



REVIEW ARTICLE

A Systemic Review: Structural Mechanism of SARS-CoV-2A and Promising Preventive Cure by Phytochemicals

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Abstract

The novel coronavirus 2019 has recently emerged as a human pathogen in the city of Wuhan in China's Hubei province, causing fever, severe respiratory illness, and pneumonia disease recently named COVID-19 [1,2].

The world experienced the outbreaks of coronavirus infection that threaten global pandemic in 2002-2003 by Severe Acute Respiratory Syndrome (SARS) and in 2011 by Middle East Respiratory Syndrome (MERS). The genomic sequence of SARS-CoV-2 showed similar, but distinct genome composition of SARS-CoV and MERS-CoV.

Phytochemicals are a powerful group of compounds, belonging to secondary metabolites of plants and including a diverse range of chemical entities such as polyphenols, flavonoids, steroidal saponins, organ Sulphur compounds, and vitamins. The potential biological benefits such as antioxidant, anti-inflammatory, anticancer, antibacterial, anti-fungal and antiviral activities.

The ideal technology would be vaccine that gives lifelong immunity with a single dose. When whole world community of scientist working hard to find out clinical solution of this problem so mean time we have to work with what we have in hand the best prevention approach and the phytonutrient could be a one of them.

Keywords

COVID-19, Phytochemical, Antiviral, Curcumin, Lock & Key mechanism

Introduction

The novel coronavirus 2019 has recently emerged as a human pathogen in the city of Wuhan in China's Hubei province, causing fever, severe respiratory illness, and pneumonia disease recently named COVID-19 [1,2].

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infection that threaten global pandemic in 2002-2003 by Severe Acute Respiratory Syndrome (SARS) and in 2011 by Middle East Respiratory Syndrome (MERS). The genomic sequence of SARS-CoV-2 showed similar, but distinct genome composition of SARS-CoV and MERS-CoV [3,4].

The World Health Organization (WHO) also declared a global emergency on January 31st due to increasing concerns over its fast spread, and on March 11th the disease was recognized as a pandemic.

As of today, 26 Apr 2020 around 3 million cases were reported that infected by coronavirus with 200,000 deaths while 840,000 has been recovered. The distribution of total cases and daily projection of cases given in [5] (Figure 1).

On an average corona hit the 1.5% to 2020 global GDP and 0.2% to long-run global GDP. We forecast a muted long-term impact because damage to productive capacity will be small, plus economic confidence should quickly return once the virus subsides [6,7] (Figure 2).

Human pathogenic subtypes of CoV are associated with mild clinical symptoms. However, severe acute respiratory syndrome related coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are the two notable exceptions. In 2012, MERS-CoV was first detected in Saudi Arabia. It was responsible for 2,494 confirmed cases, which led to 858 fatalities [8]. In 2002, a subtype of the beta-COV rapidly spread across Guangdong, China. This outbreak resulted in 8,000 infections and 774 fatalities in 37 countries [9]. The outbreak in 2020 has presented in the form of pneumonia.

Distribution of cases

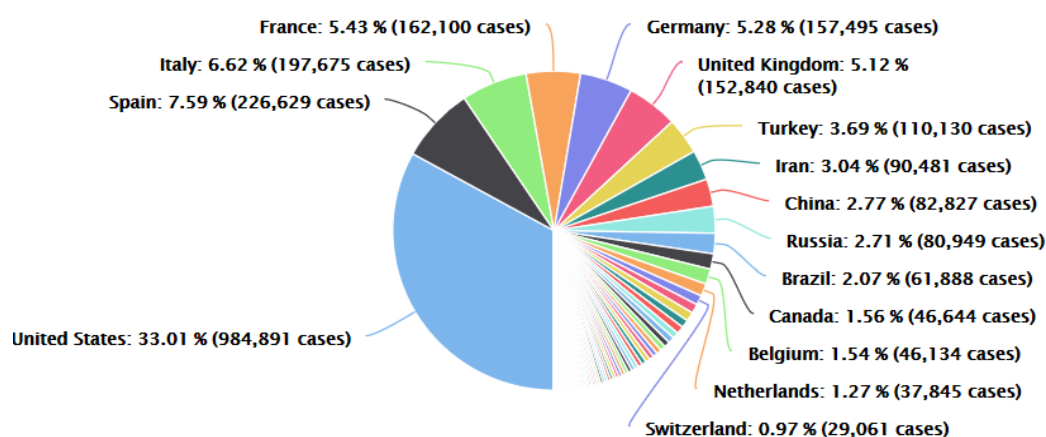


Figure 1: Worldwide distribution of COVID-19 cases [5].

