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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Response Letter to the Editor

Response to Dr. DF Naude

I appreciate your letter and the concerns that you raise regarding our statement of caution regarding the use of *Echinacea purpurea* and *E. angustifolia* by individuals during symptomatic infection or positive test results for COVID-19. This caution was based on the lack of human clinical data in combination with preclinical evidence of increased IL-1β and/or IL-18 production in infected immune cells and the need for extreme caution regarding Covid (note that this article was written very early in the Covid pandemic).

This article was initially published (Eprint) in March 2020, at the start of the Covid-19 pandemic and was clearly stated as hypothesized therapy—an opinion piece, not a standard of care based upon clinical data. Since the publication of this piece, there have been numerous additional publications, albeit still no human clinical trials on the use of Echinacea spp. in individuals with SARS-CoV-2 infection. Similarly, data has expanded on some of the other hypothesized cautions during COVID-19 illness suggesting that our hypothesized caution may no longer be justified, although the need for prospective clinical trials remains high. This is particularly true for vitamin D,[1,2] especially in individuals deficient in vitamin D.[3,4] Overall, there is still a paucity of human clinical data on the cited hypothetical therapies in patients infected with SARS-CoV-2, necessitating a cautious approach overall.

Dr. Naude points to 5 publications which describe both pro-inflammatory and anti-inflammatory effects of Echinacea, primarily Echinaforce®[1] [hydro-alcoholic extract from fresh Echinacea purpurea herb and root in a 95:5 ratio], noting that the inclusion of *Echinacea purpurea* roots is essential for the anti-inflammatory effects. Collectively, these in-vitro studies elucidate the role of N-alkylamides, found in higher concentrations in the root of *E. purpurea,* in activating cannabinoid receptor 2 (CB2), that, in turn, leads to reduced TNF-α, IL-6 and increased IL-10 expression by peripheral blood mononuclear cells and monocytes.[5,6] The immunosuppressive nature of IL-10 is indeed relevant as IL-10 production reduces IL-1, IL-6 and other inflammatory cytokines. Of note, the *induction* of peripheral blood leukocyte mRNA expression of several inflammatory cytokines, including IL-1B, IL-6, Il-8 and TNF-α, is also documented in several of these studies, although, alkylamides do appear to modulate the protein expression of TNF-α.[7] Dr. Naude cites a preliminary pilot study of 30 healthy adults who received Echinaforce® over 10 days.[8] Interestingly, this study found differential effects depending on constitutive cytokine production levels, showing an induction effect in weak cytokine producers and no effect in strong producers. The clinical significance of this in relationship to Sars-CoV-2 infection is uncertain. This is of particular importance given that both elevated and depressed levels of pro- and anti-inflammatory cytokines can contribute to the lethality of this infection depending upon the stage of infection, individual metabolic and immune variability and co-morbidities.

Overall, we would agree that a hydro-alcoholic preparation of fresh *Echinacea purpurea* that includes both aerial and root components, such as Echinaforce®, may have favorable immunodulatory effects in relation to SARS-CoV-2 infection, and that this type of extract may not merit caution in healthy individuals who are free from serious, chronic, or immune-related illnesses, characteristicare which are reflective of the study participants.

We agree that using the work by Senchina (2009) does merit additional notation that the species used in his study was *E. tennesseensis* (the *Echinacea* species that grows in Tennessee, USA). We also agree that although the *Echinacea* root extract did elevate IL-1B, in fact to the greatest extent of all extracts studied, this did not reach statistical significance. However, the high magnitude of effect from *E. tennesseensis* root extract suggests that the lack of significance may signify a statistical type II error, the result of individual variability in response. Furthermore, Senchina, et al. found that certain alkylamides isolated from the Echinacea did result in statistically significant elevations of IL-1B, TNFα and IL-10. The significance of these findings to the ingestion of an extract of the whole root is not addressed, but, again, at the time of publication, this data warranted caution. Dr. Naude points out this study was an exercise model as opposed to an infectious model, which although true, remains relevant to active individuals at risk for SARS-CoV-2 infection.

The reviews cited by Dr. Staub, which include both pre-clinical and clinical data, consistently conclude the need for further research given the potential benefit of *Echinacea* species, but also note that the risk of bias in included studies limits the current body of data.[9,10] We would agree with the need for further clinical research on the potential role for *Echinacea* spp. in Covid-19 infection.

When taken at the onset of symptoms, *Echinacea purpurea*, and possibly other *Echinacea* spp., may decrease the severity, or duration, of acute respiratory infection. Because the vast majority of studies to date have involved participants who were free from immunological disorders, serious or chronic illness, it is not possible to infer what the role of *Echinacea* spp. could be in those at highest risk of COVID-19.

So, we do agree with your references that it is not possible to conclude what the role of *Echinacea* spp. could be in those at highest risk of, or symptomatic with, COVID-19.

We thank you for your detailed response.

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