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Spices to Control COVID-19 Symptoms: Yes, but Not Only…

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Keywords

Nuclear factor (erythroid-derived 2)-like 2 · Transient receptor potential ankyrin 1 · Transient receptor potential vanillin 1 · COVID-19 · Spices · Fermented vegetables

Abstract

There are large country variations in COVID-19 death rates that may be partly explained by diet. Many countries with low COVID-19 death rates have a common feature of eating large quantities of fermented vegetables such as cabbage and, in some continents, various spices. Fermented vegetables and spices are agonists of the antioxidant transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2), and spices are transient receptor potential ankyrin 1 and vanillin 1 (TRPA1/V1) agonists. These mechanisms may explain many COVID-19 symptoms and severity. It appears that there is a synergy between Nrf2 and TRPA1/V1 foods that may explain the role of diet in COVID-19. One of the mechanisms of COVID-19 appears to be an oxygen species (ROS)-mediated process in synergy with TRP channels, modulated by Nrf2 pathways. Spicy foods are likely to desensitize TRP channels and act in synergy with exogenous antioxidants that activate the Nrf2 pathway.

Introduction

Like most diseases, COVID-19 prevalence, severity, and mortality exhibit large geographical variations which frequently remain unexplained. The COVID-19 epidemic is multifactorial, and factors like climate, population density, social distancing, age, phenotype, obesity, prevalence of noncommunicable diseases, and possibly genetic background are associated with increased incidence and mortality [1]. Diet represents only one of the possible moderating factors of the COVID-19 epidemic [2, 3].

Although there are many pitfalls in analyzing death rates for COVID-19 [3], death rates during the Spring pandemic 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 in 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 in 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]. The recent COVID-19 outbreak in Europe and the USA does not appear to exist in many Asian or African countries.

Among the spices with a beneficial effect on human health, allicin, capsaicin, curcumin, gingerol, mustard oil, piperine, and quercetin glucosides are the major ones [6]. Most of them have an antioxidant activity through different mechanisms including the direct or indirect activation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) [7], and all are TRP (transient receptor potential) agonists. However, spices may interact with SARS-CoV-2 by other mechanisms [8].

Three phases of COVID-19 have been described: (i) a viral infection lasting for 1–2 weeks; (ii) a second phase