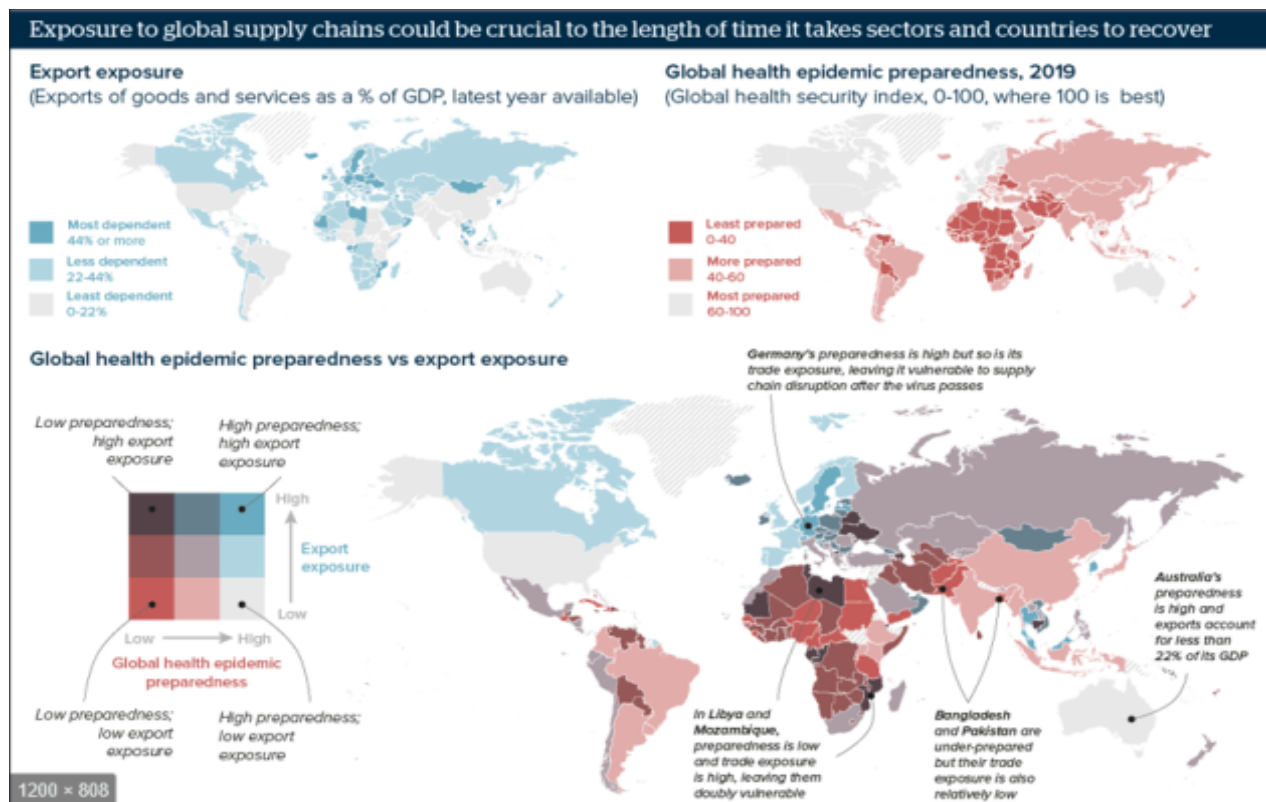


Figure 2: Health preparedness and trade affect COVID-19 exposure [8].

Initially, this virus was designated as 2019-nCoV. However, the International Committee on Taxonomy of Viruses designated it as the SARS-CoV-2 virus [10-13].

The AIDS epidemic offers an example the broad goal of course is to end the disease the highest leverage approach is prevention. The ideal technology would be vaccine that gives lifelong immunity with a single. When whole world community of scientist working hard to find out clinical solution of this problem so mean time we have to work with what we have in hand the best prevention approach and the phytonutrient could be a one of them.

Phytochemicals are a powerful group of compounds, belonging to secondary metabolites of plants and including a diverse range of chemical entities such as polyphenols, flavonoids, steroidal saponins, organ Sulphur compounds, and vitamins. The potential biological benefits such as, antioxidant, anti-inflammatory, anti-cancer, antibacterial, antifungal and antiviral activities. The high bioavailability and low cytotoxicity of natural phytochemical it would be great possible candidate in this situation. Here author intended to discuss the mechanism of antiviral properties of few phytochemical toward the SARS-COVID-19 and how it would be a preventive approach in the pandemic situation [14-17].

