Can concomitant use of zinc and curcumin with other immunity-boosting nutraceuticals be the arsenal against COVID-19?

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Dear Editor,

The recent pandemic spread of COVID-19 has socio-economically crippled the world and threatened humanity akin to World War II situation. The rise of this novel strain, SARS-CoV-2, and its exponential transmission rate has hindered the researchers to find a plausible prophylaxis and therapy to date. Therefore, slowing down the transmission rate is the only possible action plan. Hence, WHO recommended social distancing and improving personal hygiene as a protective measure, adhering to which, nations around the globe have imposed a total lockdown for its citizens.

Aging and/or immunocompromised populations, as well as polymorbid patients, are the most vulnerable towards COVID-19 according to mortality and morbidity reports around the globe (Koff & Williams, 2020). It suggests that the COVID-19 has a proximate association with innate and adaptive immune responses, which declines with age and diseases. Further scientific investigations are warranted in these directions. However, the diet has an integrated role in raising our immune responses against pathogenic invasions. Adequate and proper nutrition is required for an "activated" immune system to meet the demand for energy during periods of infection. Micronutrients and dietary components play a specific role in the development and maintenance of an effective immune system e.g. Vitamin A and Zinc (Zn), via regulating cell division, which is involved in the proliferative response of the immune cells (Childs, Calder & Miles, 2019). Whereas, Vitamin E being an antioxidant involved in the activation of protein kinase C. Similarly, prebiotic and probiotic-rich diets enrich the gut microbiota which further nourishes components of the immune system like immunoglobulin A (IgA). The majority of such immune cells reside in gut-associated lymphoid tissues, thus reflecting its importance in maintaining host health.

Lack of effective prophylaxis against COVID-19 has prompted regulatory authorities to propose boosting of immunity of individuals via nutritional supplements. While modern medicine directly confronts an antigen (via vaccination or antibiotic), in comparison nutraceuticals, food supplements, and traditional medicines activate the overall immunity of the human body. To maintain optimum health during this lockdown period, recently Ministry of AYUSH, Government of India, has also stressed upon various immunity-boosting steps concerning Ayurveda (*AYUSH*). Several suggestions from daily intake of warm water, Haldi, herbal tea etc., to practicing yoga and Pranayam, have been suggested by the Indian Government.

The hypothesis of Ayurveda or any other traditional system of medicine has been built around the concepts of practicing daily/ seasonal regimes and consuming nutrients which further nourishes us and develops overall natural resistance against pathogens. US Food and Drug Administration (FDA) has already approved various food and immunity-boosting dietary supplements as safe (GRAS) level. Reports from China validate the use of Traditional Chinese Medicine (TCM) which has found success against COVID-19. A decoction of Qing Fei Pai Du (QPD), a TCM, has proven its effectivity in COVID-19 patients. Out of 701 confirmed cases treated by QPD, 130 cured cases, 51 cases with disappeared clinical symptoms, 268 cases of improved symptoms, and 212 cases of stable symptoms were found without aggravation (*Ren et al., 2020*). Thus, we can expand our discussion by taking the example of two nutritional supplements- Curcuminoids and Zn, which have been classified under GRAS by FDA as nutraceutical and nutrient. Both molecules have a proven history of antiviral activity in both *in vitro* and *in vivo* trials thus could be leadings in developing new prophylactic candidates against COVID-19.

