Curcumin as a potential treatment for COVID-19

Dear Editor,

Although a worldwide phenomenon, severe acute respiratory syndrome (SARS) by the new coronavirus (SARS-CoV-2) infection is apparently less severe in some parts of the world with some countries presenting a surprisingly low death toll (https://coronavirus.jhu.edu/map.html; in 6 May 08:53 a.m.). No one would argue that a specific treatment with a well-defined mechanism would be the best approach to fight this pandemic. However, given the urgency, clinical trials based on pragmatism, using the prima non nocere principle, may be justified. Epidemiological observations coupled with sound basic evidence may thus provide clues in the search for such strategies. Turmeric (Indian saffron), a much-appreciated spice, has India as by far the greater producer and consumer, together with Pakistan, Malaysia, Bangladesh, Sri Lanka, Taiwan, China, Burma (Myanmar), and Indonesia (http://www.fao.org/fileadmin/user_upload/inpho/docs/Post_Harvest_Compendium_-_Turmeric.pdf downloaded in 21 March 2020). Curcuma or curcuminoids isolated from Turmeric have long been reported to have antiinflammatory and immunomodulatory activity. Due to its low bioavailability, alternatives to improve turmeric absorption have been developed. Although edible consumption may provide health benefits, pharmaceutical preparations increase curcumin absorption thus allowing pharmacodynamic and pharmacokinetic data on the serum levels of curcuminoids (Aggarwal, Gupta, & Sung, 2013). A world map of the new coronavirus disease (COVID-19) reveals that countries in Southeast Asia, which are the largest producers and consumers of curcumin, have shown a very low number of deaths attributed to SARS-CoV-2 infections. Our attention was driven to the death toll from the COVID-19 because the number of infected people is likely underestimated. We excluded Taiwan from our analysis given the apparently efficient strict rules for isolation implemented there as well as its presumed disposal of adequate health facilities. As of 23 April, the total death toll from COVID-19 reported in India, Indonesia, Pakistan, Bangladesh, Malaysia, Sri Lanka, and Burma was 3,424, being 1,695, 895, 526, 186, 107, 9, and 6 in each country, respectively (https://coronavirus.jhu.edu/map.html downloaded in 6 May, 08:53 a.m.). Let us not forget that the sum of the population in those countries represents over one quarter of the world population. At the same time, it was interesting to note that Iran has a COVID-19 death toll of 6,418 as of 6 May. Curiously, Iran, once a greater consumer of Turmeric, has experienced a shortage of this product in the last years due to economic sanctions (https://economictimes.indiatimes.com/news/economy/foreign-trade/turmeric-exports-hit-by-us-sanctions-against-iran/articleshow/70446034.cms?from=mdr; downloaded in 6 May 2020, 08:53 a.m.). Community isolation has been hard to implement in those Southeast Asian countries which, like Iran, do also experience a shortage of health facilities and supplies to face this epidemic.

We were also impressed by the great difference between the number of deaths attributed to COVID-19 in those heavy curcumin-consuming countries and those in some western European countries. We should also consider that some of those European countries have implemented severe rules restricting social activities as an attempt to mitigate disease spreading, in addition to having far better health systems available. We started this observation in the early days of March 2020, but the death toll is persistently very low in those Southeast Asian countries, thus reinforcing its relevance. There are a lot of possible confounders impacting this epidemiological observation. Why would more people die from COVID-19 in such wealthy countries and why would Iranians be so heavily penalised? Considering the excellence of health systems in most western European countries, we may assume they provide more accurate data on diagnostic testing, which are lacking in those Southeast Asian countries as well as in Iran. Thus, counting the number of deaths attributed to COVID-19 might better illustrate the burden of this disease across different populations. Although ethnicity could play a role, the large variability across those heavy curcumin consumers both within and between countries make it unlikely to be relevant. The vast geographical area at stake argues against environmental issues including temperature, altitude, and other weather conditions to explain this consistently sustained very low death toll among the curcumin consumers.

1 | POSSIBLE MECHANISMS OF ACTION OF CURCUMIN TO FIGHT SARS-COV-2

There is controversy as to whether drugs acting in the angiotensin converting enzyme (ACE) pathway worsen the clinical picture of patients affected by SARS-CoV-2 (Vaduganathan et al., 2020). This virus uses ACE2 as a cell entry and ACE blocking compounds could lead to upregulation of ACE2 expression thereby favouring virus infectivity (Wrapp et al., 2020). Currently, epidemiological data do not definitively support a linkage of the usage of renin-angiotensin-aldosterone (RAA) blocking compounds with a more severe clinical picture of COVID-19. Measurement of, ACE serum activity, which can be used to evaluate the efficacy of RAA blockers, may not reflect ACE activity at the tissue level, particularly in the lung, a major target of SARS-CoV-2 infection (Vaduganathan et al., 2020). Furthermore, after using ACE2 as a cell

