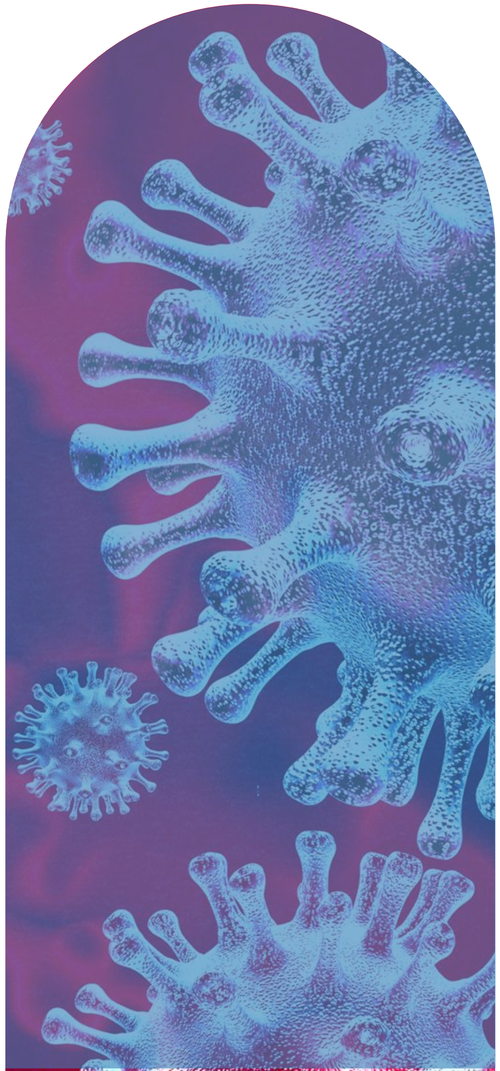
SARS-CoV-2
Characteristics

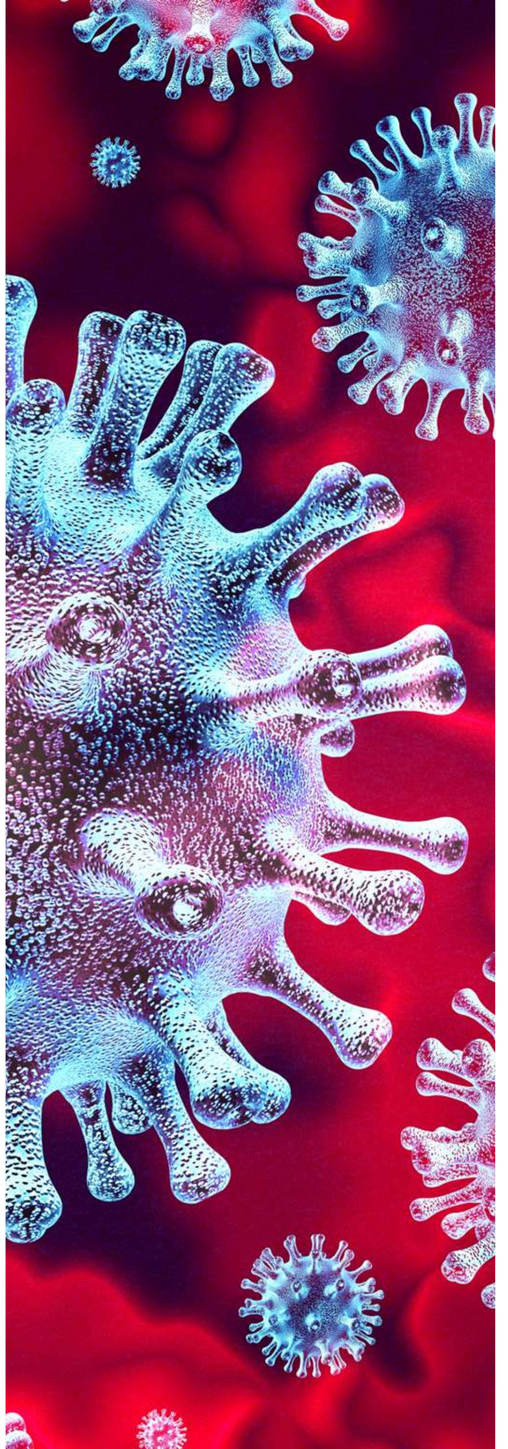
The current epidemic of the disease caused by the Coronavirus 2019 (COVID-19) began in December 2019 in China, leading to a global sanitary State of Emergency.

Coronaviruses (CoV) constitute a broad group of viruses that are taxonomically within the Coronavirinae subfamily within the Coronaviridae family (order Nidovirales); All species belonging to the genera Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus are designated under the term coronavirus.

These are viruses whose genome is made up of a single chain of RNA with positive polarity (+ ssRNA, of English single-stranded positive-sense RNA) and approximately 30,000 base pairs, which have a methylated hood at the 5 'end and a polyadenylated tail (poly-A) at the 3 'end, giving it a strong resemblance to the host's messenger RNA.







SARS-CoV-2
Characteristics

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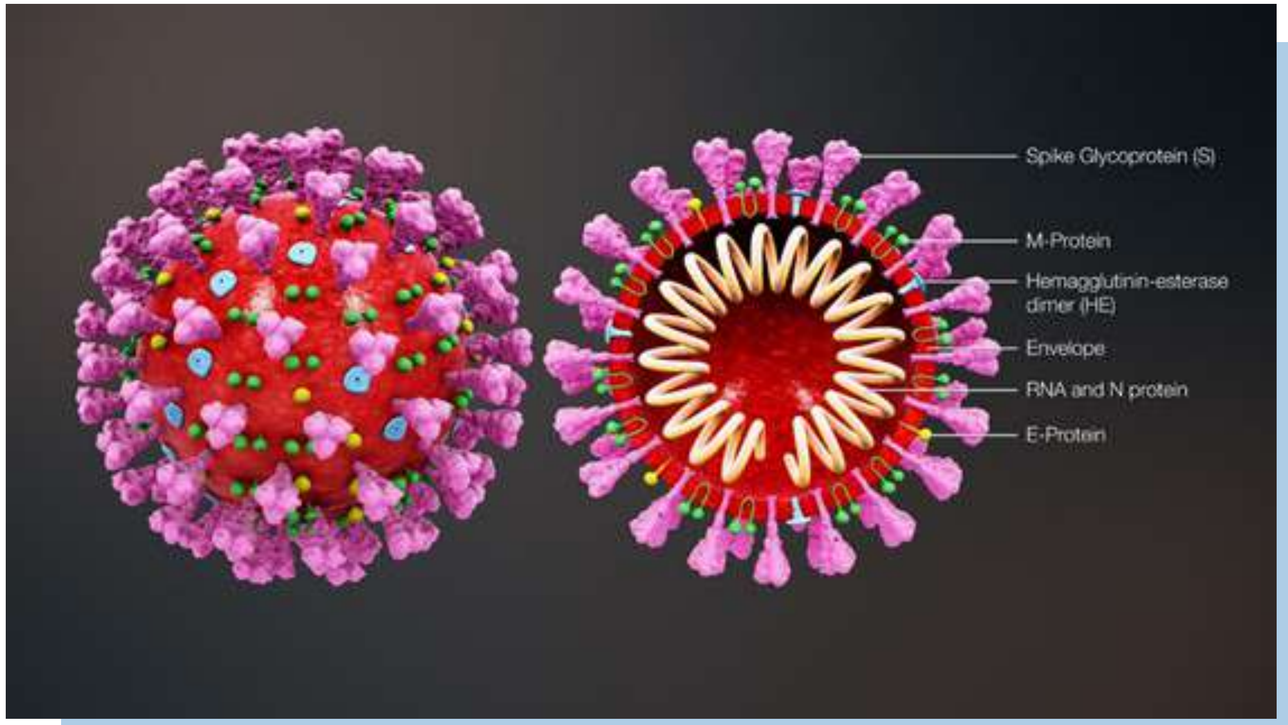


Broadly speaking, coronaviruses begin their replication with the entry of virions - the infectious form of the virus - **when they lose their envelope and deposit their viral RNA in the cytoplasm of the eukaryotic cell, where the resemblance to the host mRNA allows it to bind directly to ribosomes for translation**. There, it is used as a template to translate directly into polyprotein 1a / 1ab, in which all the proteins that will form the replication-transcription complex in double membrane vesicles are bound.

