Kimchi and Asian fermented vegetables: candidates for the partial control of the COVID-19 pandemic

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To the Editor,

A COVID-19 epidemic started in China and then disseminated to other Asian countries before becoming a pandemic. It appears that the pandemic has so far resulted in proportionately fewer deaths in China and most Eastern Asian countries. Many reasons can explain this picture. One of them is the type of diet in the low mortality countries.

This paper is the sixth of a series attempting to understand the role of diet in the differences of COVID-19 death rates between and within countries with the aim to identify potential preventive measures against COVID-19. The concept paper was followed by two ecological studies comparing death rates in European countries and the consumption of vegetables or fermented foods. We then proposed that sulforaphane from cruciferous vegetables and lactobacilli from fermented foods (submitted) were possibly involved in the reduction of insulin resistance in COVID-19.

It is noteworthy that fermented foods are largely used in Asia. It is therefore important to check whether some commonly eaten fermented foods in these countries may explain geographic differences in COVID-19. Kimchi will be used as a model of fermented cabbage.

Geographic differences in COVID-19 death rates

When comparing death rates, large differences exist between and within countries and the evolution of the pandemic differs largely between countries (Figure 1). As the temporal dynamic of the pandemic may have changed the geographical patterns observed in our previous analyses, we focus on the more recent mortality trends.

Although there are many pitfalls in analyzing death rates for COVID-19, the evolution of death rates
between May 20 and July 18 shows a dramatic increase in Latin America and some increase in European countries, certain African countries, the Middle East, India, Pakistan and some of the South East Asian countries. However, there is no change in the very low death rates of Cambodia, China, Japan, Korea, Lao, Malaysia, Taiwan, Vietnam as well as of many Sub-Saharan African countries, Australia and New Zealand. This geographical pattern is very unlikely to be totally due to reporting differences between countries.

**Ecological studies on food consumption and death rates in countries**

Although many factors are involved in COVID-19 mortality, a recent hypothesis proposed that differences between countries may partly be explained by diet with fermented foods and certain vegetables that are potent anti-oxidants. Two studies examined the association between the COVID-19 mortality rate in EU countries and diet. The consumption of fermented vegetables, head cabbage and cucumber was associated with lower death rates. Even though these are ecological studies, they support the association between diet and fatality. A healthy diet, rich in antioxidants, has been proposed as a therapeutic strategy to mitigate the cytokine storm that develops in COVID-19.

**Angiotensin-converting enzyme 2 (ACE2) and COVID-19**

COVID-19 is more severe in older adults and/or patients with comorbidities, such as diabetes, obesity, kidney disease or hypertension, suggesting a role for insulin resistance. Although differences exist between countries, the same risk factors for severity were found globally, suggesting common mechanisms. Moreover, the severe outcomes of COVID-19 - including lung damage, cytokine storm or endothelial damage - appear to exist globally, again suggesting common mechanisms.

The angiotensin-converting enzyme 2 (ACE-2) is part of the dual system, the renin-angiotensin-system (RAS), including the ACE-Angiotensin-II-ATR axis. AT1R is involved in most Angiotensin II effects, including oxidative stress generation, pro-inflammatory, pro-fibrotic effects in the respiratory system, endothelial damage and insulin resistance. SARS-CoV-2 binds to and downregulates ACE-2, enhancing the AT1R axis, likely to be associated with insulin resistance but also to severe outcomes of COVID-19.

**Fermented vegetables**

The fermentation process, a preservation method of the Neolithic age, enabled humans to survive. Fermented foods are “foods or beverages made via controlled microbial growth (including lactic acid bacteria strains (LABs) and enzymatic conversions of food components.” Many bacteria are used for the fermentation of vegetables but most traditional foods with live bacteria in the low-death rate countries are based on LAB fermentation.

Gut microbiota has an inter-individual variability due to genetic predisposition and diet. Some foods like cabbage can be fermented by the gut microbiota. Kimchi fermented from many vegetables including cabbage has several effects on insulin resistance associated diseases: anti-diabetic properties, cardiovascular diseases, dyslipidemia or ageing.

**Effects of fermented vegetables on insulin resistance**

Kimchi fermented from many vegetables including cabbage has several effects on insulin resistance associated diseases: anti-diabetic properties, cardiovascular diseases, dyslipidemia or ageing. Lactobacilli have an inconstant effect on diseases associated with insulin resistance. However, most studies are underpowered or have some methodological flaws. Moreover, not all LAB strains have the same action on insulin resistance. The redox mechanisms of Lactobacillus spp. are involved in the downregulation of reactive oxygen species (ROS)-forming enzymes and redox stress resistance proteins or genes. In addition, the nuclear factor erythroid 2-like 2 (Nrf-2) and nuclear factor kappa B (NF-κB) are two common transcription factors that also modulate oxidative stress.