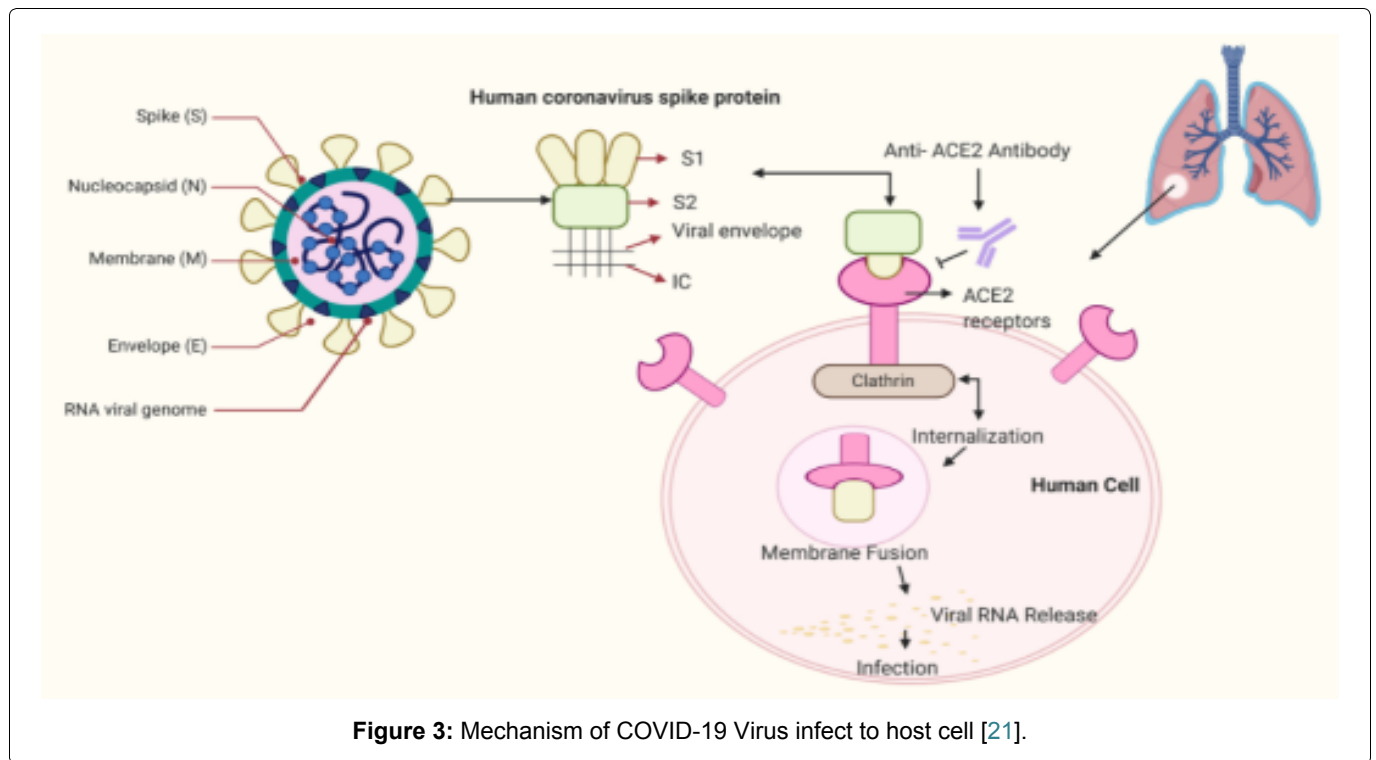


Figure 3: Mechanism of COVID-19 Virus infect to host cell [21].

