




Cabbage and fermented vegetables: From death rate heterogeneity in countries to candidates for mitigation strategies of severe COVID-19

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Abstract

Large differences in COVID-19 death rates exist between countries and between regions of the same country. Some very low death rate countries such as Eastern Asia, Central Europe, or the Balkans have a common feature of eating large quantities of fermented foods. Although biases exist when examining ecological studies, fermented vegetables or cabbage have been associated with low death rates in European countries. SARS-CoV-2 binds to its receptor, the angiotensin-converting enzyme 2 (ACE2). As a result of SARS-CoV-2 binding, ACE2 downregulation enhances the angiotensin II receptor type 1 (AT₁R) axis associated with oxidative stress. This leads to insulin resistance as well as lung and endothelial damage, two severe outcomes of

Abbreviations: ACE, angiotensin-converting enzyme; Ang II, angiotensin II; AT₁R, angiotensin II receptor type 1; COVID-19, coronavirus disease 19; GI, gastrointestinal; LAB, lactic acid bacilli; NF- κ B, nuclear factor kappa B; Nrf2, nuclear factor (erythroid-derived 2)-like 2; PEDV, porcine epidemic diarrhea virus; ROS, reactive oxygen species; SARS, severe acute respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TGEV, transmissible gastroenteritis coronavirus infection.

See the ARIA group in Appendix 1.

COVID-19. The nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is the most potent antioxidant in humans and can block in particular the AT₁R axis. Cabbage contains precursors of sulforaphane, the most active natural activator of Nrf2. Fermented vegetables contain many lactobacilli, which are also potent Nrf2 activators. Three examples are: kimchi in Korea, westernized foods, and the slum paradox. It is proposed that fermented cabbage is a proof-of-concept of dietary manipulations that may enhance Nrf2-associated antioxidant effects, helpful in mitigating COVID-19 severity.

KEYWORDS

angiotensin-converting enzyme 2, cabbage, COVID-19, diet, fermented vegetable, kimchi, *Lactobacillus*, sulforaphane

1 | INTRODUCTION

A COVID-19 epidemic started in China and then disseminated to other Asian countries before becoming a pandemic. There is a large variability across countries in both incidence and mortality, and most of the current debates on COVID-19 focus on the differences between countries. Several intertwined factors can be proposed: social distancing, health system capacity, age of the population, social lifestyle (gathering of family/friends, social behavior), testing capacity, and/or timing and intensity of the first outbreak. German fatalities are strikingly low as compared to many European countries. Among the several explanations proposed, an early and large testing of the population was put forward¹ as well as social distancing. However, little attention has been given to regional within-country differences that may propose new hypotheses.

It would appear that the pandemic has so far resulted in proportionately fewer deaths in some central European countries, the Balkans, China, in most Eastern Asian countries, as well as in many sub-Saharan African countries. Several reasons can explain this picture. One of them may be the type of diet in these low mortality countries.^{2,3}

Diet has been proposed to mitigate COVID-19.^{4,5} Some foods or supplements may have a benefit on the immune response to respiratory viruses. However, to date, there are no specific data available to confirm the putative benefits of diet supplementation, probiotics, and nutraceuticals in the current COVID-19 pandemic.⁶ News and social media platforms have implicated dietary supplements in the treatment and prevention of COVID-19, but without evidence.⁷

In this paper, we discuss country and regional differences in COVID-19 deaths. We attempt to find potential links between foods and differences at the national or regional levels. The aim is to propose a common mechanism focussing on oxidative stress that may be relevant in COVID-19 mitigation strategies. We used cabbage and fermented vegetable as a proof-of-concept.

2 | BIASES TO BE CONSIDERED

According to the Johns Hopkins Coronavirus Resource Center (<https://coronavirus.jhu.edu>), one of the most important ways of measuring the burden of COVID-19 is mortality. However, death rates are assessed differently between countries and there are many biases that are almost impossible to assess. Using the rates of COVID-19 confirmed cases is subject to limitations that are similar to or even worse than the differences in the use of COVID-19 testing.

Differences in the mortality rates depend on healthcare systems, the reporting method, and many unknown factors. Countries throughout the world have reported very different case fatality ratios—the number of deaths divided by the number of confirmed cases—but these numbers cannot be compared easily due to biases. On the other hand, for many countries, the methodology used to report death rates in the different regions is standardized across the country.

We used mortality per number of inhabitants to assess death rates, as proposed by the European Center for Disease Prevention and Control (ecdc, <https://www.ecdc.europa.eu/en>), and to report trends with cutoffs at 25, 50, 100, and 250 per million.

Our hypothesis is mostly based on ecological data that are hypothesis-generating and that require confirmation by proper studies.

3 | MULTIFACTORIAL ORIGIN OF THE COVID-19 EPIDEMIC

Like most diseases, COVID-19 exhibits large geographical variations which frequently remain unexplained.⁸ The COVID-19 epidemic is multifactorial, and factors like climate, population density, age, phenotype, and prevalence of noncommunicable diseases are also associated with increased incidence and mortality.⁹ Diet represents only one of the possible causes of the COVID-19 epidemic, and its importance needs to be better assessed. Some risk factors for the COVID-19 epidemics are proposed at the individual and country levels in Table 1.