SARS-CoV-2
Pathogenesis

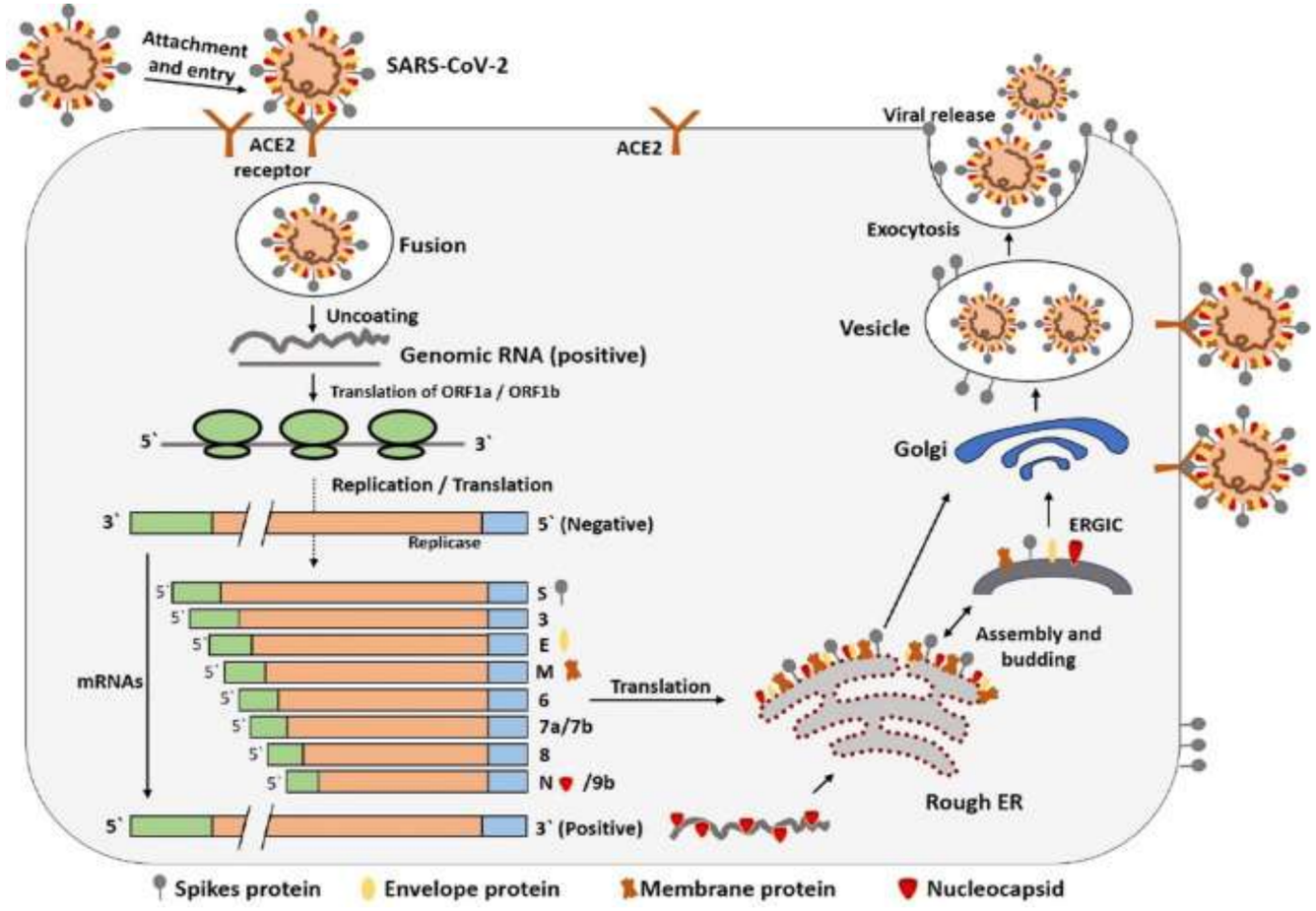
SYMPTOMS

FEVER | COUGH | SHORTNESS OF BREATH | SORE THROAT | HEADACHE

The clinical manifestations of a coronavirus infection largely depend on the type of virus and the person's state of health, but the most common clinical signs include those of a **common cold, highlighting fever, cough, and respiratory symptoms** (**dyspnea and other breathing disturbances**). **Gastrointestinal symptoms**, including diarrhea, have also been reported. In the most severe cases, the infection can cause **bronchitis or pneumonia** (either direct viral pneumonia or favor secondary bacterial pneumonia), **severe acute respiratory syndrome, kidney failure or failure, and even death**. As with many other viruses, there is currently no specific treatment for the disease caused by new coronaviruses.

However, many of the symptoms can be managed clinically, so treatment must be individualized based on the patient's condition and must ensure life support in case of complications. **Recombinant interferons or rivabirin have only limited effects on coronavirus infections**. The possibility of using antiretroviral drugs (such as lopinavir or ritonavir) or remdesivir - an antiviral drug initially developed for the treatment of Ebola virus infection - has recently been considered, but for now there are no conclusive results regarding its effectiveness.

SARS-CoV-2 Mechanism of entry



Shereen M, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. Journal of Advanced Research. 2020;24:91-98.

LIFE CYCLE

Fig. 3. The life cycle of SARS-CoV-2 in host cells

It begins its life cycle when S protein binds to the cellular receptor ACE2. After receptor binding, the conformation change in the S protein facilitates viral envelope fusion with the cell membrane through the endosomal pathway. Then SARS-CoV-2 releases RNA into the host cell. Genome RNA is translated into viral replicase polyproteins pp1a and 1ab, which are then cleaved into small products by viral proteinases. The polymerase produces a series of subgenomic mRNAs by discontinuous transcription and finally translated into relevant viral proteins. Viral proteins and genome RNA are subsequently assembled into virions in the ER and Golgi and then transported via vesicles and released out of the cell. ACE2, angiotensin-converting enzyme 2; ER, endoplasmic reticulum; ERGIC, ER–Golgi intermediate compartment.

