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Potential Interplay between Nrf2, TRPA1, and TRPV1 in Nutrients for the Control of COVID-19

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Keywords

COVID-19 · Nrf2 · TRAP-1 · Broccoli · Pungent foods · Cough challenge

Abstract

In this article, we propose that differences in COVID-19 morbidity may be associated with transient receptor potential ankyrin 1 (TRPA1) and/or transient receptor potential vanilloid 1 (TRPV1) activation as well as desensitization. TRPA1 and TRPV1 induce inflammation and play a key role in the physiology of almost all organs. They may augment sensory or vagal nerve discharges to evoke pain and several symptoms of COVID-19, including cough, nasal obstruction, vomiting, diarrhea, and, at least partly, sudden and severe loss of smell and taste. TRPA1 can be activated by reactive oxygen species and may therefore be up-regulated in COVID-19. TRPA1 and TRPV1 channels can be activated by pungent compounds including many nuclear factor (erythroid-derived 2) (Nrf2)-interacting foods leading to channel desensitization. Interactions between Nrf2-associated nutrients and TRPA1/TRPV1 may be partly responsible for the severity of some of the COVID-19 symptoms. The regulation by Nrf2 of TRPA1/TRPV1 is still unclear, but suggested from very limited clinical evidence. In COVID-19, it is proposed that rapid desensitization of TRAP1/TRPV1 by some ingredients in foods could reduce symptom severity and provide new therapeutic strategies.

Introduction

The transient receptor potential (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 co-localized in sensory neurons, and interact to modulate function. They co-localize with neuropeptides such as substance P, CGRP and the receptor for nerve growth factor, and have a low threshold for various inflammatory mediators such as bradykinins, histamines, and eicosanoids. They are also expressed in many non-neuronal cells such as vascular smooth muscle, monocytes, lymphocytes, keratinocytes, epithelial cells, and endothelium [1].

TRPA1, an excitatory ion channel originally associated with the receptor of mustard oil in sensory neurons [2], plays a pivotal role in detecting cysteine-reactive irritants and in augmenting sensory or vagal nerve discharges to evoke pain and cough. TRPA1 induces inflammation, plays a key role in the physiology of almost all organs [3], 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 [4]. Its function is modulated by multiple factors, including Ca^{2+} , trace metals, pH, reactive oxygen species (ROS), nitrogen, and carbonyl species.

TRPV1, also known as the capsaicin receptor, has a major function in the detection and regulation of body temperature [5]. TRPV1 provides a sensation of heat and pain (nociception). In primary afferent sensory neurons,

it cooperates with TRPA1 to mediate the detection of noxious environmental stimuli [6]. It can also be activated by some endogenous lipid-derived molecules, PGE₂, acidic solutions, pungent chemicals, food ingredients such as capsaicin, and toxins [7]. TRPV1 is a sensor of oxidative stress, but to a lesser extent than TRPA1.

COVID-19 morbidity cannot be appreciated across countries because there is no common method of assessment. However, death rates may be a proxy for COVID-19 severity. There have been large country variations in COVID-19 death rates [8, 9]. Some of the very low death rate settings, such as those of Eastern Asia, Central Europe, the Balkans and Africa, have a common feature of eating large quantities of fermented vegetables [10] and, in some countries, spices. There appears to be an inverse correlation between spice consumption and COVID-19 mortality [11], and the same countries are often those with a high consumption of fermented vegetables and spices [12, 13].

A common denominator in all clinical manifestations associated with COVID-19 appears to be the oxidative stress storm [14]. The intake of fermented vegetables is associated with activation of the nuclear factor (erythroid-derived 2) (Nrf2)-like antioxidant transcription factor [10, 15, 16]. There are many Nrf2-interacting nutrients [17] (berberine, curcumin, epigallocatechin gallate, genistein, quercetin, resveratrol, and sulforaphane) that act similarly to reduce insulin resistance, endothelial damage, lung injury, and cytokine storm (Bousquet et al. [10], submitted). It has been proposed that Nrf2-interacting foods and nutrients can re-balance insulin resistance and have a significant effect on COVID-19 severity [10, 18–20]. However, other mechanisms may also be involved as pungent foods and spices interact through TRPA1 and TRPV1 [21]. Activation of TRP channels (TRPV1, TRPV4, TRPM3, TRPM8, and TRPA1) enables cross talk between neurons, immune cells, and epithelial cells to regulate a wide range of inflammatory actions [22].

In this article, we examined whether (i) TRPA1 and/or TRPV1 may be associated with COVID-19 symptoms and morbidity; (ii) TRPA1 and/or TRPV1 may be involved in COVID-19 risk factors (obesity and diabetes), lung injury, and endothelial damage; (iii) TRPV1 may be associated with TRPA1 in COVID-19; (iv) Nrf2, the most potent antioxidant system of the human body, may regulate TRPA1 and/or TRPV1; (v) Nrf2-interacting nutrients act on TRPA1 and/or TRPV1; and (vi) the results of 3 clinical cases treated with broccoli seed capsules (broccoli) containing glucoraphanin might be explained by TRPA1 and/or TRPV1.

