Metadichol ® a novel nano lipid that inhibits In Vitro, SARS-COV-2 and a multitude of pathological viruses

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Research Article

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EDITORIAL NOTE:

10 October, 2023 Editorial note (correction). This submission initially contained a declaration of no competing interests for this submitted work; however, the author has now provided a corrected competing interest declaration as follows: The author, PR Raghavan, is the CEO of Nanorx Inc., the manufacturer of the Metadichol® supplement mentioned in this work, and, as such, has professional and financial interests related to research outcomes of this supplement.

Abstract

New pathogenic virus outbreaks with increasing regularity are leading us to explore novel approaches, which will reduce the reliance on a time-consuming vaccine mode to halt the strike. The requirement is to find a universal approach to disarm any new and as yet unknown viruses as they appear. A promising approach could be by targeting the lipids membranes, common to all viruses and bacteria.

The ongoing pandemic of the SARS-coronavirus 2 (SARS-CoV-2) has restated the importance of interactions between components of the host cell plasma membrane and the virus envelope as a critical mechanism of infection. Metadichol ®, a nano lipid emulsion, has been examined and shown to be a strong candidate to help stop the proliferation of the SARS-COV-2.

Naturally derived substances, such long chain saturated lipid alcohols reduce the infectivity of various types of viruses, including the coronavirus like SARS-COV-2, by modifying the lipid-dependent attachment to human host cells. SARS-COV-2 uses the receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming.

Metadichol®, a nano lipid formulation of long-chain alcohols, has been shown to inhibit TMPRSS2 (EC50 of 96 ng/ml). Compared to the inhibitor Camostat Mesylate (26000 ng/ml), it is 270 times more potent. Also, Metadichol ® is a moderate inhibitor of ACE2 @ 31 µg/ml. In the SARS-COV2 antiviral assay using CACO2 cells, it has an EC90 of 0.16 µg/ml.

Introduction

There is today an increasing need for a broad-spectrum antimicrobial agent, which could inactivate human pathogens such as bacteria and viruses. Rapid resistance has propelled this approach by microorganisms to focused drugs. The most recent trigger is the fear of a future pandemic caused by new, poorly studied virulent strains, like the present SARS-COV–2.

Background to SARS-COV–2

The severe acute respiratory syndrome coronavirus 2 (SARS-COV–2) (COVID–19), is a pandemic *1,* which has caused global havoc within a few months. To medically control a rapidly spreading viral pandemic utilizing specific Antivirals and vaccines will prove expensive, time-consuming, and carries with it compromise on the safety and efficacy. An alternative approach is to test molecules that are already proven safe and tested to be effective against SARS-COV–2. Among the candidates being tested are Camostat

mesylate (a 35year Japanese drug) Avigan (another Japanese Drug) and Gilead Science Inc's Remdesivir [2] To enter a host cell, the SARS COV–2 needs TMPRSS2 [3], a serine protease, and ACE 2 [4] to bind and thus facilitate its entry. Blocking both receptors can effectively stop the cell entry' mechanism used by the virus.

TMPRSS2 is a protease that primes the spike protein of SARS-CoV, and the Middle East respiratory syndrome-related coronavirus (MERS-CoV). Camostat mesylate (CM), an inhibitor of TMPRSS2, inhibited SARS-CoV in a

mouse model [5,6] Hoffmann et al., [7] determined that the SARS-CoV–2 requires TMPRSS2. They showed that CM blocks the virus entry into the lungs. So far, there are no clinical data on the use of CM in patients.

The other receptor used by viruses to gain entry into the host cell is ACE2. SARS-CoV–2 has a spike (S) protein on its viral envelope (exterior) that binds to the transmembrane protein angiotensin-converting enzyme 2 (ACE2), which is present in human cells. ACE2 protein is essential for viral entry. However, ACE2 also regulates blood pressure and blood volume; blocking ACE2 would be detrimental to health. A solution that partially regulates ACE2 in concert with inhibition of TMPRSS2 would thus be an ideal solution.

Lipids and Viruses

Viral envelope lipid plays a role in both viral stability as well as its infective capabilities. For example, substances that affect the lipid envelop like Phospholipases, organics solvents, and surfactants like soaps have shown to affect the viral infectability. Causing envelope disintegration, they stop the virus transmission to a new host. Active ingredients [8] in a number of the cleaning agents, wipes, and tissues target the viral lipid envelop to render the virions non-viable. Snipes and coworkers [9] showed that saturated alcohols could inactivate viruses with chain lengths from 10 to 14 carbons. Their studies established that inactivation of enveloped viruses by lipids varies greatly, depending on both the nature of the lipid and the type of virus.Â

Hilmarsson et al. 10,11,12 studied the virucidal effects of medium and long-chain (8 to 18 carbon) fatty alcohols and corresponding lipids against HSV–1 and HSV–2 respiratory syncytial virus (RSV) and human virus type 2 (HPIV2) and enveloped viruses, at various concentrations, times and pH levels. After 10-minute incubation at 37 deg C and ten mM concentration, 14 of the lipids tested caused a 100 000-fold or more significant reduction in HSV titer. Testing between pH 7 and 4.2 showed that the pH to 4.2 caused a more rapid inactivation of HSV–1 virus titer in one minute. These long-chain alcohols may act by penetrating the envelope of the virus by hydrophobic effect, making it permeable to small molecules and thus inactivating the virus, the degree of penetration into lipid membranes due to the chain length of a lipid compared with the thickness of the membrane.13.

Metadichol is a nano lipid formulation of long-chain alcohols[14.] Metadichol has been shown to inhibit viruses in vitro and in vivo 15,16,17. Metadichol was tested for its inhibitory actions against ACE2, TMPRSS2, and antiviral assay with SARS-COV–2.

Experimental Methods And Results

All assays were on a fee for service contract basis and outsourced to Bioanalytical testing companies worldwide. Antiviral assay was done by a Bio-Safety Level 3 (BSL3) facility in USA.

Antiviral assay

Metadichol was serially diluted using eight half-log dilutions in test medium (MEM supplemented with 2% FBS and 50µg/mL gentamicin) so that the starting (high) test concentration was 100 µg/ml. Each dilution was

added to 5 wells of a 96-well plate with 80–100% confluent CACO–2 cells.

Three wells of each dilution were inoculated with virus, with two wells uninoculated (as toxicity controls), six wells were inoculated and untreated (as virus controls), and six wells were uninoculated and untreated (as cell controls). The SARS-CoV–2 virus was prepared to achieve the lowest possible multiplicity of infection (MOI) that would yield >80% cytopathic effect (CPE) within five days. M128533 (Protease specific for SARS virus.) was tested in parallel as a positive control. Plates were incubated at 37±2°C, 5% CO2. On day three post-infection, once untreated virus control wells reached maximum CPE, plates were stained with neutral red dye for approximately 2 hours (±15 minutes). Supernatant dye was removed, and wells rinsed with PBS, and the incorporated dye was extracted in 50:50 Sorensen citrate buffer/ethanol for

>30 minutes, and the optical density was read on a spectrophotometer at 540 nm.