SARS-CoV-2 Mechanism of entry

Figure 1

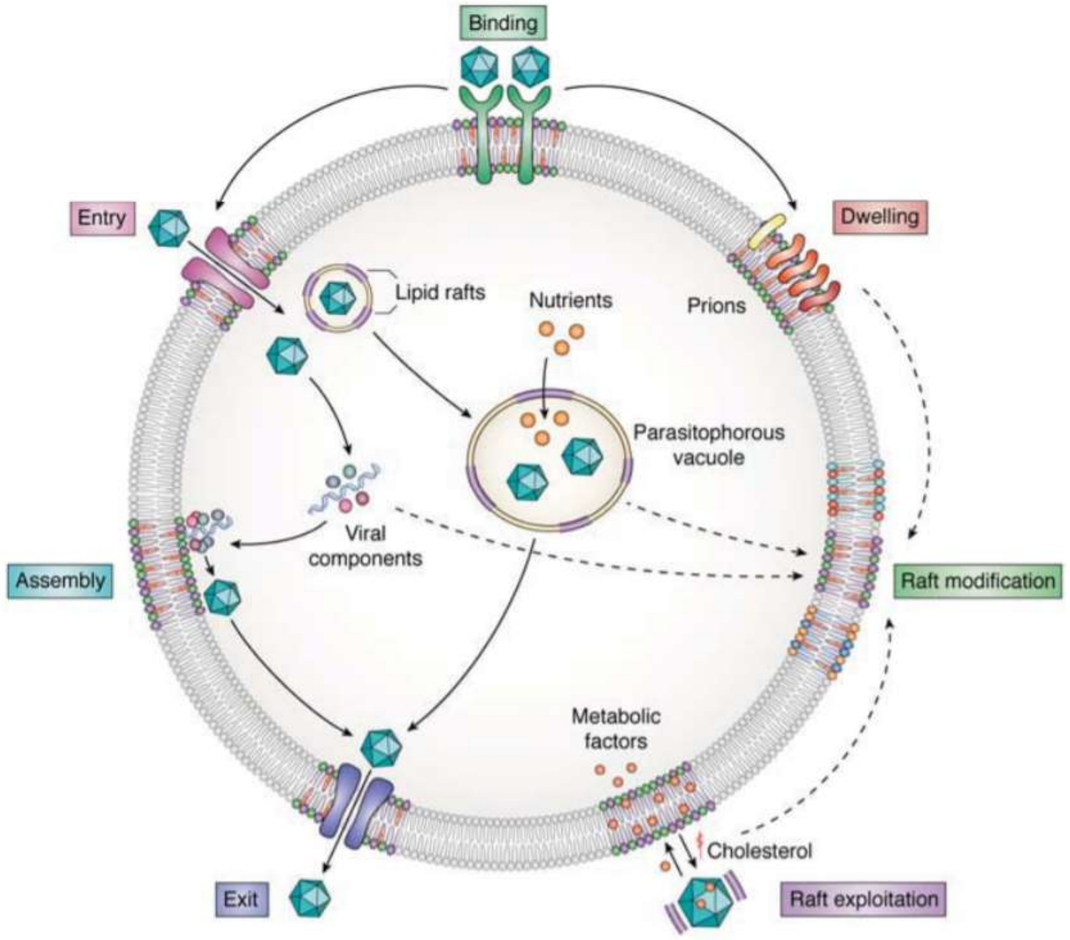
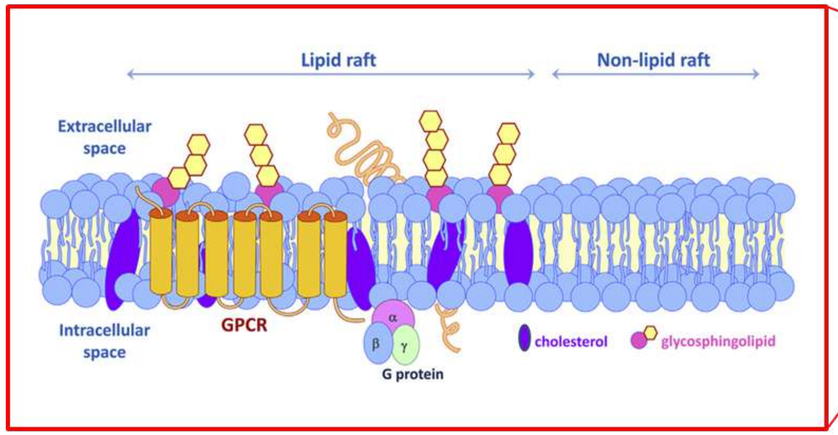


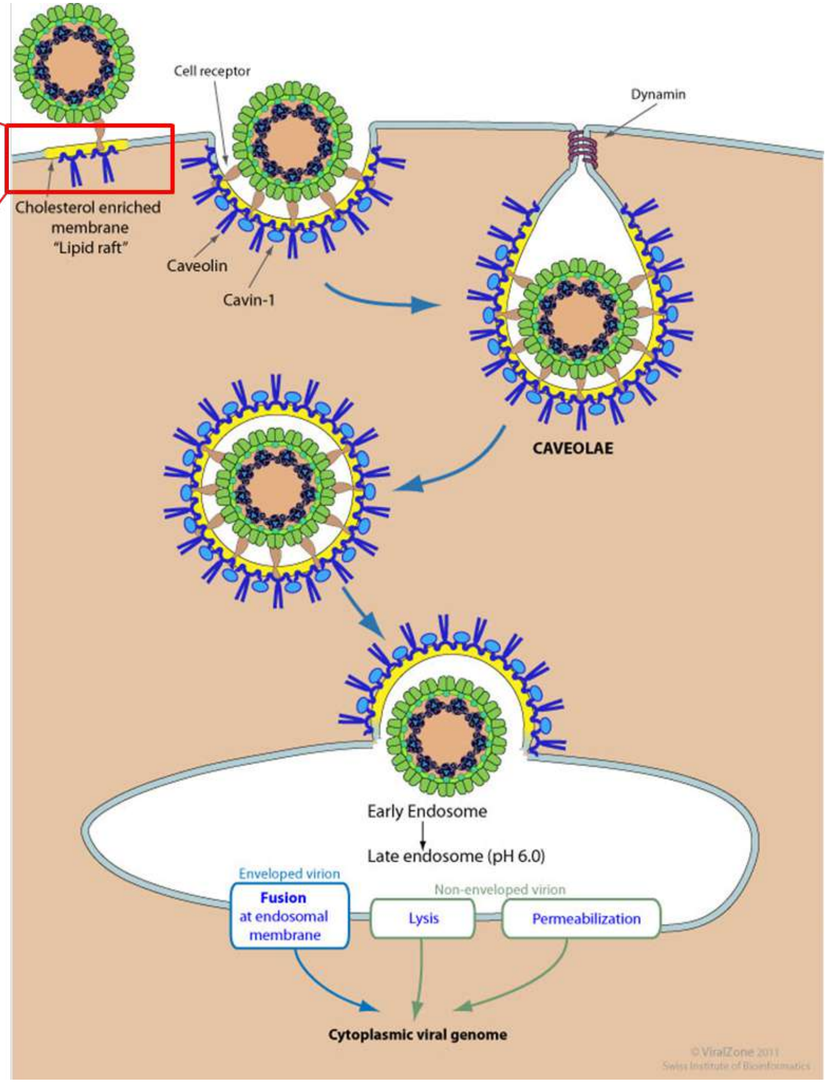
Figure 1. Overview of interaction of pathogens with host lipid rafts.

Various pathogens use high concentrtion of outward looking receptors in lipid rafts as a binding site, and raft associated endocitosis machinery as a pathway to get inside of the host cell. Some intracelular parasites take rafts with them during internalization and use them to communicate with the host cell and to prevent maturation or fusión of microbe-containing endocytic vesicle (e-g- parasitophorous vacoule) with lysosomes. Prions find high concentration of physiologically folded proteins in rafts converting them into pathological form.

Many pathogens modify lipid rafts, throught releasing raft-modifying factors. Viruses ofthen use lipid rafts as a platform to facilitate self-assembly, and various pathogens exploit involvement of lipid rafts in exocytosis to get out.

SARS-CoV-2 Mechanism of entry





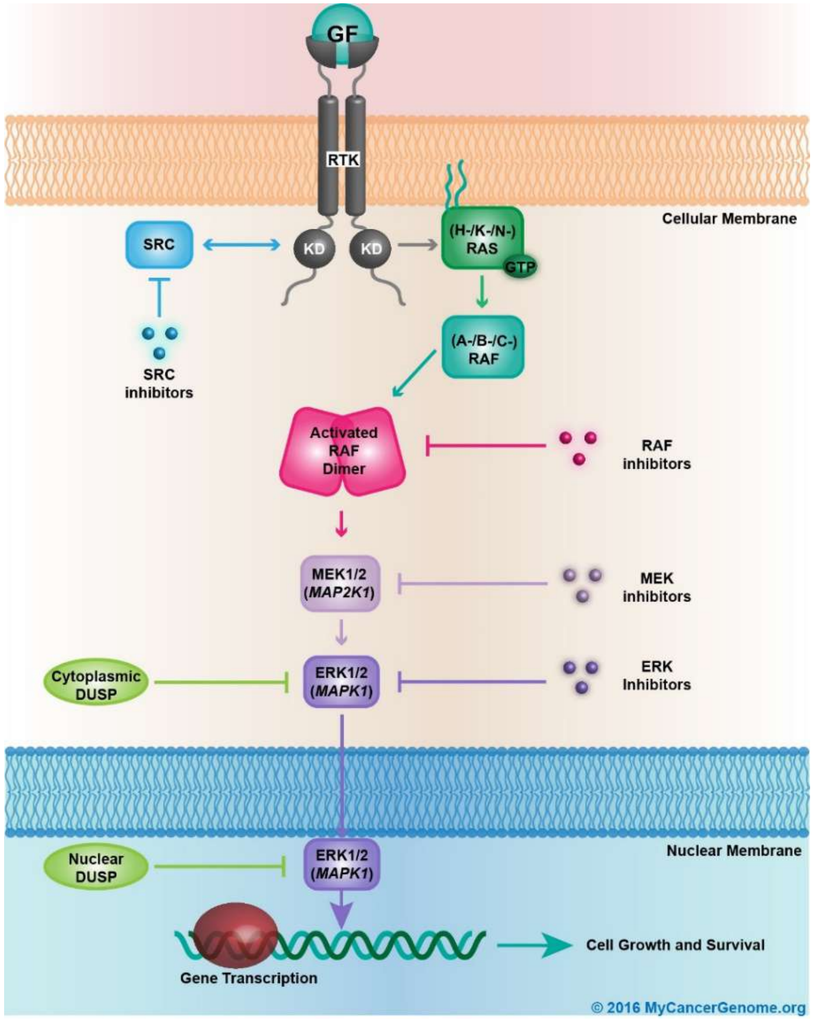
Virus internalization by the host cell via caveolae, which are specialized lipid rafts that form 50-70 nm flask-shaped invaginations of the plasma membrane. Internalized viruses bound to their host cell receptor are delivered to the early endosome. It has been first thought that bound viruses were first taken to pH-neutral organelles in the cytoplasm called caveosomes and finally delivered to the ER, but this has been refuted in. Caveolae represent a low capacity but highly regulated pathway.