TABLE 1 Possible risk factors for COVID-19 infection explaining geographical differences

	Measure	Individual level	Country/region level
A	Contact with a SARS-CoV-2 infected individual	++++	Case zero identified ++++ For example, Lombardy
A	Intensity of social contacts	++	+++
A	Intensity of occupational contacts	+++	++
A	Confinement (level)	+++	+++ For example, the United States versus EU Sweden vs Nordic countries
A	Confinement (early measures)	+++	+++ For example, the UK versus EU
A	Climatic conditions (temperature, humidity)	?	++ Hot and humid temperature may reduce infection but epidemic bursts in Brazil, Peru, and Ecuador
A	GDP of a country/region	?	+
A	Vitamin D	?	+
B	Diet	?	+ The map of COVID-19 deaths in Europe and the low prevalence in Asia and Africa suggest a role for diet
B	Food	++?	+ Bibliographic analysis suggests a role for some fermented foods. Raw cabbage can be fermented in the intestine. Kefir is largely used in many low-prevalence countries.
B	Long food chain supply	++?	+ In Italy and Spain, there may be an association with long-chain supply. This may be relevant since food quality differs.
B	Traditional fermented food (example of food)	++?	++ This may be a relevant issue. In former Eastern European countries, in the Balkans, in Africa, and in many Asian countries with low COVID-19 prevalence, traditional fermented foods are common (in line with short food chain supply)
B	Air pollution	+?	+?
B	Underserved area	++	++
A and C	Age	+++	+ to ++++ In countries where population is young, fewer people have a severe disease (e.g., Africa)
C	Comorbidities (severity of COVID-19)	+++	++
C	Sex	++	
C	Institutionalized person	++	

Note: A: risk factors at a country level, B: environment, nutrition, C: individual level; + to ++++: Proposed relative importance.

4 | ECOLOGICAL DATA ON 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). Although there are many pitfalls in analyzing death rates for COVID-19,³ the evolution of death rates between May 20 and July 18 shows a dramatic increase in Latin America and only 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, and Vietnam and 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.

In some high death rate countries such as Italy (Figure 2), variations are extremely large from 50 per million in Calabria to over 1600 in Lombardia. In Switzerland, the French- and Italian-speaking cantons have a far higher death rate than the German-speaking ones (*Office fédéral de la santé publique, Switzerland*) (Figure 3). It may be proposed that the high death rate cantons were contaminated by French and Italian people. However, the Mulhouse airport serves the region of Basel (Switzerland), the Haut-Rhin department (France), and the region of Freiburg (Germany). There was a COVID-19 outbreak in the Haut-Rhin department, in particular in Mulhouse and Colmar. The death rate for COVID-19 (May 20, 2020) was 935 per million inhabitants in France but only 10 to 25 in Switzerland and 7 in Germany. It is important to

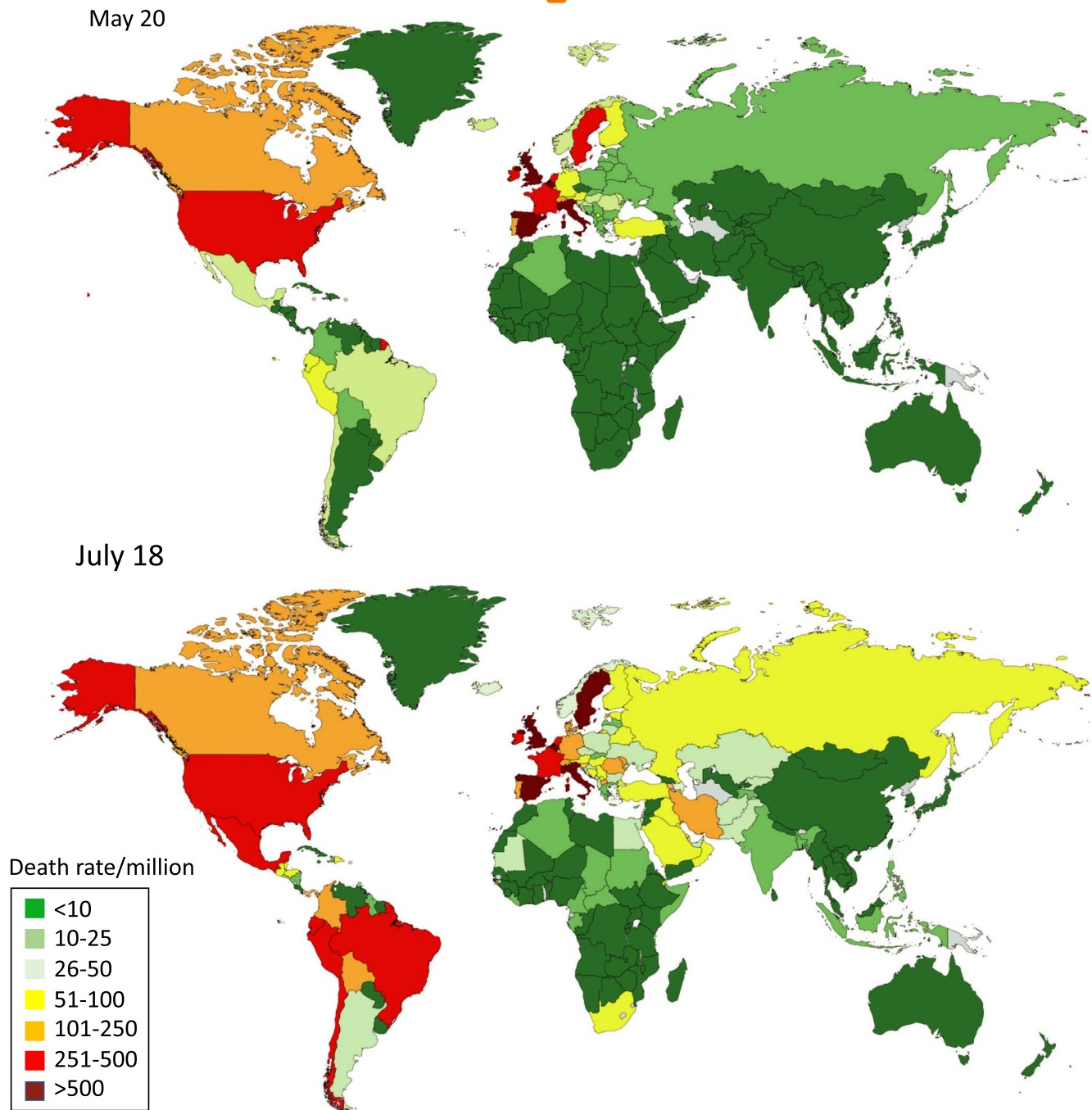


FIGURE 1 COVID-19 deaths per million inhabitants (from Johns Hopkins Coronavirus Center)

consider these regional differences since reporting of deaths is similar within the country and many factors may be considered.