Optical densities were converted to percent of cell controls, and the concentration of compound that would cause 50% cell death (CC50) in the absence of a virus was calculated by regression analysis. The selective index (SI) is the CC50 divided by EC90. Results in Table 1

For virus yield reduction (VYR) assay, the supernatant fluid from each compound concentrations was collected on day three post-infection, before neutral red staining (3 wells pooled) and tested for virus titer using a standard endpoint dilution CCID50 assay in Vero 76 cells and titer calculations using the Reed- Muench (1948) equation. The concentration of compound required to reduce virus yield by one log10 was calculated by regression analysis (EC90). The selective index (SI) is the CC50 divided by EC90.

Table 1. In vitro antiviral results

	CC50	EC90	SI90
Metadichol (µg/ml)	4	0.15	20
M128533 (µg/ml)	>10	0.2	>33

CC50; 50% cytotoxic concentration of compound without virus added, EC50: 50% effective antiviral concentration.

EC90: Calculated concentration to reduce virus yield by 1 log (90%), SI = CC50/EC50

Table 2. Shows Cytotoxicity and virus yield data for each concentration of Metadichol tested

Metadichol Concentration Titer (µg/ml)	Cytotoxicity (%)	Virus Titer (CCID50 per 0.1 ml)
100	100%	<0.7
32	100%	<0.7
10	83%	<0.7
3.2	54%	0.7
1	17%	4.3
0.3	26%	1.5
0.1	26%	5.7
0.03	26%	5.3

As shown in Table 2, the virus reduction assay did not follow a typical dose-response, with virus reduction seen at a concentration of 0.3 µg/ml and 3.2 µg/ml, but no reduction seen at a concentration of 1 µg/ml.

Assuming that breakthrough of the virus at one µg/ml was an outlier. The calculated SI ratio was 20 (Table 1), indicating EC 90 of 0.15 µg/ml.

TMPRSS2 Inhibition assay

Procedure

TMPRSS purified from LNCaP cells (Cayman Chemicals) was used as an enzyme source. The reaction mixture contains the purified TMPRSS2 protease in TBS buffer with or without a range of various concentrations from 1.56 to 100 ng/ml of test sample or inhibitor. The reaction mixture was incubated for 10 mins and at 37°C. To the reaction mixture, 1µl of 10mM fluorogenic trypsin substrate Cbz-Gly-Gly-Arg-AMC was added and the kinetic fluorescence reading was recorded after 2 mins incubation at 37°C at 383ex and 455em at 5–10 mins using Spectramax i3X, Molecular devices. Change in fluorescence (delta RFU) was calculated to determine the inhibitory effects of the test sample. Camostat mesylate at a two-fold range of concentrations from 1.56 to 100nM was used as a positive control for TMPRSS2 protease.

Figure. 1.Camostat mesylate
Figure 2. Metadichol

Table 3. TMRSS2 assay data

Sample	Concentration	RFU	% Inhibition	IC 50
Control	0	43233358	0.00	
Metadichol (ng/ml)	1.56	41305150	4.46	96.65 ng/ml
	3.12	39329385	9.03	
	6.25	36713767	15.08	
	12.5	33778222	21.87	
	25	30695684	29.00	
	50	26087008	39.66	
	100	16009312	62.97	
Camostat mesylate (µg/ml)	0.78	37984828	12.14	26.46 ug/ml
	1.56	35235186	18.50	
	3.125	31685728	26.71	
	6.25	29234396	32.38	
	12.5	23276839	46.16	
	25	18931887	56.21	
	50	8797988	79.65	

ACE2 Inhibition assay

The ACE2 Inhibitor Screening Assay Kit, Catalog no 79923 (BPS biosciences, San Diego USA) was to measure the exopeptidase activity of ACE2 and inhibition by Metadichol and control inhibitor DX600. The inhibitory activity was measured based on the fluorescence emitted by the cleavage of the chromogenic substrate.

Procedure:

Enzyme (ACE2) stocks were prepared and from the supplied kit. 20µl of enzyme solution (0.5ng/µl) was added to all the wells designated for the assay. DX600, a potent ACE2 inhibitorwas used as a positive control for ACE2 inhibition at various concentrations ranging from 0.0156µg/ml to 1µg/ml. The test sample at a range of concentrations from 0.125µg/ml to 40µg/ml was used. To each well consisting of enzyme solution, 5µl of inhibitor solutions was added to respective designated wells. The reaction mixture was incubated at room temperature for 5 minutes room temperature. Post incubation, 25µl ACE2 substrate was added to the mixture and incubated for 1hr at room temperature. The RFU of cleavage of the substrate was read at Ex555nm and Em585nm using Spectramax i3x, Molecular devices. The IC50 values were calculated based on based on the readings obtained.

Figure 3 DX 600 (control)

Figure 4. Metadichol

Table 4. ACE2 assay data

Sample	Concentration ug/ml	RFU	% Inhibition	IC50 ug/ml
Control	0	308315546	0.00	
Metadichol	0.125	290309918	5.84	30.15
	0.25	260064163	15.65	
	0.5	249149792	19.19	
	1	240301136	22.06	
	10	212275253	31.15	
	20	187702504	39.12	
	40	139821100	54.65	
DX600	0.0156	252855648	17.99	0.1027
	0.031	231028864	25.07	
	0.0625	193810784	37.14	
	0.125	145881248	52.68	
	0.25	127485752	58.65	
	0.5	111498760	63.84	

Discussion

The results reported open the gateway to effective and safe therapies for COVID–19. Metadichol inhibits ACE2 sufficiently to prevent SARS-CoV–2 entry into host cells. and at the same time, the concentrations for inhibition of viral passage are not high enough to affect the physiological functions of the host.

The results also demonstrate Metadichol's direct antiviral effect against the SARS-COV–2 virus itself, in CACO–2 cells with an EC90 of 0.15 µg/ml. Comparatively, this result gives it a 2000 fold higher effectiveness than Remdesivir and 4000 fold potency over Hydroxychloroquine phosphate 18.

Metadichol also inhibits TMPRSS2, as is seen to be 270-fold more potent than Camostat Mesylate 19. Metadichol inhibits moderately ACE2 and, in combination with TMPRSS2 inhibition, likely leading to a pronounced synergistic effect in overcoming viral entry. The antiviral assay shown in Table 5, suggest that it is toxic to cells at concentrations above Units are µg/ml unless noted.

But Metadichol is not toxic as the LD 50 is 5000 mg/kilo 20,21,22. It is likely that Metadichol at higher concentrations behaves in a soap mimicking manner, by disrupting the lipid membrane, and at lower

concentrations, it neutralizes the virus by a different mechanism. A previously published work (see ref 15) on antiviral assay this same “toxicity” was seen, and this is shown in Tables 5 and 6.

Raw data from Cytotoxicity of Metadichol without a virus present in Vero cells as measured by neutral red assay. When >75% “toxicity” occurred in the absence of a virus, no viral CPE value was reported.

It is not the toxicity of Metadichol on cell lines, but rather it behaves as a “detergent” in neutralizing the SARS-COV–2 and other pathogenic viruses, as shown in Table 7. Also, Metadichol® targets cancer cells in CACO–2 cells. In a previous study, 23 of Klotho gene expression of cancer cell lines Mia-Paca, Colo 205, and Panc1, where it was also seen to be toxic to cell lines above one µg/ml. It is also toxic at 10 µg/ml in Leukemia cancer cells 24.