Curcumin is a natural bioactive polyphenolic compound isolated from the dried powder of *Curcuma longa* rhizomes, commonly known as turmeric (*Haldi* in Hindi), and widely used worldwide for cooking. Ayurveda mentioned the use of turmeric for numerous therapeutic purposes like blood coagulation to immune stimulation. An array of systemic antioxidant properties has been attributed to curcumin containing nutraceuticals. For example-it exerts an anti-inflammatory action in arthritis and inflammatory bowel diseases, reduces lipid levels in cardiovascular diseases and address oxidative stress in skins disorders (Pagano, Romano, Izzo et al., 2018). Curcumin has an established track record as an antiviral agent against several viruses like Influenza Type A, Hepatitis A, Zika, HIV etc. Mode of action of curcumin includes- inhibition of viral entry into cells, suppression of viral replication, stimulation of interferons (IFNs) and other cytokines and inhibition of viral protein expression. *In-silico* studies have also revealed that curcumin binds directly with receptor binding domain of viral spike protein (*involved in host cell binding*) and the cognate host cell receptor angiotensin-converting enzyme-2 (*serves as a medium of viral entry*) of SARS-CoV-2 virus (Fig. 1). Moreover, curcumin has been reported to inhibit the release and suppress numerous cytokines like IL-1β, IL-6, IL8, TNFα, MCP-1 etc. When investigated in various viral infection set up, the mode of cytokine suppression by curcumin can be correlated with clinical improvement in conditions associated with cytokine storm (Sordillo & Helson, 2015). Following the suggested interaction with these key components of viral lifecycle and immune system, it is apparent that curcumin could prevent the COVID-19 infection. Moreover, in recent years blood coagulation properties of curcumin (by inhibiting platelet aggregation, cyclooxagenase pathway and blocking of calcium signaling) has been utilized in designing various materials and devices (Keihanian et al., 2018). As the SARS-CoV-2 corona virus

infection can be associated with a disseminated intravascular coagulopathy, hence curcumin can be an effective agent against this pathological condition. It should also be noted that there is the possibility that studies on curcumin have not been carried out according to more recent scientific qualitative standards for plant-derived products (Heinrich et al., 2020). Therefore, there is the chance that high implausible concentrations in vitro or doses in vivo have been used.

Zn is an essential micronutrient and its deficiency influences both the natural and acquired immune system and causes oxidative stress. Physiologically, Zn is found in bound form in intracellular metallothionein proteins. Supplementation of Zn augments metallothionein expression. This leads to direct antiviral actions of metallothionein against an array of viruses by sequestering Zn away from viral metalloproteins or by acting as Zn chaperones and facilitating antiviral signaling indirectly (*Read et al., 2019*). In *in-vitro* study Zn was also found to interfere with the viral replication cycle by free viral inactivation, inhibiting viral uncoating, interfering with viral genome transcription, protein translation, and polyprotein processing. These antiviral properties of zinc need further validation in a clinical setup. In elderly patients, zinc deficiency is concomitant with susceptibility to infections. On supplementation of zinc, a significant drop in infection rate was observed in patients of 55-87 years along with low production of tumour necrosis factor and oxidative stress markers, further establishing the association of zinc deficiency and cell-mediated immune dysfunction (*Prasad et al., 2007*). Zn supplementation can also make a positive contribution to chloroquine and other antiviral treatments applied today. Zn^{2+}along with Zn ionophores found to limit the replication of SARS-CoV, by blocking RNA synthesis via inhibiting RNA-dependent RNA-polymerase (RdRp) (Fig. 1). Consequently, Zn

supplementation directed in a proper strategy can significantly protect against both chronic and acute viral infections.

One of the feasible strategies by antiviral therapeutics is to target pathways/ viral mechanisms that are shared among multiple viral species (for example, cellular entry or RNA genome replication). A recent study revealed the phylogenetic resemblance of surface spike glycoprotein between SARS-CoV-2 and SARS-CoV, which raises the possibility of the existence of cross-reactive epitopes (*Yuan et al., 2020).* The availability of such conserved domains may serve not only as a lead towards the development of SARS-CoV-2 vaccine, but also for cross-protective antibody responses against future corona virus epidemics. Similar therapeutic approaches could be hypothesized by fusing broad-spectrum antiviral properties of curcumin (e.g. *inhibition of viral entry*) with Zn (e.g. *RNA polymerase inhibition*). Zn in combination with polyphenols like curcumin may form ionophore complex and result in a concerted antiviral action. Thus, these supplements as a part of the food, nutraceutical, or traditional medicines may pave the way towards developing a therapeutic strategy against the COVID-19 pandemic.