SARS-CoV-2

Mechanism of replication

It is well-documented that lipid rafts act as signalling platforms and initiate a variety of signal transduction processes. Previous reports have documented **hyperphosphorylation of Src tyrosine kinase** in JEV infection and therefore we investigated how the SFKs are distributed in the different membrane fractions isolated from control and JEV infected C17.2 (30 min and 3 h p.i.). Full activation of c-Src requires phosphorylation at Tyr416, which then allows p-Src to associate with inner leaflet of the membrane (Brown and Cooper 1996; de Diesbach et al. 2008).

The **association of Src with lipid rafts has been shown to be correlated with their ability to signal to PI3K and lead to subsequent activation of protein kinase B (PKB)/Akt signaling** (de Diesbach et al. 2008). A number of viruses activate PI3K/Akt signaling in a bid **to slow down apoptosis** of the infected cell **and prolong viral replication** in both acute and persistent infections (Cooray 2004). Such activation of the PI3K/Akt pathway and inhibition of cell death pathway has been observed in Flaviviral infections like JEV (Lee et al. 2005).

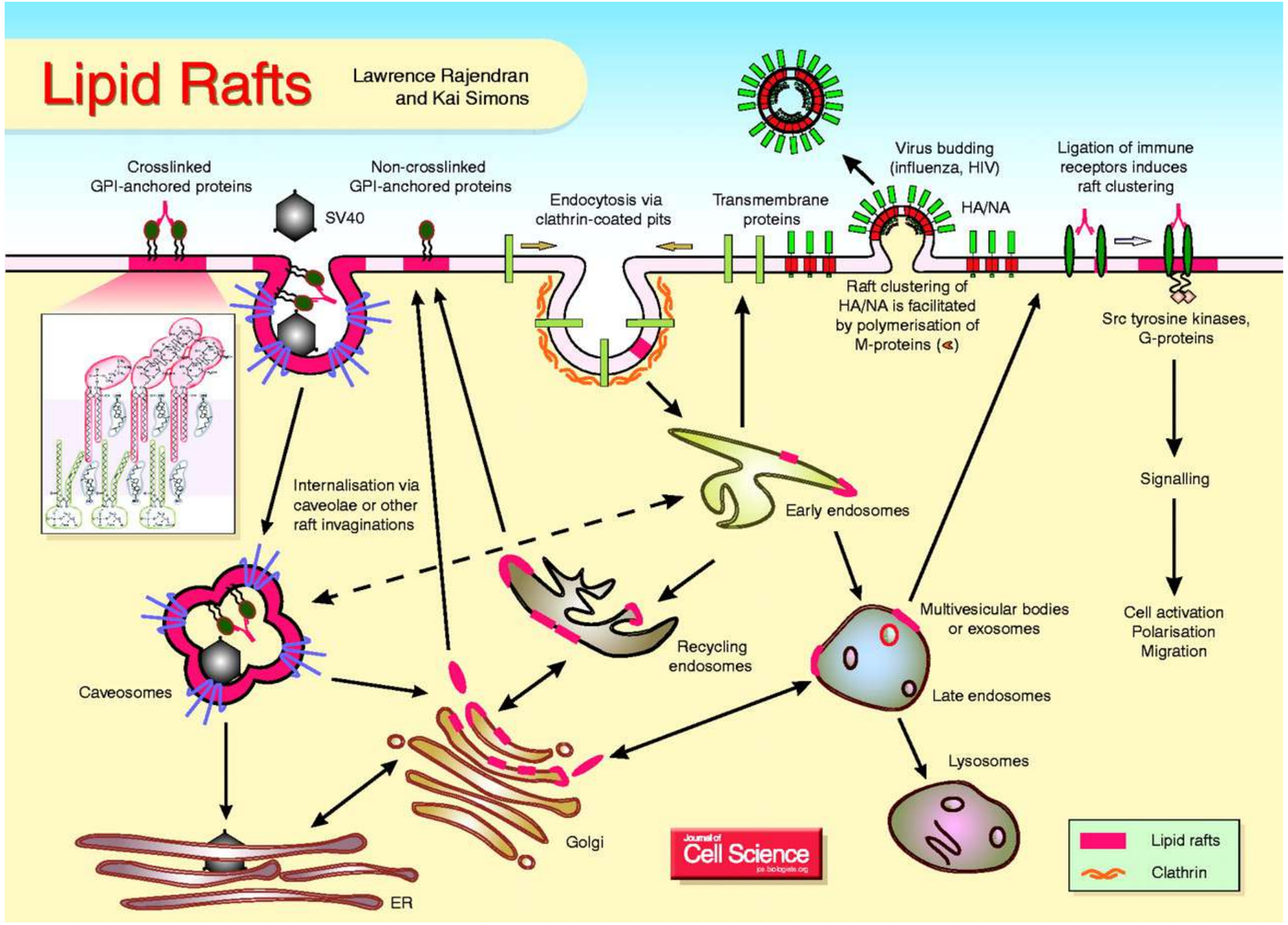


Das S, Chakraborty S, Basu A. Critical role of lipid rafts in virus entry and activation of phosphoinositide 3′ kinase/Akt signaling during early stages of Japanese encephalitis virus infection in neural stem/progenitor cells. Journal of Neurochemistry. 2010;115(2):537-549.

SARS-CoV-2

Mechanism of entry & replication

The **Src-family tyrosine kinases** (e.g. Lck, Fyn and Lyn), which are anchored to the inner leaflet via their dual acylation modification (Simons and Toomre, 2000); palmitoylated and myristoylated proteins such as flotillins (Rajendran et al., 2003); cholesterolbinding proteins such as caveolins (Kurzchalia and Parton, 1999) and hedgehog (Karpen et al., 2001); heterotrimeric G proteins; and phospholipid-binding proteins such as annexins (Babiychuk et al., 2002).



Rajendran L. Lipid rafts and membrane dynamics. Journal of Cell Science. 2005;118(6):1099-1102.

VIUSID

Glycyrrhizic acid

- **It stops viral replication as a result of inhibition of the activity of the Src Family of Kinases.**
- **Irreversible inhibitor of the Src protein kinase family.**

Ohtsuki and Iahida:
Inhibitory effect of Glycyrrhizin on Polypeptide Phosporylation by Polypeptide-dependent Protein Kinase (Kinase P) in vitro. *Biochem Biophys Res Commun. 1988 Dec 15;157(2):597-604.*

DOES NOT GENERATE RESISTANCE AFTER USE, EVEN IF TREATMENT IS STOPPED

Rajendran L. Lipid rafts and membrane dynamics. Journal of Cell Science. 2005;118(6):1099-1102.