COVID-19 Symptoms

Several COVID-19 Symptoms Are Associated with TRPA1 and/or TRPV1

Cough is a major COVID-19 symptom [23], but is not necessarily associated with severity. The cough reflex is induced by the activation of airway sensory nerves and TRP ion channels related to the vanilloid (TRPV) family and TRPA1 [24–26]. TRPA1 is abundantly expressed on the innervations of the entire respiratory tract. These include the C-fibers of the trigeminal and vagal ganglia as well as nasal, tracheal, bronchial, and alveolar epithelial cells, bronchial smooth muscle cells and CD⁴⁺ T cells [27]. C-fibers largely “sense” the presence of potentially toxic inhaled irritants and toxicants. TRPA1 represents a gateway to airway irritation and reflex responses induced by inhaled oxidants [28], air pollutants, and tobacco smoking [29]. Capsaicin has been largely used in cough provocation tests related to airway mucosal TRPV1 receptors in sensory nerves, reacting to noxious stimuli [24]. Both TRPA1 and TRPV1 mediate cigarette smoke-induced damage of the bronchial and alveolar epithelial cells via modulation of oxidative stress, inflammation, and mitochondrial damage [30]. This suggests a complex regulatory role of TRPA1 and TRPV1 in acute and chronic airway inflammation [31].

Smell and taste disorders are very common in COVID-19 [32–37]. TRPA1 and TRPV1 are among the TRP channels involved in nociception and are excited by pungent odorous substances [38]. Associations have been observed between TRPA1 genetic variants and increased sensitivity to thermal pain stimuli or increased olfactory sensitivity [39]. Capsaicin is also partly involved in smell and taste perception with sensory (olfactory) and sensitive (trigeminal) perceptions coming together [40]. In addition, most odorants have sensitive (trigeminal) characteristics, this being linked with nasal hyper-reactivity to strong odorants (sometimes identified as “hyperosmia” by patients with sino-nasal inflammation). The intranasal trigeminal system is a third chemical sense in addition to olfaction and gustation. In the nasal cavity, high levels of trigeminal receptor expression were found for TRPV1 and TRPA1 [38]. The sensitivity of the intranasal trigeminal system to chemicals was found to be partly mediated by TRPA1 [41]. The mammalian taste system consists of taste buds found throughout the oral cavity. TRP channels are important in gustatory processing [42]. They are very sensitive to changes in temperature and are activated by many compounds found in plants, often used as spices

[43]. TRPA1 is mostly an acid-sensing and epithelial sodium channel [44], whereas TRPV1 is also sensitive to temperature and bitter taste [45].

Loss of appetite is common [46] and may be severe in COVID-19. It has been suggested that TRPA1 may play a role in food intake and satiety [47–50]. In animals, TRPA1 activation increases appetite [51]. TRPV1 can have an impact on appetite through control of appetite hormone levels or modulation of gastrointestinal vagal afferent signalling [52].

Nasal obstruction alone is relatively common in COVID-19. In 2 studies, nasal obstruction was frequently reported, but not correlated with olfactory dysfunction [53, 54]. In rhinitis, nasal itch is related to TRPV1 [55]. Patients suffering from rhinitis exhibit a decreased threshold to the TRPA1 agonist allyl isothiocyanate (AITC). This correlates with symptoms and, in animals, is resolved after chemical destruction of the nasal sensory nerves [56–58]. Capsaicin was found to be an option for the treatment of nonallergic rhinitis [59].

Nausea, vomiting, and/or diarrhea are relatively common symptoms of COVID-19 [46]. TRPA1 is expressed in both dorsal root ganglions and nodose ganglion neurons innervating the stomach, as well as in nerve fibers of the gastric wall. Gastric administration of garlic powder containing the TRPA1-agonist allicin induces specific epigastric symptoms and gastric relaxation in healthy subjects [60]. Capsaicin can induce gastroesophageal and abdominal pain, heartburn, bloating, and/or dyspepsia through TRPV1 [61–63].

COVID-19 is often associated with myalgia, back pain, widespread hyperalgesia, and headache [34, 64]. TRPA1 and TRPV1 are involved in acute and chronic pain and in migraine [3, 65, 66]. They may also be partly involved in some of the COVID-19 symptoms. Some of the other COVID-19 symptoms, such as fever or fatigue, appear less likely to be associated with TRPA1 and/or TRPV1.

COVID-19 Risk Factors, TRPA1, and TRPV1

Obesity and, to a lesser extent, diabetes are risk factors for COVID-19 severity. The importance of TRPA1 on the metabolic syndrome, obesity, and diabetes is usually indirect using agonists that have multiple actions including TRPA1 and TRPV1. It is therefore difficult to differentiate the 2 TRP channels. Animal models are of importance for a more precise assessment of the mechanisms [67, 68].

