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Review Article

Food as Coronavirus Prophylaxis

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Abstract

The global human coronavirus-2 epidemic requires rapid response, and the scientists are searching for prevention and treatment.

The epidemiologic data collected during the epidemic show that in China COVID-19 has a lethality rate of 3.5% versus 1.19% in Japan; or 4.9% in Italy versus 0% in Germany, as of March 2nd , there may be many reasons for these differences in lethality, and diet may be one of them. COVID-19 is a β-coronavirus, like SARS and MERS, and the spread resembles the 2003 and 2012 epidemics from the same family of virus. The finding of the COVID-19 receptor angiotensin-converting enzyme 2 (ACE2) permits to repurpose drugs used for its inhibition.

Herein we explored natural drugs that have shown to inhibit ACE2 and CD26 and prevented MERS and COVID-19 cellular entry. We propose a diet rich in niacin (vitamin B3) and berberine as prophylaxis for COVID-19 and β-coronavirus infections.

Keywords: *Human Coronavirus (2019-hCoV); Niacin; Berberine; ACE2; CD26; COVID19*

Introduction

Given the magnitude of the 2019 human coronavirus (2019-hCoV) epidemic and its fast expansion around the world, the scientific community is obliged to give a rapid response, which is against normal procedures for reliable science.

Repurposing drugs that have already passed the clinical trials, and are safe, is a reasonable path, although their efficacy for patients infected with 2019-hCoV has yet to be determined. However, there is always another first-line response: food; even before those drugs are necessary, there are naturally occurring small molecules, with proven antiviral activity, present in food can prevent infection, even upon contact with the virus.

Food may be used as first-line prophylaxis, as well as a treatment since it does not require clinical trials or safety testing. To that end, we have to understand the viral entry mechanism, molecular targets, and small molecules used for the treatment of coronaviruses of the same phylogeny. The targets for treatment should be the same used on these proteins even for other purposes, luckily viruses have few proteins encoded and high homology within a group.

Viral tropism

Coronaviruses infect different species such as bats, birds, pigs, monkeys, including humans, and several different tissues. Their versatility facilitates expansion across species [1-3] comprising a wide range of infections that are acute, in the lung, intestine or brain, like pneumonia, gastroenteritis, and encephalitis; or chronic like chronic hepatitis or multiple sclerosis caused by lymphocytes, from

previous infections, reactivated by basic myelin protein [4-6]. Given the lethality of some of its forms, and the long term consequences for survivors, prevention becomes key to population well being.

The several types of coronaviruses are classified as: α, that produces gastrointestinal disorders in human, dogs, pigs, and cats; β, include the Bat coronavirus (bCoV), the human Severe Acute Respiratory Syndrome (SARS-hCoV) virus, the Middle Eastern Respiratory Syndrome coronavirus (MERS-hCoV), and 2019-hCoV; γ, which infect avian spices; and δ that infects avian and mammals [7,8].

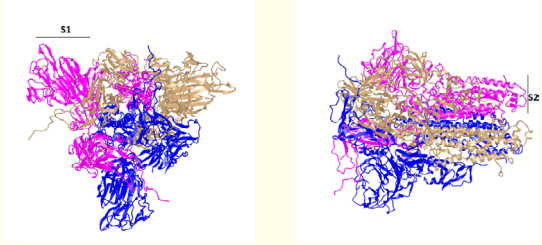
Epidemiology

β-coronaviruses are responsible for the recent epidemic such as the 2003 worldwide pandemics caused by SARS-hCoV, with a 10% fatality rate [9]; the 2012 outbreak, in the Arabian Peninsula, named MERS-hCoV with 35% to 50% lethality [6,10,11]; and the 2019 epidemic in China caused by SARS-hCoV-2, also known as 2019-hCoV or COVID19, with 3.5% fatality rate in China that has spread to 26 countries with 4.9% lethality in Italy, the highest lethality been 8.3% reported in Argentina over 12 cases and the lowest 0% in Germany over 1040 cases reported, Japan also has a low lethality rate, 1.19% in 502 cases, probably due to high soy consumption. World wide there are 109 963 cases and 3824 death and 3.5% global lethality rate, as 2nd of March 2020 [12-14].

Viral structure

2019-hCoV is an enveloped, positive-sense, single-stranded RNA β-coronavirus of 29700 bases and 6 - 7 x 10^6 molecular weight, capped at the 5´-terminus with 7-methylguanylate, and polyadenine at the 3´-end. There are 3 well defined viral proteins from coronavirus, a nucleocapsid (60 kD) that is phosphorylated by a virion-bound protein kinase; an envelope glycoprotein (23 KD) and a larger petal-like spike structures (90 KD) that forms a trimer with the crown-like shape (Figure 1a), which attaches to the host cell [15-17], therefore characterization of the spike protein is important to establish the viral entry mechanism.