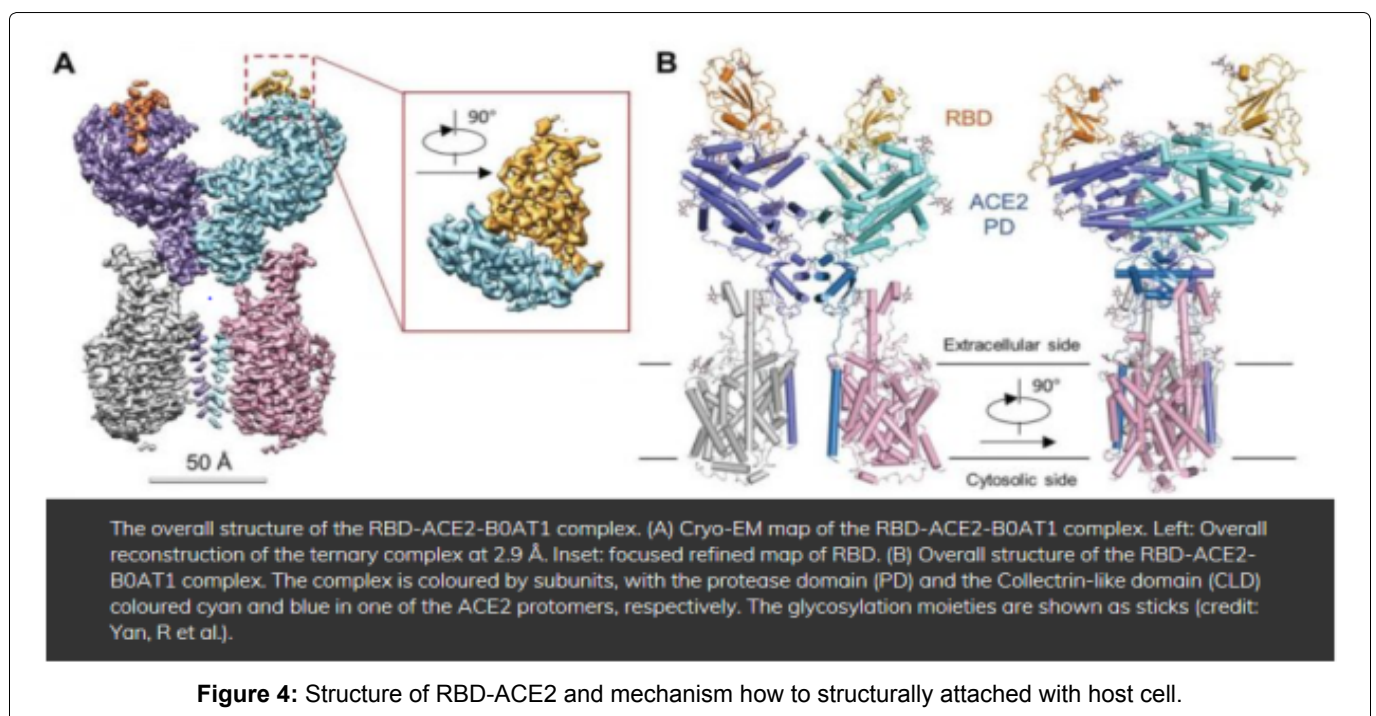


Figure 4: Structure of RBD-ACE2 and mechanism how to structurally attached with host cell.

Clinical Mechanism of SARS Spike Protein in Host Cell

Coronavirus (CoV) is a large family of positive-sense, single-stranded RNA virus that. Their viral RNA genome ranges from 26 to 32 kilobases in length [18]. The virus has four important structural proteins which are (E) the envelope protein (M) the membrane protein (S) the spike protein and (N) the nucleocapsid protein, which are required to regulate the function and viral structure [19] among these virus S and N will help to attachment of virus with host cells. The attachment of virus to the host cells [20].

The S protein has three major sections which are the

large ectodomain, a single-pass trans-membrane anchor and a short intracellular tail. These play a major role in anchoring the host cells. Among these sections have two subunits which are the S1 receptor-binding subunit and S2 the membrane fusion subunit.

During infection, the S protein is cleaved into subunits, S1 and S2. S1 contains the receptor binding domain (RBD) which allows coronaviruses to directly bind to the peptidase domain (PD) of ACE2. S2 then likely plays a role in membrane fusion [20,21] (Figure 3).

Studies, suggests ACE2 needs to dimerism to be active. The resultant homodimer has two PDs, able to bind two COVID-19 S protein trimmers simultaneously in the

current study, the team identified that the structures could only bind if the PD interacts with the up RBD [22].

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They further compared how SARS-CoV-2-RBD binding is different to other SARS-CoV-RBDs binding; showing that some changes in the sequence may make associations tighter in COVID-19, while others could reduce the binding affinity.

This virus belongs to β -coronavirus, a large class of viruses prevalent in nature. Similar to other viruses, SARS-CoV-2 has many potential natural hosts, intermediate hosts and final hosts.

Cytokine release syndrome is a vital factor that aggravates disease progression. A higher levels of IL-6 and IL-10, and lower levels of CD4+T and CD8+T are observed in COVID-19 patients parallel with the severity of the disease [7].

Mechanism of Antiviral Activities of Phytochemicals

Phytochemical compound works as a legend and -protein at the site where it was known to get involved in host cell binding. Their binding interaction is more stable than with that of recently available drug. Similarly, it was also seen that these molecules attach to those sites of ACE2 which were involved in serving a medium of viral entry. Thus, it is apparent from the present study that viral infection can be prevented by Phytochemicals.

Phytochemicals bind to S this would rather serve dual inhibitory machinery by blocking host cell receptor to virus and viral protein entry. Moreover, some of

the phytochemicals are more potent immunostimulant and have been reported to induce autophagy, another important mechanism of viral clearance that promotes elimination or neutralisation of viral infection [23].