In many Western countries, large cities (eg, London, Madrid, Milan, New York, Paris) have been the most affected. This seems to be true also for many countries in which the rural areas have much fewer cases.

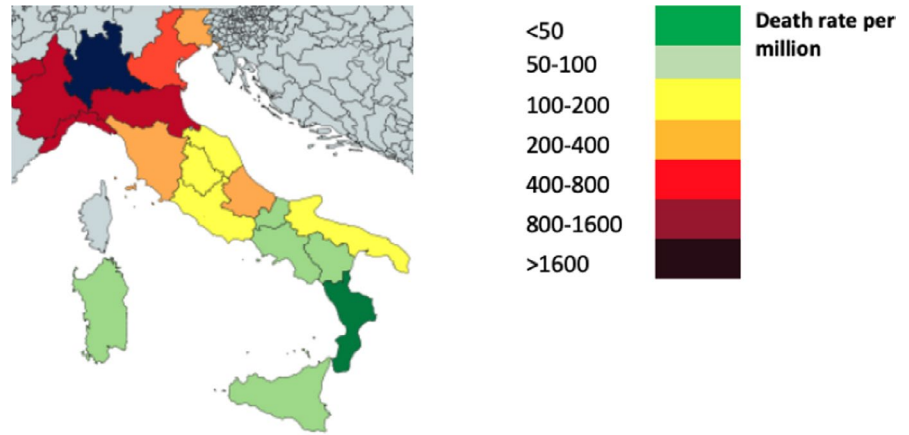
The number of deaths is relatively low in sub-Saharan Africa compared to other regions, and the low population density (which applies in rural areas but not in megacities such as Cairo or Lagos) or the differences in health infrastructure are unlikely to be the only explanation.¹⁰ It has been proposed that hot temperature may

reduce COVID-19, but, in Latin American countries, death rates are high (eg, Brazil, Ecuador, Peru, and Mexico).

5 | IS DIET PARTLY RESPONSIBLE FOR DIFFERENCES BETWEEN AND WITHIN COUNTRIES?

Nutrition may play a role in the immune defense against COVID-19 and may explain some of the differences seen in COVID-19 between

FIGURE 2 Regional differences of death rates in Italy (from Worldometer)



Switzerland



May 20, 2020	Deaths	Population	Deaths/million
Basel city (Sw)	49	198,000	25
Basel-Lands (Sw)	30	298,000	10
Freiburg (DE)	15	213,000	7
Haut-Rhin (F)	715	765,000	935

Deaths per million

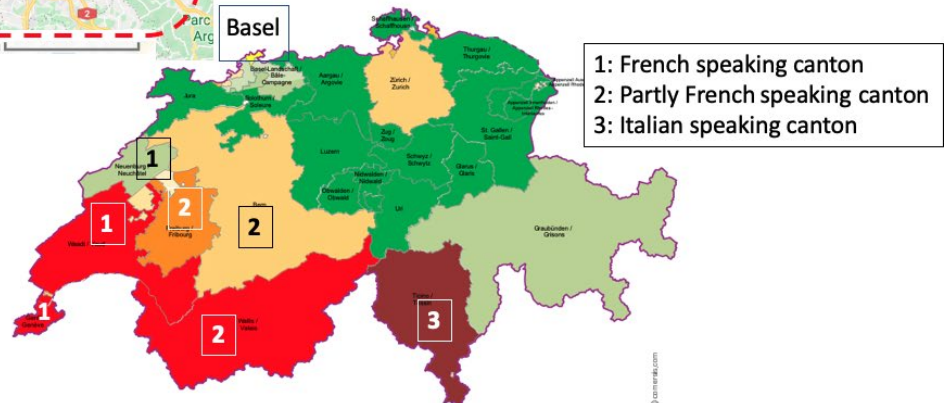
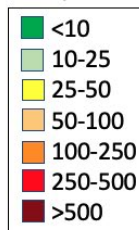


FIGURE 3 Regional differences of death rates (May 20) (from Office fédéral de la santé publique, Switzerland, Gouvernement français, Lander Bade Wurtemberg)

and within countries.³ In this concept paper, raw and fermented cabbage was proposed as a candidate.

To test the potential role of fermented foods in the COVID-19 mortality in Europe, an ecological study, the European Food Safety Authority (EFSA) Comprehensive European Food Consumption Database, was used to study the country consumption of fermented vegetables, pickled/marinated vegetables, fermented milk, yoghurt, and fermented sour milk.¹¹ Of all the variables considered, including confounders, only fermented vegetables reached statistical significance with the COVID-19 death rate per country. For each g/day increase in consumption of fermented vegetables of the country, the mortality risk for COVID-19 was found to decrease by 35.4% (Figure 4).

A second ecological study has analyzed cruciferous vegetables (broccoli, cauliflower, head cabbage (white, red, and savoy cabbage),

leafy brassica) and compared them with spinach, cucumber, courgette, lettuce, and tomato.¹² Only head cabbage and cucumber reached statistical significance with the COVID-19 death rate per country. For each g/day increase in the average national consumption of some of the vegetables (head cabbage and cucumber), the mortality risk for COVID-19 decreased by a factor of 11, to 13.6%. The negative ecological association between COVID-19 mortality and consumption of cabbage and cucumber supports the a priori hypothesis previously reported. However, these are ecological studies that need to be further tested.