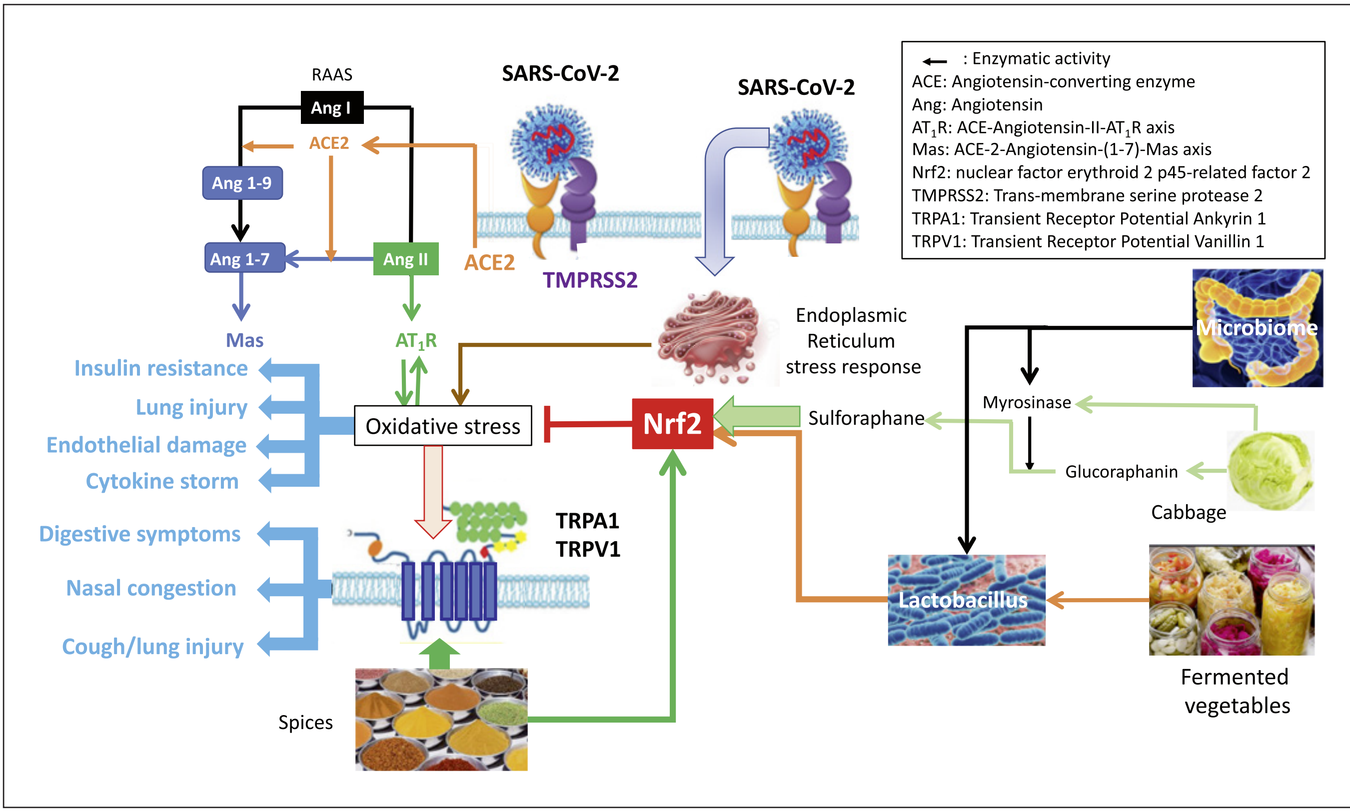

Fig. 1. Interactions between foods and COVID-19. ←, enzymatic activity; ACE, angiotensin-converting enzyme; Ang, angiotensin; AT_1R, ACE-angiotensin-II-AT_1R axis; Mas, ACE-2-angiotensin-(1–7)-Mas axis; Nrf2, nuclear factor erythroid 2 p45-related factor; TMPRSS2, transmembrane serine protease 2; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanillin 1; ER, endoplasmic reticulum.

characterized by an intertwined cytokine and oxidative stress storm, independent of infection; and (iii) a recovery phase that may last for some months. Spices may interact differently during these 3 phases.

COVID-19: From Oxidative Stress to TRPs

Oxidative Stress

A common denominator in all conditions associated with COVID-19 appears to be the impaired redox homeostasis, responsible for the accumulation of reactive oxygen species (ROS) [9]. Among many others, 2 important mechanisms can be involved [7, 10].

The angiotensin-converting enzyme 2 (ACE2) receptor is part of the dual system – the renin-angiotensin-system – consisting of an ACE-Angiotensin-II-AT_1R axis and an ACE-2-Angiotensin-(1–7)-Mas axis. SARS-CoV-2 binds to ACE2 and its receptor, and ACE2 downregulation enhances the AT_1R axis [11] leading to oxidative stress generation [12]. As a result, this is associated with insulin resistance as well as with lung and endothelial damage and cytokine storm, 3 severe outcomes of COVID-19 [13–15] (shown in Fig. 1).

When SARS-CoV-2 enters the cell, it triggers endoplasmic reticulum (ER) stress responses associated with increased oxidative stress and unfolded protein response (UPR) [16, 17]. As for other viral infections, ER stress and sustained UPR signalling may be major contributors to the pathogenesis of COVID-19 [18, 19] (shown in Fig. 1).

Nrf2 is the most potent antioxidant in humans [20, 21] and can downregulate the oxidative stress from the AT_1R axis as well as in the ER [7, 22]. In particular, the upregulation of Nrf2 signalling inhibits the overproduction of IL-6, proinflammatory cytokines, and chemokines. It also limits the activation of nuclear factor-kappa b (NFκB). Other transcription factors involved in oxidative stress

Table 1. Examples of Nrf2, TRPA1, and TRPV1 interacting spices

	Foods	Nrf2	TRPA1	TRPV1
Allicin	Garlic, leek, onion		[59]	[59]
Capsaicin	Red pepper	[60, 61]	[62]	[63]
Cinnamaldehyde	Cinnamon	[64]	[65]	[66]
Curcumin	Turmeric	[67, 68]	[69]	[69]
Gingerol	Ginger	[70]	[71]	[72]
Mustard oil	Mustard seeds		[73]	
Piperine	Black and long pepper	[74]	[75]	[76]
Wasabi	Japanese horseradish	[77]	[78]	[78]

Nrf2, nuclear factor (erythroid-derived 2)-like 2; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanillin 1.

are activator protein 1 and NFκB. There is an amplification loop in oxidative stress. Excess ROS induces inflammatory cell recruitment under the effect of IL-6, IL-8, and TNF-α, the activation of which generates more ROS(O_2^-) produced in the mitochondria and ER.