TRPV1 and TRPA1 have been associated with control of weight, pancreatic function, hormone secretion, thermogenesis, and neuronal function. This suggests a potential therapeutic value of these channels in obesity and di-

abetes [69, 70]. Cinnamaldehyde (in cinnamon) may have an adjunct future potential role in the treatment of diabetes and its complications [12]. A garlic supplement plays a positive and sustained role in blood glucose, total cholesterol, and in high/low density lipoprotein regulation in the management of diabetes [71]. However, these effects can be mediated by multiple pathways. As an example, cinnamaldehyde exerts its effects through its action on multiple signalling pathways [70], including TRPA1-ghrelin [72] and Nrf2.

Lung Injury

Acute respiratory distress syndrome is one of the major causes of mortality associated with COVID-19. TRP ion channels are involved in lung injury. It has been proposed that morbidity, severity of the disease, and underlying physiological events leading to mortality are closely linked with the TRPV1-expressing neuronal system (afferent/efferent neurons) in the lungs [73]. TRPV1 and TRPV4 are involved in pulmonary chemical injuries [74]. In mouse acute lung injury models, the bacterial endotoxin LPS involves both TRPV1 and TRPA1 [31, 73, 75]. Ventilator-induced lung injury contributes to mortality in patients with acute lung injury by increasing inflammation. In a rat model of ventilator-induced lung injury, a TRPA1 inhibitor significantly reduced both inflammation in the lung tissues and the generation of ROS [76]. Unsaturated aldehydes generated during incomplete combustion – such as acrolein – are highly toxic for the lungs. TRPA1 protects against high-level acrolein-induced toxicity in mice [77]. The simultaneous activations of TRPA1 and TRPV1 by their respective selective agonists are far more effective than single agonists taken separately [78]. In a mouse model, liquiritin, a novel inhibitor of TRPV1 and TRPA1, protects against LPS-induced acute lung injury [75]. TRPA1 may be involved in the development and progression of heart failure, myocardial ischemia-reperfusion injury, myocardial fibrosis, and arrhythmia that may aggravate lung injury [79].

TRPA1/TRPV1 and Nrf2

TRPA1/TRPV1 Are Sensory Receptors for Multiple Products of Oxidative Stress

Oxidative stress, characterized by an imbalance between oxidants and antioxidants in favour of oxidants, leads to the disruption of redox signalling and physiological function. Redox signalling-induced changes are performed by ROS and reactive nitrogen species (RNS) [80].

ROS is a collective term that includes superoxide ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl radical (OH^{\cdot}), singlet oxygen (1O_2), peroxy radical (LOO^{\cdot}), alkoxy radical (LO^{\cdot}), lipid hydroperoxide (LOOH), hypochlorous acid (HOCl), and ozone (O_3), among others [81].

TRPA1 also functions as a sensor, activated by ROS and modulated by the occurrence of intracellular changes in oxygen levels. Multiple agents produced during oxidative stress can activate TRPA1 expressed in sensory neurons [82]. Besides ROS, TRPA1 channels are also activated by RNS, including nitric oxide (NO) [83]. Although many studies have been performed, the relevance of TRPA1 activation for cell signalling in oxidative stress is still unclear [84]. In the upper and lower airways, TRPA1, found in vagal sensory endings responsive to hypoxic conditions, may serve as a rapid alarm system during abnormal oxidative conditions [84].

The potential links between TRPA1 and TRPV1 with ROS production has been proposed in chronic diseases. In endothelial cells, TRPV1 stimulation activates endothelial NO synthase (eNOS) [85] and NO production, leading to smooth muscle relaxation and vasodilation, and concomitant protection of endothelial cells from leukocyte adhesion. On vascular smooth muscle cells, capsaicin reduces the accumulation of lipids and cholesterol uptake in a Ca^{2+} -, calcineurin- and protein kinase A-dependent manner, via increased expression of ATP-binding cassette transporter A1 and reduced expression of LDL-related protein 1 [86]. In in vivo models, dietary capsaicin treatment improves atherosclerosis by reducing the inflammatory events that cause atherosclerotic plaque formation. Since oral capsaicin treatment cannot cause the increase in blood levels of capsaicin needed to act directly on cardiac or intravascular TRPV1 receptors, a remote activation should be suggested, which likely involves TRPV1 receptors localized on the capsaicin-sensitive sensory nerve terminals [87]. Indeed, experimental evidence proposes the protective roles of cardiac capsaicin-sensitive afferents and sensory TRPV1 receptors in myocardial protection through the release of sensory neuropeptides [88]. The chronic administration of systemic capsaicin induces sensory desensitization [89], leading to a model of Heart Failure with preserved Ejection Fraction (HFpEF). Mechanistically, this phenotype is due to reduced basal cardiac NO, superoxide, and peroxynitrite ($ONOO^-$) formation, with impairment of the filling properties of the heart. The protective roles of the capsaicin-sensitive nerves and TRPV1 receptors on cardiac function are suggested.