Glycyrrhizic acid

Pompei R et al: **Glycyrrhizinic acid inhibits virus growth and inactivates virus particles**. *Nature 281: 689–690, 1979.*

Hirabayashi K et al: **Antiviral activities of Glycyrrhizin and its modified compounds against Human Immunodeficiency Virus Type (HIV-1) and Herpes simplex Virus Type 1 (HSV-1), in vitro**. *Research laboratory, Minophagen Pharmaceutical, Japan, 1990.*

Badam L et al: **In vitro studies of the effect of Glycyrrhizin from Indian Glycyrrhiza glabra Linn. on some RNA and DNA viruses.** *Indian-J- Pharmacology, 1994.*

Ohtsuki and Iahida: **Inhibitory effect of Glycyrrhizin on Polypeptide Phosporylation by Polypeptide-dependent Protein Kinase (Kinase P) in vitro.** *Biochem Biophys Res Commun. 1988 Dec 15;157(2):597-604.*

Sasaki H et al: **Effect of glycyrrhizin, an active component of licorice roots, on HIV replication in cultures of peripheral blood mononuclear cells from HIV-seropositive patients.** *Pathobiology. 2002-2003;70(4):229-36.*

Cristina Fiore et al: **Antiviral Effects of *Glycyrrhiza species.*** *Phytother. Res. 22, 141–148 (2008). Review Article.*

VIUSID

Glycyrrhizic acid

- Glycyrrhizin did not inhibit NF-κB and IRF3 activation induced by MyD88 or TIRF.
- Glycyrrhizin did not affect the function of CD14 or expression of TLR4.
- Glycyrrhizin could disrupt the formation of lipid rafts by depleting cholesterol.
- Glycyrrhizin inhibited the translocation of TLR4 to lipid rafts.

VIUSID

Glycyrrhizic acid

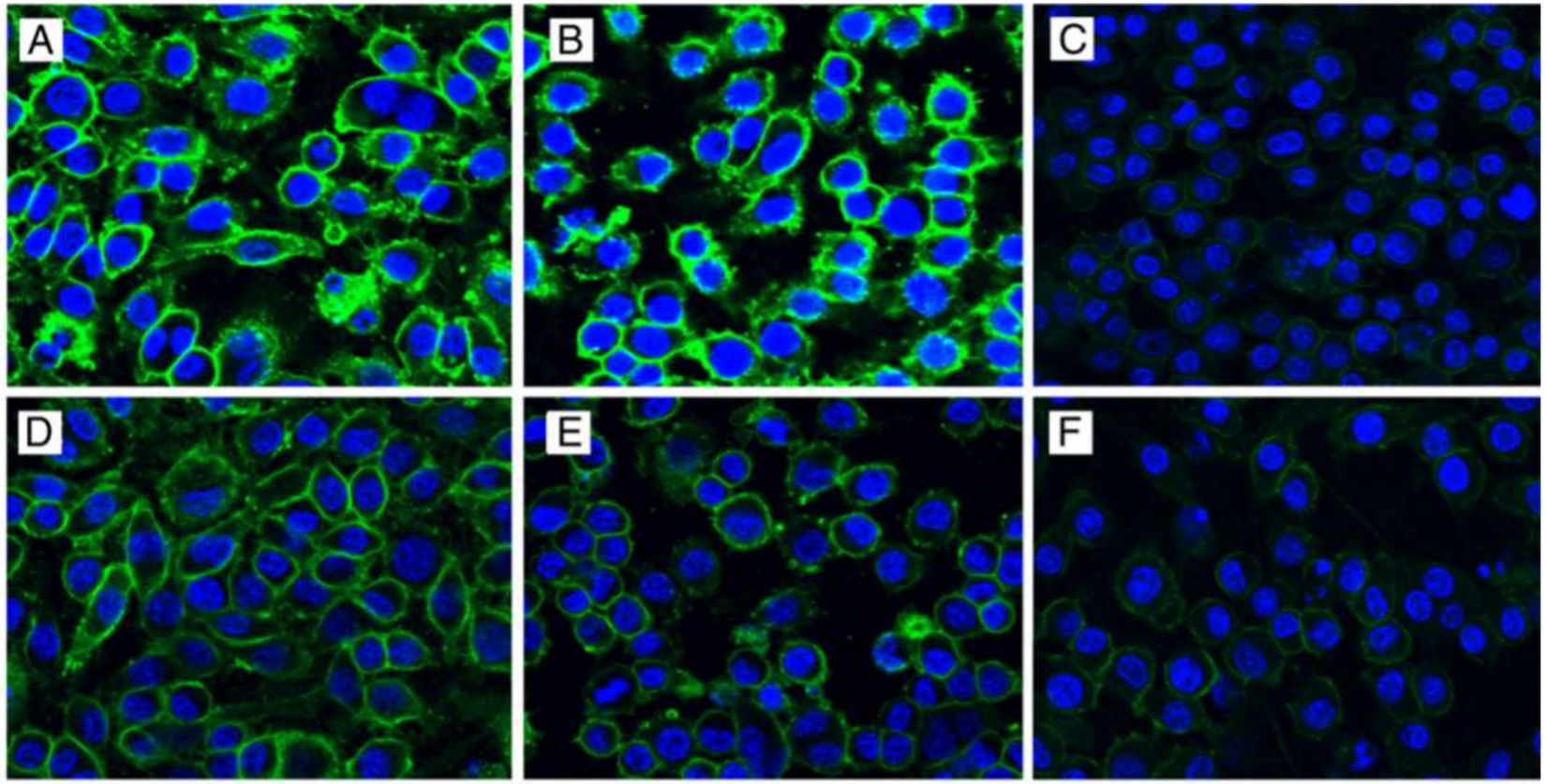
In vivo, the results showed that glycyrrhizin can improve survival during lethal endotoxemia. In vitro, glycyrrhizin dose-dependently inhibited the expression of TNF-α, IL-6, IL-1β and RANTES in LPS-stimulated RAW264.7 cells. Western blot analysis showed that glycyrrhizin suppressed LPS-induced NF-κB and IRF3 activation. However, glycyrrhizin did not inhibit NF-κB and IRF3 activation induced by MyD88-dependent (MyD88, IKKβ) or TRIF-dependent (TRIF, TBK1) downstream signaling components. Moreover, glycyrrhizin did not affect the expression of TLR4 and CD14 induced by LPS. **Significantly, we found that glycyrrhizin decreased the levels of cholesterol of lipid rafts and inhibited translocation of TLR4 to lipid rafts. Moreover, glycyrrhizin activated ABCA1, which could induce cholesterol efflux from lipid rafts.**

Fu Y, Zhou E, Wei Z, Song X, Liu Z, Wang T et al. Glycyrrhizin inhibits lipopolysaccharide-induced inflammatory response by reducing TLR4 recruitment into lipid rafts in RAW264.7 cells. Biochimica et Biophysica Acta (BBA) - General Subjects. 2014;1840(6):1755-1764.

VIUSID
Glycyrrhizic acid

The inhibition of membrane cholesterol levels by glycyrrhizin.

The cells were preincubated with glycyrrhizin (50, 100, 200 μg/ml) for 1 h, followed by treatment with 1 μg/ml LPS for 1 h. The lipid rafts (green) were stained with Alexa Flour 488-conjugated CTxB and the nucleus was stained with Hoechst. (A) control group, (B) LPS group, (C) LPS + MβCD group, (D) LPS + glycyrrhizin 50 μg/ml, (E) LPS + glycyrrhizin 100 μg/ml, (F) LPS + glycyrrhizin 200 μg/ml.



