LETTER TO THE EDITOR

WILEY

An approach of fatty acids and resveratrol in the prevention of COVID-19 severity

Dear Editor

Pooled evidence from several systematic reviews and meta-analyses have consistently reported the positive association between underlying diseases and the severity among COVID-19 patients (Gheblawi et al., 2020; Jung, Choi, You, & Kim, 2020; Zhang, Penninger, Li, Zhong, & Slutsky, 2020). In our previous network meta-analysis, we found that chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), cancer, cerebrovascular accident (CVA), diabetes, hypertension, and chronic kidney disease were significantly associated with critical conditions of COVID-19, with relative risks (RRs) (95% confidence intervals [CIs]) of 4.22 (3.12–5.69), 3.00 (2.41–3.73), 2.91 (2.16–3.91), 2.86 (1.95–4.19), 2.10 (2.16–3.91), 2.02 (1.82–2.23), and 2.00 (1.36–2.94), respectively (Hoang & Tran, 2020).

Given that nutritional status either are associated with the risk of several chronic disease, thus, results in the risk of disease progression among COVID-19 patients or directly interacts with COVID-19 severity, we summarized current evidence of nutritional factors in the association with both comorbidity and COVID-19, with the focus on fatty acids and resveratrol.

1. | NUTRITION AND COMORBIDITIES

1.1. | Fatty acids

In relation to lung conditions, especially COPD, dietary intake of *n-3* polyunsaturated fatty acid (FUFA) has been suggested to improve the lung function due to anti-inflammatory and antioxidative stress effects (Rawal & Yadav, 2015). Results from two large cohort studies in the United States of 120,175 participants showed a significantly reduced risk of newly diagnosed COPD among subjects more frequent fish intake (hazard ratio [HR] = 0.71, 95% CI = 0.54–0.94) (Varraso, Barr, Willett, Speizer, & Camargo Jr., 2015). However, the effect of fatty acids as well as *n-3* FUFAs was found to be nonsignificant (Varraso et al., 2015). Like *n-3* FUFAs, epidemiological evidence for the effect of *n-6* FUFAs on COPD prevention was inconsistently reported (Hirayama et al., 2010; McKeever et al., 2008; Varraso et al., 2015). In addition, data from the National Health and Nutritional Examination Survey of 11,180 participants did not show any significant association between dietary saturated fatty acids (SFA) and lung function (Cornell et al., 2019).

Regarding CVD risk, a recent meta-analysis of cohort studies found the borderline effect of dietary total fat, saturated fatty acid (SFA), monounsaturated fatty acid (MUFA), and FUFA, with HRs (95% CIs) of 0.97 (0.93–1.01) (N = 45), 0.97 (0.93–1.02) (N = 56), 0.97 (0.93–1.01) (N = 43), and 0.97 (0.93–1.00) (N = 45) (Zhu, Bo, & Liu, 2019). Among FUFAs, *n-3* FUFA was found to significantly reduce the risk of CVD, with RRs (95% CIs) ranging between 0.89 (0.82–0.98) to 0.90 (0.85–0.96), whereas findings for *n-6* FUFA and total FUFAs did not reach the consistency in the umbrella review (Chareonrungrueangchai, Wongkawinwoot, Anothaisintawee, & Reutrakul, 2020). Pooled estimates from another meta-analysis found that *n-3* FUFA supplementation was associated with lower risks of coronary heart disease (RR = 0.90, 95% CI = 0.85–0.96) and myocardial infarction (RR = 0.89, 95% CI = 0.80–0.99), but not for total CVD (RR = 0.98, 95% CI = 0.95–1.01) and stroke (RR = 0.88, 95% CI = 0.71–1.10) (Hoang & Kim, 2020).

Furthermore, data of 28,100 women reported that dietary intake of *n-3*, *n-6*, total PUFAs, MUFA, and SFA were not associated with incident hypertension, with RRs (95% CIs) of 1.01 (0.96–1.07), 0.99 (0.94–1.05), 1.03 (0.98–1.10), 1.05 (0.99–1.12), and 1.04 (0.97–1.11), respectively (Wang et al., 2010). Besides, dietary intake of fish and marine *n-3* FUFAs in Asian populations and regular-fat dairy foods in Western populations was shown to related to a reduced risk of diabetes (Rice Bradley, 2018).