Table 5. Raw data for cytotoxicity of Metadichol without virus present, as measured by neutral red assay

Units are µg/ml unless noted								
µg/ml Metadichol	Adenovirus	Tacaribe	Rift valley	SARS	Japanese Encephalitis	West nile virus	Yellow Fever	Powassan virus
500	95%	98%	96%	96%	100%	100%	100%	100%
160	92%	98%	96%	95%	100%	100%	100%	100%
50	90%	97%	97%	95%	100%	100%	100%	100%
16	85%	95%	81%	92%	88%	77%	98%	100%
5	0%	23%	26%	35%	33%	28%	35%	44%
1.6	0%	2%	10%	15%	12%	14%	19%	6%
0.5	0%	3%	9%	0%	2%	3%	2%	0%
0.16	0%	17%	3%	0%	0%	0%	4%	0%
CC50	9.90	7.30	8.40	6.70	7.20	8.50	5.00	5.1

Table 6; Antiviral assay of Metadichol vs. various viruses as measured by Neutral red assay

ug/mL Metadichol	Adenovirus	Tacaribe	Rift Valley Fever	SARS	Japanese Encephalitis	West Nile	Yellow Fever	Powassan
5	100%	31%	100%	0%	56%	84%	70%	53%
1.6	100%	69%	100%	52%	87%	100%	73%	100%
0.5	100%	97%	100%	100%	100%	100%	95%	100%
0.16	100%	100%	100%	100%	100%	100%	96%	100%
EC50	>9.9	2.8	>8.4	1.7	>7.2	>8.5	>5	>5.1

Table 7. List of Viruses Inhibited by Metadichol In Vitro

Adenovirus	Rift valley
Japanese Encephalitis	Marburg
Tacaribe	SARS
Powassan	Respiratory Syncytial Virus
Zika	Chikungunya
Ebola	Influenza A (H1N1)
Yellow fever	Dengue
West Nile Virus	HIV

Vitamin D and SARS-COV–2 infection.

An out of control inflammatory response to SARS-COV–2 is the major cause of disease severity and death in patients with COVID–19 25 and is associated with high levels of circulating cytokines, TNF, CCl2,, CRP, Ferritin. Metadichol (see Ref 14) is an inhibitor of CCl2 (also known as MCP–1), TNF, NF-kB, and CRP which, is a surrogate marker for cytokine storm 26 and is associated with Vit D deficiency.

Vitamin D3 is generated in the skin through the action of UVB radiation, reaching 7-dehydrocholesterol in the skin, followed by a thermal reaction. Vitamin D3 is converted to 25(OH)D in the liver and then to 1,25(OH)2D (calcitriol) in the kidneys. Calcitriol binds to the nuclear vitamin D receptor; a DNA binding protein interacts with regulatory sequences near target genes that participate genetically and epigenetically in the transcriptional output of genes needed for functioning 27. Vitamin D reduces the risk of infections.by

mechanisms that include inducing cathelicidins and defensins 28, resulting in lowered viral replication rates and reducing concentrations of pro-inflammatory cytokines. 29. Supplementation with 4000 IU/d of vitamin D

decreased dengue virus infection 30. Inflammatory cytokines increase in viral and bacterial infections, as seen in COVID–19 patients. Vitamin D can reduce the production of pro-inflammatory Th1 cytokines, such as tumor necrosis factor and interferon 31.

Vitamin D is a modulator of adaptive immunity 32 and suppresses responses mediated by the T helper cell type 1 (Th1) by primarily repressing the production of inflammatory cytokines IL–2 and interferon-gamma (INF) 33. Additionally, 1,25(OH)2D3 promotes cytokine production by the T helper type 2 (Th2) cells, which helps enhance the indirect suppression of Th1 cells by complementing this with actions mediated by a multitude of cell types 34.

1,25(OH)2D3 promotes the T regulatory cells' induction, thereby inhibiting inflammatory processes 35. It is known that COVID–19 infection is associated with the increased production of pro-inflammatory cytokines, C-reactive protein, increased risk of pneumonia, sepsis, acute respiratory distress syndrome, and heart failure 36. Case fatality rates (CFR's) in China were 6%–10% for those with cardiovascular disease, chronic respiratory tract disease, diabetes, and hypertension 37.

Telomerase and Viral infections

Metadichol increases h-TERT (telomerase) at one picogram by 16 fold 38. Viral infection puts a significant strain on the body. CD8 T cells that mediate adaptive immunity 39 to protect the body from microbial invaders can easily reach their Hayflick limit by depleting their telomeres 40. This is more so if telomeres are

already short, then this is more likely to happen. Infections put enormous strain on immune cells to replicate. Naive T and B cells are particularly important when our bodies encounter new pathogens like the like

SARS-COV–2. The quantity of these cells is crucial for useful immune function.

Aryl Hydrocarbon receptor and Viral Infections

One of the major issues with infected COVID–19 patients has been a respiratory failure. It has been suggested that the Aryl Hydrocarbon receptor (AHR) is activated during coronavirus infections, impacting antiviral immunity, and lung cells associated with repair 41. signaling via AHR may dampen the immune response against coronavirus 42. It has been reported that although some signaling is needed for coronavirus replication, excessive activation of this Pathway may be deleterious for the virus. AHR limits activation and interferes with multiple antiviral immune mechanisms, including IFN-I production and intrinsic immunity. Yamada et al., 43 suggested AHR (Constitutive aryl hydrocarbon receptor) signaling constrains type I

interferon-mediated antiviral innate defense and suggested a need to block AHR constitutive activity and only an inverse agonist can dampen this. We have shownMetadichol® binds to AHR as an inverse/protean agonist 44. Metadichol is an inverse/protean agonist (see Ref 14) of vitamin D receptor and thus can reduce complications attributed to out of control inflammation and cytokine storm.

Vitamin C and its role in viral infections

In infectious diseases, there is also a need to boost Innate and adaptive immunity. Micronutrients with the most robust evidence for immune support are vitamins C and D. Vitamin C is essential for a healthy and well functional host defense mechanism. The pharmacological application of vitamin C enhances immune function 45. Vitamin C has antiviral properties leading to inhibition of replication of herpes simplex virus

type 1, poliovirus type 1, influenza virus type 46, and rabies virus in vitro 47.

Vitamin C deficiency reduces cellular 48–52 and humoral immune responses, and treatment of healthy subjects promoted and enhanced natural killer cell activities 53 underlining the immunological importance of vitamin C 54,55 and supports its role as a crucial player in various aspects of immune cell functions, such as

immune cell proliferation and differentiation, besides its anti-inflammatory properties. Moreover, the newly characterized hydroxylase enzymes, which regulate the activity of the hypoxia-and inducible factor), gene transcription, and cell signaling of immune cells need vitamin C as a cofactor for optimal activity 56,57,58.

Metadichol increases Vitamin C levels endogenously by recycling Vitamin C and reaches levels not reached by oral intake. The levels reached to bring about changes in improving diverse biomarkers. 59,60,61.

Gene Cluster Network analysis.

The present drug discovery paradigm is based on the idea of one gene-one target, one disease. It has become clear that it is hard to achieve single target specificity. Thus, a need to transition from targeting a single gene to multiple targeting of genes is likely to be more active, leading to blocking multiple paths of disease progression 62,63. An analysis of the gene network analysis can provide a minimum set of genes that can form the basis for targeting diseases. This clustering network of genes can modulate gene pathways and biological networks. We used www.ctdbase.org 64 that has curated genes relevant to COVID–19. Table 9 genes and diseases states that they are involved in as far as infectious diseases are concerned.

