

May the concurrent use of indomethacin and an antioxidant in the SARS-CoV-2 infection treatment induce an exacerbation of COVID-19?

To the Editor,

Apparently, associating vitamins and plant-derived nutraceuticals with a conventional anti-inflammatory therapy against coronavirus disease 2019 (COVID-19) should deal to an improvement in the pharmacological effectiveness and in a prompt healing from the illness, at least according to some recent reports.^{1,2} Yet, none of these studies, has dissected the effect of nutraceuticals from the one from a pharmaceuticals, to better investigate the biochemical effect of plant-derived bioactive substances in the development of the COVID-19 pathogenesis.

Moreover, recent literature has reported that the effect of some vitamins, such as vitamin C,² is not completely harmless on the effect of some anti-inflammatory drugs, such as indomethacin.³

A look on the epithelia lining the gut, that is, the enteric epithelium, should suggest a possible key to address the counteracting action of ascorbate towards some nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin.³ This epithelium works also as an immune barrier, where local innate immunity and commensal bacteria localization, that is, internalization and translocation, are fundamental to adjust the barrier functionality and ensure the correct activity of NSAIDs at this first line of defense. Indomethacin, via a mild increase in the production of reactive oxygen species (ROS), facilitates bacteria translocation and the subsequent enforcement in the activity of the immune barrier in the gut epithelia, via the mitochondria activation and production of ROS. Anti-oxidants such as ascorbate (vitamin C) and flavonoids, disrupt this mechanism, weakening the activity of the immune barrier of the epithelia and, therefore, increasing the susceptibility to infections and inflammatory mechanisms via the gastro-intestinal tract, despite the use of NSAIDs.³

Dysfunction in the gut immune barrier leads to an exacerbation in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.⁴ Both dysbiosis in the gut microbiome and dysfunction in the gut immune barrier, may play a role in the pathophysiology of COVID-19, as the host immunity homeostasis is impaired.⁴

A forecast calculation of the relative risk (RR) of incoming a COVID-19 worsening and being hospitalized, based on data publicly available from the Italian Ministry of Health, if people were treated with an NSAID such as indomethacin associated with vitamin C, gave RR = 4.1907 (95% confidence interval = 4.0337–4.3539, $z = 73.524$, $p < 0.0001$). This calculation is, yet, only presumptive, based on

forecast and probability calculations on data publicly retrievable and regarding the prolonged use of nutraceuticals and its association with indomethacin, when a SARS-CoV-2 infection occurs.

The use of NSAIDs in Italy to address SARS-CoV-2 infection in the earliest stages of the illness, usually when the patient is still at home, remains largely infrequent during mild COVID-19 symptomatology, where pharmaceuticals having a simple pain relief action, such as antipyretics, are much commonly considered.⁵ Therefore, besides people recurring to paracetamol, whose risk to be hospitalized has previously been thoroughly reviewed,^{6,7} patients diagnosed as SARS-CoV-2 positive and showing the earliest COVID-19 symptoms, may increase the risk of being hospitalized if treated with indomethacin and an antioxidant, such as vitamin C or a flavonoid, at least theoretically.

This effect might be even worsened by the use of omeprazole, as it can widely modify the gut colonic microflora.⁸ Certainly, changes in the gut microflora have been associated with severity in patients with COVID-19 and even with immune dysfunction in the gut immune barrier.⁹

A further clinical trial or observational investigation should shed light on this issue and ascertain if the use of nutraceuticals associated with a FANS in the treatment of COVID-19 may exacerbate the development of the pathology due to the impact of a prolonged nutraceutical assumption on the intestinal gut barrier.

Plant-derived anti-oxidants are notoriously toxic compounds, which can elicit a “stress-response” promoting benefits, only in healthy conditions. Yet, further data about the interfering role of plant-derived phytochemicals on the gut immune barrier, need to be updated. Despite flavonoids are retained as health-promoting compounds for gut epithelia,¹⁰ the complex homeostatic regulation of the gut microbiome itself and the host's gut immunity are particularly crucial for subjects undergoing a SARS-CoV-2 infection.^{11,12}

While it is particularly wise to prevent the use of nature-derived anti-oxidants as the only therapy against SARS-CoV-2 infection, the association of NSAIDs with anti-oxidants might even worsen the development of the COVID-19 etiopathogenesis, as previously suggested,¹³ and therefore this issue should be further elucidated. Data on the gastrointestinal function of patients undergoing a merged NSAID + antioxidant therapy or treated with NSAIDs while they are daily up-taking since long time nutraceutical formulas should

be crucial to ensure their prompt recovery, without simplifying the therapeutic protocol with nature-derived compounds usually considered harmless, with a naïve attitude.²

The correct pharmacology of COVID-19 must consider the complex etiopathogenesis of the SARS-CoV-2 infection, which is quite far from a simple, easily addressable flu infection.

AUTHOR CONTRIBUTION

The manuscript was conceived, wrote, validated, and submitted by Salvatore Chirumbolo.

CONFLICT OF INTEREST

The author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

Data regarding this manuscript are available on request to the author

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