Nonalcoholic fatty liver disease has been the leading cause of chronic liver disease. A high dietary intake of MUFAs or PUFAs was found to be beneficial for the prevention of nonalcoholic fatty liver disease, whereas a possible harmful effect was observed for a high dietary intake of SFAs (Perdomo, Fruhbeck, & Escalada, 2019; Ullah et al., 2019). Despite the lack of evidence from different populations, dietary PUFA intake from the Southern Community Cohort Study of 1,074 cases and 3,230 controls was shown to be not associated with end-stage renal disease, with RRs (95% CIs) of 0.93 (0.71–1.21), 0.81 (0.61–1.06), and 0.79 (0.60–1.05) for *n-3*, *n-6*, and total PUFAs, respectively (Malhotra et al., 2016). In terms of cancer risk, a recent umbrella review of 57 meta-analyses reported nonsignificant or weak associations between *n-3* PUFAs and different cancer types (Lee et al., 2020).

1.2. | Resveratrol

Overlapping mechanisms for the effect of resveratrol on both lung and muscle might suggest the potential benefit of resveratrol in COPD patients (Beijers, Gosker, & Schols, 2018). Several inflammatory cytokines such as nuclear factor kappa B, tumor necrosis factor, and matrix

TABLE 1 Summary of the impact of fatty acids on immune responses

Immune responses	Cell type	Fatty acids	Effects
Innate immune responses	Epithelium	*n-3* PUFAs	Downregulation of barrier permeability, mucus production, pro-inflammatory cytokine production, and oxidative stress Upregulation of tight junctions and healing
	Macrophages	PUFAs	Activation of M-2 phenotype shift and phagocytosis Inhibition of nucleotide oligomerization domain-like receptor protein 3 inflammasome activation, apoptosis, cytokine production, and macrophage frequency Activation or inhibition of receptor-dependent prostaglandin production
		SFAs	Activation of nucleotide oligomerization domain-like receptor protein inflammasome and receptor-dependent prostaglandin production Inhibition of M-2 phenotype shift
	Dendritic cells	PUFAs	Activation of tolerogenic dendritic cells Inhibition of T-cell stimulation, cytokine production, maturation, antigen presentation, and phagocytosis
		SFAs	Activation of nucleotide oligomerization domain-like receptor protein 3 inflammasome, reactive oxygen species production, T-cell stimulation, cytokine production, maturation, antigen presentation, and phagocytosis Inhibition of tolerogenic dendritic cells
	Neutrophils	PUFAs	Activation of chemotaxis, reactive oxygen species production, phagocytosis, neutrophil frequency, resolvins release, cytokine production, and neutrophil extracellular traps production
		SFAs	Activation of neutrophil extracellular traps production Inhibition of reactive oxygen species production, phagocytosis, and neutrophil frequency
Adaptive immune responses	T-cells	PUFAs	Activation of T regulatory cells Inhibition of migration to periphery, type 1 helper cells, type 17 helper cells, proliferation, and cytokine production
		SFAs	Activation of migration to periphery, type 1 helper cells, type 17 helper cells, and cytokine production Inhibition of regulatory T cells

Abbreviations: PUFAs, polyunsaturated fatty acids; SFAs, saturated fatty acids.

metalloprotease-9 protein expression in lymphocytes were observed to be higher in COPD patients than in healthy controls and were reduced after treatment with resveratrol (Beijers et al., 2018). Additionally, antioxidant properties of resveratrol on both lung and muscle would be beneficial to reduce the lung injury in COPD (Beijers et al., 2018).

Dyck et al. recently reviewed the effect of resveratrol on different conditions related to CVD (Dyck, Raj, Zieroth, Dyck, & Ezekowitz, 2019). Since the evidence from randomized controlled trials for the endothelial improvement and plasma low-density lipoprotein cholesterol lowering effects has still been contradictory, further studies were suggested to confirm the effect of resveratrol on CVD prevention (Dyck et al., 2019).

In terms of hypertension, meta-analyses revealed that resveratrol supplementation might have the blood pressure lowering effect at high doses (Dyck et al., 2019). Regarding diabetes, a meta-analysis of 11 individual studies showed that resveratrol consumption significantly reduced fasting glucose, insulin, glycated hemoglobin, and insulin resistance levels in the subgroup of diabetes patients (Dyck et al., 2019; Ma et al., 2017). However, these significant findings were not observed in the subgroup of nondiabetes subjects (Ma et al., 2017).

Furthermore, the evidence for the beneficial effect of resveratrol on other comorbidities including chronic liver diseases (Ma et al., 2017), chronic kidney diseases (Den Hartogh & Tsiani, 2019; Kitada & Koya, 2013), and cancer prevention has still limited, as most evidences

from preclinical studies were available only (Ko et al., 2017; Vervandier-Fasseur & Latruffe, 2019; Xiao et al., 2018).