Oxidative stress in the airways occurring through inflammatory mechanisms or following the inhalation of

noxious agents causes cellular dysfunction. Oxidative stress activates vagal sensory C-fibers, initiating nerve action potentials that lead centrally to unpleasant sensations (e.g., cough, dyspnea, and chest-tightness) and to the stimulation/modulation of reflexes (e.g., cough, bronchoconstriction, respiratory rate, inspiratory drive). There is a key role for TRPA1, although TRPV1 may also play a role [83, 90].

Nuclear factor (erythroid-derived 2)

Nrf2 is the major regulator of cellular resistance to oxidants. Nrf2 is mainly regulated by the Kelch-like ECH-associated protein 1. Nrf2 activation, through constitutive mechanisms, is carried out by electrophilic compounds and oxidative stress, where some cysteine residues in Kelch-like ECH-associated protein 1 are oxidized. This results in a decrease in Nrf2 ubiquitination and an increase in its nuclear translocation and activation. In the nucleus, Nrf2 induces a variety of genes involved in the antioxidant defence [91].

Interactions between Nrf2 and TRPA1

It is possible that Nrf2 may play a major role in the modulation of TRPA1 by ROS. However, there are few studies assessing the interactions between Nrf2 and TRPA1, and their results are sometimes conflicting. Specific signalling pathways of lung ischemia-reperfusion injury impair Nrf2-antioxidant response and activate oxidative stress in the brainstem, thereby leading to the amplification of TRPA1, most likely via ROS [92]. Polysulfides (H_2Sn) occur in the brain, activate TRPA1, and facilitate the translocation of Nrf2 [93]. TRPA1 knockdown exacerbates the infiltration of activated macrophages, renal inflammation, and renal injury in mice after ischemic reperfusion injury [94]. In different animal models, neuroprotection has been observed and associated with the activation of the Nrf2 pathway via antioxidative signalling pathways [95–98]. A neuronal redox-sensing Ca^{2+} -influx channel, overexpressed in human cancer, upregulates Ca^{2+} -dependent anti-apoptotic pathways to promote ROS resistance. Nrf2 directly controls TRPA1 expression, thus providing an orthogonal mechanism for protection against oxidative stress, together with canonical ROS-neutralizing mechanisms [99].

Interactions between Nrf2 and TRPV1

There are few studies assessing the interactions between Nrf2 and TRPV1, and their results are sometimes conflicting. Capsaicin induces the production of ROS, which can induce Nrf2 activation and the induction of

heme oxidase-1 expression [100]. TRPV1 activation induces calcium influx associated with an increasing expression of Nrf2-responsive antioxidant enzymes [101]. Ultraviolet irradiation causes cellular oxidative stress, stimulates 12-lipoxygenase and the product 12-hydroxyicosatetraenoic acid, and then activates TRPV1. A Ca^{2+} influx via TRPV1 is responsible for UVB irradiation-induced Nrf2 degradation [102].

Activation and Desensitization of TRPA1 and TRPV1

Neurotropism of SARS-CoV-2

Coronaviruses are neurotropic. The expression of ACE2 in human neurons supports the neuro-invasive potential of SARS-CoV-2 [103–105]. In a human induced pluripotent stem cell-derived BrainSphere model, ACE2 was detected and SARS-CoV-2 was found to replicate [106]. In an animal study assessing olfactory damage, ACE2 and the protease TMPRSS2 were expressed in the sustentacular cells of the olfactory epithelium, but much less in most of the olfactory receptor neurons [107]. These results propose a dual model: direct viral invasion or a bystander injury after the infection of epithelial/endothelial cells [108].

Many Nrf2-Interacting Nutrients Are TRPA1 and TRPV1 Agonists

TRP channels are polymodal channels and most of the superfamily members can be activated by a multitude of stimuli [109]. Several Nrf2-interacting nutrients are direct TRPA1 activators [21, 110]. These include: (i) allyl isothiocyanates (AITC: pungent components of mustard, horseradish, and wasabi [2]), (ii) cinnamaldehyde from cinnamon [70], (iii) allicin, an organosulfur compound from garlic [111], (iv) green tea polyphenols [112, 113], and (v) 3 glucosinolates from *Sisymbrium officinale* (isopropylisothiocyanate and 2-buthylisothiocyanate) or *Moringa oleifera* (4-[(α -l-rhamnosyloxy) benzyl] isothiocyanate) [114, 115]. Sulforaphane, an AITC and the most potent natural Nrf2 activator, does not appear to interact with TRPA1. The plant polyphenol resveratrol [116] may have an agonist or antagonist effect [117]. An indirect agonist effect [118] was found via the N-methyl-D-aspartate receptor in vivo [119]. TRPA1 may serve as a downstream target of pro-nociceptive ion channels such as N-methyl-D-aspartate receptors [120] (Table 1).

