Received: 6 May 2020 | Revised: 9 May 2020 | Accepted: 13 May 2020
DOI: 10.1002/ptr.6745

LETTER TO THE EDITOR

WILEY

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 process 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 angiotensin, 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, administration of curcumin to rats subjected to angiotensin II infusion attenuated 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 blocking 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 antiinflammatory 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 anticytokine 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 evidence 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 consumption of saffron has long been incorporated into the culture of those countries. Provided that in vitro data prove curcumin to be effective, 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 wrote, revised, and approved the final version of the manuscript.

Francisco Airton Castro Rocha[1]
Marcos Renato de Assis[2,3]

[1]*Department of Internal Medicine, Faculdade de Medicina, Universidade Federal do Ceará, Fortaleza, Brazil*
[2]*Department of Internal Medicine, Faculdade de Medicina de Marília (FAMEMA), Marília, Brazil*
[3]*Department 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 bioavailable blocker of TNF and other pro-inflammatory biomarkers. *British 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 supplementation of ginger and turmeric rhizomes on angiotensin-1 converting 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 curcumin 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/NEJMsr2005760

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.