Another diet component potentially relevant in COVID-19 mortality may be the food supply chain and traditional groceries.¹³ The impact of the long supply chain of food on health is measurable by an increase in metabolic syndrome and insulin resistance.¹⁴ Therefore,

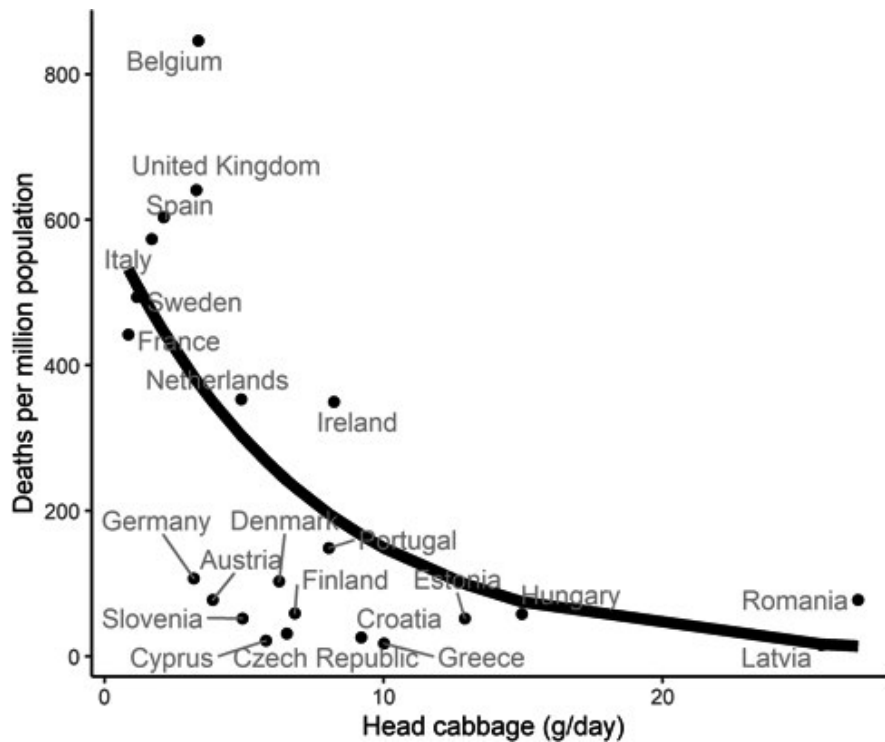


FIGURE 4 Consumption of head cabbage and COVID-19 death rate at a country level (from Fonseca et al¹²)

areas that are more prone to short supply food and traditional groceries may have been able to better tolerate COVID-19 with a lower death toll. These considerations may be partly involved in the lower death rates of Southern Italy compared to the northern part (Figure 2).

6 | FERMENTED FOODS, MICROBIOME, AND LACTOBACILLI

The fermentation process, born as a preservation method in the Neolithic age, enabled humans to eat not-so-fresh food and to survive.¹⁵ Indigenous fermented foods such as bread, cheese, vegetables, and alcoholic beverages have been prepared and consumed for thousands of years. They are strongly linked to culture and tradition, especially in rural households and village communities, and are consumed by hundreds of millions of people.¹⁶ Fermented foods are “foods or beverages made via controlled microbial growth (including lactic acid bacteria (LAB)) and enzymatic conversions of food components.”¹⁷ Not all fermented foods contain live cultures, as some undergo further processing after fermentation: pasteurization, smoking, baking, or filtration. These processes kill or remove the live microorganisms in foods such as soy sauces, bread, most beers, and wines as well as chocolate. Live cultures can be found in fermented vegetables and fermented milk (fermented sour milk, yoghurt, probiotics, etc.).

Most traditional foods with live bacteria in the low death rate countries are based on LAB fermentation.¹⁸ A number of bacteria are involved in the fermentation of kimchi and other Korean traditional fermented foods, but LAB—including *Lactobacillus*—are the dominant species in the fermentation process.^{19,20} *Lactobacillus* is

also an essential species in the fermentation of sauerkraut, as well as in Taiwanese,²¹ Chinese,²² or other fermented foods.²³ Lactobacilli are among the most common microorganisms found in kefir, a traditional fermented milk beverage,²⁴ milk, and milk products.^{25,26} During fermentation, LAB synthesize vitamins and minerals, and produce biologically active peptides with antioxidant activity.^{17,27–31}

Humans possess two protective layers of biodiversity, and the microbiome has been proposed as an important actor of COVID-19.³² The environment (outer layer) affects our lifestyle, shaping the microbiome (inner layer).³³ Many fermented foods contain living microorganisms and modulate the intestinal microbiome.^{17,31,34–36}

The composition of microbiomes varies in different regions of the world.³⁷ Gut microbiota has an inter-individual variability due to genetic predisposition and diet.³⁸ As part of the gut microbiome, *Lactobacillus* spp. contributes to its diversity and modulates oxidative stress in the GI tract. Some foods like cabbage can be fermented by the gut microbiota.³⁹

Westernized foods usually lack fermented vegetables, and milk-derived products have less biodiversity than traditional ones. Urbanization in Western countries was associated with changes in the gut microbiome and with intestinal diversity reduction.^{38,40–43} Westernized food in Japan led to changes in the microbiome and in insulin resistance.⁴⁴ The gut microbiome of westernized urban Saudis had a lower biodiversity than that of the traditional Bedouin population.⁴⁵ Fast food consumption was characterized by reduced Lactobacilli in the microbiome.⁴⁶

The links between gut microbiome, inflammation, obesity, and insulin resistance are being observed, but further large studies are needed for a definite conclusion.^{47–49}

Some COVID-19 patients have intestinal microbial dysbiosis⁵⁰ with decreased probiotics such as *Lactobacillus* and *Bifidobacterium*.⁵¹ Many bacteria are involved in the fermentation of vegetables but most traditional foods with live bacteria in the low death rate countries are based on LAB fermentation.^{18-20,23,30} Lactobacilli are among the most common microorganisms found in milk and milk products.²⁴⁻²⁶

