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Curcumin as a Complementary Treatment in COVID-19

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Dear Editor,

Curcumin is an herbal spice and coloring food additive extracted from *Curcuma longa* that has been evaluated as a complementary tool in the scenery of COVID-19[1-8]. *C. longa* (turmeric) is a plant used as a traditional Indian medicine with antiviral, analgesic, antimicrobial, antiproliferative, and anti-inflammatory properties[1-8]. Moreover, turmeric is one of the most popular spices worldwide, mainly in India[1,2,5,7,8]. Curcumin chemoprotection and cytoprotection are due to the free radicals scavenging, and also to the antioxidant, anti-inflammatory, anticancer, and antimicrobial actions[1-8]. Moreover, it can exert antithrombotic effects via the inhibition of thrombin and FXa, and might be a complementary option to prevent post-Covid thromboembolism[2,3,5,8]. Curcumin can modify pro-inflammatory cytokines, apoptotic proteins, cyclooxygenase, endothelin-1, malondialdehyde, phosphorylase kinase, glutathione, prostaglandin, C-reactive protein, pepsinogen, transferrin receptor, and the transforming growth factor[1]. Curcumin can regulate molecules related to the inflammatory mechanisms, including cellular pathways, transcription factors, chemokines and cytokines, kinases, enzymes, and regulators of inflammasomes[2,3,6,8]. Curcumin has usefulness to countervail toxic manifestations of medicines as anti-tuberculosis, chemotherapy, analgesics, psychiatric and anesthetic drugs; as well as substances heavy metals, insecticides, nicotine, benzopyrene, alcohol, and aflatoxins[1]. Researchers have been actively seeking for some really effective prophylaxis and treatment to employ in SARS-CoV-2 infection[2,8]. Until consistent data of the studies on a definite treatment schedule for COVID-19, the evidence suggests curcumin as a promising alternative prophylactic management[2,8]. Curcumin may have antiviral activity against SARS-CoV-2 by the envelope disruption; action in viral membrane proteins; inhibition of proteases; antiviral responses induction; and targeting the NF-κB, inflammasome, IL-6 trans-signaling, and HMGB1 pathways[2]. The novel genome research utilizing Clustered Regularly Interspaced Short Palindromic Repeats Cas9 (CRISPR-Cas9) revealed that the High Mobility Group Box 1 (HMGB1) is a significant pro-viral host factor in SARS-CoV-2 infection[8]. This non-histone nuclear protein can bind with DNA and regulate transcription; its major role in danger-related molecular patterns is to enhance the inflammatory responses by binding to Toll-like receptors and the activation of the inflammasome[2,8]. The severity of COVID-19 is directly related to cytokine release syndrome (CRS), and authors have described the role of inflammasome activation involved in driving CRS[2]. Many studies confirmed the potency of curcumin to block inflammasome activation; this property is due to curcumin (diferuloylmethane), the most abundant bioactive pharmacological of curcuminoids; bisdemethoxycurcumin, or demethoxycurcumin[2,6,8]. HMGB1 antagonists might be potential alternatives for protection against SARS-CoV-2

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infection, reducing HMGB1 expression and the mediated proinflammatory responses[2]. Curcumin may inhibit SARS-CoV 3CL protease activity, vital for viral replication; and interacts with S protein and ACE2 protein intervening on the viral entry in lung cells[2,8]. Then, it may protect from COVID-19 by down-regulating the ACE2 expression[2,4,5,7,8]. As a promising agonist of transcription factor NRF2, curcumin can activate the NRF2 pathway in the lung of mice, an indication of antiviral activity against SARS-COV-2[2]. The increased survival of infected mice treated with curcumin was related to lower levels of interleukins (IL-1beta and IL-6) and tumor necrosis factor alpha in bronchopulmonary and blood samples[2]. Curcumin is an adjuvant to control risk factors for COVID-19 as immunosuppression; diabetes; hypertension; heart, lung, cerebrovascular, and renal diseases; and cancer[1,3-6]. Worth of note, curcumin may be also effective against human influenza A virus, Respiratory Syncytial virus infection, SARS-CoV *in vitro*, as well as other acute and chronic respiratory disorders and in sepsis, by mechanisms involving the oxidative stress[2].

Pawar *et al*. studied the effects of associated curcumin/piperine in the management of COVID-19; and the evolution of 70 controls under conventional COVID-19 treatment and probiotics was compared to that of 70 patients receiving the conventional treatment plus association twice daily[3]. The authors concluded that curcumin/piperine can improve the COVID-19 management, and their use reduced the time of hospitalization and the number of deaths[3]. Saber-Moghaddam *et al*. performed a nonrandomized trial about the use of curcumin in hospitalized COVID-19 patients[4]. During 2 weeks 41 patients were evaluated: 21 used nano-curcumin (curcuminoids 40 mg as nanomicelles, two capsules twice daily), and 20 patients of the control group[4]. No patients died in both groups as well as none of the treatment group had clinical deterioration, which occurred in 40% of those of the control group during follow-up[4]. The authors commented that over 300 clinical trials showed protective effects of curcumin on cardiovascular, pulmonary, metabolic, and liver diseases, besides cancer[4]. They concluded that nano-curcumin can be useful to COVID-19 control without significant adverse reactions, and contribute to the reduction of hospital permanence of mild to moderate cases[4].

Based on the data here commented, authors suggest more clinical trials to evaluate the curcumin preventive and therapeutic role as an alternative or complementary medication against COVID-19.

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