Many TRPV1 agonists also interact with Nrf2 and/or TRPA1. TRPV1 is a sensor stimulated by several spices including capsaicin (red pepper), piperine (black pepper), gingerol, and zingerone (ginger), pungent com-

pounds from onion and garlic, eugenol (clove), and camphor. TRPV1 is also activated by AITC, present in mustard, horseradish, and wasabi [121], and by resiniferatoxin, a toxin of tropical *Euphorbia* plants [122].

There is a substantial overlap of electrophilic ligands between TRPA1 and Nrf2 [21]. However, not all Nrf2-interacting nutrients are activators of TRPA1. For example, mustard oil does not interact with Nrf2, whereas sulforaphane does not interact with TRPA1 or TRPV1.

Desensitization of TRP

The pungent effects of chili and other spices are rapidly reduced by high or repeated doses [21]. This was first described for capsaicin, an active component of chili peppers [165]. Desensitization of TRPV1 underlies the paradoxical analgesic effect of capsaicin. The TRPV1 receptors begin a refractory state, commonly termed as desensitization, that leads to the inhibition of receptor function [21]. The acute desensitization of TRPV1 accounts for most of the reduction in responsiveness occurring within the first few (~20) seconds after the vanilloids are administered to the cell for the first time. Several signalling pathways including calcineurin, calmodulin, or the decrease of phosphatidylinositol 4,5-bisphosphate [166] are involved in TRPV1 desensitization. Oxidative stress decreases phosphatidylinositol 4,5-bisphosphate [167], and receptor desensitization may possibly be obtained at lower doses of agonists in COVID-19. Another form of desensitization is “tachyphylaxis,” which is a reduction in the response to repeated applications of vanilloid [168].

TRPA1 is desensitized by homologous (mustard oil; a TRPA1 agonist) or heterologous (capsaicin; a TRPV1 agonist) agonists via Ca^{2+} -independent and Ca^{2+} -dependent pathways in the sensory neurons [169]. There is a heterologous desensitization of TRPA1 via a TRPV1 pathway [170, 171]. Resveratrol or AITC act as activators and desensitizers of TRPA1 channels [153]. High concentrations of para-benzoquinone caused rapid activation of TRAP1 followed by fast decline in a cysteine-dependent desensitization mechanism [172]. The contractile effect of TRAP1 in isolated mouse intestine can be induced by AITC. Repeated doses induce desensitization [173]. The electrophilic fatty acid NO_2 -OA acts on TRP channels to initially depolarize and induce firing in sensory neurons followed by desensitization and suppression of firing [174]. NO_2 -OA attenuates intracellular oxidative stress through Nrf2 and suppression of NADPH oxidase [175].

Although data are sometimes conflicting, interactions between TRPA1 and TRPV1 can modulate receptor de-

Table 1. Examples of Nrf2-, TRPA1-, and TRPV1-interacting nutrients

	Foods	Nrf2	TRPA1	TRPV1
Alliin	Garlic, leek, onion		[123]	[123]
Berberine	European barberry, goldenseal, goldthread, Oregon grape, phellodendron, goldenseal, poppy, and tree turmeric	[124]		[125]
Capsaicin	Red pepper	[100, 126]	[127]	[128]
Cinnamaldehyde	Cinnamon	[129]	[70]	[130]
Curcumin	Turmeric	[131, 132]	[133]	[133]
Epigallocatechin gallate	Green tea, apple skin, plums, onions, hazelnuts, pecans, and carob powder	[131]	[113]	[134]
Genistein	Soy-based foods including tofu, tempeh, and miso	[131]	[135]	[136]
Gingerol	Ginger	[137]	[138]	[139]
Lactobacillus	Fermented foods	[140]		[141]
Mustard oil	Mustard seeds		[142]	
N-acetyl cysteine		[143]	[144]	[145]
NO		[146]	[147]	[147]
Piperine	Black and long pepper	[148]	[149]	[150]
Quercetin	Fruits (cranberries, lingonberries, black plums), vegetables (broccoli, capers, kale, red onion, radish, sorrel, watercress), leaves (fennel), seeds, and grains	[131]	[151]	[152]
Resveratrol	Skin of grapes, blueberries, raspberries, mulberries, and peanuts	[131]	[116, 153]	[117]
Selenium		[154]	[155]	[156]
Sulforaphane (from glucoraphanin)	Cruciferous vegetables such as broccoli, Brussels sprouts, and cabbages	[131]		
Vitamin C		[157]		[158]
Vitamin D		[159]		[160]
Wasabi	Japanese horseradish	[161]	[162]	[162]
Zinc		[154, 157]	[163]	[164]

TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1; Nrf2, nuclear factor (erythroid-derived 2); NO, nitric oxide.

sensitization. Using patch-clamp electrophysiology, the co-expression and interaction of TRPA1 with TRPV1 proved to be the most critical for the differential sensitization of sensory neurons for pain [176]. On the other hand, the selective TRPA1 agonist (AITC) resulted in the restoration of sensitivity to capsaicin TRPV1 channels (resensitization TRPV1 channels) [177]. The attenuation of experimental colitis by capsazepine (capsaicin-induced denervation CPZ) is attributed to its antagonistic action on TRPV1. It exerts its anti-inflammatory effects via profound desensitization of TRPA1 [178].