Table 8. COVID–19 and 13 Curated genes

CCL2	IL6	IL7
TNF	TMPRSS2	ACE2
IL10	CCL3	AGT
IL2	IL8	IL2RA
CSF3		

Table 9. Diseases network of the 13 curated genes

Disease Name	Disease Categories	P-value	Corrected P-value	Annotated Genes Quantity	Annotated Genes
COVID-19	Respiratory tract disease, Viral disease	4.49E-50	3.10E-47	13	ACE2,AGT,CCL2,CCL3,CSF3,CXCL10,IL10,IL2,IL2RA,IL6,IL7,TMPRSS2,TNF
Pneumonia, Viral	Respiratory tract disease,Viral disease	6.28E-49	4.34E-46	13	ACE2,AGT,CCL2,CCL3,CSF3,CXCL10,IL10,IL2,IL2RA,IL6,IL7,TMPRSS2,TNF
Coronaviridae Infections	Viral disease	2.51E-47	1.74E-44	13	ACE2,AGT,CCL2,CCL3,CSF3,CXCL10,IL10,IL2,IL2RA,IL6,IL7,TMPRSS2,TNF
Coronavirus Infections	Viral disease	2.51E-47	1.74E-44	13	ACE2,AGT,CCL2,CCL3,CSF3,CXCL10,IL10,IL2,IL2RA,IL6,IL7,TMPRSS2,TNF
Nidovirales Infections	Viral disease	2.51E-47	1.74E-44	13	ACE2,AGT,CCL2,CCL3,CSF3,CXCL10,IL10,IL2,IL2RA,IL6,IL7,TMPRSS2,TNF
RNA Virus Infections	Viral disease	7.12E-30	4.92E-27	13	ACE2,AGT,CCL2,CCL3,CSF3,CXCL10,IL10,IL2,IL2RA,IL6,IL7,TMPRSS2,TNF
Virus Diseases	Viral disease	2.51E-28	1.73E-25	13	ACE2,AGT,CCL2,CCL3,CSF3,CXCL10,IL10,IL2,IL2RA,IL6,IL7,TMPRSS2,TNF
Sexually Transmitted Diseases, Viral	Viral disease	1.99E-15	1.38E-12	7	CCL2,CCL3,IL10,IL2,IL2RA,IL6,TNF
HIV Infections	Immune system disease,Viral disease	2.26E-15	1.56E-12	7	CCL2,CCL3,IL10,IL2,IL2RA,IL6,TNF
Lentivirus Infections	Viral disease	2.26E-15	1.56E-12	7	CCL2,CCL3,IL10,IL2,IL2RA,IL6,TNF
Retroviridae Infections	Viral disease	2.26E-15	1.56E-12	7	CCL2,CCL3,IL10,IL2,IL2RA,IL6,TNF
HIV Wasting Syndrome	Immune system disease,Metab olic disease,Nutriti on disorder,Viral disease	5.79E-07	4.00E-04	2	IL6,TNF
Coxsackievirus Infections	Viral disease	1.45E-06	0.001	2	IL6,TNF
Enterovirus Infections	Viral disease	6.36E-06	0.0044	2	IL6,TNF
Picornaviridae Infections	Viral disease	7.52E-06	0.00519	2	IL6,TNF

We can filter the 13 genes to a set 4 genes: TNF, CCL2, ACE2, and TMPRSS2 are modulated by Metadichol and AGT that is part of RAS (Renin-Angiotensin System) network that ACE2 is part of (Figure 5). A similar analysis

of these network genes shows that they are closely networked in diseases with a highly significant p-value. These five genes are closely related, and the network can be disease Name

generated as shown in (Figure 6) using www.innatedb.org 65 This integrates known interactions and pathways from major public databases.

Figure 5. Minimum Gene set to be Targeted to treat SARS-COV–2 infection

Table 10. Disease network of genes implicated in Sars-COV–2 infection

Disease Name	P-value	Corrected P-value	Genes	Annotated Genes
COVID-19	1E-18	5.44E-16	5	ACE2,AGT,CCL2,TMPRSS2,TNF
Pneumonia, Viral	1.56E-18	8.46E-16	5	ACE2,AGT,CCL2,TMPRSS2,TNF
Coronaviridae Infections	3.4E-18	1.85E-15	5	ACE2,AGT,CCL2,TMPRSS2,TNF
Coronavirus Infections	3.4E-18	1.85E-15	5	ACE2,AGT,CCL2,TMPRSS2,TNF
Nidovirales Infections	3.4E-18	1.85E-15	5	ACE2,AGT,CCL2,TMPRSS2,TNF
Pneumonia	9.42E-15	5.11E-12	5	ACE2,AGT,CCL2,TMPRSS2,TNF
Respiratory Tract Infections	3.13E-13	1.7E-10	5	ACE2,AGT,CCL2,TMPRSS2,TNF
RNA Virus Infections	2.46E-12	1.34E-09	5	ACE2,AGT,CCL2,TMPRSS2,TNF
Virus Diseases	9.48E-12	5.15E-09	5	ACE2,AGT,CCL2,TMPRSS2,TNF

Figure 6 Network analysis of genes involved in SARS-COV–2 Infections. Figure 7. SARS-COV–2 related genes in RAS and VDR network

The circled ones are circle in black. The highlighted ones are SIRT1, AR, and FOS. Gilinsk 66 suggested that Vitamin D, as a potential mitigation agent in preventing SARS-COV–2 entry. Metadichol binds to VDR, which controls the expression of FOS 67. AR also controls the expression of FOS as well as TMPRSS2.

Figure 7 generated below using PACO 68 below shows the gene network and regulation relationship sa.VDR controls FOS expression, FOS controls AGT, AGT controls expression of AGTR1 and ACE, and AR controls expression of TMPRSS2.

Goren et al.69 suggested that SARS-CoV–2 infection is likely to be androgen-mediated. The first step to infectivity is the priming of the spike proteins in SARS-COV–2 by transmembrane protease serine 2 (TMPRSS2), which also cleaves angiotensin-converting enzyme 2 (ACE2) for augmented viral entry. This is seen in the network (Fig 7). SIRT1, which plays an active role in enhancing immunity in viral infections

70.

Proteases like Furin 71 and Adam–17 have been described to activate the spikes in vitro, for viral spread and pathogenesis in the infected hosts. The VDR controls Furin expression, mediated through its interaction with SRC 72. Adam–17 is regulated via CEPBP 73,74, which is involved in the regulation of genes involved in immune and inflammatory responses. Recently Ulrich and Pilalt 75 proposed that CD147 is another receptor used as a viral entry like ACE2. CD147 is a known receptor 76 for the parasite that causes Malaria in humans “plasmodium falciparum”, Metadichol (See Ref 6, US patent 9,006,292) inhibits the malarial parasite.

The key to entry into cells by SARS-COV–2 is ACE2 which, when endocytosed with SARS-CoV, results in

Figure 8. RAS and VDR network

a reduction of ACE2 on cells, and an increase of serum Angiostensin II 77. Angiostensin II acts as vasoconstrictor and a pro-inflammatory cytokine (Figure 1) via AT1R 78. The Angiostensin II-AT1R axis leads to pro-inflammatory state 79. leading to infections in through activation of NF-KB leading to increased IL–6 to multiple inflammatory and autoimmune diseases 80 .

