Paracetamol low dose, broccoli seeds, curcumin and black pepper capsules control some but not all symptoms of COVID-19

To the Editor

Diet represents one possible moderating factor of the COVID-19 symptoms.[1] Foods that are agonists of the antioxidant transcription factor, the nuclear factor (erythroid-derived 2)-like 2 (Nrf2),[2,3] and TRPA1/V1 (Transient Receptor Potential Ankyrin 1 and Vanillin 1) have been proposed to help COVID-19 symptom control. [4 5]

In three COVID-19 clinical cases, broccoli seed capsules containing glucoraphanin, the precursor of suforaphane, (Nrf2 activator) and paracetamol (benzoquinone metabolites are TRPA1/V1 agonists) improved COVID-19 symptoms within minutes.[6] The relative roles of Nrf2 and TRPA1/V1 agonists, were confirmed in N-of-1 induced cough challenges. [7] A cross-talk between Nrf2 and TRPA1/V1 may be related to the rapid and long-term effect of foods in COVID-19 induced cough.

An open labelled clinical study was carried out to determine for which symptoms Nrf2 and TRPA1/V1 agonists are effective.

Methods

Following the two initial proof-of-concept studies,[6 7] this third study enrolled 10 volunteers with demonstrated COVID-19. Three times daily, the volunteers ingested broccoli seed capsules (14 µmol of glucoraphanin) and paracetamol, and some added curcumin (51 mg) and black pepper (8 mg). The doses were those recommended. The patients were followed for 7 days to assess their COVID-19 symptoms (Figure 1).

The classical COVID-19 symptoms (cough, fever, sense of taste and smell, appetite, dyspnea, respiratory rate, fatigue, aches, headache, chills, digestive symptoms, nasal obstruction) were assessed before ingestion of the nutrients and after 10, 30, 60 minutes and 2 hours. The symptoms (except fever) were quoted from 0 (none) to 10 (worst) using a visual analogue scale as previously reported. [6]

Results

Patients ranged in age from 18 to 74 years and eight were at risk of severe COVID-19 due to their age, obesity and/or diabetes. Eight were in blood group A. The most common symptoms were fatigue and loss of appetite (100%), followed by cough, hyposmia or loss of taste (80%) or digestive symptom problems (70%). Nutrients were effective in cough (100%), digestive symptom problems (100%) and to a lesser extent fatigue and loss of appetite. Nutrients were completely ineffective on hyposmia or loss of taste (Figure 1 and Table 1).

Severe respiratory symptoms were specifically scrutinized. Three patients had dyspnea that was fully controlled 10-30 minutes after ingestion of the nutrients. None of the nine patients who measured respiratory rate had a level of over 24/minute.

Figure 1: Characteristics of the patients and individual symptom response to nutrients

Case		2*	3*	4	5	6	7	8	9	10
Age	74	62	64	48	46	18	48	61		36
Sex	M	F	M	M	F	F	F	M	F	F
BMI	24	24	28	40	37	22	34	22	21	33
Blood group	A+	A+	A-	A+	A+	A+	O+	A+	A+	O+
Co-morbidity	T2D		HTN				HTN			
COVID phase	1-2	2	1	2	2	2	2	2	2	2
RT-PCR	+	+	+	+	+	Neg.	+	+	+	+
Broccoli + Para	+	+	+	+	+	+	+	+	+	+
Spices				C+P	C+P	C+P	C+P	C+P	C+P	
Cough										
Fever										
Hyposmia										
Dysgeusia										
Dyspnoea										
Respiratory Rate >24/min										ND
Fatigue										
Aches										
Headache										
Chills										
Digestive symptoms										
Nasal obstruction										
Loss of appetite										

Size of circles: VAS 0 (best: no circle) to 10 (worst: largest circle), black: COVID-19 symptoms, green: improvement, black + green: partial improvement
C: Curcumin, P: Black pepper, Para: Paracetamol, HTN: Hypertension, T2D: Diabetes, ND: Not determined