Nicotine activates TRPA1 [179] and TRPV1 [180]. The prevalence of smoking among hospitalized COVID-19 patients is low [181]. Although many different mechanisms are proposed, the desensitization of TRPA1/TRPV1 by nicotine may be one possibility. If this were the case, it would show that TRPA1/TRPV1 may be involved in severe COVID-19.

Sensory receptors like TRPA1 or TRPV1 may serve as gate-keepers in optimizing spice intake, thereby avoiding over-exposure and exemplifying the sensory and metabolic interactions of spicy nutraceuticals. In this scenario,

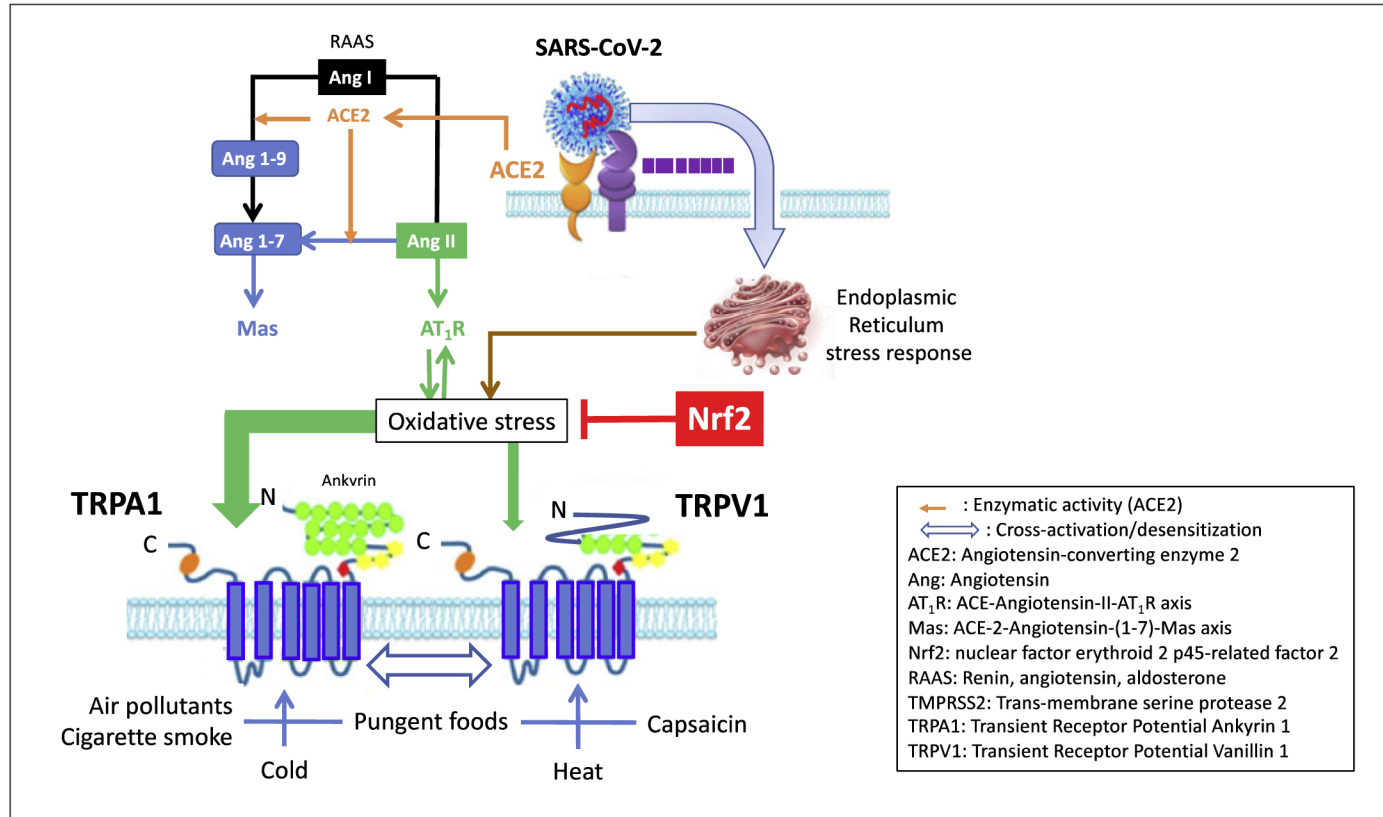


Fig. 1. Interactions between TRPs and oxidative stress in COVID-19 (modified from [10, 110]). SARS-CoV-2 binds to the cell through ACE2 that is downregulated. Angiotensin I is transformed in angiotensin II AT₁R pathways, inducing oxidative stress. When SARS-CoV-2 enters the cell, it induces an endoplasmic reticulum stress response, inducing an oxidative stress among other pathways. The oxidative stress is inhibited by many antioxidants, but