The dysregulation of angiotensin 2 downstream of ACE2 leads to cytokine release that is seen in COVID–19

patients, resulting in increases TNF that leads to IL6, CCl2,, and CRP levels. The cytokine storm *81* results in ARDS (Acute respiratory distress syndrome).

Controlling the Cytokine storms

A cytokine storm develops after an initial immune response by the induction of cytokines. The response to SARS-CoV–2 leads to inflammation.. There are increased levels of the proinflammatory cytokines interleukin–6 (IL–6), IL–18, tumor necrosis factor (TNF), and IL–1-beta by macrophages, and of IFN-gamma by natural killer (NK) cells. '

Figure 9; Cytokine relationship and network

Figure 9 generated by use of PACO (*www.pathwcommons.org)* the cytokines relationship network The cytokines can activate T cells, which lead to tissue damage and infection in the lungs. Infiltration of T cells can also result from the up regulation of adhesion molecules like ICAM1 by lung endothelial cells.

Metadichol being an inhibitor (see ref 14, US patent 8,722,093) in vivo of TNF alpha, ICAM1 and CCl2 shuts down the hyper inflammatory cytokine response caused by SARS-CoV–2 and, at the same time, enhances innate and adaptive immunity through the VDR pathways and increased Vitamin C levels.

Metadichol, by its binding to VDR, leads to a network of genes control of the cytokine storms in figure 9 bringing about homeostasis

Clinical

A pilot study (outside the USA) on five COVID–19 patients with minor symptoms showed the absence of a virus after 2–4 days of Metadichol @ 20 mg per day. To validate this further, we have been initiated a study in

collaboration with government agencies. We have initiated a trial of 200 patients in 2 continents with Metadichol vs. comparable control groups, with only Standard Care. We hope to communicate these results in the near future..

Summary And Conclusions

Metadichol thus inhibits SARS-CoV–2 entry into host cells by inhibiting TMPRSS2 and partial inhibition of ACE2 and boosts the antiviral response by enhancing innate and adaptive immunity through Vitamin D pathway and also anti-viral activity by increasing endogenously Vitamin C. In addition Telomerase activity can also play a key role in maintaining levels of naive T and B cells needed to fight infections. Metadichol modulates the cytokine storms as it is an inhibitor of TNF, ICAM1 and also CCL2 which as shown play a key role with other cytokines. Co morbidities associated [82,83] with COVID–19 like Hypertension, diabetes [84,85] are also controlled by Metadichol and this could certainly improve long term prognosis for the effcted patient population. This actions on multiple genes and also via multiple pathways bring about homeostasis and prevent SARS-COV–2 infections. Metadichol's [86] actions on multiple genes and proteins lead to over 2000 unique interactions with other genes and resulting in a network that help bring about Homeostasis.

Metadichol is a safe, non-toxic product, made from renewable sources and commercially available for the last six years, with no reported side effects. This unique property allows for the use of Metadichol as a immune modulator to prevent future occurrence of SARS-COV–2 and possibly other infections being predicted and allow a rapid return to normal human social and economic activity worldwide.

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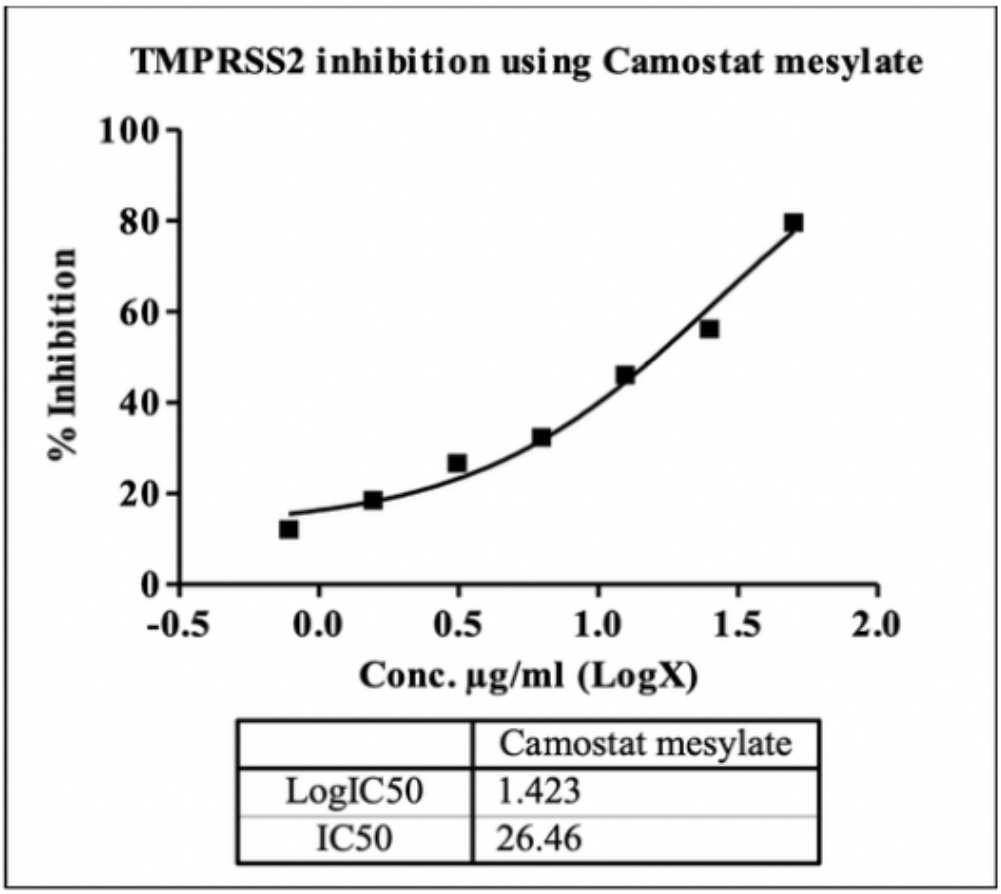
Glossary Of Gene Descriptions

Gene	description
VDR	vitamin D receptor
AHR	aryl hydrocarbon receptor
TERT	telomerase reverse transcriptase
KL	klotho
PAI1 (SERPINE1)	serpin family E member 1
HIF 1 alpha	Hypoxia-inducible factor 1-alpha
CCL2	C-C motif chemokine ligand 2
ICAM1	intercellular adhesion molecule 1
TNF	tumor necrosis factor
ACE	angiotensin I converting enzyme
ACE2	angiotensin I converting enzyme 2
AGTR1 (ANG1)	angiotensin II receptor type 1
AGTR2 (ANG2)	angiotensin II receptor type 2
TMPRSS2	Ttansmembrane serine protease 2
SIRT1	sirtuin 1
TNF	tumor necrosis factor
FURIN	furin, paired basic amino acid cleaving enzyme
CD 147 (BSG)	Basigin (BSG) also known as extracellular matrix metalloproteinase inducer
IL6	interleukin 6
IL10	interleukin 10
CCL3	C-C motif chemokine ligand 3
IL2	interleukin 2
IL7	interleukin 7
CSF3	colony stimulating factor 3
IL2RA	interleukin 2 receptor subunit alpha
CXCL8	C-X-C motif chemokine ligand 8