Blocking mechanism by the Activity of viral RNA

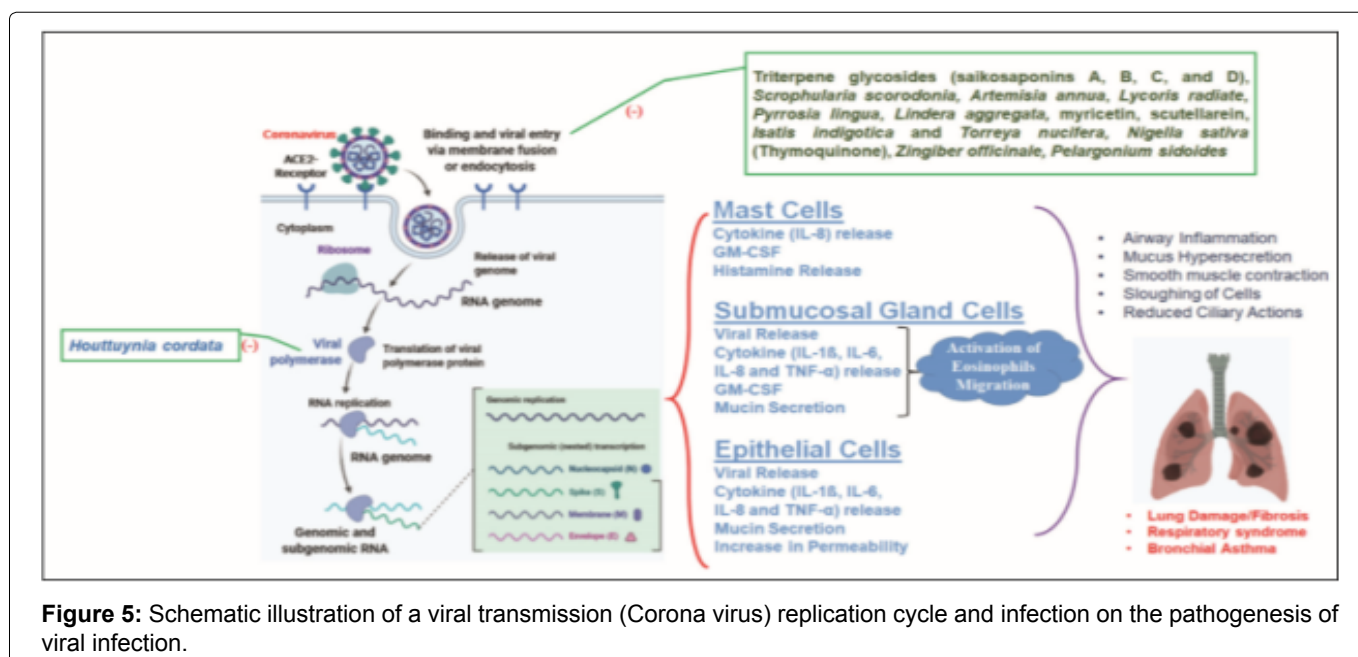
Some of the myricetin, scutellarein, and phenolic compounds work as natural inhibitors against the SARS-Covid-19. They show the different antiviral mechanisms against SARS-CoV that include inhibiting the viral 3CL protease and blocking the activity of viral RNA-dependent RNA polymerase29 (Figure 5).

Molecular docking is a computational method which aims to identify non-Covalent binding between protein (receptor) and a small molecule (ligand/Inhibitor). Docking predicts the mode of interaction between a target protein and a small ligand for an established binding site [24].

Phytochemical compound works as a legend. The SARS-CoV-2S is a surface glycoprotein. This protein plays important roles during viral attachment, fusion and entry into the host cells [25]. Biologically this protein exists in a heterotrimeric form with three separate polypeptide chains: Chain A, B and C, forming each monomer [26]. Ligands to investigate their binding affinity with SARS-CoV-2S chain A as the receptor target protein [21,26,27].

Therapeutic Activity of Few Phytochemical-SARS COVID-19

Medicinal plant compounds are already used to successfully treat numerous viral diseases. Currently no effective treatment is available for COVID-19. Phytochemicals could be an effective tool by increase the Immunity and can transform in to the clinical drug. Thus, it is necessary to further examine the topic of antiviral phytochemicals, highlighting drug delivery applications



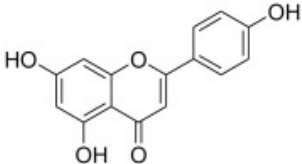
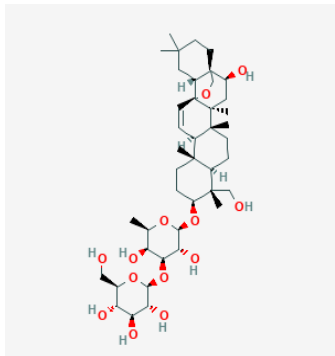
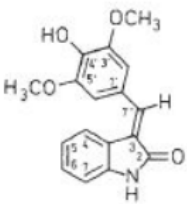
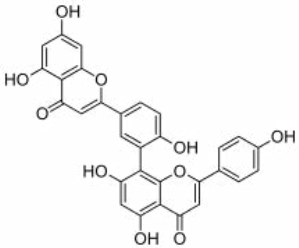
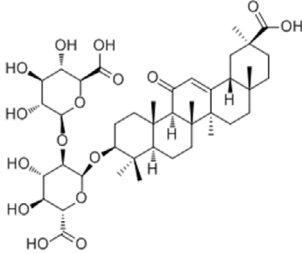
in overcoming the multiple biological barriers existing for antiviral agents to successfully reach their intended site(s) of action. Here author focus to explain about few phytochemical they could be a next possible treatment against the pandemic situation.