2. | NUTRITION AND COVID-19

2.1. | Possible interaction with angiotensin-converting enzyme 2

Several previous studies have reported the mediation effect of angiotensin-converting enzyme 2 (ACE2) in COVID-19 (Behl et al., 2020; Ni et al., 2020; Verdecchia, Cavallini, Spanevello, & Angeli, 2020). The SARS-CoV-2 can enter the host cells by binding their spike glycoprotein on the viral envelope with ACE2 receptors on the membrane of several organisms, such as heart, vessels, gut, lung, kidney, testis, and brain (Ni et al., 2020; Verdecchia et al., 2020). Despite the lack of research on human, animal models have examined the impact of a high-fat diet with 50% to 60% fat of the total energy intake (Horne & Vohl, 2020). Research in the retroperitoneal adipose tissue of postnatal rats showed a downregulation effect of the high-fat diet on ACE2 gene expression (Horne & Vohl, 2020). It was also reported the ACE2 expression lowering effect of the high-fat diet in mice liver, male mice kidney, and female mice with ovariectomy (Horne & Vohl, 2020). Additionally, a six-week intervention study of 46 healthy and nonobese twin pairs revealed that the high-fat diet was associated with a 15% increased serum level of ACE and an increased ACE expression in adipose tissue (Schuler et al., 2017). Furthermore, results from in vivo studies showed the upregulating ACE2 effect of resveratrol, with an increased ACE2 level in mice or rats fed resveratrol, compared to the control group (Horne & Vohl, 2020).

2.2. | Possible interaction with immune system

In the aspect of the immune system and COVID-19, evidences have been demonstrated for the contribution of dysregulation in the innate immune response to the clinical feature of patient with severe COVID-19 infection (Indini et al., 2020). Particularly, the "cytokine storm" as high levels of several proinflammatory cytokines (such as IL-1, IL-2, IL-6, IL-7, IL-8, IL-10, IL-21, G-CSF, IP-10, MCP-1, MIP-1A, and TNF) were observed in these patients, which resulted in the accumulation of cells and fluid in the respiratory system (Indini et al., 2020). Besides, SARS-CoV-2 can also dysregulate the human immune response through lymphocytes by producing proinflammatory cytokines (Indini et al., 2020). Recently, Radzikowska et al. comprehensively reviewed the effect of fatty acids on innate and adaptive immune responses (Table 1), which might therefore suggest their potential influence in COVID-19 severity (Radzikowska et al., 2019). However, most of the evidences for their possible beneficial effects were thoroughly demonstrated in mechanistic in vitro and in vivo studies focusing on the specific cell populations, with uncertain findings from experimental and clinical studies (Radzikowska et al., 2019).

Another dietary item, resveratrol, has been reported to regulate the immune response by interfering with immune cell regulation, proinflammatory cytokines, and gene expression (Malaguarnera, 2019). The influence of resveratrol on several immune cells was comprehensively review by Malaguarnera (Malaguarnera, 2019). The effects included upregulation of the activity of natural killer cells and macrophages, downregulation the activity of B cells, regulatory B cells, natural killer cells, T 17 helper cells, and M2-like cells, and bidirectional way the activity of T cells and regulatory T cells (Malaguarnera, 2019). Additionally, resveratrol could enhance the apoptosis of MERS-CoV by downregulating the FGF-2 signaling (Lin et al., 2017). The results from an in vitro model showed that resveratrol might have the antiviral effect by reducing the cell death caused by MERS-CoV, reducing the RNA expression and viral yield of MERS-CoV, inhibiting existing MERS-CoV infection and nucleocapsid expression, and inhibiting Caspase 3 cleavage induced by MERS-CoV infection (Lin et al., 2017), which suggested for their potential effect on SARS-CoV-2 infection.

3. | SUMMARY

In summary, findings from observational studies suggested the potentially protective effect of polyunsaturated fatty acids on cardiovascular disease and diabetes, but not for lung disease, hypertension, liver disease, and cancer. While the protective effect of resveratrol on cardiovascular disease, hypertension, and diabetes needs further confirmation studies, the effect on other diseases are limited from preclinical studies only. Furthermore, the interaction of fatty acids and resveratrol with angiotensin-converting enzyme 2 as well as immune system in COVID-19 were discussed. Further studies are needed to fully understand the effect of fatty acids and resveratrol on chronic diseases and COVID-19 infection.

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