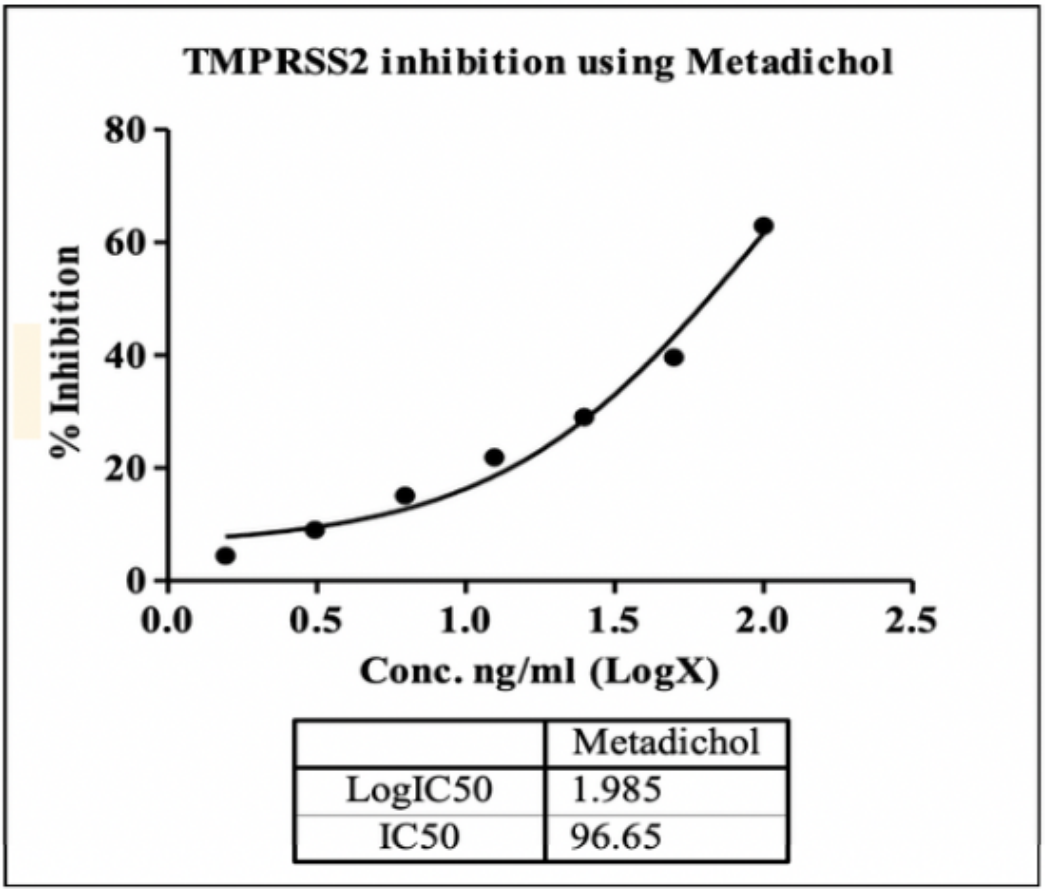
Figures



	Camostat mesylate
LogIC50	1.423
IC50	26.46

Figure 1

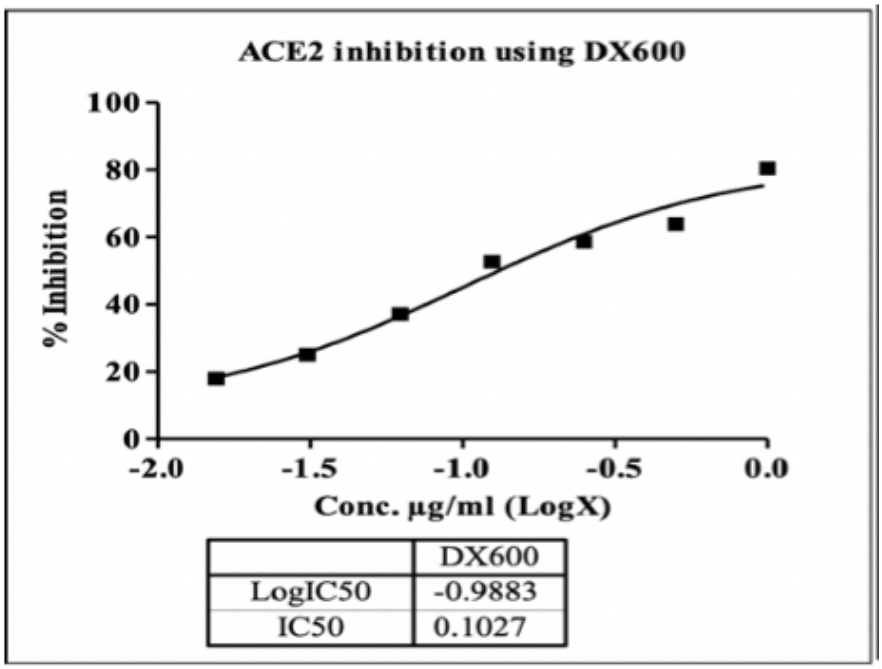
TMPRSS2 Assay: Control Camostat mesylate