7 | 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, or hypertension, suggesting a role for insulin resistance.⁵² Although differences exist between countries, the same risk factors for severity were found globally, suggesting common mechanisms. A strong relationship between hyperglycemia, impaired insulin pathway, and cardiovascular disease in type-2 diabetes is linked to oxidative stress and inflammation.⁵³ Lipid metabolism has an important role to play in obesity, in diabetes and its multi-morbidities, and in aging.⁵⁴ The increased severity of COVID-19 in diabetic, hypertensive, obese, or elderly individuals may be related to insulin resistance, with oxidative stress as a common pathway.⁵⁵ 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 (ACE2) receptor is part of a dual system—the renin-angiotensin-system (RAS)—consisting of an ACE-Angiotensin-II-AT₁R axis and an ACE-2-Angiotensin-(1-7)-Mas axis. AT₁R is involved in most of the effects of Ang II, including oxidative stress generation,⁵⁶ which in turn upregulates AT₁R.⁵⁷ In metabolic disorders and with older age, there is an up-regulation of the AT₁R axis leading to pro-inflammatory, pro-fibrotic effects in the respiratory system and to insulin resistance.⁵⁸ SARS-CoV-2 binds to its receptor ACE2 and exploits it for entry into the cell. The ACE2 downregulation, as a result of SARS-CoV-2 binding, enhances the AT₁R axis⁵⁹, likely to be associated with insulin resistance^{60,61} but also to severe outcomes of COVID-19 (Figure 5A).

8 | ANTIOXIDANT ACTIVITIES OF FOODS LINKED WITH COVID-19

Many foods have an antioxidant activity,⁶²⁻⁶⁴ and the role of nutrition has been proposed to mitigate COVID-19.⁶⁵ Many antioxidant mechanisms have been proposed, and several foods can interact with transcription factors related to antioxidant effects such as the nuclear factor (erythroid-derived 2)-like 2 (Nrf2).⁴ Some processes like fermentation increase the antioxidant activity of milk, cereals, fruit, vegetables, meat, and fish.²⁹

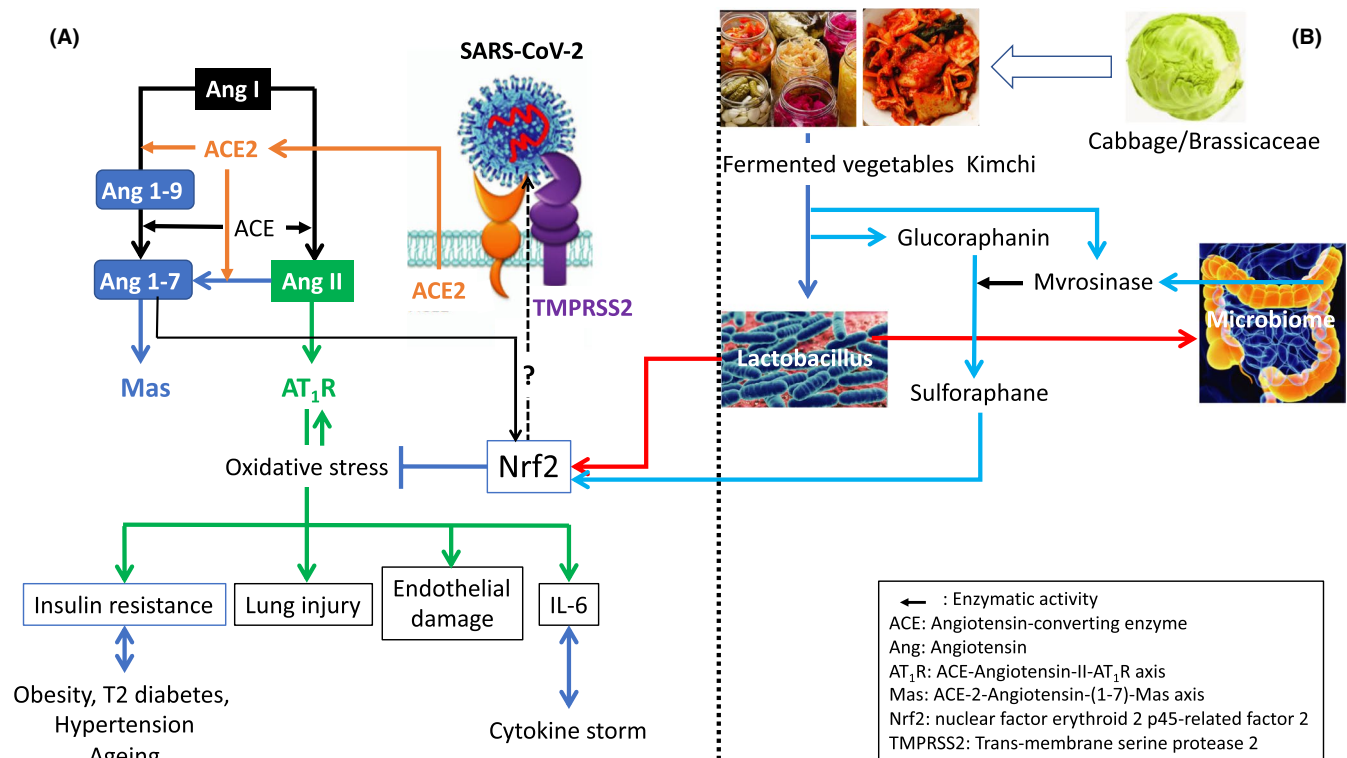


FIGURE 5 Putative mechanisms of fermented or Brassica vegetables against COVID-19. (A) Oxidative stress induced by SARS-CoV-2 after its binding to ACE2. (B) Preventive effects of cabbage and fermented vegetables through Nrf2