Nrf2 is the most potent one. The oxidative stress senses TRPA1 and, to a lesser extent, TRPV1. The activated TRPs are prone to be hyper-activated by various natural stimuli. Foods can activate Nrf2 and desensitize TRPs. TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1; Nrf2, nuclear factor (erythroid-derived 2).

desensitization might be an attempt to maintain an optimal intake of pungent compounds in spite of priming the metabolizing enzymes and a substantial higher and/or faster inactivation by metabolic clearance [21]. We propose that electrophilic ligands may activate and desensitize TRPA1 or TRPV1.

TRPA1-TRPV1 and Acetaminophen

Paracetamol (acetaminophen) has TRPA1-independent antipyretic effects [182] and TRPA1-dependent effects on pain [183]. The electrophilic metabolites N-acetyl-p-benzoquinone imine (NAPQI, hepatotoxic metabolite) and p-benzoquinone, but not paracetamol itself, activate TRPA1 [82]. They also activate and sensitize TRPV1 by interacting with intracellular cysteines [184, 185]. NAPQI also directly activates Nrf2 [186], and benzoquinone desensitizes TRPA1 [172].

The physiological and toxicological responses of paracetamol form a continuum coordinated by the Wnt and Nrf2 pathways. Therapeutic doses produce reactive ROS and NAPQI in the cytoplasm but result in little permanent damage [187]. At high doses, paracetamol can induce oxidative stress-mediated hepatotoxicity which is reduced by enhancing the Nrf2 pathway [188–190].

Conclusions: Hypothetic Interactions of Nrf2, TRPA1/TRPV1, and COVID-19

A common denominator in symptoms associated with COVID-19 appears to be the impaired redox homeostasis responsible for ROS accumulation [191]. Several mechanisms have been proposed involving, among others, the renin-angiotensin-aldosterone system [10] and/or endo-

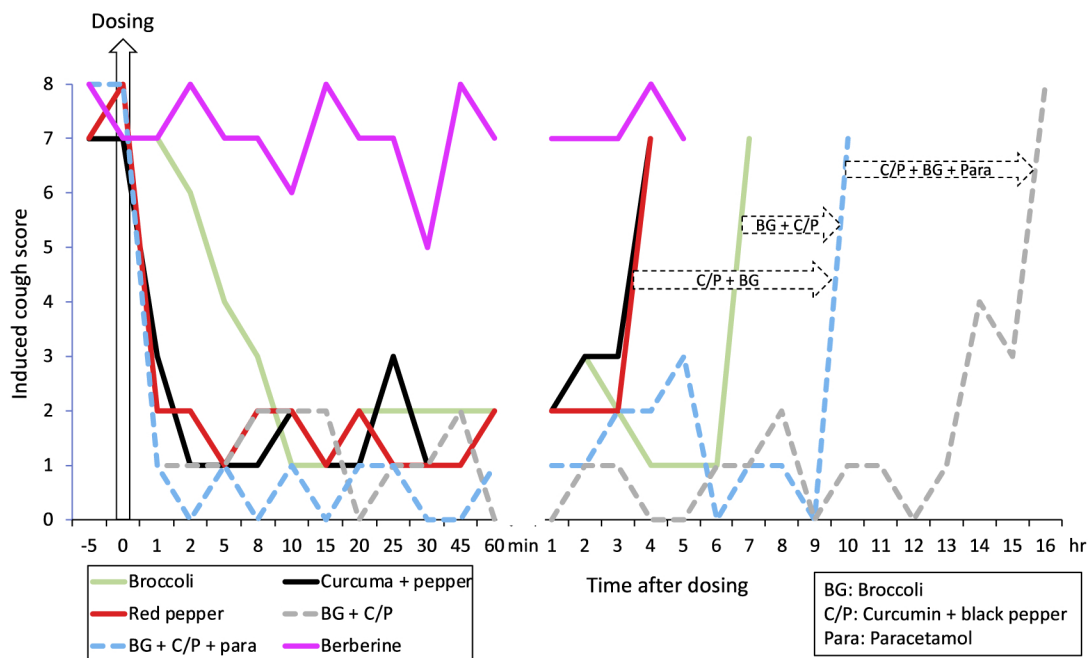


Fig. 2. Induced cough challenges with Nrf2, TRPA1 and/or TRPV1 agonists (from [194]). In the same patients, open-labelled induced cough challenges were carried out before dosing with an agonist before challenge (-5 min), and after 1, 2, 5, 8, 10, 15, 30, 25, 30, 45, and 60 minutes and every hour until the cough score was ≥ 7 . The cough challenge was validated in a double-blind, placebo-controlled study [193]. Berberine (Nrf2) was ineffective. Red pepper 20 mg (Nrf2 low + TRPV1 high) or curcumin 100 mg + black pepper 16 mg (Nrf2 low + TRPA1 high + TRPV1 low) were effective within 1-2 minutes, and their effect persisted for up to 3 hours.

plasmic reticulum stress [192]. It has, however, never been proposed that TRPA1/TRPV1 may be involved in COVID-19 (Fig. 1).