There are other products in fermented vegetables that can potentiate the effect of LABs. Kimchi, when fermented for a long time, reduces insulin intolerance to a greater extent than fresh kimchi, indicating that newly formed products during fermentation are important. In particular, Kimchi from cabbage and
Chinese cabbage contains several glucosinolates\(^1,^{42,43}\) that can be transformed in sulforaphanes either in the plant itself or by the human microbiome\(^24\). Sulforaphanes were suggested to be effective in diseases associated with insulin resistance\(^1,^{44-46}\).

**Proposed mechanisms of action of Kimchi and fermented vegetables in COVID 19**

Reactive oxygen species (ROS), such as hydrogen peroxide and superoxide anion, exert beneficial and toxic effects on cellular functions. Nrf2 is a key regulator of the anti-oxidative response.\(^47\) Nrf2 activity in response to chemical insults is regulated by a thiol-rich protein named KEAP1 (Kelch-like ECH-associated protein 1). The KEAP1-Nrf2 system is the body’s dominant defense mechanism against ROS.\(^48\) Sulforaphane is the most potent activator of Nrf2\(^3,^{34}\). “Ancient foods”, and particularly those containing *Lactobacillus*, activate Nrf2.\(^49\) In different animal models, several strains of *Lactobacillus* were found to regulate Nrf2.\(^50-52\) *In vitro* studies have shown an effect of *Lactobacillus* on Nrf2.\(^53-55\)

A putative mechanism may be proposed (Figure 2). SARS-CoV-2 downregulates ACE2 inducing an increased insulin resistance associated with oxidative stress through the AT\(_1\)R pathway. Fermented vegetables are often made from cruciferous (*Brassica*) vegetables that release glucoraphanin converted by the plant or by the gut microbiome into sulforaphane which activates Nrf2 and subsequently reduces insulin intolerance by its potent antioxidant activities. Fermented vegetables contain a high content of *Lactobacillus* that can activate Nrf2 and impact on the microbiome. Nrf2 may be involved in diseases associated with insulin-resistance\(^24,^{56-58}\) and may have a role in COVID-19.\(^59\) Sulforaphane and LABs both have the ability to reduce insulin resistance.

Other putative actions on COVID-19 severity may be postulated. The down-regulation of ACE2 reduces the Ang-1,7 anti-oxidant activity that was found to activate Nrf2.\(^60,^{61}\) Nrf2 protects against hallmarks of severe COVID-19. It has anti-fibrotic effects on various organs including the lungs,\(^62\) protects against lung injury and acute respiratory distress syndrome,\(^63\) and endothelial damage.\(^64\) Finally, Nrf2 can block IL-6 in different models of inflammation\(^65\) and might play a role in the COVID-19 cytokine storm.

These different mechanisms may explain the importance of fermented cabbage in preventing the severity of COVID-19. It is clear that other nutrients, vitamin D and many different foods act on NRF2.

It is not yet known whether sulforaphane and/or LABs may act on the infectivity of SARS-CoV-2. Disulfide bonds can be formed under oxidizing conditions and play an important role in the folding and stability of some proteins. The receptor-binding domain of the viral spike proteins and ACE2 have several cysteine residues. Using molecular dynamics simulations, the binding affinity was significantly impaired when all of the disulfide bonds of both ACE2 and SARS-CoV/CoV-2 spike proteins were reduced to thiol groups. This computational finding possibly provides a molecular basis for the differential COVID-19 cellular recognition due to the oxidative stress.\(^66\)

**Kimchi and Asian fermented foods as candidates for the partial control of severe COVID-19**

Mainstream COVID-19 control strategies including social distancing, confinement and intensive case finding, testing, tracing and isolating are so far not enough to provide a SARS-CoV-2-free environment and restore a safe social life. There are hopes for a safe and effective vaccine, but this is unlikely to become available. So, there is a need to explore other potentially useful strategies. An area that has not been sufficiently considered is diet, both as a preventive and/or therapeutically useful intervention, encouraging people to eat more traditional foods containing fermented vegetables. We have suggested that fermented vegetables could be associated with a lower COVID-19 mortality due to their potent antioxidant effect among which sulforaphane and LABs are important. However, many other foods may have a similar activity. It should be noted that dietary supplements that over-activate Nrf2 may have side-effects.\(^67\)

Robust evidence from observational studies would be helpful to formally investigate associations between fermented foods and clinical outcomes in COVID-19. State-of-the-art methods, including the use of DAGs (Directed Acyclic Graphs), may be needed to help assess whether the associations seen are likely to represent causal relationship\(^68\). A faster approach would be to develop large clinical trials in the appropriate populations. Interventions based on diets with a high intake of fermented foods like Kimchi or other fermented
foods are unlikely to present ethical difficulties. Furthermore, the fact that a precise mechanism has been proposed would facilitate adding reliable biomarkers to the relevant clinical outcomes. Moreover, new drugs based on the components of these fermented foods may be of interest.

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Conflict of interest: the authors have no COI to declare.

References


Figure 1: COVID-19 death rates (Johns Hopkins Coronavirus Resource center)
Figure 2: proposed mechanisms of fermented vegetables against COVID-19 (adapted from \textsuperscript{1})

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mechanisms of COVID-19 severity.pptx available at https://authorea.com/users/322406/articles/