8.1 | Nrf2, a central antioxidant system

Reactive oxygen species (ROS), such as hydrogen peroxide and superoxide anion, exert beneficial and toxic effects on cellular functions. Nrf2 is a pleiotropic transcription factor at the center of a complex regulatory network that protects against oxidative stress and the expression of a wide array of genes involved in immunity and inflammation, including antiviral actions.⁶⁶ 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.⁶⁷ Induction of the antioxidant responsive element and the ROS-mediated pathway by Nrf2 reduces the activity of the nuclear factor kappa B (NF- κ B),⁶⁸ whereas NF- κ B can modulate Nrf2 transcription and activity, having both positive and negative effects on the target gene expression.⁶⁹

Natural compounds derived from plants, vegetables, fungi, and micronutrients (eg, curcumin, sulforaphane, resveratrol, and vitamin D) or physical exercise can activate Nrf2.^{70,71} However, sulforaphane is the most potent activator of Nrf2.^{3,34} "Ancient foods," and particularly those containing *Lactobacillus*, activate Nrf2.⁷²

Nrf2 may be involved in diseases associated with insulin resistance.^{60,73-75} Nrf2 activity declines with age, making the elderly more susceptible to oxidative stress-mediated diseases.⁷⁶ Nrf2 is involved in the protection against lung⁷⁷ or endothelial damage.⁷⁸ Nrf2-activating compounds downregulate ACE2 mRNA expression in human liver-derived HepG2 cells.⁷⁹ Genes encoding cytokines, including IL-6 and many others specifically identified in the "cytokine storm", have been observed in fatal cases of COVID-19. ACE2 can inhibit NF- κ B and activate Nrf2.⁸⁰

8.2 | Sulforaphane, the most potent Nrf2 natural activator

Isothiocyanates are stress response chemicals formed from glucosinolates in plants often belonging to the cruciferous family, and, more broadly, to the Brassica genus including broccoli, watercress, kale, cabbage, collard greens, Brussels sprouts, bok choy, mustard greens, and cauliflower.⁸¹ The formation of isothiocyanates from glucosinolates depends on plant-intrinsic factors and -extrinsic postharvest factors such as industrial processing, domestic preparation, mastication, and digestion.⁸²

Sulforaphane [1-isothiocyanato-4-(methylsulfinyl)butane] is an isothiocyanate occurring in a stored form such as glucoraphanin in cruciferous vegetables.^{83,84} Sulforaphanes are also found in fermented cabbage.^{31,85} Present in the plant as its precursor, glucoraphanin, sulforaphane is formed through the actions of myrosinase, a β -thioglucosidase present in either the plant tissue or the mammalian microbiome.^{86,87}

Sulforaphane is a clinically relevant nutraceutical compound used for the prevention and treatment of chronic diseases and may be involved in aging.⁸⁸ Along with other natural nutrients, sulforaphane

has been suggested to have a therapeutic value for the treatment of coronavirus disease 2019 (COVID-19).⁸⁹

One of the key mechanisms of action of sulforaphane involves the activation of the Nrf2-Keap1 signaling pathway.⁹⁰ Sulforaphane is the most effective natural activator of the Nrf2 pathway, and Nrf2 expression and function are vital for sulforaphane-mediated action.^{91,92} Sulforaphanes were suggested to be effective in diseases associated with insulin resistance.^{1,93-95} It has been proposed that SARS-CoV-2 downregulates ACE2 and that there is an increased insulin resistance associated with oxidative stress through the AT₁R pathway. Fermented vegetables and Brassica vegetables release glucoraphanin, converted by the plant or by the gut microbiome into sulforaphane, which activates Nrf2 and subsequently reduces insulin intolerance (Figure 5B).

8.3 | Lactic acid bacteria

8.3.1 | Antioxidant activity of *Lactobacillus*

The gastrointestinal (GI) tract is challenged with oxidative stress induced by a wide array of factors, such as exogenous pathogenic microorganisms and dietary aspects. Redox signaling plays a critical role in the physiology and pathophysiology of the GI tract.⁹⁶ The redox mechanisms of *Lactobacillus* spp. are involved in the downregulation of ROS-forming enzymes,^{97,98} and redox stress resistance proteins or genes differ largely between LAB species. In addition, Nrf-2 and NF- κ B are two common transcription factors, through which *Lactobacillus* spp. also modulates oxidative stress.⁹⁹

8.3.2 | Do lactobacilli prevent insulin resistance?

Hundreds of studies have attempted to find an efficacy of LAB on insulin resistance-associated diseases. However, most of them are underpowered or have some methodological flaw. Moreover, not all LAB strains have the same action on insulin resistance¹⁰⁰ and new better designed studies with an appropriate LAB are required. A large meta-analysis found that the intake of probiotics resulted in minor but consistent improvements in several metabolic risk factors in subjects with metabolic diseases, and particularly in insulin resistance.¹⁰¹ Another recent meta-analysis found that an oral supplementation with probiotics or synbiotics has a small effect in reducing waist circumference but no effect on body weight or body mass index (BMI).¹⁰² Kefir, a fermented milk product, was not found to be more effective than yoghurt in the glycemic control of obesity, possibly because there are insufficient differences between both.¹⁰³

8.3.3 | *Lactobacillus* and Nrf2

Nrf2 may be involved in diseases associated with insulin resistance.⁷³⁻⁷⁵ "Ancient foods," and particularly those containing