Recent sequencing reports from the whole human coronavirus 2019 (NC_045512.2), from Wuhan, China, showed 91.1% of protein homology with the Bat virus (bCoV, MG772934.1), 79.7% with Bat virus 6 (bCoV-6, DQ022305.2) and 77.1% with the SARS-hCoV (NC_004718.3) proteome [18,19]. This homology helps to narrow the search for viral receptors and small molecules that can inhibit the viral attachment, to treat or prevent infection. Although the Spike protein was the least conserved region, in the viral genome, 2019-hCoV had 80%, amino acid sequence homology with the bat virus, 76% for bCoV-6 and 76% for SARS-hCoV (NC_004718.3) [18,20]. This similarity indicates the same receptors will be targets for 2019-hCoV infection.



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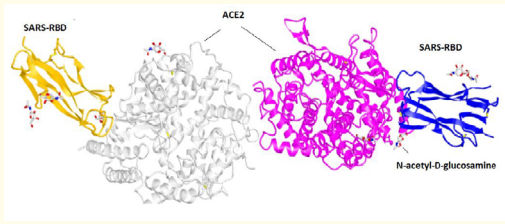

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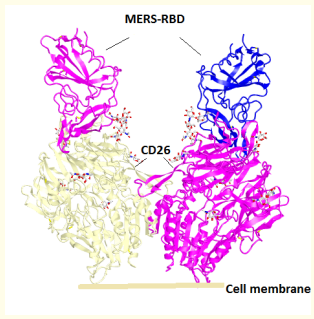

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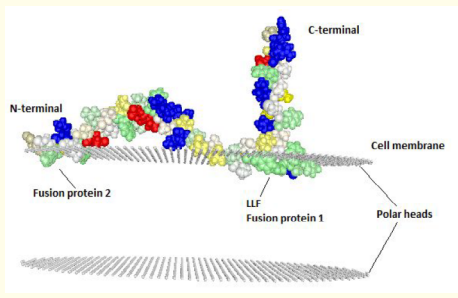

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Figure 1: *(a) The spike protein structure from the human coronavirus (Protein Data Bank ID: 5I08) [48]. (b) Angiotensin-converting enzyme 2 (ACE2) complexed with the receptor-binding domain (RBD) from SARS-hCoV spike protein (MMDB ID: 78776) [49]. (c) CD26 complexed with the receptor-binding domain (RBD) from MERS-hCoV spike protein, complex (MMDB ID: 111699) [50]. (d) The fusion protein of SARS-CoV (PDB ID: 5XJK) [51].*

β-coronavirus receptor structure

There are two known β-coronavirus receptors in humans (Figures 1b and 1c), angiotensin-converting enzyme 2 (ACE2) for SARS-hCoV, and dipeptidyl peptidase IV (DPP4 or CD26) for MERS-hCoV [21,22] and a most recent publication confirmed ACE2 as 2019- hCoV receptor [19]. β-coronavirus entry to the host cell is via a receptor-binding domain within S1 (Figure 1a), from the spike protein, which attaches to the host-cell receptor and is responsible for spice and tissue tropism (Figures 1b and 1c) [23-30]. The viral fusion to the host membrane occurs at the S2 domain via the fusion protein (42,43) (Figures 1a and d), which are highly conserved sequences within a viral group [31,32]. SARS-hCoV cysteine C822 and C833 with the LLF motif are highly conserved within the β-coronavirus (Figure 1d) and mutations of LLF to AAA prevent infection [33]. The fusion protein region interacts with the polar heads of the phospholipids in the bilayer from the host membrane, in a Ca^{+2} dependent manner, ordering the lipid layer below, increasing the ratio of protein/lipid [34,35]. This finding is relevant since chelating extracellular Ca^{+2} with EDTA reduces 2.9 times SARS-hCoV entry to the cells [34]. Chelating therapy could be considered for preventive treatment in cases of high risk, like health care personnel; 4 gr per day of EDTA orally is used for heavy metals poisoning and has been tested for safety, but it should be used with caution since it is also anticoagulant [36,37].

After binding ACE2, there are conformational changes (Figure 1d), the fusion protein is embedded into the host membrane; a proteolytic cleavage site on S protein is directly upstream of the fusion peptide and is a essential determinant of the intracellular site of fusion [38-42]. Some scientist propose that cleavage is an obligatory event for coronavirus entry [43] which is then phagocyted and entries through the lysosomal pathway, however, MERS-hCov does not seem to use this pathway.