Transient Receptor Potential

The TRP vanilloid 1 (TRPV1) and ankyrin 1 (TRPA1) are members of the TRP superfamily of structurally-related, nonselective cation channels. TRPV1 and TRPA1 are frequently colocalized in sensory neurons and interact to modulate function. They are also expressed in many non-neuronal cells such as vascular smooth muscle, monocytes, lymphocytes, keratinocytes, epithelial cells, and endothelium [23].

TRPA1 induces inflammation, plays a key role in the physiology of almost all organs [24], and exhibits the highest sensitivity of TRPs to oxidants. TRPA1 can be activated by cold, heat, pungent compounds, mechanical stimuli, endogenous signals of inflammation, and oxidative stress [25].

TRPV1, also known as the capsaicin receptor, has a major function in the detection and regulation of body temperature [26]. It can be activated by some endogenous lipid-derived molecules, acidic solutions, pungent chemicals, food ingredients such as capsaicin, and toxins [27]. TRPV1 is a sensor of oxidative stress, but to a lesser extent than TRPA1.

TRPA1 and TRPV1 augment sensory or vagal nerve discharges to evoke several symptoms of COVID-19, including cough, nasal obstruction, pain, vomiting, diarrhea, and, at least partly, sudden and severe loss of smell and taste [24]. The modulation by Nrf2 of TRPA1/V1 is still unclear but suggested from very limited clinical evidence.

Foods Interacting with Nrf2 and TRPs

Natural compounds derived from plants, vegetables, and fungi and micronutrients or physical exercise can activate Nrf2 [28, 29]. Many foods have antioxidant properties, and many mechanisms may be involved. However, the activation of Nrf2 may be of primary importance [7, 30, 31]. Differences in COVID-19 death rates among countries may partly be associated with Nrf2 and Nrf2-interacting nutrients like spices and raw or fermented vegetables that could reduce COVID-19 severity [2–4] (shown in Table 1). Nrf2-interacting foods and nutrients may rebalance oxidative stress and have a significant effect on COVID-19 severity [4, 32–34]. On the other hand, many Nrf2 medications were found to be toxic as the balance between oxidant/antioxidant is difficult to obtain.

TRPA1 and TRPV1 can be activated by pungent compounds including many, but not all, Nrf2-interacting nutrients [24]. Spices and aromatic herbs have potent antibacterial and antiviral activities [35–37]. Spices can also interact with many other mechanisms in COVID-19 including the entry of SARS-CoV-2 into the cell and autophagy processes [7, 38].

Clinical Data Supporting the Hypothesis

A few patients have been studied in order to assess their response to foods. Seven COVID-19 patients received either broccoli and paracetamol (submitted, available online) [39] or broccoli with TRPA1/V1 and paracetamol during the first 2 phases of the infection. It was consistently found that these nutrients reduced cough, gastrointestinal symptoms, and nasal symptoms very rapidly (within minutes). Fatigue was usually largely improved 1 h after ingestion. Loss of smell and taste were mostly unchanged. Pain and headache were inconstantly improved. The effect of the nutrients ranged from 4 to 8 h, after which patients had a reoccurrence of symptoms.

