Thinking about Coronavirus from an Infectious Disease Perspective
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As the medical community frantically scrambles to address SARS-CoV2, we in the natural community can also be investigating the tools we have that may be helpful during this pandemic. As a scientist who is not a clinician, my opinions come from research, not clinical experience. Given that there is not yet research on most (if any) natural therapies for SARS-CoV2, this conversation is going to be based on past research of other viruses.

Let's start with the SARS-CoV2 virus.

At this point in time (March 20, 2020), we know that SARS-CoV2 enters the body through the ACE2 receptor. The ACE2 receptor is on many cells in the body, including the vascular epithelium, lung, and gut tissue. It's expressed at lower levels in the renal system and the central nervous system. The implications are that people who already have disease in these systems may experience worse symptoms as the virus interferes with ACE2 receptor.

One strategy we've used for past viral infections is block the viral-human receptor interface. For influenza, the virus binds to sialic acid, and antivirals block this interaction. For HIV, the virus binds to CCR5 or CXCR4 and CD4. Again, antivirals designed for HIV can block this interaction.

What could block SARS-CoV2 and ACE2?

The first promising data came from hydroxychloroquine. This is a drug used for malaria. While in vitro data looks promising[1], the side effects[2] are not great and it hasn't shown in vivo effects with SARS-CoV2. This hasn't stopped the general public from buying hydroxychloroquine.

The natural source of chloroquine is the bark of the Cinchona tree.[3] Cinchona is available as a supplement, however it has not been studied for SARS-CoV2. Some individuals are trying other antimalarials, such as *Artemisia anna*. If Artemisia works on SARS-CoV2, it would likely be through a different mechanism than blocking viral uptake, as it doesn't work like on malaria like hydroxychloroquine.[4]

The research community is looking at other strategies for blocking viral uptake, including ACE2 receptor antibody. Competitive inhibition is another strategy, so recombinant ACE2 receptors are be synthesized to test as a potential drug.

Viral Infection in Cells

Once SARS-CoV2 is inside the cell, it goes through its viral life cycle.[5] SARS-CoV2 is a retrovirus, thus our comparison is between SARS-CoV2 and HIV infection. As with all retroviruses, SARS-CoV2 RNA must be transcribed into RNA. Reverse transcriptase inhibitors and other antivirals that are used for HIV were tested in the past for SARS-CoV.[6] Betaferon, Alferon, Multiferon, Wellferon, and ribavirin showed promise in the 2004 study. Derivatives of these drugs are being

tested both alone and in combination.[7] The protease inhibitors for HIV are not likely to work on SARS-CoV2 as the proteases are very different. However, some of the other antiretrovirals such as nucleotide inhibitors and interferon beta may have an effect.

There are no natural nucleotide inhibitors. However, there are natural antivirals that impact HIV as well as natural antivirals that affect other upper respiratory viruses.

Berberine is an antiviral that has shown activity in HIV, influenza, and respiratory syncytial virus.

Berberine, from Goldenseal and Oregon Grape Root, inhibits ER stress, which has two effects on infection in vitro. It decreases production of inflammatory cytokines TNF-alpha and IL-6. It also decreases production of HIV proteases at the level of protein production.[8] Thus berberine is indirectly acting as a protease inhibitor.

Other in vitro studies of berberine in influenza demonstrate a reduction of inflammation in mouse lung.[9] Berberine has a different mechanism of action in influenza. It reduces inflammation through inhibition of the TLR7, MyD88, NF-kB, pathway.[9]

Respiratory Syncytial Virus (RSV) is also affected by berberine. In the case of RSV, berberine reduces phosphorylation of P38 MAPK (map kinase) early in infection which reduces viral replication.[10] In addition, berberine reduces IL-6 mRNA, suggesting that it is reducing inflammation.[10]

Together these studies suggest that berberine could inhibit SARS-CoV2 infection – although it hasn't been studied specifically for SARS-CoV2.

Antiviral Evidence for Elderberry (*Sambucus nigra*)
While there haven't been large clinical trials looking at Elderberry, there have been two small clinical trials that demonstrate that elderberry extract shortens the length of infection when compared to placebo.[11] In both studies, Elderberry decreased the length of infection by four days.[12,13]

Elderberry's effect on virus is different than many other herbs. It appears to affect lipid rafts, which means that it can inhibit viral uptake and viral budding.[14,15] This is mechanism that would make elderberry important for any viral infection, including SARS-CoV2.

Elderberry does not stimulate a cytokine storm in any research study. In fact, elderberry can reduce reactive oxygen species (ROS) and inflammatory cytokine secretion by blocking NF-kB pathways.[16] While this study was not in an infectious disease model, the lack of reports of cytokine storms is significant considering that clinical trials have been completed.

Astragalus – Antiviral and more
Astragalus membranaceus has been used for thousands of years for lung health and upper respiratory infection. Interestingly, astragalus is used for treating bird flus and has been studied

in several avian infections.[17–19] Research on astragalus suggests that it's blocking several TLRs (the receptors that indicate danger to your immune system and launch the inflammatory pathway).[20,21] Importantly, one of the components of astragalus, astragaloside IV, is cardioprotective.[22]

Astragalus has also been used for HIV, but as one component of a Chinese herbal formula. In this study, the viral load decreased, and the herb combo (which included Glycyrrhiza glaba L., Artemisia capillaris Thumb., Morus alba L., Astragalus membranaceus(Fisch.) Bge., Carthamus tinctorius L.) was shown to be safe.[23]

Echinancea – one of the most recognized antivirals
The antiviral activities of Echinacea purpea are evident in an aqueous extract. It's been shown to prevent influenza A, avian flu, and swine flu.[24] For influenza viruses, echinacea may be impacting the hemagglutinin, which wouldn't be relevant to SARS-CoV2. However, echinacea can kill HIV-1, through blocking viral integrase.[24] And echinacea has also been shown to be active against herpes simplex 1 and 2 in vitro.[24] Together this suggests that echinacea has broader antiviral effects.

Echinacea also has a variety of immunological effects. We will discuss the implications of these activities in another discussion.

Mint family (Lamiaceae) – spearmint, peppermint, lemon balm, self-heal
Several aqueous extracts, peppermint, lemon balm and sage, from the mint family have been shown to decrease HIV infectivity at very low doses of herb.[25] What is especially interesting about the mint family is that it inactivates HIV before it binds to cells and infects them. In fact, once the HIV virus binds to cell, the herbs are no longer effective. This data suggests that the mint family is directly viral toxic.[25]

Lemon balm (Melissa offinalis) extract can inhibit protein synthesis in Herpes I infection, again inhibiting attachment.[26] Because of its potent antiviral activity, lemon balm has been tested as an alternative to oseltamivir (a pharmaceutical antiviral). In this study, lemon balm inhibits viral replication at multiple stages of the viral replication cycle.[27]

Other members of the Lamiaceae family, such as Oregano, may also be effective.[28] Less is known about the mechanism, however it has shown efficacy against respiratory syncytial virus, coxsackie virus B3, and HSV1.[28]

Summary

This discussion is meant to demonstrate that there are several herbal therapies that could demonstrate similar antiviral activity to pharmaceutical approaches. There are other antiviral herbs, including green tea, pomegranate, licorice root, and milk thistle to name a few. This is not meant to be a comprehensive review. Instead, this discussion is meant to suggest that there

are tools that can be tested against SARS-CoV2. A future discussion will include herbs that may affect the Immune response to SARS-CoV2.

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