Lactobacillus, activate Nrf2.⁷² The microbiome is highly related to insulin resistance. In mice, several strains of *Lactobacillus* were found to regulate Nrf2 in models of aging,¹⁰⁴ in cardioprotective effects,¹⁰⁵ and in nonalcoholic fatty acid liver disease.¹⁰⁶ *Lactobacillus plantarum* CQPC11—isolated from Sichuan pickled cabbages—antagonizes oxidation and aging in mice.¹⁰⁷ *Lactobacillus* protects against ulcerative colitis by modulation of the gut microbiota and Nrf2/Ho-1 pathway.¹⁰⁸ The sugary kefir strain, *Lactobacillus mali* APS1, ameliorates hepatic steatosis by regulation of Nrf2 and the gut microbiota in rats.¹⁰⁹ In vitro studies have also found an effect of *Lactobacilli* mediated by Nrf2.^{110–112} Interestingly, the symbiotic combination of prebiotic grape pomace extract and probiotic *Lactobacillus* sp reduces intestinal inflammatory markers.¹¹³

8.3.4 | Coronavirus disease in animals and lactic acid bacteria

The porcine epidemic diarrhea virus (PEDV) and the transmissible gastroenteritis coronavirus infection (TGEV) are worldwide-distributed coronaviruses. Low levels of *Lactobacillus* were found in the intestine of piglets infected by TGEV¹¹⁴ or PEDV. *Lactobacillus* inhibits PEDV or TGEV effects in vitro.^{115,116}

8.4 | 7-4-Nrf2 and COVID-19

Nrf2 can act on the endoplasmic reticulum stress and the AT1R pathway. A putative mechanism may be proposed for the AT1R pathway (Figure 5). SARS-CoV-2 downregulates ACE2, inducing an increased insulin resistance associated with oxidative stress through the AT₁R pathway. This may explain risk factors for severe COVID-19.

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.¹¹⁷ Sulforaphane and LAB both therefore have the ability to reduce insulin resistance.

Other putative actions on COVID-19 severity may be postulated. The downregulation of ACE2 reduces the Ang-1,7 antioxidant activity that was found to activate Nrf2.^{118,119} Nrf2 protects against hallmarks of severe COVID-19. It has anti-fibrotic effects on various organs including the lungs,¹²⁰ and protects against lung injury, acute respiratory distress syndrome,¹²¹ and endothelial damage.⁷⁸ Finally, Nrf2 can block IL-6 in different models of inflammation¹²² 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,¹²³ and many different foods act on NRF2 and that mechanisms other than Nrf2 may be operative.

It is not yet known whether sulforaphane and/or LAB 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 both 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.¹²⁴

It is likely that foods with antioxidant activity can interact with COVID-19 and that fermented or cruciferous vegetables represent one of the possible foods involved. If some foods are found to be associated with a prevention of COVID-19 prevalence or severity, it may be of interest to study their LAB and/or sulforaphane composition in order to eventually find some common mechanisms and targets for therapy.

9 | MAY DIETARY MODIFICATIONS CHANGE THE COURSE OF COVID-19?

9.1 | Fermented vegetables and Kimchi

It is tempting to propose that countries where traditional LAB-fermented vegetables are largely consumed are those showing lower COVID-19 death rates and that fermented vegetables represent one possible preventive approach. Other nutrients are found in these products that may enhance their effect (eg, vitamin K¹²⁵). Kimchi fermented from many vegetables including cabbage has several effects on insulin resistance-associated diseases: anti-diabetic properties,^{126,127} cardiovascular diseases,²⁸ dyslipidemia,¹²⁸ or aging.¹²⁹ Kimchi, when fermented for a long time, reduces insulin intolerance to a greater extent than fresh kimchi,¹²⁶ indicating that newly formed products during fermentation are important. In particular, Kimchi from cabbage and Chinese cabbage contains several glucosinolates^{60,130,131} that can be transformed into sulforaphanes either in the plant itself or by the human microbiome.⁶⁰ In central European countries, raw and fermented cabbage is commonly consumed.

In sub-Saharan Africa, although young age is an important factor, people commonly eat fermented foods, mainly cereal-based foods like sorghum, millet and maize, and roots such as cassava, fruits, and vegetables. Fermented cassava products (like *gari* and *fufu*) are a major component of the diet of over 800 million people and, in some areas, these products constitute over 50% of the diet.¹⁶

It is clear that sauerkraut is consumed in Alsace (France) where a COVID-19 outbreak has been identified, but it is not a regular meal.

9.2 | Westernized diet

Westernized diets contain reduced amounts of fermented vegetables^{43,132} and the population may be prone to increasing insulin resistance^{44,133}, to diseases associated with it,¹³⁴ and thereby to severe COVID-19.

In the Mediterranean diet, well known for reducing insulin resistance,¹³⁵ Nrf2 appears to play an important role.^{71,136} The COVID-19 death rate differences in Italian (Figure 2) and Spanish³ regions suggest a role for Mediterranean diet and short-chain food supply. This also indicates that many foods can have an effect and that cabbage and fermented foods represent a proof-of-concept. Nrf2 is also involved in the Okinawan-based diet,⁷¹ active on insulin intolerance.¹³⁷ Taken altogether, it is possible that diet is partly involved in the COVID-19 death clusters found in large Western cities where traditional diet is often replaced by long-chain food supply.

It is clear that diet is not the only risk factor and should be considered in the context of COVID-19 in a given setting. For example, Nordic/central European people socialize less than the Mediterraneans and simultaneously may consume more fermented vegetables.

9.3 | The COVID-19 slum paradox

It was expected that the COVID-19 pandemic would be catastrophic if it reached deprived areas of low- and middle-income countries, in

particular informal settlements (slum areas) where social distancing and lockdown are almost impossible to set up.¹³⁸

In the United States, highly populated, regional air hub areas, minorities, and poverty had an increased risk of COVID-19-related mortality.¹³⁹ It was proposed that the inequality might be due to the workforce of essential services, poverty, access to care, or air pollution.¹⁴⁰ These are common risk factors in mortality observed in deprived areas of the United States.¹⁴¹ Moreover, in the United States and the UK, there are unique health issues facing black, Asian, and minority ethnic communities.^{142,143} This greater risk of hospitalization in these populations was not explained by socioeconomic or behavioral factors.¹⁴⁴ Social distancing is an important factor to be considered¹⁴⁵ but diet may also be involved.