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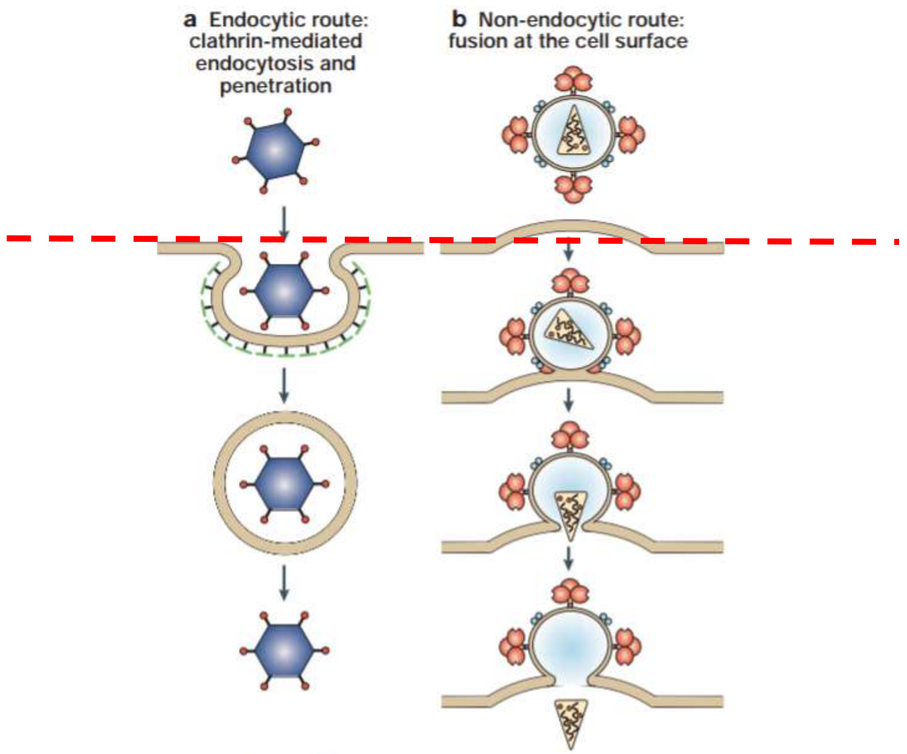
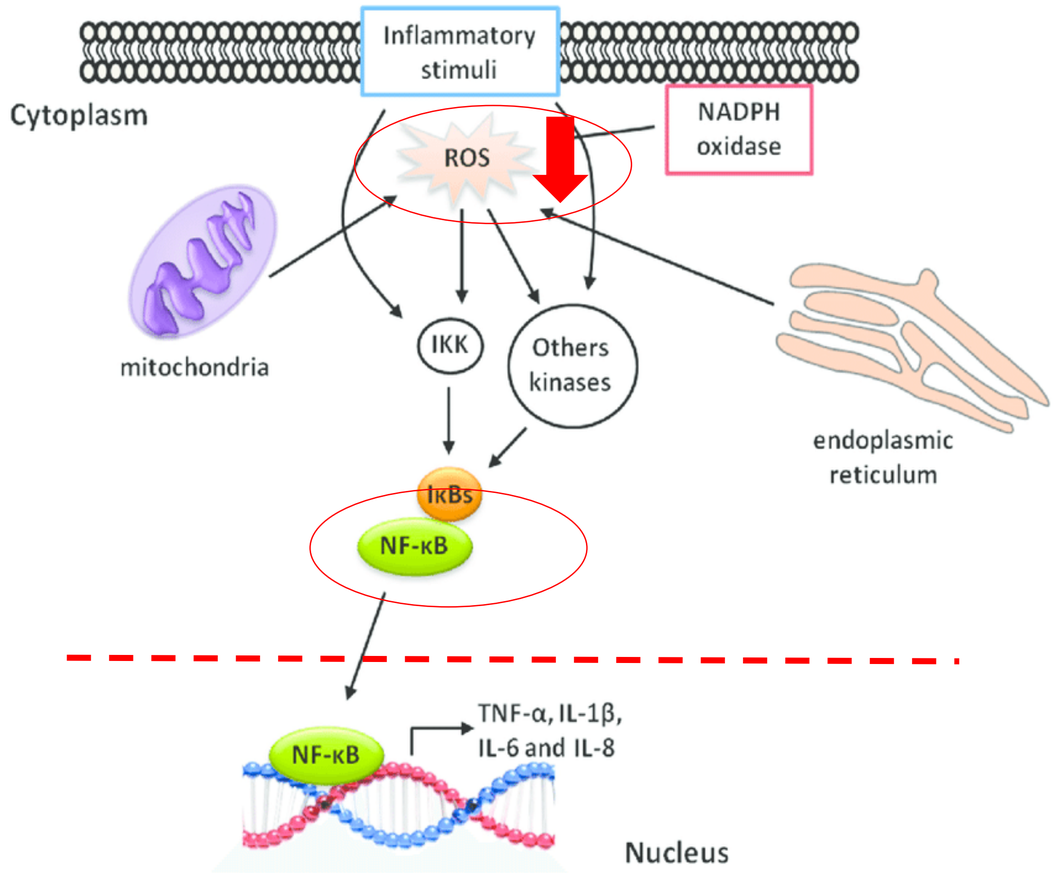


Figure 1 | **Two main virus entry pathways. a** | Clathrin-mediated endocytosis, for example, adenovirus. Endocytosis by caveolae can also occur, for example, SV40. **b** | Fusion at the cell membrane, for example, HIV. Fusion can also occur from inside an endosome, for example, influenza.



SARS-CoV-2
Pathogenesis

Initial plasma **IL1B, IL1RA, IL7, IL8, IL9, IL10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNFα, and VEGF** concentrations were **higher** in both ICU patients and non-ICU patients than in healthy adults (appendix pp 6–7). Plasma levels of IL5, IL12p70, IL15, Eotaxin, and RANTES were similar between healthy adults and patients infected with 2019-nCoV. Further comparison between ICU and non-ICU patients showed that plasma concentrations of **IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα** were **higher in ICU** patients than non-ICU patients.

