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LETTER TO THE EDITOR

Ingestion of beta-glucans could stimulate longer-lasting cellular immunity upon administration of COVID-19 vaccines

We read with interest the article by Basak and Gokhale (2021) which reviewed the immunity boosting nutraceuticals and functional foods in the context of coronavirus disease 2019 (COVID-19), one of them being beta-glucans. The authors described several immune-modulating effects of beta-glucans, and went on to propose that beta-glucans can act as a nutraceutical-based intervention to boost the immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative pathogen of COVID-19. Indeed, as previously reported, yeast (1,3)-(1,6)-beta-glucan supplements can decrease the incidence of symptomatic common cold infections and also the severity and/or duration of symptomatic upper respiratory tract infection in healthy cohorts (Shokri-Mashhadi et al., 2021). Nevertheless, considering that the SARS-CoV-2 replicates predominantly in upper respiratory epithelia where angiotensin-converting enzyme 2 is expressed and thus facilitates its cellular entry, it might be too far-fetched to expect the immune-stimulatory activities of beta-glucans to augment adequate antiviral innate immunity to protect against the acquisition of COVID-19.

We would like to complement the discussion of the authors (Basak & Gokhale, 2021) about the potential of beta-glucans to stimulate adaptive immunity to protect against the acquisition of COVID-19, which is more relevant in the current context where COVID-19 vaccines have been rolled out. The humoral immunity (mediated by B cells) and cellular immunity (mediated by T cells) are two types of adaptive immune response which are of utmost importance to eliminate SARS-CoV-2. Nevertheless, the relative contribution of B cells and T cells to the immunity to SARS-CoV-2 merits further discussion. Previous studies have indicated the decline in antibody levels in patients with COVID-19 after clearance of SARS-CoV-2 infection (Sharma et al., 2020; Ward et al., 2021). For instance, a community study in England of over 365,000 adults demonstrated that adjusted antibody prevalence declined from 6.0% to 4.4%, which represents a fall of 26.5% over 3 months of the study (Ward et al., 2021). In a population-based seroepidemiological study in India of over 12,000 adults, it was reported that adjusted antibody prevalence declined from 28.4% to 24.7%, which represents a fall of 13.0% over 3 months of the study (Sharma et al., 2020).

Attention has thus been shifted toward cellular immunity, which has been previously reported to maintain for a longer period than the humoral immunity in patients infected with SARS-CoV-1 (Channappanavar et al., 2014). Indeed, available studies to date indicated the same in patients infected with SARS-CoV-2 (Bilich et al., 2021; Zuo et al., 2021). A recent analysis of 100 patients with previous SARS-CoV-2 infection demonstrated the presence of T-cell responses in the serum samples of all participants at 6 months following the primary infection, which was characterized by significant CD4+ T-cell responses with strong cytokine (interleukin-2) expression (Zuo et al., 2021). Another study of 51 patients with previous SARS-CoV-2 infection even reported the increment of the frequency of detectable T-cell responses from 93% to 100% over a median period of about 4 months and the increment of the intensity of CD4+ T-cell responses over the same period (Bilich et al., 2021).

It seems that eliciting T-cell responses (cellular immunity) may be the key for COVID-19 vaccines to provide long-term protection. In fact, there is a recent study which investigated T cell immunity in patients with documented SARS-CoV-2 infection and individuals who had been fully vaccinated with BNT162b2 vaccine (1 month after the second vaccine dose) reported that induced T cell reactivity to Spike-specific peptides in vaccinated individuals was equivalent to that of infected patients after recovery (Jordan et al., 2021). We are still learning how long can the available vaccines protect against COVID-19 in real-world conditions, especially on hospitalization and death from COVID-19. However, based on current observations, vaccine adjuvants that could specifically stimulate T-cell responses should be explored. In addition to its ability to promote trained immunity, beta-glucan could also augment cellular immunity, and has been previously touted to be promising as oral anti-infective vaccine adjuvants (Jin et al., 2018). β-Glucans as vaccine adjuvants have been found to enhance the immunogenicity of hepatitis B vaccine and influenza vaccine in animal studies (Dong et al., 2007; Le et al., 2011). Indeed, the potential of oral beta-glucans supplementation to stimulate cellular immunity upon administration of COVID-19 vaccines to provide long-term protection is suggested in an observational study of healthy adults aged 50 or older, whereby supplementation with active hexose correlated compound (mixture of alpha- and beta-glucans; 3 g/day for 60 days) increased the frequency of peripheral CD4+ and CD8+ T cells producing interferon-gamma and/or tumor necrosis factor-alpha at 30 and 60 days compared to baseline and such findings were still observed at 30 days upon discontinuing the supplementation (Yin et al., 2010).

In the current context where herd immunity should be achieved as soon as possible due to the emergence of different variants of concern of SARS-CoV-2 which might one day completely escape neutralization by the available COVID-19 vaccines, attention should be focused on the armamentarium that we possess currently, where we can recommend oral beta-glucans supplementation among

COVID-19 vaccine recipients to enhance cellular immune responses, in order to provide more long-lasting protection. We believe that this wide spectrum vaccine adjuvant approach to COVID-19 with beta-glucans acting as biosimilars warrants more in-depth investigations to prove its efficacy (Ikewaki et al., 2021).

CONFLICT OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

AUTHOR CONTRIBUTIONS

Chia Siang Kow: Conceptualization; Writing-original draft; Writing-review & editing. **Dinesh Sangarran Chia Ramachandram:** Writing-original draft; Writing-review & editing. **Syed Shahzad Hasan:** Writing-original draft; Writing-review & editing.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Chia Siang Kow[1,2]
Dinesh Sangarran Ramachandram[2]
Syed Shahzad Hasan[3,4]

[1]*School of Postgraduate Studies, International Medical University, Kuala Lumpur, Malaysia*
[2]*School of Pharmacy, Monash University Malaysia, Jalan Lagoon Selatan, Bandar Sunway, Subang Jaya, Selangor, Malaysia*
[3]*School of Applied Sciences, University of Huddersfield, Huddersfield, United Kingdom*
[4]*School of Biomedical Sciences & Pharmacy, University of Newcastle, Callaghan, New South Wales, Australia*

Correspondence
Chia Siang Kow, School of Postgraduate Studies, International Medical University, Kuala Lumpur, Malaysia.
Email: chiasiang_93@hotmail.com

ORCID

Chia Siang Kow https://orcid.org/0000-0002-8186-2926

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