

# Potential Health Benefits of Fermented Foods in Covid-19 Patients

Velat Çelik<sup>1</sup> and Muserref Celik<sup>1</sup>

<sup>1</sup>Trakya University Faculty of Medicine

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To the Editor, The coronavirus disease 2019 (COVID-19) pandemic is a significant, global threat to human life<sup>1</sup>. Because there is no established prevention or treatment protocol for COVID-19, all potential therapeutics and prevention strategies, which may reduce the severity of infection, are of vital importance. Nutritional therapy may be considered as one possible tool. Fermented foods have been a well-established part of the human diet for thousands of years. The health benefits associated with the fermentation process may be the result of direct interactions between the ingested live microorganisms and the host (probiotic effect), or indirectly as a result of ingestion of microbial metabolites produced during the fermentation process (biogenic effect)<sup>2</sup>.

The presence of several comorbidities, such as hypertension, diabetes, hypercholesterolemia, and cardiovascular diseases severely influence the mortality rate reported in COVID-19 patients<sup>1</sup>. Fermented foods contain angiotensin converting enzyme (ACE) inhibitor peptides and they are recommended as a non-pharmacological strategy for the management of hypertension<sup>3</sup>. Angiotensin-converting enzyme 2 (ACE2) was identified as a receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)<sup>1</sup>. ACE inhibitors have the capacity to upregulate the expression and activity of ACE2 in the lungs. The higher level of ACE2 might increase the susceptibility of cells to SARS-CoV-2 viral host entry and propagation. On the other hand, the activation of ACE2 might ameliorate the acute lung injury.<sup>4,5</sup> ACE inhibitor peptides in fermented foods may have similar dual effects. Although it was previously thought that ACE inhibitors would increase susceptibility to SARS-CoV-2 infection, the available evidence does not seem to support the hypothesis<sup>4,5</sup>. After all, hypertension is a risk factor for severe COVID-19, and the hypertension-preventing diet can be one strategy to prevent and/or alleviate severe COVID-19. Moreover, fermented foods can lower the serum LDL-cholesterol values, hypertension, coronary heart disease and insulin resistance, which are other risk factors for severe COVID-19<sup>3</sup>.

It was shown that fermented foods and probiotics clinically effective in reducing the incidence, severity and duration of upper respiratory tract infections<sup>6</sup>. While none of these effects or mechanisms have been tested on the new SARS-CoV-2 virus, the effects of probiotics against other coronavirus strains have been reported<sup>6</sup>. Furthermore, secondary bacterial infections during COVID-19 infection are important causes of morbidity and mortality. Many species of LAB isolated from fermented vegetable and milk products have antibacterial activities due to the production of antimicrobial compounds such as bacteriocin and pediocin. It stands to reason that fermented foods may offer COVID-19 patients some protection against secondary bacterial infections.

Fermented foods may modulate the gut microbiota with the probiotic bacteria they contain, and their biological ingredients, such as fiber and short chain fatty acids<sup>3</sup>. The gut microbiota and lung microbiota interact, which is called the Gut Lung Axis (GLA)<sup>6</sup>. GLA can shape immune responses and interfere with the course of respiratory diseases<sup>6</sup>. As reports from China indicate that COVID-19 might be associated with intestinal dysbiosis which causes inflammation and weakened response to pathogens. It is feasible that consumption of fermented foods could further influence and restore gut homeostasis and GLA<sup>6</sup>. Two randomized controlled trials showed that modulating gut microbiota can reduce ventilator-associated pneumonia (NOT specifically

COVID-19) which can be evidence of gut-lung axis<sup>7</sup>. During the COVID-19 pandemic, 2–47% of infected patients required invasive mechanical ventilation<sup>7</sup>. Accordingly, we can speculate that COVID-19-related pneumonia may be alleviated in the same manner. Furthermore, aging is associated with a significant reduction in microbiome diversity. This may explain, at least partially, the different impacts of viral infections in elderly individuals.

The inflammatory response plays a crucial role in the clinical manifestations of COVID-19. Post SARS-CoV-2 entry, host factors trigger an immune response against the virus. If left uncontrolled, this response may result in pulmonary tissue damage. This extremely high level of inflammatory response is called the cytokine storm<sup>5</sup>. Subsequently, there is the activation of transcription factors NF- $\kappa$ B, pathway that induce the expression of inflammatory factors<sup>5</sup>. It is important to determine the optimal of reducing inflammation. Fermented foods have anti-inflammatory properties, and may suppress pro-inflammatory cytokine production and increase Treg cells. Chen et al. showed that treatment with kefir peptides decreased the particulate matter-induced inflammatory cell infiltration and the expression of the inflammatory mediators IL-1 $\beta$ , IL-4 and TNF- $\alpha$  in lung tissue by inactivating NF- $\kappa$ B signaling<sup>8</sup>. Reactive oxygen species also play a crucial role in the inflammatory response. As such, utilizing compounds with antioxidant properties may also be considered as a way to reduce the cytokine storm<sup>5</sup>. Fermented foods contain high amounts of antioxidants, such as proline, conjugated linoleic acid and phenolic compounds. These antioxidants also contribute to their anti-inflammatory effects<sup>3</sup>. Cytokine storm syndrome could be strictly linked with coagulopathy, generating acute pulmonary embolism caused by in-situ thrombosis. A 20% reduction in mortality was observed when patients with D-dimer exceeding 3.0  $\mu$ g/mL were treated with prophylactic doses of heparin<sup>9</sup>. Some fermented food products have antithrombotic or fibrinolytic activity which have the potential to reduce mortality in COVID-19 patients.

Mortality is one of the most important ways of measuring the burden of COVID-19, and it differs between countries<sup>4</sup>. Among many factors, diet differs considerably between low and high mortality countries. Traditional dietary habits may be associated with these different mortality rates. Fermented cabbage is largely consumed in low-death rate European countries, Korea and Taiwan. It might be considered as one factor in the lower death rates. Consumption of fermented milk is common in Greece and Bulgaria, and they have very low death rates across European countries<sup>4</sup>. Fermented milk and cabbage are common in Turkey<sup>2</sup> and Turkey is another low-death rate country<sup>4</sup>.

In summary, based on the current evidence and clinical observations, we speculate that it is plausible to assume that these anti-inflammatory, antithrombotic, antioxidant, and antimicrobial effects could potentially contribute, at least partially, or in combination with other medications, in the prevention and/or alleviation of COVID-19-related symptoms. There is a need for well-designed, randomized controlled clinical trials to measure the effects of fermented foods in COVID-19.

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**Velat Celik**, M.D. Trakya University Faculty of Medicine, Department of Pediatric Allergy and Immunology, Edirne, Turkey

**Muserref Celik**, Trakya University Faculty of Medicine, Department of Pediatric Allergy and Immunology, Edirne, Turkey

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