A series of cough-induced challenges were carried out on one of the patients during the recovery phase. Eight double-blind, placebo-controlled challenges showed that broccoli was effective in reducing cough within 10 min (submitted, available online) [39]. Forty-nine open-label induced cough challenges were subsequently carried out on the same patient. Nutrients with various Nrf2 and TRPA1/V1 agonist activity were used: broccoli (potent Nrf2 agonist and mild TRPA1 activity), berberine (Nrf2 only), black pepper, curcumin, ginger, green tea, resveratrol, and zinc (potent TRPA1 agonists and variable Nrf2 agonists) as well as red pepper (potent TRPV1 agonist and Nrf2 agonist). Berberine and zinc were not effective. All of the other nutrients except resveratrol were rapidly effective (1–10 min). The effect of TRPA1/V1 agonists disappeared in 1–4 h. Broccoli induced a longer duration of action (5–7 h). The duration of the effect increased to around 10 h when low doses of TRPA1/V1 agonists were added to low-dose broccoli. Paracetamol low dose (its metabolites, *N*-acetyl-*p*-benzoquinone imine and *p*-benzoquinone, but not paracetamol itself, are TRPA1/TRPV1 agonists [40]) increases the duration of action of the TRPA1/V1-broccoli combinations to over 14 h.

The results of the challenges suggest a rapid short-lasting TRPA1/V1 desensitization (papers submitted and available online [39, 41]): (i) the clinical effect found in challenges carried out with curcumin and black pepper, ginger, or green tea (all TRPA1 agonists) and capsaicin (TRPV1 agonist) was extremely rapid; (ii) the duration of action of the compounds was relatively short; (iii) short-lasting and mild episodes of cough were observed during the challenges, suggesting a resensitization-desensitization of receptors; and (iv) gastroesophageal symptoms were experienced when cough reoccurred at the end of the challenges with red and black pepper.

The results of the clinical studies presented herein cannot be taken as formal evidence. However, they have contributed to developing a proof of concept for the hypothesis that combined Nrf2-TRPA1/V1 foods may be beneficial for some COVID-19 symptoms and that there is a synergy between Nrf2 and TRPA1/V1 agonists. Before any conclusion can be drawn and these treatments recommended for COVID-19, the data warrant confirmation. In particular, the benefits of the foods need to be assessed in more severe and/or hospitalized patients through large and properly designed studies with a double-blind, placebo-controlled design. These immediate effects cannot be related to the blockage of the virus entry into the cells or to autophagy [7].

Spices in COVID-19 Control: Yes, but…

In COVID-19, a rapid desensitization of TRAP1/V1 by spices is likely to reduce disease severity. However, Nrf2 agonists expand the duration of action of spices. Very high doses of spices regularly consumed in Asian or sub-Saharan countries could reduce COVID-19 infection and/or severity. However, in Western countries, except possibly in Hungary, most people usually eat less spicy foods, and doses ingested elsewhere cannot be given rapidly due to side effects (mostly gastrointestinal intolerance). In these countries, it would be advantageous to combine Nrf2-TRP agonists.

In countries where large amounts of spices are eaten, the consumption of fermented vegetables is also high. This is the case for cassava in Africa or many fermented vegetables in Asia. Different types of fermented foods are widely consumed in Eastern Asian countries. Among them, kimchi is the most popular Korean traditional food. Kimchi is prepared by fermenting baechu cabbage with other cruciferous vegetables containing precursors of sulforaphane, the most active natural activator of Nrf2 [42]. Subingredients such as garlic, ginger, leaf mustard, and red pepper powder are TRPA1/V1 potent agonists [43]. During fermentation, lactic acid bacteria produce biologically active peptides with antioxidant activity [44–49] and Nrf2 interaction [50]. In such countries, it is possible that another form of TRP desensitization, "tachyphylaxis," may be important. This is the reduction or disappearance in the response to repeated applications of agonists [51–53].

Nrf2-TRPA1/V1 agonists may have some relevance for the treatment of persistent cough following viral infections [54–56], both in nonallergic rhinitis [57, 58], and also possibly in some symptoms of the common cold. We do however urgently need to go from empiricism to science with appropriate mechanistic and clinical studies.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.B. proposed the concept and discussed it with J.M.A., T.Z., and W.C. J.M., H.B., J.P.C., Rdl.T., V.L.M., N.P.L., and A.B. were part of the think tank group. S.C.F. and G.I. discussed the food data, H.J.C. and H.J.K. discussed the kimchi data, and I.A., C.A.A., G.W.C., A.A.C., A.F., J.F., B.G., T.H., J.C.I., M.J., L.K., P.K., D.L.L., E.M., Y.O., N.G.P., O.P., J.R., Y.R., P.P.R., B.S., A.S., S.T.S., and A.V. were requested to comment on the concept and to review the paper. All authors accepted the paper.

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