Antioxidants inducing Nrf2 activation have been proposed to treat COVID-19 [10, 18-20]. Antioxidants may be of interest, but their clinical benefits are unlikely to be seen in minutes, and the effect may not be optimal. In 3 clinical cases of proven COVID-19, capsules of broccoli seeds containing glucoraphanin and paracetamol were found to induce a rapid improvement (minutes) of some symptoms such as cough (submitted, published online [193]). Double-blind, placebo-controlled induced cough challenges in 1 patient showed a reduction of cough within 10 minutes.

Other hypotheses can also be proposed. TRPA1/TRPV1 are involved in several common COVID-19 symptoms. TRPA1 more than TRPV1 can be activated by

Broccoli 300 mg (Nrf2 high + TRPA1 low) was effective within 10 minutes and its effect persisted for up to 6 hours. Broccoli 150 mg + curcumin 50 mg + black pepper 6 mg were effective for up to 9 hours. Broccoli 150 mg + curcumin 50 mg + black pepper 6 mg + paracetamol 250 mg (paracetamol metabolites: TRPA1 + TRPV1) were effective for up to 16 hours. These results suggest a very fast TRPA1-TRPV1 desensitization and a cross talk with Nrf2 to increase the duration of the effect. TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1; Nrf2, nuclear factor (erythroid-derived 2).

ROS and may therefore be upregulated in COVID-19. Reducing ROS by Nrf2 will most likely reduce TRPA1 hyperreactivity, thereby reducing TRPA1 activation by exogenous or endogenous agents. However, such a mechanism is likely to take time and cannot be involved in very rapid-onset clinical benefits. It may take an hour or more to find this synergy.

The activation of TRPA1/TRPV1 by exogenous agents can lead to a rapid dose-dependent desensitization that may be effective within minutes and for up to a few hours, suggesting a symptomatic improvement. This rapid-onset mechanism may be sustained by antioxidants or other products. This proposal seems to be substantiated by preliminary clinical studies, but these observations need to be confirmed through formal studies. Double-blind, open labelled induced cough challenges in 1 patient showed a reduction of cough within 2 minutes with TRPA1/V1 ag-

onists (green tea, curcumin, ginger, and red pepper) and suggested a synergy with Nrf2 (broccoli) for an increased duration of the effect (Fig. 2, submitted, available online [194]).

Another form of TRP desensitization is “tachyphylaxis,” which is a reduction or the disappearance in the response to repeated applications of agonists [168, 195, 196]. In Asian or Sub-Saharan countries, large amounts of spices are regularly eaten and it is likely that TRPA1/TRPV1 receptors are permanently desensitized or may have been reduced in numbers, allowing people to eat large amounts without side effects. In this model, Nrf2 and antioxidants may play an important additive role in reducing ROS. It is therefore possible that TRPA1/V1 tachyphylaxis may reduce the severity of COVID-19 symptoms, and even possibly reduce infection by SARS-CoV-2. The long-term consumption of kimchi, which contains pungent nutrients and fermented cabbage, could be a prototype.

The results of these limited clinical studies cannot be taken as formal evidence. However, they have contributed to developing a proof-of-concept for the hypothesis that combined Nrf2-TRPA1 foods may be beneficial for some COVID-19 symptoms and that there is a synergy between Nrf2 and TRPA1 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 studies employing a double-blind, placebo-controlled design.

There are several unknown issues. The first is the interplay between TRPA1 and TRPV1 in desensitization. The second is the regulation of these channels by oxidative stress and the synergistic role of Nrf2. TRPV1 desensitization by capsaicin patches may be of benefit for COVID-19. It may also be of interest to combine Nrf2-potent agonists such as broccoli. However, again, these hypotheses cannot be used in practice before obtaining the results of mechanistic studies and formal clinical trials.

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 W.C., J.M.A., and T.Z. H.B., J.P.C., R.d.l.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. N.P.Z., V.L.M., I.A., C.A.A., G.W.C., A.A.C., A.F., J.F., S.F., B.G., T.H., J.C.I., M.J., L.K., P.K., D.L.L., A.M., E.M., Y.O., N.G.P., O.P., F.R., J.R., Y.R., P.P.R., B.S., A.S., S.T.S., A.V., H.J.C., and H.J.K. were requested to comment on the concept and to review the paper. All authors accepted the paper.

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