On the other hand, a recent report of the Municipal Corporation of Greater Mumbai (Public Relation Department, 28-07-2020) found that 57% of subjects tested in the slum area had antibodies against SARS-CoV-2 but only 16% in the nonslum areas. The fatality rate in slum areas was very low (0.05%-0.1%).¹⁴⁶ Although precise data are lacking, in Brazilian favelas, the spread of COVID-19 is not noticed.¹⁴⁷ Temperature does not seem to be an important factor for containing the pandemic. Young age of the population may be important. Fermented foods are popular throughout the world, and, in many regions, they represent a widespread tradition. They also contribute significantly to the diet of millions of individuals.¹⁴⁸ This is the case in slum areas, and it is possible that fermented foods may explain, at least partly, the paradox.

Social distancing, age (population, individual), lockdown, sex, other factors

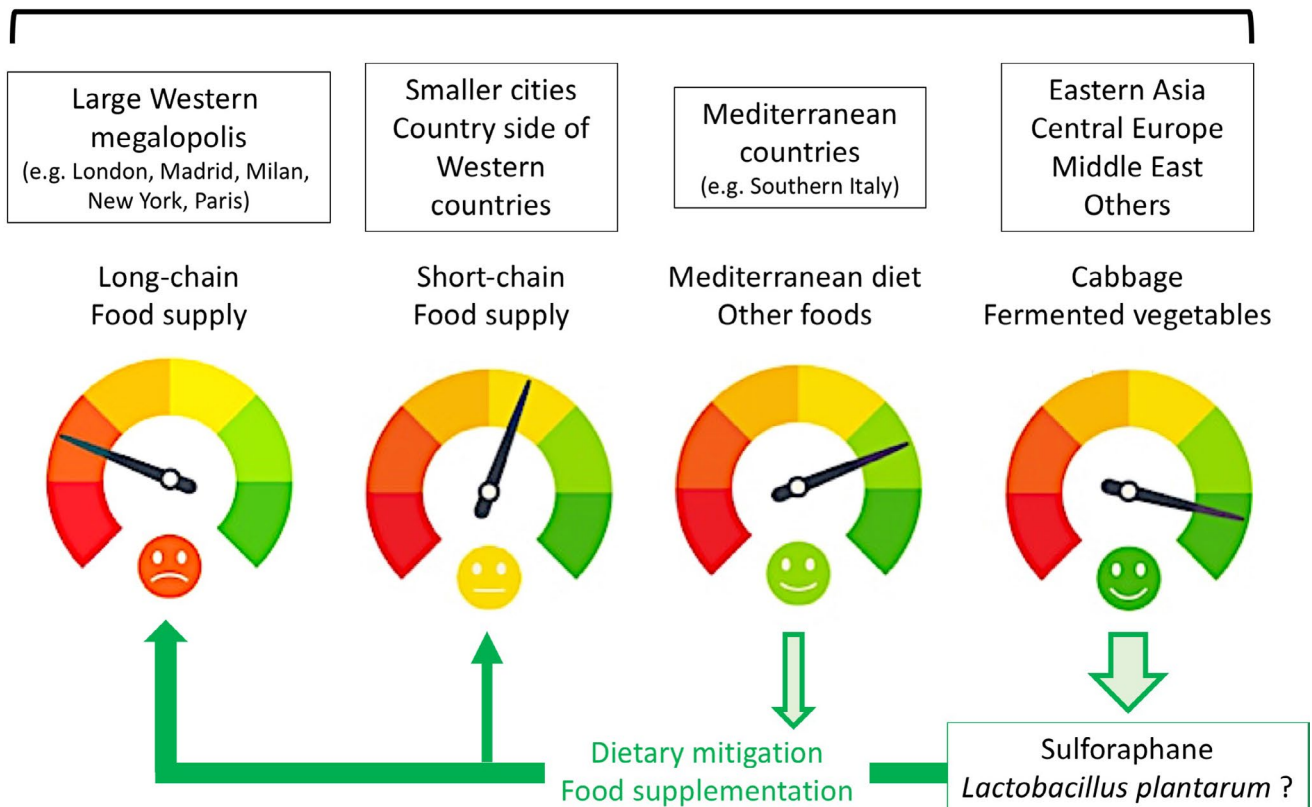


FIGURE 6 Putative role of diet in COVID-19

10 | CONCLUSION

Cabbage contains precursors of sulforaphane, the most active natural activator of Nrf2. Fermented vegetables contain many lactobacilli, also potent Nrf2 activators. It is proposed that fermented cabbage is a proof-of-concept of dietary manipulations that may enhance Nrf2-associated antioxidant effects helpful in mitigating COVID-19 severity.

Mainstream COVID-19 control strategies including social distancing, confinement, 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 rapidly 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 therapeutically useful intervention, encouraging people to eat more traditional foods containing fermented vegetables (Figure 6). 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 LAB are important. However, many other foods may have a similar activity. It should be noted that dietary supplements that overactivate Nrf2 may have side effects.¹⁴⁸

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.¹⁴⁹ 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.

If the hypothesis is proved, COVID-19 will be the first infectious disease outbreak associated with a loss of "nature"¹⁵⁰ and to be ascribed as a disease of the Anthropocene.¹⁵¹ Imbalance in the gut microbiota is responsible for the pathogenesis of various disease types including allergy, asthma, rheumatoid arthritis, different types of cancer, diabetes mellitus, obesity, and cardiovascular disease.¹⁵² Fermentation was introduced during the Neolithic age and was essential for the survival of humankind. When modern life led to eating reduced amounts of fermented foods, the microbiome drastically changed,¹⁵³ allowing SARS-CoV-2 to spread or to be more severe.¹⁵⁴ It is time for mitigation.¹⁵⁵

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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APPENDIX 1

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