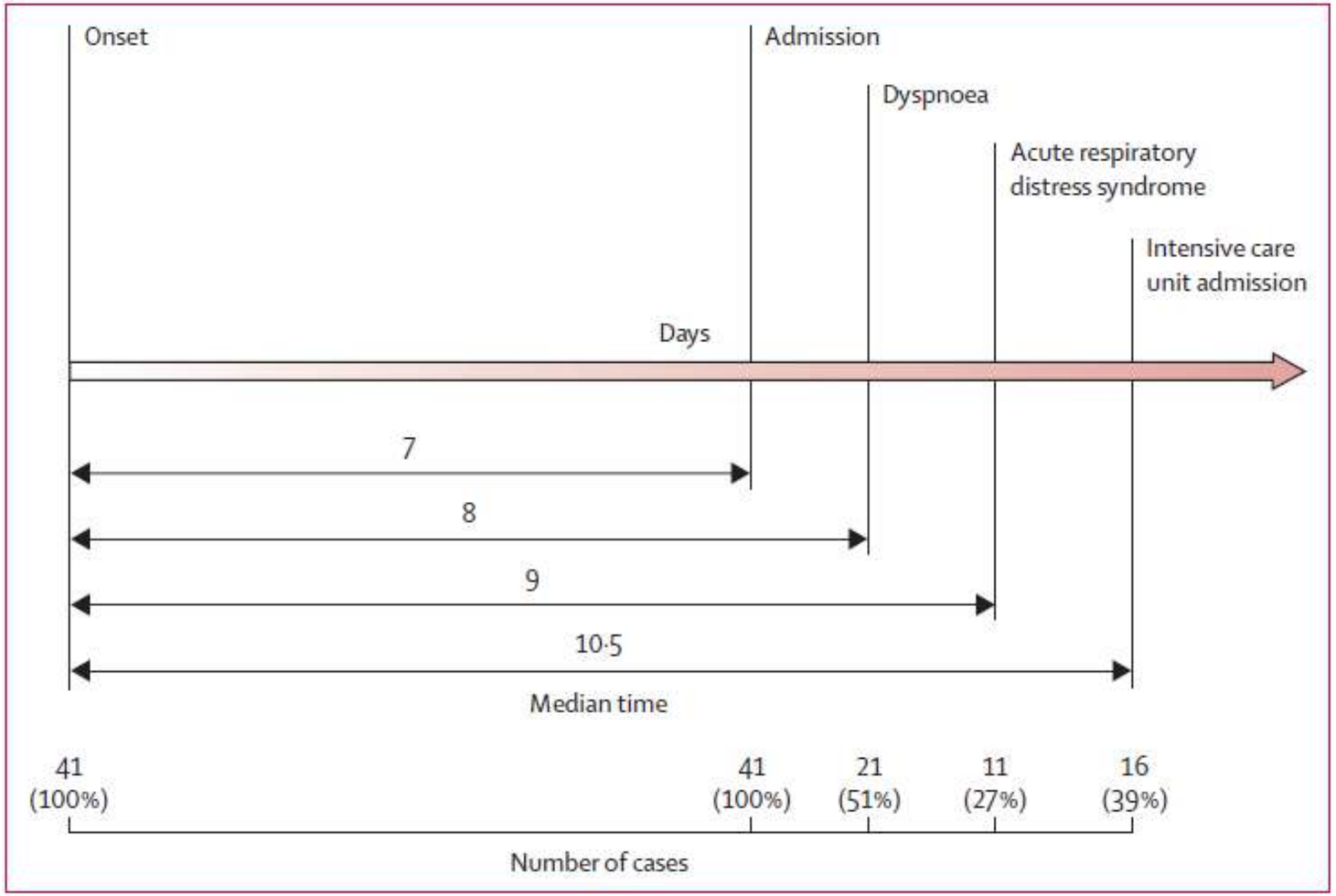
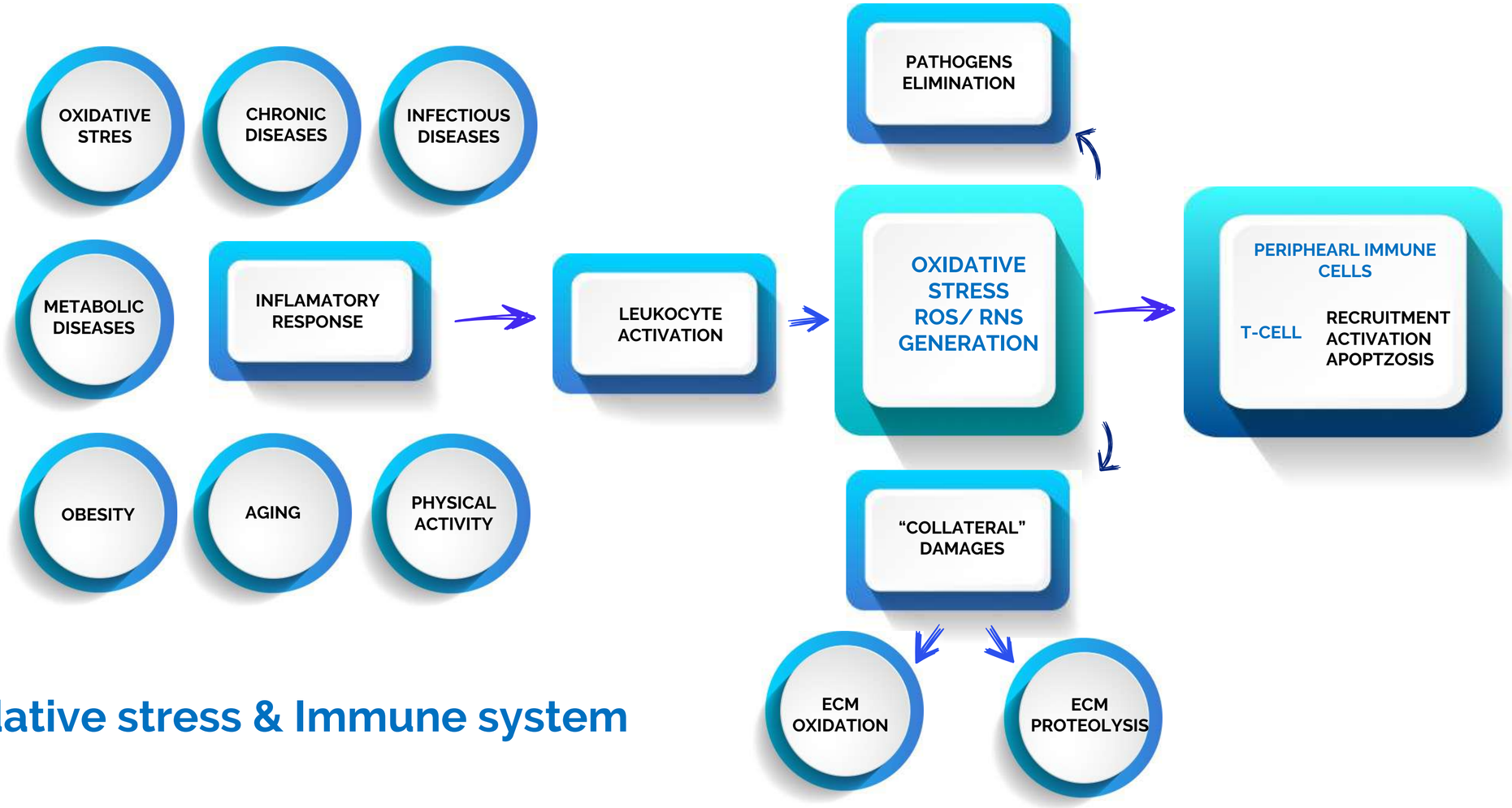


Figure 2: **Timeline of 2019-nCoV cases after onset of illness**

Fu Y, Zhou E, Wei Z, Song X, Liu Z, Wang T et al. Glycyrrhizin inhibits lipopolysaccharide-induced inflammatory response by reducing TLR4 recruitment into lipid rafts in RAW264.7 cells. Biochimica et Biophysica Acta (BBA) - General Subjects. 2014;1840(6):1755-1764.

Schematic representation of the relationship among inflammation, oxidative stress, and leukocytes. ROS = reactive oxygen species; ECM = extracellular matrix; RNS: reactive nitrogen species.



Oxidative stress & Immune system

Inhibition of prostaglandin E_2 in damaged tissue.

Kawakami F et al.:

"Characterization of complement C3 as a glycyrrhizin (GL)-binding protein and the phosphorylation of C3alpha by CK-2, which is potently inhibited by GL and glycyrrhetinic acid in vitro"

J Biochem (Tokio) 133(2):231-7, 2003.

Induces the production of interferons
› ↑ macropaghes and immune cells

cells activation › ↑ phagocytic and bactericide properties

Interferons effect › antiviral, anti-proliferative.

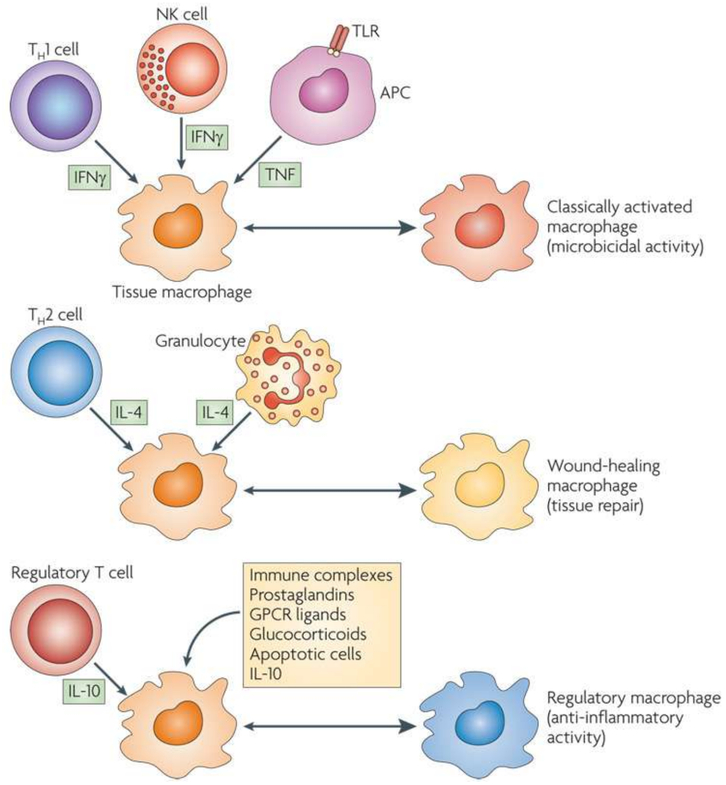
Abe N, Ebina T, Ishida N.:

"Interferon induction by glycyrrhizin and glycyrrhetinic acid in mice."

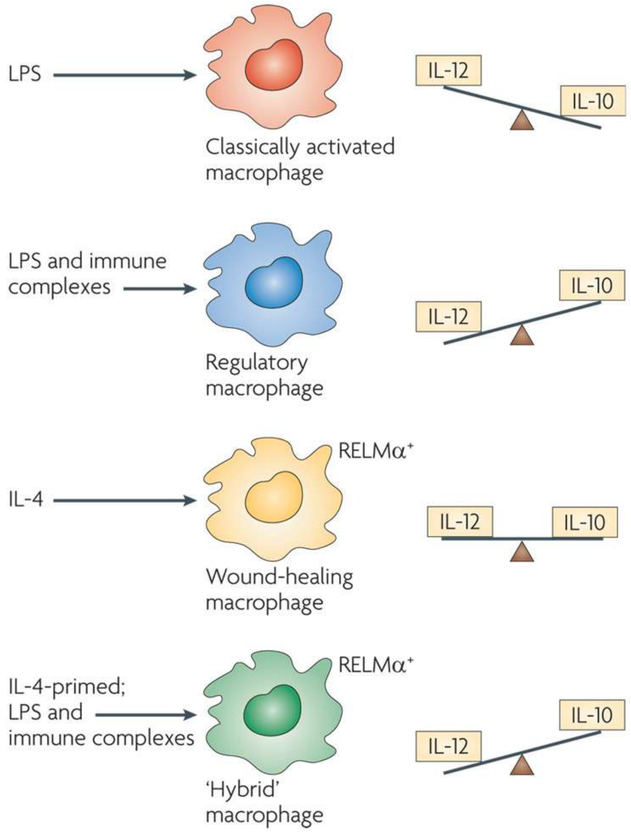
Microbiol Immunol 1982;26:535-9.

