Kimchi, a possible food prototype for the control of COVID-19 by nutrients due to an interplay between Nrf2, TRPA1 and TRPV1

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There are large country variations in COVID-19 death rates. Like most diseases, COVID-19 exhibits large geographical variations which frequently remain unexplained. The COVID-19 epidemic is multifactorial, and factors like climate, population density, social distancing, age, phenotype, obesity and prevalence of non-communicable diseases are associated to increased incidence and mortality [1]. Diet represents only one of the possible causes of the COVID-19 epidemic [2,3].

Although there are many pitfalls in analyzing death rates for COVID-19, [3] death rates were low or very low in Central European countries, Eastern Asian countries, many Sub-Saharan African countries, the Middle East, India and Pakistan as well as Australia and New Zealand. This geographical pattern is very unlikely to be totally due to reporting differences between countries. Some very low death rate settings (but not Australia or New Zealand) have a common feature of eating large quantities of fermented vegetables such as cabbage [2-4] and, in some continents, various spices [5].

A common denominator in all conditions associated with COVID-19 appears to be the impaired redox homeostasis responsible for reactive oxygen species (ROS) accumulation [6]. Many foods have antioxidant properties and many mechanisms may be involved. However, the activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) anti-oxidant transcription factor may be of primary importance.[7,8] Differences in COVID-19 death rates among countries may in part associated with Nrf2 and Nrf2-interacting nutrients like fermented vegetables could reduce COVID-19 severity [2-4]. Many Nrf2-interacting nutrients such as spices are TRPA1 (transient receptor potential ankyrin 1) and/or TRPV1 (transient receptor potential vanillin 1) agonists [9]. TRPA1, an excitatory ion channel, plays a pivotal role in augmenting sensory or vagal nerve discharges, evoking several COVID-19 symptoms [9]. In COVID-19, rapid desensitization of TRAP1/TRPV1 may reduce symptom severity (papers submitted and available online [10,11]). TRPV1 is another TRP channel often co-localized and interacting with TRPA1 and also possibly involved in COVID-19 symptoms.

Seven clinical cases showed the rapid effect of curcuma (100 mg) + black pepper (16.5 mg) or ginger (gingerol mg) (TRPA1 agonist) or red pepper (10 to 30 mg) (TRPV1 agonist) on some COVID-19 symptoms but not on loss of taste and smell. These effects occurred within two minutes and lasted less than 3 Hours. These spices were used at a rather low dose to avoid side effects. Broccoli (Nrf2 agonist) is acting within 10 minutes, at a lesser extent and for 5-6 hours. Mixing broccoli and curcuma + black pepper or ginger, red pepper (TRPV1 agonist) we showed a synergy between Nrf2 and TRP nutrients for their long standing effect (up to 10 hours) [10]. It is likely that TRPA1/TRPV1 agonists act by receptor desensitization. These results are of interest since they show that TRPA1/TRPV1 agonists can be used at lower doses with Nrf2 nutrients thereby reducing side effects from high dose spices.

These results cannot be taken as formal evidence. However, they have contributed to developing a proof-of-concept for the hypothesis that combined Nrf2-TRPA1/TRPV1 foods may be beneficial for some COVID-19 symptoms and that there is a synergy between Nrf2 and TRPA1/TRPV1 agonists. Before any conclusion can be drawn, these data warrant confirmation, in particular for assessing the benefits of these foods in more severe and/or hospitalized patients, in large and properly designed studies with a double-blind, placebo-controlled design.

Different types of fermented foods such as chongkukjang, doenjang, ganjang, gochujang, and kimchi are widely consumed in north eastern Asian countries including Korea. Among them, kimchi is the most popular Korean traditional food. Kimchi is prepared by fermenting the baechu cabbage with other vegetables [12]. The major ingredients of kimchi are cruciferous vegetables and other healthy functional foods such as garlic, ginger, red pepper powder added as sub-ingredients to enhance taste, flavor, nutritional value and texture [13]. Cabbage and cruciferous vegetables, contain precursors of sulforaphane, the most active natural activator of Nrf2 whereas many sub-ingredients are TRPA1 agonists. Many bacteria are involved in the fermentation of kimchi, but lactic acid bacteria (LAB) become dominant while the putrefactive bacteria are suppressed during salting and fermentation [13]. During fermentation, LAB synthesize vitamins and minerals, and produce biologically-active peptides with anti-oxidant activity [14-19]. LABs possess an oxidative stress tolerance and antioxidant capacity [20]. LABs are potent Nrf2 activators [21] (Table 1).

Kimchi may be one of the major reasons for low COVID-19 death rates and severity in Korea. It might also prevent infection by SARS-CoV-2. These benefits may be related to Nrf2 and TRAP1/TRPV1 agonists. Kimchi may therefore represent a possible food prototype for the control of COVID-19 by nutrients.

Table 1: Effects of Kimchi ingredients on Nrf2 and TRPA1 and TRPV1

	Nrf2	TRPA1	TRPV1	Autophagy	Compounds in Baechu kimchi
Allicin		74	74	75	Garlic, leek [12,76]
Berberine	45		77	78	
Curcumin	47,48	79	79	80,81	
EGCG	47	82	83	84	
Genistein	47	85	86	81	
Gingerol	87	88	89	90	Ginger [12,91]
Lactobacillus	51		92	93	Fermentation
Mustard oil		94			Baechu and Gat Kimchi [91]
N-acetyl cysteine	95	96	97	98	
Nitric oxide	99	100	100	99	
Piperine	101	102	Weak [103]	104	
Quercetin	47	105	106	106,107	108
Red pepper (capsaicin)	109,110	111	112	113	All kimchi [11]
Resveratrol	47	114,115	116	81	
Selenium	117	118	119	81	
Sulforaphane (from glucoraphanin)	47			120	Cabbage [11]

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