Inhibitors of viral entry

The relevance of the host receptor for prevention is demonstrated by the infective capacity of the virus, according to the ACE2 tissue distribution within spice, organ, and cell type. The murine expression of ACE2 is low in endothelial lung cells and blood cells (Figure 2a and 2b; Table 1). Consequently, SARS-CoV infects mouse cells inefficiently [44,45].

Furthermore, understanding the host receptor structure, function, and viral interaction is necessary for proper viral inhibitor selection. ACE2 is a carboxypeptidase of 805 amino acids, with a Zn^{+2}-binding motif, that is involved in autophagy [46]. ACE2 studies in heart and kidney tissue, as the target for hypertension treatments, shows that angiotensin II is the substrate that ACE2 cleaves to angiotensin [1-3,47]. When ACE2 is down-regulated, by cigarette smoke [47,52], angiotensin II accumulates, which is responsible for pulmonary hypertension. Similar results are obtained by DX600 or MLN4760 mediated ACE2 inhibition [52,53]. Nicotinamide isolated from soybean inhibits 100% ACE2 activity at 900 nM. The half-maximal inhibitory concentration is 84 nM for hydrolysis of His-Pro-Lys-containing substrate.

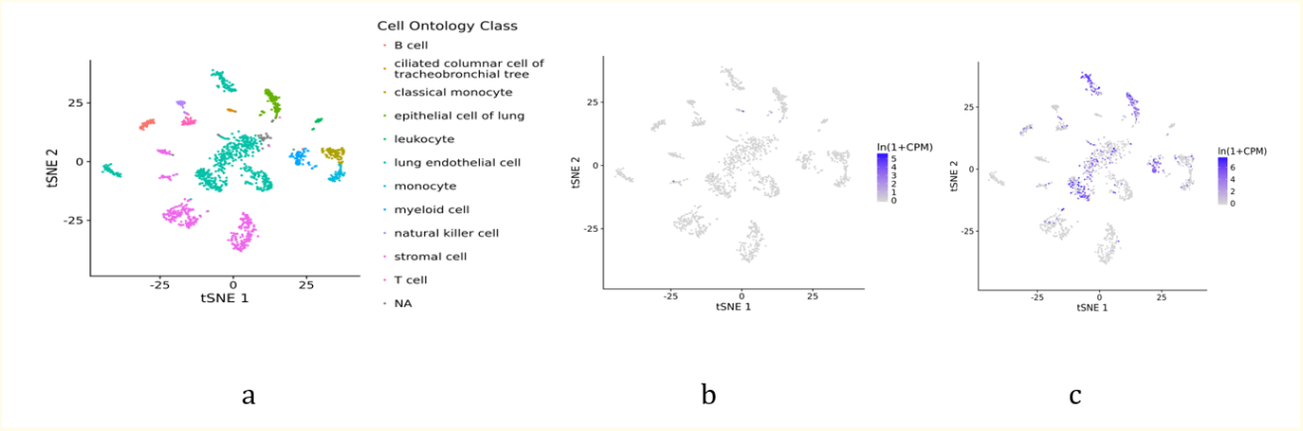

Figure 2: *(a) The t-distributed stochastic neighbor embedding (t-SNE) projection of the normal lung, primary-colored by cell type and (b) Intensity of expression Ln(1+cpm) of ACE2 and (c) CD26 expression on each cell in mouse lung tissue (n = 53,760 cells from 8 mice) [54]. https://tabula-muris.ds.czbiohub.org/.*

Although the ACE2 proteolytic activity is not required for SARS-hCoV attachment, blocking the ACE2 catalytic site, which cleaves the sequence His-Pro-Lys, prevents binding to the receptor-binding domain from CoV and the subsequent viral infection [48].

The importance of ACE2 in 2019-hCoV infection indicates that food containing natural inhibitors, such as soybeans, would be suitable for food prophylaxis [55]. Nicotinamide, also known as niacinamide, is the B3 vitamin present in yeast meat, milk, and green vegetables besides soybeans, at a concentration of 84 nM in blood would block 2019-entry to the tissue. There is a distribution between 1000 and 10000 copies of mRNA of ACE2 in human lung [56], achieving 84 nM concentration of niacinamide would not cause damage to the person and could prevent 2019-hCov infection.