OXIDATIVE STRESS & IMMUNE SYSTEM

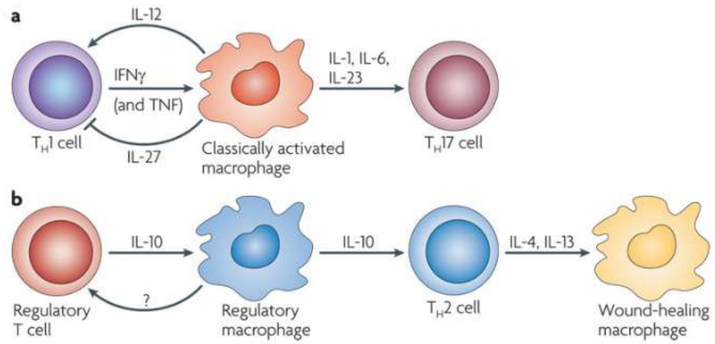
Cytokines produced by immune cells can give rise to macrophages with distinct physiologies



The plasticity of activated macrophages



Interactions between macrophage and T cells



Mosser D, Edwards J. Exploring the full spectrum of macrophage activation. Nature Reviews Immunology. 2008;8(12):958-969.

VIUSID

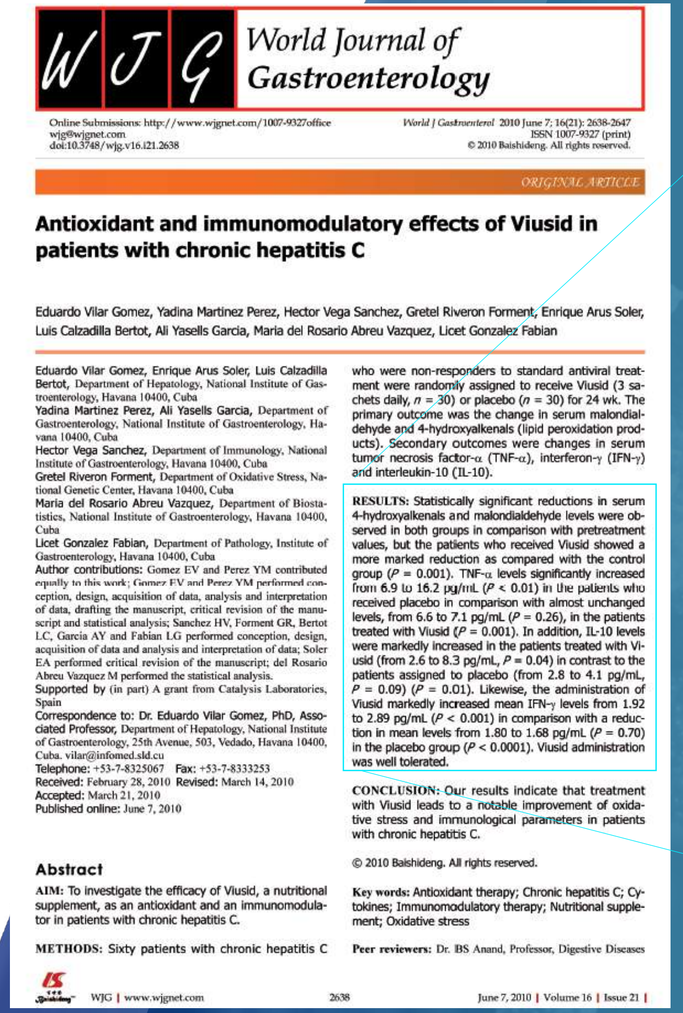
Oxidative stress & Immune system

Viusid immunomodulatory effect

Patients treated with Viusid, controlled the levels of TNF-α (pro-inflammatory cytokine); increased levels of IL-10 (anti-inflammatory interleukin that regulates macrophage and dendritic cell activation); they increased the mean of IFN-γ (interferon produced by NK and T lymphocytes to activate macrophages).

Pro-inflammatory cytokines

Anti-inflammatory cytokines



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ORIGINAL ARTICLE

Antioxidant and immunomodulatory effects of Viusid in patients with chronic hepatitis C

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Abstract

AIM: To investigate the efficacy of Viusid, a nutritional supplement, as an antioxidant and an immunomodulator in patients with chronic hepatitis C.

METHODS: Sixty patients with chronic hepatitis C who were non-responders to standard antiviral treatment were randomly assigned to receive Viusid (3 sachets daily, $n = 30$) or placebo ($n = 30$) for 24 wk. The primary outcome was the change in serum malondialdehyde and 4-hydroxyalkenals (lipid peroxidation products). Secondary outcomes were changes in serum tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ) and interleukin-10 (IL-10).

RESULTS: Statistically significant reductions in serum 4-hydroxyalkenals and malondialdehyde levels were observed in both groups in comparison with pretreatment values, but the patients who received Viusid showed a more marked reduction as compared with the control group ($P = 0.001$). TNF-α levels significantly increased from 6.9 to 16.2 pg/mL ($P < 0.01$) in the patients who received placebo in comparison with almost unchanged levels, from 6.6 to 7.1 pg/mL ($P = 0.26$), in the patients treated with Viusid ($P = 0.001$). In addition, IL-10 levels were markedly increased in the patients treated with Viusid (from 2.6 to 8.3 pg/mL, $P = 0.04$) in contrast to the patients assigned to placebo (from 2.8 to 4.1 pg/mL, $P = 0.09$) ($P = 0.01$). Likewise, the administration of Viusid markedly increased mean IFN-γ levels from 1.92 to 2.89 pg/mL ($P < 0.001$) in comparison with a reduction in mean levels from 1.80 to 1.68 pg/mL ($P = 0.70$) in the placebo group ($P < 0.0001$). Viusid administration was well tolerated.

CONCLUSION: Our results indicate that treatment with Viusid leads to a notable improvement of oxidative stress and immunological parameters in patients with chronic hepatitis C.

Key words: Antioxidant therapy; Chronic hepatitis C; Cytokines; Immunomodulatory therapy; Nutritional supplement; Oxidative stress

Peer reviewers: Dr. IBS Anand, Professor, Digestive Diseases

RESULTS: Statistically significant reductions in serum 4-hydroxyalkenals and malondialdehyde levels were observed in both groups in comparison with pretreatment values, but the patients who received Viusid showed a more marked reduction as compared with the control group ($P = 0.001$). TNF-α levels significantly increased from 6.9 to 16.2 pg/mL ($P < 0.01$) in the patients who received placebo in comparison with almost unchanged levels, from 6.6 to 7.1 pg/mL ($P = 0.26$), in the patients treated with Viusid ($P = 0.001$). In addition, IL-10 levels were markedly increased in the patients treated with Viusid (from 2.6 to 8.3 pg/mL, $P = 0.04$) in contrast to the patients assigned to placebo (from 2.8 to 4.1 pg/mL, $P = 0.09$) ($P = 0.01$). Likewise, the administration of Viusid markedly increased mean IFN-γ levels from 1.92 to 2.89 pg/mL ($P < 0.001$) in comparison with a reduction in mean levels from 1.80 to 1.68 pg/mL ($P = 0.70$) in the placebo group ($P < 0.0001$). Viusid administration was well tolerated.

Prevention

Stay at home when you are sick

Avoid close contact with people who are sick.

Wash your hands at least 20 seconds.

Cover your cough or sneeze with a tissue.

Don’t eat raw food, throughly cook meat & egg.

Avoid touching eyes, nose, & mouth with unwashed hands.

Clean & disinfect frequently touched object & surfaces.

Avoid Crowd Places.

Symptoms


THANK YOU
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