	Metadichol
LogIC50	1.985
IC50	96.65

Figure 2

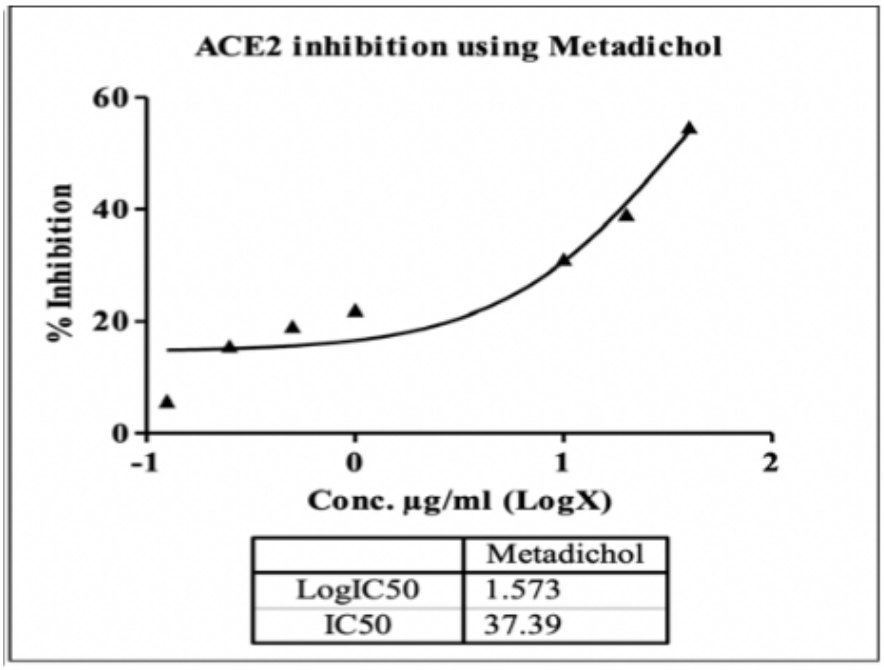
TNPRSS2 assay: Metadichol



	DX600
LogIC50	-0.9883
IC50	0.1027

Figure 3

ACE2-assay; Control



	Metadichol
LogIC50	1.573
IC50	37.39

Figure 4

Ace 2 Assay: Metadichol

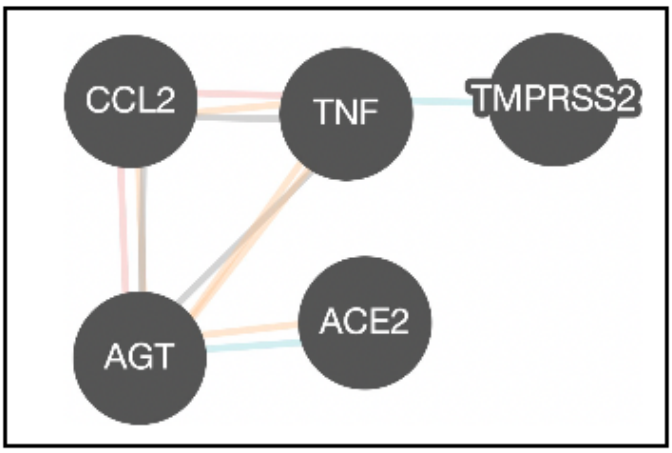


Figure 5

Five genes and their network relationships

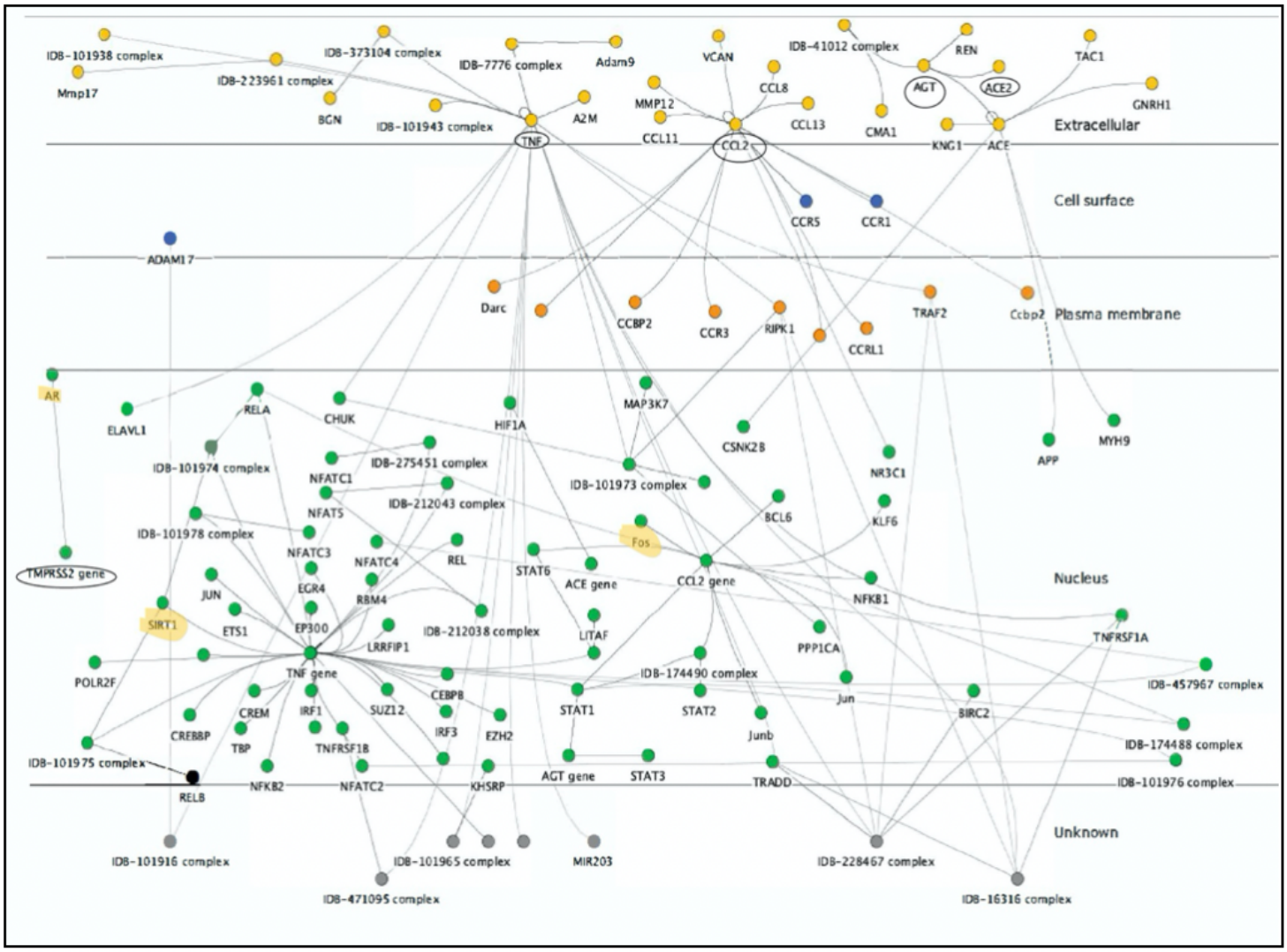


Figure 6