Table 1: Global results

	N	Compound efficacy			Comments
	10	Complete	Partial	None	
Risk factors • Age>60 • BMI>30 • Diabetes	 4 4 1				

Positive rRT-PCR	9				The patient with a negative rRT-PCR had pathognomic COVID-19 symptoms
Blood group A	8				
Broccoli + paracetamol	10				
Curcuma + pepper	6				
Cough	10	5	5	0	
Fever	9	0	6	3	Possibly due to paracetamol, small effect
Hyposmia	8	0	0	8	Almost always anosmia
Loss of taste	8	0	2	6	Very small effect, short term, difficult to assess
Dyspnea	3	3	0	0	
Respiratory rate >24	0/9	-	-	-	Patient 10 did not measure RR
Fatigue	10	0	9	1	In 9 cases, very intense
Aches	5	0	4	1	Inconsistent effect even when compound was effective
Headache	5	0	4	1	
Chills	3	1	1	1	
Digestive SX	7	6	0	1	
Nasal obstruction	8	3	2	2	Highly variable from complete relief to none
Loss appetite	10	0	9	1	

Discussion

The present study extends the reports of the first three clinical cases reported [6] and shows that (i) there is a heterogeneity across COVID-19 symptoms. (ii) Most symptoms were present but only three patients had transient dyspnea and none had a severe lung impairment. It is possible that nutrients may have reduced respiratory symptoms. This is in line with the effect of curcumin on the COVID-19 cytokine storm. [8] (iii) Some but not all COVID-19 symptoms were rapidly improved, indicating that there was no verum effect on symptom relief. (iv). Cough was rapidly reduced suggesting a TRPA1/V1 effect. [4] (v) Loss of smell and taste were not improved by the nutrients in any of the patients. Smell and taste are regulated by a complex neural network and TRPA1/V1 at the doses administered do not appear to be of significant value. (vi) Blood group A was found in 8/10 patients. However, the low number of patients and their selection prevents any firm conclusion.

This proof-of-concept study cannot be considered as a definite conclusion but it will help to design appropriate trials to confirm the hypothesis that some nutrients induce a cross talk between Nrf2 and TRPA/V1 in order to improve some but not all COVID-19 symptoms and may be of interest in preventing severe lung injury.

References

1. Bousquet J, Anto JM, Iaccarino G, et al. Is diet partly responsible for differences in COVID-19 death rates between and within countries? *Clin Transl Allergy.* 2020;10:16.
2. Bousquet J, Cristol JP, Czarlewski W, et al. Nrf2-interacting nutrients and COVID-19: time for research to develop adaptation strategies. *Clin Transl Allergy.* 2020;10(1):58.
3. Cuadrado A, Pajares M, Benito C, et al. Can Activation of NRF2 Be a Strategy against COVID-19? *Trends Pharmacol Sci.* 2020.
4. Bousquet J, Czarlewski W, Zuberbier T, et al. Spices to Control COVID-19 Symptoms: Yes, but Not Only. *Int Arch Allergy Immunol.* 2020:1-7.

5. Bousquet J, Anto JM, Czarlewski W, et al. Cabbage and fermented vegetables: from death rate heterogeneity in countries to candidates for mitigation strategies of severe COVID-19. *Allergy*. 2020.
6. Bousquet J, Le-Moing V, Blain H, et al. Efficacy of broccoli and glucoraphanin in COVID-19: From hypothesis to proof- of-concept with three experimental clinical cases. *World Allergy Organ J*, *https://authorselseviercom/sd/article/S1939-4551(20)30401-4*. 2020.
7. Bousquet J, Czarlewski W, Zuberbier T, de-la-Torre R, Anto J. Induced cough challenges in a single patient with COVID-19 showing an interplay between Nrf2, TRPA1 and TRPV1 agonists 2020;https://www.ga2len.net.
8. Valizadeh H, Abdolmohammadi-Vahid S, Danshina S, et al. Nano-curcumin therapy, a promising method in modulating inflammatory cytokines in COVID-19 patients. *Int Immunopharmacol*. 2020;89(Pt B):107088.

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