Abbreviations: ACE, angiotensin converting enzyme; COVID-19, coronavirus disease; SARS-CoV-2, severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2.
entry mechanism, SARS-CoV-2 downregulates ACE2 expression, a pro-
cess that has been associated with enhanced inflammation in the lungs. 
Apparently, the subsequent activation of the RAA system via increased 
activity of angiotensin II, which would no longer be converted to angio-
tensin, could increase vascular permeability, yielding pulmonary edema and 
SARS. Discussing this issue would be too speculative given that the 
relevance of ACE2 expression during a COVID-19 infection is yet to be 
clarified (Vaduganathan et al., 2020). There are data showing that curcumin 
may either increase or decrease ACE in vivo activity. Curcumin has 
been shown to protect rats subjected to thioacetamide-induced 
hepatotoxicity via downregulation of ACE gene expression (Fazal, 
Fatima, Shahid, & Mahboob, 2015). Rats subjected to induced systemic 
arterial hypertension were protected by pre-treatment with ginger and 
turmeric rhizome supplementation, a response that was associated with 
reduced ACE activity (Akinyemi et al., 2015). On the other hand, admin-
istration of curcumin to rats subjected to angiotensin II infusion attenu-
ated the development of myocardial fibrosis, which was associated 
with increased protein levels of ACE2 in the myocardium (Pang et al., 
2015). We are not aware of any specific study on curcumin and 
SARS-CoV-2. However, previous reports have shown that curcumin 
presents both direct and indirect antiviral activity against the human 
immunodeficiency virus (HIV) by inhibiting virus replication or via block-
ing inflammatory pathways operating in the acquired immunodeficiency 
syndrome (Prasad & Tyagi, 2015). It has also been shown that curcumin 
has antiviral activity against Chikungunya and Zika virus (Mounce, 
Cesaro, Carrau, Vallet, & Vignuzzi, 2017). Curcumin possesses 
antinflammatory and immunomodulatory activities by inhibiting the 
release of inflammatory mediators, namely prostanoids and cytokines, 
thereby showing anticancer, antiarthritic and antiatherosclerotic effects 
(Aggarwal et al., 2013). Its antioxidant activities were protective in 
inflammatory bowel disease and it also provides lipid-lowering effects 
that help tackling cardiovascular and metabolic diseases (Pagano, 
Romano, Izzo, & Borrelli, 2018). Antithrombotic properties of 
curcuminoids could benefit COVID-19 patients given the reported high 
number of thrombotic events in such patients (Wichmann et al., 2020). 
Curcumin may also help in lung involvement following SARS-CoV-2 
infection both through its anti-inflammatory and antifibrotic activities (Lelli, 
Sahebkar, Johnston, & Pedone, 2017). Despite robust preclinical data, 
there is criticism concerning clinical studies performed with curcumin 
particularly regarding translation of in vitro concentrations and in vivo 
animal dosages to reproducible, achievable concentrations in humans 
(Heinrich et al., 2020). Thus, well-controlled studies are crucial to assess 
any possible curcumin benefit in COVID-19. Hard times pose hard 
problems that demand urgent policies. Health authorities worldwide 
are struggling to decide what is best to prevent people from getting 
COVID-19 infection and, when the disease unleashes, which approaches to preserve lives. Using the best rationale to look for evi-
dence about the therapeutic effects of turmeric in COVID-19, we can 
do an exercise on Hill’s causality criteria. The strength of the association 
is high, based on the incidence map, and has been a repeated pattern in 
many countries with similar consumption of turmeric. There is some 
consistency between epidemiological and laboratory findings given that 
curcumin may interfere with the major pathway for COVID-19 cell 
entry. We cannot yet claim specificity or biological gradient (dose-
response relationship). Temporality is guaranteed because the con-
sumption of saffron has long been incorporated into the culture of 
those countries. Provided that in vitro data prove curcumin to be effect-
ive, preferably showing a defined mechanism, clinical studies could 
then be proposed. However, the excellent safety profile of curcumin 
shown in various human studies (Aggarwal et al., 2013) may justify a 
pragmatic clinical protocol using the primum non nocere principle.

ACKNOWLEDGEMENT
This work was supported by Conselho Nacional de Desenvolvimento 
Científico e Tecnológico (CNPQ), Brasil (Grant 308429/2018-4).

CONFLICT OF INTEREST
The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS
Francisco Airton Castro Rocha conceived, wrote, revised, and 
approved the final version of the manuscript. Marcos Renato de Assis 
went, revised, and approved the final version of the manuscript.