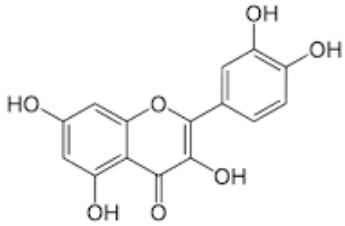
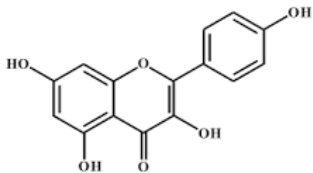
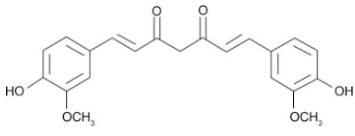
Ginger, *Zingiber officinale*, is a widely used has been found active against Human Respiratory Syncytial Virus (HRSV)-induced plaque formation on the epithelium of the airways through blocking viral attachment and internalization. Interestingly, an extract of *Pelargonium sidoides* reduces rhinovirus infection through modulation of viral binding proteins on human bronchial epithelial cells. For the management of acute bronchitis

and acute respiratory tract infections [28].

It's reported these natural compounds effectively prevent the early stage of HCoV-22E9 infection, including viral attachment and penetration. *Saikosaponins* (A, B2, C, and D), which are naturally occurring triterpene glycosides isolated from medicinal plants such as *Bupleurum* spp. *Heteromorpha* spp., and *Scrophularia scorodonia* exert antiviral activity against HCoV-22E9. Natural inhibitors against the SARS-CoV enzymes, such as the nsP13 helicase and 3CL protease, have been identified as well and include myricetin, scutellarein, and phenolic compounds from *Isatis indigotica* and *Torreya nucifera* [29-38] (Table 1).

Table 1: Phytochemical source and mode of action.

Name of Phytochemical	Mode of Action	Structure	Source	Reference
Apigenin	Apigenin inhibited EV-A71 infection by suppressing viral internal ribosome entry site (IRES) activity.		Fruit and vegetable parsley, Celery, Celeriac and Chamomile tea	[29]
Saikosaponins (A)	Early stage of HCoV-22E9 infection, Including viral attachment and penetration.		Triterpene glycosides Radix Bupleuri medicinal plant	[30]
<i>Isatis indigotica</i>	SARS-CoV 3CL protease inhibitor		Phenolic compound woad dyer's woad or Glastum	[29]
Amentoflavone	SARS-CoV 3CL protease inhibitor		<i>Torreya nucifera</i> japease nutmag	[31]
<i>Glycyrrhiza glabra</i>	Inhibition of viral replication; Modulation of membrane fluidity		Licorices	[32]

Vitex trifolia	Reduction		–	[34]
Quercetin	Reduced RNA and Protein synthesis and Antioxident activity.		Red (grape) wines, Leaves of radish (<i>Raphanus raphanistrum</i> subsp. <i>sativus</i>) and fennel (<i>Foeniculum vulgare</i>), seeds of pepper (<i>Capsicum annuum</i>)	[33,35,36]
Kaempferol	Inhibit 3a ion channel of coronavirus		Raspberry (<i>Rubus idaeus</i>), Capers (<i>Capparis spinosa</i>), Brussels sprout (<i>Brassica oleracea</i>), Black bean (<i>Phaseolus vulgaris</i>) and Fruit of grapes	[37,45]
Curcumin	By interference of Viral replication machinery or Suppression of cellular signaling pathways essential for Viral replication		Turmeric Indian spice	[42,43]

Ashwagandha (*W. somnifera*)

It has been reported *W. somnifera* compound, with anone, docked very well in the binding interface of AEC2-RBD complex, and was found to move slightly towards the interface center on simulation. With anone significantly decreased electrostatic component of binding free energies of ACE2-RBD complex. Two salt bridges were also identified at the interface; incorporation of with anone destabilized these salt bridges and decreased their occupancies. We postulate, such an interruption of electrostatic interactions between the RBD and ACE2 would block or weaken COVID-19 entry and its subsequent infectivity [39].

Curcumin

Due to the lack of preventive and therapeutic options for many viral infections, numerous studies have been conducted to investigate the antiviral potential of various natural compounds [25,40,41]. Accumulated evidence indicated curcumin plays an inhibitory role against infection of numerous viruses including hepatitis viruses, influenza viruses and emerging arboviruses like the Zika virus (ZIKV) or chikungunya virus (CHIKV), human immunodeficiency virus (HIV), herpes simplex virus 2 (HSV-2) and human papillomavirus (HPV) [20]. Various studies shows the mechanisms involve either a direct interference of viral replication machinery or suppression of cellular signaling pathways essential for viral replication, such as PI3K/Akt, NF- κ B [21]. Inosine monophosphate dehydrogenase (IMPDH) enzyme due to rate-limiting activity in the *de novo* synthesis of guanine nucleotides is suggested as a therapeutic target for antiviral compounds [42,43].