The MERS-hCoV binds CD26 (Figure 1c) expressed on several different types of cells; antibodies directed against human CD26 inhibits infection of primary human bronchial epithelial cells [2,57]. The Spike receptor binding domain in the S1, strongly binds CD26, with a dissociation constant (Kd) of 16.7 nM, but not to SARS-hCoV [58]. Hence, CD26 inhibitors are useful for treating and preventing MERS-hCoV. Table 1 shows the CD26 distribution on different cell types in the lung, intestine, and brain tissues; the mice lung has a higher intensity of CD26 than ACE2. This leaves the murine lung susceptible to MERS-hCoV infection but not to 2019-hCoV, which had to be transfected with ACE2 to be infected for research purposes [59]. Sitagliptin, a drug used to treat diabetes, a regulator of glucose, is a CD26 inhibitor that could be used to prevent infection, although a natural inhibitor of CD26 would be more suitable like berberine, a natural alkaloid (Figure 3), isolated from the Chinese herb, *Coptis chinensis* (Huanglian), it is commonly used for diarrhea treatment. The high intestine expression of CD26 (45%), coincides with the use of berberine for the treatment of β-coronavirus infections [60].

Lung					Intestine			Brain		
	CD26		ACE2		CD26			CD26		
Cell type	IE[a]	%[b] > 0	IE	% >0	Cell type	IE	% > 0	Cell type	IE	% > 0
Myeloid	3.02	69.41	0.00	0.00	Enteroendo-crine	2.06	45.76	Endothelial	0.81	19.72
Epithelial	2.87	68.14	0.10	3.54	Epithelial	1.86	49.08	Neuron	0.1	3.91
Endothelial	1.65	34.05	0.01	0.58	Goblet	1.63	45.86	Pericyte	0.04	3.21
T	1.02	22.64	0.02	1.89	Enterocyte of Epithelium	0.37	12.03	Oligodendrocyte	0.03	2.22
B	0.71	15.79	0.00		Brush Cell of Epithelium	0.02	1.59	Astrocyte	0.02	2.08
Classical Monocyte	0.71	17.78	0.01	1.11				Oligodendrocyte Precursor	0.01	1.97
Natural Killer	0.61	27.03	0.03	2.7				Bergmann glial	0.00	0.00
Monocyte	0.45	10.77	0.01	1.54						
Leukocyte	0.28	5.71	0.00	0.00						
Stromal	0.20	5.44	0.02	0.95						
Ciliated Columnar Cell of Tracheo-Bronchial Tree	0.19	4.00	0.17	4						

Table 1: *ACE2 and CD26 mRNA expression in single cells isolated from different tissue quantified by t-SNE [54].*

[a]: IE: Intensity of expression. [b]: % > Percentage of cell expressing the receptor.

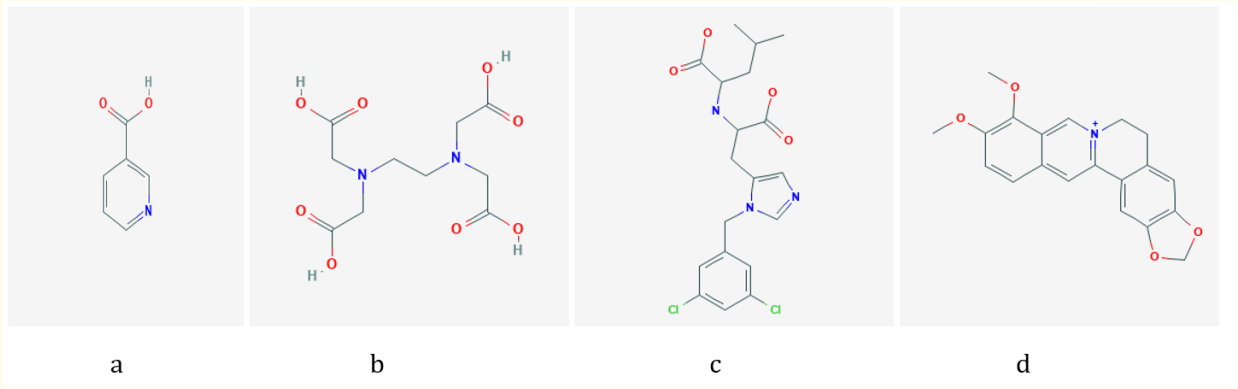

Figure 3: *Structure of (a) niacin (CID 938) [61], (b) EDTA (CID 6049) [62], (c) © Sitagliptin (CID 4369359) [63] and (d) berberin (CID 2353) [64].*

Conclusion

Prevention of β-coronavirus infections with chelating therapy, EDTA 4 g/day could be used, with caution, for healthcare personnel in contact with the virus. Niacin, 84 nM (vitamin B3) in blood and 16.7 nM of berberine, from natural sources, should protect from β-coronavirus infections, including COVID-19, SARS and MERS. These concentrations have shown to be effective, are safe to use and available from food. At this point we have not, scientifically, quantified the amount of these molecules in the different food sources, to calculate the amount to be consumed to reach this threshold in blood. Food with a high content of vitamin B3 and berberine should be consumed regularly for prophylaxis of coronavirus infections.

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