Francisco Airton Castro Rocha1
Marcos Renato de Assis2,3

1Department of Internal Medicine, Faculdade de Medicina, Universidade 
Federal do Ceará, Fortaleza, Brazil
2Department of Internal Medicine, Faculdade de Medicina de Marilia 
(FAMEMA), Marília, Brazil
3Department of Rheumatology, Faculdade de Medicina de Assis (FEMA), 
Assis, Brazil

Correspondence
Francisco Airton Castro Rocha, Laboratório de Investigação em 
Osteoartropatias, Instituto de Biomedicina, Rua Cel. Nunes de Melo, 
1315-1, Andar, Rodolfo Teófilo, 60430-270, Fortaleza, CE, Brazil. 
Email: arocha@ufc.br

ORCID
Francisco Airton Castro Rocha https://orcid.org/0000-0003-4370-3294
Marcos Renato de Assis https://orcid.org/0000-0002-6567-4570

REFERENCES
Aggarwal, B. B., Gupta, S. C., & Sung, B. (2013). Curcumin: An orally bio-
available blocker of TNF and other pro-inflammatory biomarkers. Brit-
ish Journal of Pharmacology, 169, 1672–1692.
Akinyemi, A. J., Thome, G. J., Morsch, V. M., Stefanello, N., Goularte, J. F., 
Belló-Klein, A., ... Schetinger, M. R. C. (2015). Effect of dietary supple-
mentation of ginger and turmeric rhizomes on angiotensin-I conver-
ting enzyme (ACE) and arginase activities in L-NAME induced 
hypertensive rats. Journal of Functional Foods, 17, 792–801. https:// 
doi.org/10.1016/j.jff.2015.06.011
Fazal, Y., Fatima, S. N., Shahid, S. M., & Mahboob, T. (2015). Effects of cur-
cumin on angiotensin-converting enzyme gene expression, oxidative 
stress, and antioxidant status in thioacetamide-induced hepatotoxicity.
Journal of the Renin-Angiotensin-Aldosterone System, 16, 1046–1051. https://doi.org/10.1177/1470320314545777
Heinrich, M., Appendino, G., Efferth, T., Fürst, R., Izzo, A. A., Kayser, O., ..., Viljoen, A. (2020). Best practice in research - Overcoming common challenges in phytopharmacological research. Journal of Ethnopharmacology, 246, 112230. https://doi.org/10.1016/j.jep.2019.112230 Epub 2019 Sep 14.
Lelli, D., Sahebkar, A., Johnston, T. P., & Pedone, C. (2017). Curcumin use in pulmonary diseases: State of the art and future perspectives. Pharmacological Research, 115, 133–148. https://doi.org/10.1016/j.phrs.2016.11.017 Epub 2016 Nov 22.
Mounce, B. C., Cesaro, T., Carrau, L., Vallet, T., & Vignuzzi, M. (2017). Curcumin inhibits Zika and chikungunya virus infection by inhibiting cell binding. Antiviral Research, 142, 148–157. https://doi.org/10.1016/j.antiviral.2017.03.014
Pagano, E., Romano, B., Izzo, A. A., & Borrelli, F. (2018). The clinical efficacy of curcumin-containing nutraceuticals: An overview of systematic reviews. Pharmacological Research, 134, 79–91. https://doi.org/10.1016/j.phrs.2018.06.007
Pang, X. F., Zhang, L. H., Bai, F., Wang, N. P., Garner, R. E., McKallip, R. J., & Zhao, Z. Q. (2015). Attenuation of myocardial fibrosis with curcumin is mediated by modulating expression of angiotensin II AT1/AT2 receptors and ACE2 in rats. Drug Design, Development and Therapy, 11(9), 6043–6054. https://doi.org/10.2147/DDDT.S95333
Prasad, S., & Tyagi, A. K. (2015). Curcumin and its analogues: A potential natural compound against HIV infection and AIDS. Food & Function, 6, 3412–3419. https://doi.org/10.1039/c5fo00485c
Vaduganathan, M., Vardeny, O., Michel, T., McMurray, J. J. V., Pfeffer, M. A., & Solomon, S. D. (2020). Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. The New England Journal of Medicine, 382, 1653–1659. https://doi.org/10.1056/NEJMra2005760
Wichmann, D., Sperhake, J. P., Lütgehetmann, M., Steurer, S., Edler, C., Heinemann, A., ..., Kluge, S. (2020). Autopsy findings and venous thromboembolism in patients with COVID-19: A prospective cohort study. Annals of Internal Medicine. https://doi.org/10.7326/M20-2003. [Epub ahead of print].
Wrapp, D., Wang, N., Corbett, K. S., Goldsmith, J. A., Hsieh, C. L., Abiona, O., ..., McLellan, J. S. (2020). Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science, 367, 1260–1263.