Glycyrrhizin

Glycyrrhizin inhibits SARS-associated coronavirus (SARS-CoV) replication in Vero cells with a selectivity in-

dex of 67. In addition to inhibition of virus replication, glycyrrhizin is able to inhibit adsorption and penetration of the virus during the early steps of the replicative cycle. The studies from show that glycyrrhizin induces nitrous oxide synthase in Vero cells and that virus replication is inhibited when a nitrous oxide donor (DETANO-nate) is added to the culture medium [32,35,44].

Quercetin

Quercetin compound with phenolic group occurs widely in nature, found in berries, fruits, grains, onion, kale and vegetables. It neutralizes potentially damaging free radicals through the donation of a hydrogen atom. The antioxidant activity is a key interest in current situation. Computer modeling techniques to identify these molecules as conceivably block the “ACE2 receptors” on cells to which the coronavirus that causes COVID-19 attaches, much like a key fits into a lock. Once the virus enters a cell it hijacks the cellular machinery and uses it to reproduce and crank out more viruses. Based on its molecular structure, quercetin could be a “key” that fits the lock and blocks other “keys” [37].

Studies reveals kaempferol has high bioavailability. In particular, The fact that these drugs not only block the 3a channel, thus counteracting virus production, but that they also interfere with other steps of the viral life cycle emphasizes the importance of multi-target phytochemical. The glycosides of kaempferol seem to be highly potent candidates for development as anti-coronaviral agents [37,38,45].

Conclusion

This is an unfortunate truth that a lot of world population will contract SARS-CoV infection. While specific treatment is not yet coming soon, individual preventive and protective measures drive the personal risk of getting the disease. Due to high bioavailability, efficacy

phytochemicals is a promising preventive option in this situation. Include phytochemical rich food like curcumin, Ginger below the daily intake limit could be prevent the un-effected population of world by the pandemic situation. Author not support to take any kind of those .more attention, research development and clinical trial would be need to became a rising clinical option and development of safe drugs. Authors promote to avoid COVID-19 in addition to a healthy diet, following precautions provided by the Centers for Disease Control and Prevention can help keep you safe.

Conflicts of Interest

The authors report no conflicts of interest in this work.