In conclusion, the novel coronavirus infection has brought the concept of boosting individual immunity at the forefront. Unless until a vaccine is discovered and "herd immunity" is brought upon masses, social isolation is the only resort to remain uninfected. The success story of TCM is continuously inspiring us to test food supplements and raise individual immunity. Can we fit curcumin and zinc into this continuing puzzle?

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Declaration of competing interest

The authors declare that there is no competing interest to disclose.

Author's contribution

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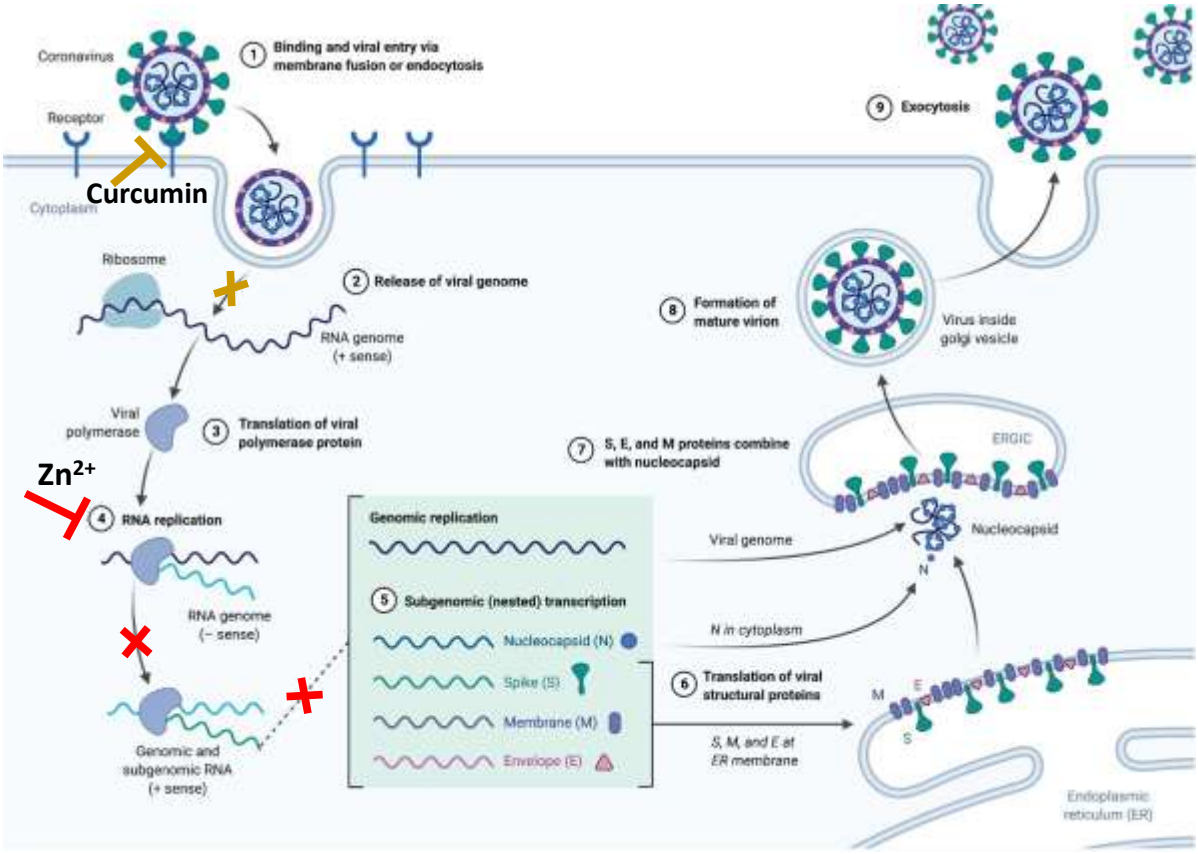

Fig.1. Potential mechanisms by which Curcumin and Zinc can exert therapeutic effects against COVID-19. Curcumin inhibits SARS-CoV-2 entry by binding directly to the receptor-binding domain (RBD) of Spike (S) protein of the virus. Whereas, Zn^{2+} causes inhibition of RNA-dependent RNA-polymersase (RdRp) and reduction in template binding.