Network analysis of genes involved in SARS-COV-2 Infections

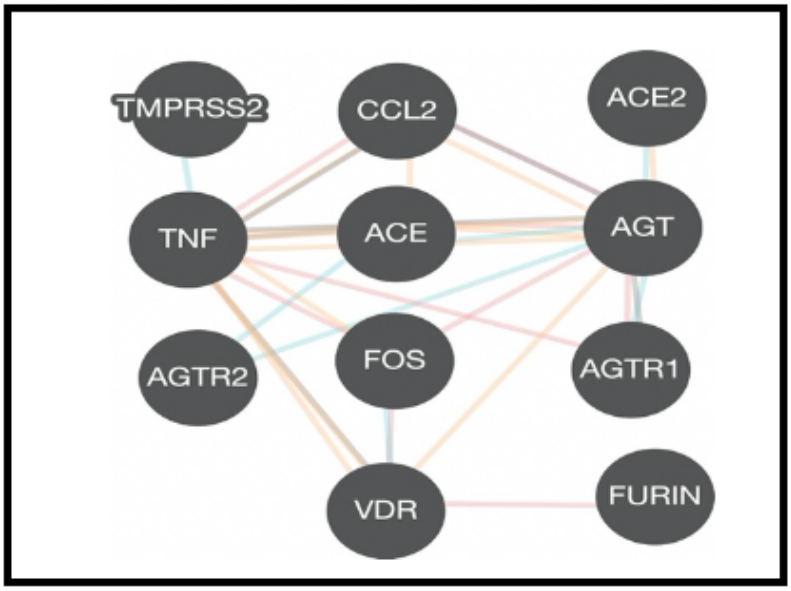


Figure 7

SARS-COV-2 related genes and RAS and VDR network

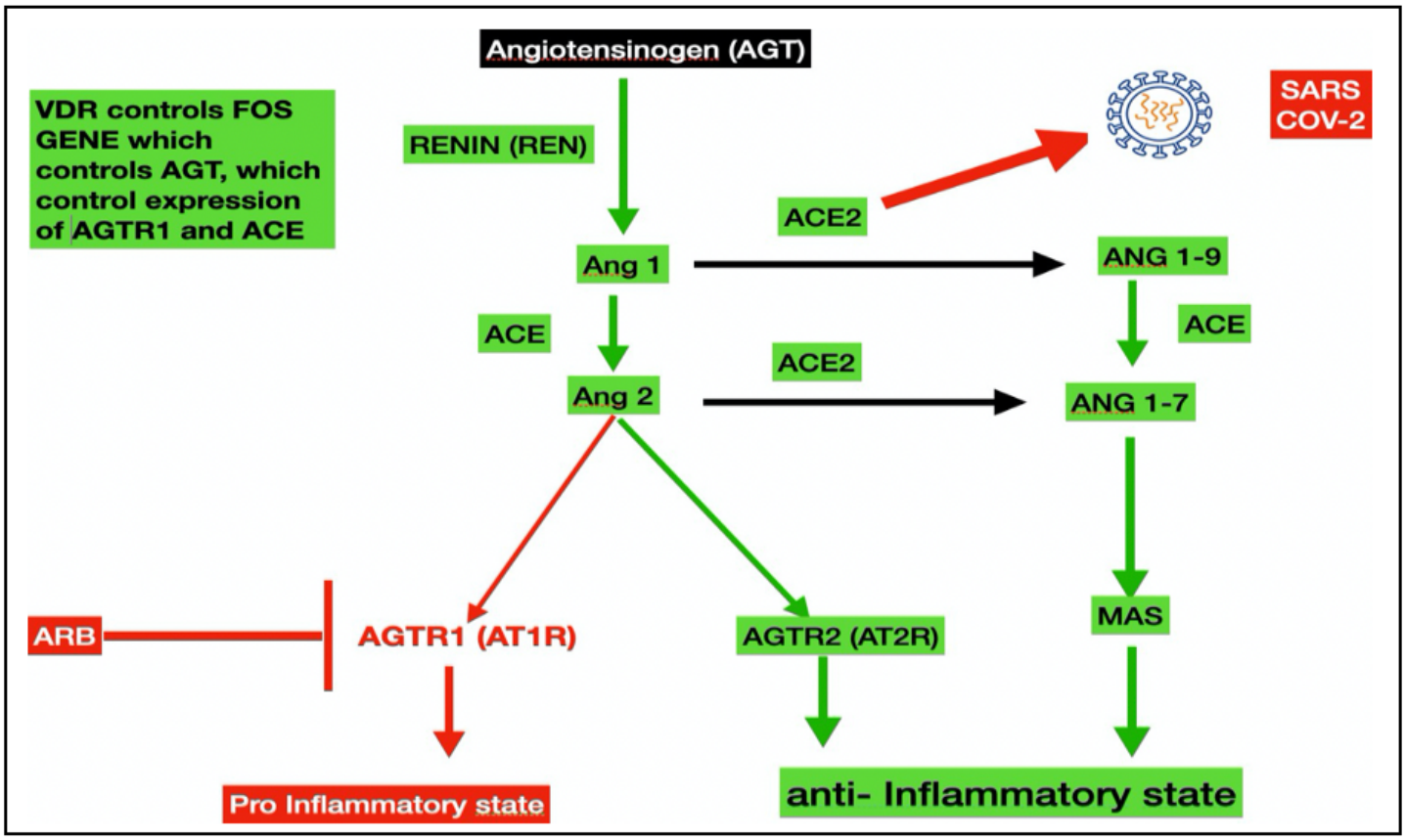


Figure 8

RAs-VDR network

Figure 9-Cytokine relationship network

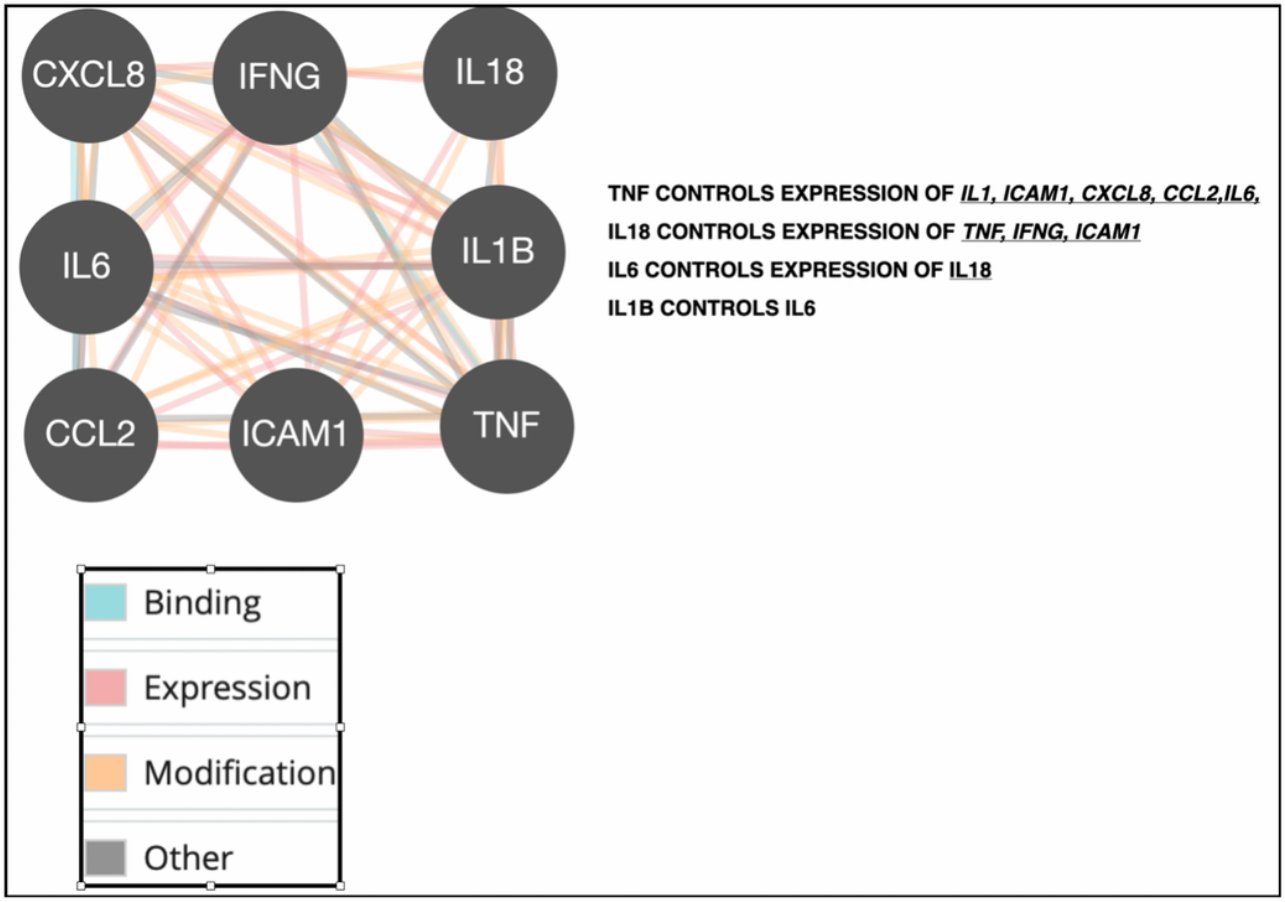


Figure 9

Cytokine relationship network

Supplementary Files

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