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References

- Nimesh Sing, Archana Panday (2020) Corona Virus: A review article to identify novel drug for treatment. IJSR.
- Jasper Fuk-Woo Chan, Shuofeng Yuan, Kin-Hang Kok, Kelvin Kai-Wang To, Hin Chu, et al. (2020) A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: A study of a family cluster. *Lancet* 395: 514-523.
- Chaolin Huang, Yeming Wang, Xingwang Li, Lili Ren, Jianping Zhao, et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395: 497-506.
- (2020) Did pangolins spread the China coronavirus to people?.
- <https://www.nature.com/articles/d41586-020-00364-2>
- <https://www.worldometers.info/coronavirus/>
- (2020) Morning star view: The impact of coronavirus on the economy.
- (2020) Health preparedness and trade affect COVID-19 exposure.
- (2020) Scientists demonstrate how COVID-19 infects human cells.
- Li-sheng Wang, Yi-ru Wang, Da-wei Ye, Qing-quan Liu (2020) Review of the 2019 Novel Coronavirus (COVID-19) based on current evidence. *International Journal of Antimicrobial Agents*.
- Organization WH (2020) Coronavirus disease (COVID-2019) situation reports.
- Chan JF, To KK, Tse H, Jin DY, Yuen KY (2013) Interspecies transmission and emergence of novel viruses: Lessons from bats and birds. *Trends Microbiol* 21: 544-555.
- Zhu N, Zhang D, Wang W, Li X, Yang B, et al. (2020) A novel coronavirus from patients with pneumonia in China, 2019. *The New England Journal of Medicine*.
- Thevarajan I, Nguyen THO, Koutsakos M, Julian Druce, Leon Caly, et al. (2020) Breadth of concomitant immune responses prior to patient recovery: A case report of non-severe COVID-19. *Nat Med*.
- Forni C, Facchiano F, Bartoli M, Pieretti S, Facchiano A, et al. (2019) Beneficial role of phytochemicals on oxidative stress and age related diseases. *BioMed Research International*.
- Panche AN, Diwan AD, Chandra SR (2016) Flavonoids: An overview. *Journal of Nutritional Science*.
- Kumar S, Pandey AK (2013) Chemistry and biological activities of flavonoids: An overview. *The Scientific World Journal*.
- Hassan S, Sheikh FN, Jamal S, Jude K Ezech, Ali Akhtar (2020) Coronavirus (COVID-19): A review of clinical features, diagnosis, and treatment. *Cureus* 12: e7355.
- D Schoeman, BC Fielding (2019) Coronavirus envelope protein: Current knowledge. *Virology J*.
- AC Walls, YJ Park, MA Tortorici, A Wall, AT McGuire, et al. (2020) Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell*.
- Balachandar Vellingiri, Kaavya Jayaramayyab, Mahalaxmi Iyer, Arul Narayanasamy, Vivekanandhan Govindasamy, et al. (2020) COVID-19: A promising cure for the global panic. *Science of the Total Environment*.
- Campbell GR, Pasquier E, Watkins J, Bourgarel-Rey V, Vincent Peyrot, et al. (2004) The glutamine-rich region of the HIV-1 Tat protein is involved in T-cell apoptosis. *J Biol Chem* 279: 48197-48204.
- Zhou Y, Simmons G (2012) Development of novel entry inhibitors targeting emerging viruses. *Expert review of anti-infective therapy* 10: 1129-1138.
- DeLano W (2002) The PyMOL molecular graphics system. *Schrodinger LLC*.
- Steinmann J, Buer J, Pietschmann T, Steinmann E (2013) Anti-infective properties of epigallocatechin-3-gallate (EGCG), a component of green tea. *Br J Pharmacol* 168: 1059-1073.
- Rane Jitendra Subhash, Chatterjee Aroni, Kumar Abhijeet, Ray Shashikant (2020) Targeting SARS-CoV-2 Spike Protein of COVID-19 with naturally occurring phytochemicals: An in silico study for drug development. *ChemRxiv*.
- Belouzard S, Millet JK, Licitra BN, Whittaker GR (2012) Mechanisms of coronavirus cell entry mediated by the viral spike protein. *Viruses* 4: 1011-1033.
- <https://www.researchsquare.com/article/rs-22057/v1>
- Thomas T Yoshikawa, Kevin P (2001) Nutritional strategies to boost immunity and prevent infection in elderly individuals. *High Clinical Infectious Diseases* 33: 1892-1900.
- Zorofchian Moghadamtousi S, Hajrezaei M, Abdul Kadir H, Zandi K (2013) *Loranthus micranthus* Linn: Biological activities and phytochemistry. *Evidence-Based Complementary and Alternative Medicine*.
- (2013) World Health Organization.
- SY Li, C Chen, HQ Zhang, HY Guo, H Wang, et al. (2005) Identification of natural compounds with antiviral activities against SARS-associated coronavirus. *Antivir Res* 67: 18-23.
- C Fiore, M Eisenhut, R Krausse, E Ragazzi, D Pellati, et al. (2008) Antiviral effects of *Glycyrrhiza* species. *Phytother Res* 22: 141-148.

34. J Liou, CY Cheng, KW Yeh, YH Wu, WC Huang (2018) Protective effects of casticin from *Vitex trifolia* alleviate osinophilic airway inflammation and oxidative stress in a murine asthma model. *Front Pharmacol* 635.
35. Salima Lalani, Chit Laa Poh (2020) Flavonoids as Antiviral Agents for Enterovirus A71 (EV-A71). *Viruses* 12: 184.
36. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, et al. (2003) Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. *The Lancet* 14: 2045-2046.
37. Liang-TzungLin, Wen-ChanHsu, Chun-ChingLin (2014) Antiviral natural products and herbal medicines. *J Tradit Complement Med*.
38. <https://www.mcgill.ca/oss/article/health/quercetin-take-or-not-take>
39. Chandel V, Raj S, Rathi B, Kumar D (2020) In Silico Identification of Potent COVID-19 main protease inhibitors from FDA approved antiviral compounds and active phytochemicals through molecular docking: A drug repurposing approach. Preprints.
40. (2020) European Review for Medical and Pharmacological Sciences 24.
41. Acharya Balkrishna, Subarna Pokhrel, Jagdeep Singh, Anurag Varshney (2020) Withanone from *Withania somnifera* May Inhibit Novel Coronavirus (COVID-19) Entry by Disrupting Interactions between Viral S-Protein Receptor Binding Domain and Host ACE2 Receptor.
42. Dimas Praditya, Lisa Kirchhoff, Janina Bruning, Heni Rachmawati, Joerg Steinmann (2019) Anti-infective Properties of the Golden Spice Curcumin. *Front Microbiol*.
43. Mathew D, Hsu WL (2018) Antiviral potential of curcumin. *Journal of Functional Foods*.
44. CW Lin, FJ Tsai, CH Tsai, CC Lai, L Wan, et al. (2005) Anti-SARS coronavirus 3C-like protease effects of *Isatisindigotica* root and plant-derived phenolic compounds. *Antivir Res* 68: 36-42.
45. Silvia Schwarz, Daniel Sauter, Kai Wang, Ronghua Zhang, Bing Sun, et al. (2014) Kaempferol Derivatives as Antiviral Drugs against the 3a Channel Protein of Coronavirus. *Planta Med*.