Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Resveratrol-zinc nanoparticles or pterostilbene-zinc: Potential COVID-19 mono and adjuvant therapy

Mina T. Kelleni [1]

Pharmacology Department, College of Medicine, Minia University, Egypt

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ABSTRACT

In this manuscript we provide the scientific basis to adopt a novel combination of two widely available nutraceuticals; resveratrol and zinc in management of COVID-19 recommending their administration using a nano-carrier based drug-delivery system. Resveratrol, a well-known antioxidant and anti-inflammatory triphenolic stilbene, is abundant in red grapes, red wine, dark chocolate, and peanut butter. Alternatively, pterostilbene-zinc combination might be also considered without using a nano-carrier. We recommend conducting prompt clinical trials to assess the potential of the suggested combinations as a monotherapy for mild COVID-19 with a potential to prevent its progression to moderate-severe disease for which we recommend their trial as an adjuvant therapy. Furthermore, the suggested combinations might also possess a pharmacotherapeutic potential that exceeds COVID-19 to various inflammatory, immunologic, and oncologic diseases.

Zinc was suggested to be beneficial for prevention and/or adjuvant treatment of COVID-19 relying on its antiviral properties that restore the body homeostasis through positive modulation of its inflammatory and immunological response especially as regards to reduction of spontaneous inflammatory cytokine release, restoration the balance and function of T cells as well as interferon gamma production [1,2]. However, no significant clinical benefits were reported when randomized clinical trials using either 50 mg elemental zinc (zinc sulfate 220 mg) [3] or 7 mg elemental zinc (50 mg of zinc gluconate) [4] were conducted. Importantly, latent and manifest zinc deficiency affect millions of people both in developed and developing countries and is more frequently encountered with increased age, ingestion of high amounts of coffee or tea, cereals, legumes, malabsorption syndromes, diabetes mellites, alcoholism, chronic renal diseases and some drugs including ACEI and diuretics which are known to decrease uptake and/or increase loss of zinc [5].

Interestingly, a preprint that is being under revision for a relatively long time has suggested that only when zinc was co-administered with an ionophore, a significant clinical benefit was achieved, as ionophore was claimed to be necessary to achieve effective intracellular zinc levels. However, the researchers used hydroxychloroquine as the co-administered ionophore and a potential harmful effect of administering hydroxychloroquine alone was also suggested [6]. Furthermore, lack of efficacy of hydroxychloroquine in management of COVID-19 [7] as well as serious adverse effects including mortality have been reported [8].

Thus, we recommend considering another ionophore to be tested with zinc for management of mild COVID-19; resveratrol which is a well-known pluripotent triphenolic stilbene abundant in red grapes, red wine, dark chocolate, and peanut butter. Notably, resveratrol was previously suggested to enhance zinc bioaccumulation in prostate [9] and a complex of zinc(II) with a hexadentate ligand containing a simple phenol; quinol was suggested to possess a synergistic antioxidant activity [10], thus we suggest that resveratrol is among the best candidates to be considered, as besides its well documented antioxidant and anti-inflammatory effects [11,12], it was also shown to inhibit SARS CoV-2 in vitro [13,14]. Additionally, resveratrol has been experimentally shown to antagonize IL-1β, IL-6, TNF-α, NF-κB signaling pathways as well as to reduce COX-1 and/or COX-2 enzymes expression in some murine models [12,15] which might overlap with COVID-19 pathogenesis [16,17]. Furthermore, a preprint showing the results of an observational study has suggested that a combination of resveratrol and copper at doses of 5.6 mg and 560 ng, respectively, orally, once every 6 h has significantly reduced the mortality of severe COVID-19 patients [18] but from a pharmacokinetic and pharmacotherapeutic point of view, we highly recommend to use nano-carrier based drug-delivery systems of this combination [11,19]. Interestingly, numerous well designed clinical trials have confirmed the safety and suggested potential efficacy of

E-mail addresses: drthabetpharm@yahoo.com, mina.kelleni@mu.edu.eg.
[1] https://orcid.org/0000–0001-6290–6025

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resveratrol in various diseases [20,21] Alternatively, pterostilbene; a resveratrol analogue with similar favorable pharmacotherapeutic profile and additional enhanced bioavailability might be also trialed in doses of 100–250 mg daily for adults in combination with zinc [22]. Importantly, we not only agree with a pharmacovigilant panel recommendation against using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial [https://www.covid19treatmentguidelines.nih.gov/supplements/zinc/] but we also suggest that it would be more vigilant to opt for a likewise attitude [https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/] when co-administering zinc with resveratrol in any performed clinical trial as abnormal zinc homeostasis, either deficiency or excessive, might negatively affect the body immune response [23].

Taken together, we recommend prompt clinical trials to evaluate resveratrol or pterostilbene zinc combinations as described to be tested as a monotherapy for mild COVID-19 with a potential to prevent its progression to moderate-severe disease for which we suggest testing the combination as an adjuvant treatment. Finally, we suggest that seeking a "holy grail" to combat COVID-19 through inexpensive and readily available therapeutics or nutraceuticals should always be prioritized and we also suggest that the described combinations with their known pharmacologic anti-inflammatory and immunomodulatory properties possess pharmacotherapeutic potentials that might exceed COVID-19 to various other medical disciplines and diseases related to inflammation, immunity and/or oncogenesis.

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Conflict of interest statement

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