

## LETTER TO THE EDITOR



## Boron enhances the antiviral activity of the curcumin against SARS-CoV-2

ION ROMULUS SCOREI<sup>1)</sup>, ANDREI BIȚĂ<sup>1,2)</sup>, GEORGE DAN MOGOȘANU<sup>1,2)</sup>

<sup>1)</sup>BioBoron Research Institute, S.C. Natural Research S.R.L., Podari, Dolj County, Romania

<sup>2)</sup>Department of Pharmacognosy & Phytotherapy, Faculty of Pharmacy, University of Medicine and Pharmacy of Craiova, Romania

Dear Editor,

Unfortunately, today we are in the situation during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic that there are no standardized vaccines or treatments yet [1]. In addition, the long incubation period of 3–7 days of virus infection, without clear evidence of the disease and the very high ability to spread the infection, made SARS-CoV-2 one of the most dangerous, especially for elderly patients and those who have meet major health problems. For now, it is known that SARS-CoV-2 invades the host cell through two receptors: angiotensin-converting enzyme 2 (ACE2) and cluster of differentiation 147 (CD147) [1–4]. Probably, there are other receptors, still undiscovered, which might have a major significance in the fight against coronavirus disease 2019 (COVID-19). Recent studies report that the neuropilin-1 receptor and the humanized transferrin receptor (an omnipresent expressed host receptor on cell membranes) represent host factors for COVID-19 infection [5–7]. In the past, CD147 has been identified as a receptor for red blood cells for infection with the *Plasmodium falciparum* parasite (protozoan causing malaria in humans) [8]. Recent research shows that human red blood cells are strongly involved in the pathophysiology of COVID-19 [9].

Over the years, curcumin solutions or turmeric extracts have been used as coloring analytical reagents to assess the amount of boron in soil, water, and food [10]. Curcumin can be found in two tautomeric conformations (keto- and enol-), with many *cis* and *trans* isomers, which can vary depending on pH, solvent polarity, temperature. These conformations play a very important role in the antioxidant activity of curcumin, as well as on its physical and chemical properties [11]. Curcumin is insoluble in water at neutral pH, so it has low bioavailability and also decomposes and/or crystallizes into acidic or alkaline pH solutions. When taken orally, the largest amount of curcumin never reaches the bloodstream, being barely absorbed from the intestine, rapidly metabolized, and excreted in the feces. Although curcumin has been evaluated in numerous laboratory and clinical studies, it has not yet established medical uses. According to a 2017 scientific review that covered more than 120 studies, curcumin was not successful in any clinical trials, leading the authors to conclude that curcumin is an unstable, reactive compound with low bioavailability and therefore in its natural form it is extremely unlikely to be used as a medicine [12].

Then, the interactive potential of curcumin with spike ('S') protein binding was demonstrated only theoretically, *in silico*, which revealed that curcumin could prevent the attachment of SARS-CoV-2 to the host surface, inhibiting this virus in the range of 3–10  $\mu\text{M}$  concentrations. This concentration is similar to that of nelfinavir (an important antiviral drug) [13]. Recently, *in silico*, it has also been shown that curcumin together with hydroxychloroquine can destabilize the structural integrity of SARS-CoV-2 surface proteins, resulting in a hypothesis for the *in vivo* combined therapy of curcumin together with hydroxychloroquine [14]. Other theoretical experiments *in silico* show that curcumin, capsaicin and piperine bind strongly to the 3C-like protease (3CL<sup>pro</sup>) protein of SARS-CoV-2 and promote important structural changes in this viral protease [15].

Due to its special chemical structure, curcumin can be an excellent chelating agent (the chemical binding process of metal ions) [16]. When combined with boric acid, its esters form a complex called rosocyanine, which is regularly used to assess the amount of boron in various organic and inorganic matrices [17]. The use of rosocyanine for the development of antibacterial, anticancer, and antifungal drugs has led to an increased presence of boron in the pharmaceutical industry [18]. At pH 2, rosocyanine proves a charged structure due to the two OH<sup>+</sup> functional groups of the benzene ring, while at pH 3–5 it has a nonionic structure [18]. The use of boron-based compounds by reaction with curcumin, it improves its stability *in vivo* without loss of bioactivity. Recently, a study showed that the drug bortezomib co-administered with curcumin determines the synergistic and therapeutic activity for the treatment of multiple myeloma. Moreover, the combination of 2-aminoethyl diphenyl borate with curcumin has been shown to increase the *in vitro* and *in vivo* stability of curcumin [19].

It is well known that curcumin's inhibition activity on human immunodeficiency virus (HIV)-1 and HIV-2 proteases was reduced, while when rosocyanine was used its inhibition activity on HIV-1 and HIV-2 proteases increased more than 10-fold [20]. As a result, boron compounds with curcumin began to be investigated more and more, discovering remarkable biological properties (antitumor, antiviral, antioxidant, antithrombotic). It is believed that in the future these compounds could be used as drugs in the prophylaxis of pandemic viral attacks, such as SARS-CoV-2, as well as to improve blood circulation in the body. Considering the scientific arguments presented above and also the ability of curcumin to form boron complexes, several boron-based compounds could be prepared for the prevention of COVID-19 viral disease [21].

Heterozygous beta-thalassemia (HBT) is a benign genetic deficiency of the blood caused by a hereditary reduction in beta-globin synthesis. HBT is prevalent in many regions of the world, including the Mediterranean countries, the northern coast of Africa, the Middle East, Central Asia, Southeast Asia, the Far East, and South America. The highest frequencies carrying beta-thalassemia were reported in Cyprus (14%), Sardinia (10.3%) and Southeast Asia (Cambodia, Bangladesh, Thailand, Laos, etc.) [22]. The population with HBT has developed a defense mechanism for bacteria and viruses that attack the blood through the action of two toxic factors: low blood iron levels and the presence of free hemin [porphyrin that contains iron(III) and chloride]. Probably the same mechanism is happening in case of SARS-CoV-2 infection too. The above-mentioned countries had and still have a very small population infected with SARS-CoV-2 [23, 24].

In order to help elucidating future treatment decisions for COVID-19, we are proposing that the HBT model to protect the blood against SARS-CoV-2 infection. Thus, we propose to utilize the following two classes of natural compounds suited for defending the blood against SARS-CoV-2: hemin and boron–curcumin complexes. The advantages of the HBT model in identifying prophylactic and therapeutic strategies against COVID-19 are related to the following physiological aspects:

(i) HO-1 has a significant activity in the spleen of HBT patients in the degradation of hemoglobin during red blood cells recycling (0.8% of the red blood cells fund per day), which represents approximately 80% of the production of endogenous carbon monoxide (CO)-derived heme [25].

(ii) HBT patients have hemin concentration in the blood, while normal people have a total lack of free hemin [23].

(iii) In HBT patients, erythropoietin (EPO), the hormone that regulates erythrocyte production, is also dramatically increased in response to anemia and hypoxia. EPO-induced HO-1 expression is likely to provide cytoprotection against oxidative stress [26]. These effects are actually a link between EPO and HO-1. In addition to HO-1 induction, EPO can exert its antioxidant effects by inducing antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase [27, 28].

(iv) Two platelet function markers belonging to the group of membrane glycoproteins – selectin P and serum soluble cluster of differentiation 40 ligand (sCD40L) – were present at lower levels in individuals with HBT compared to controls [29]. Subjects with HBT have a lower frequency of cardiac and cerebral ischemic events than controls in some studies and this difference was supported by a meta-analysis and recently multiple sclerosis is very low in thalassemics [30].

HO-1 is a metabolic enzyme that catalyzes the degradation of heme into CO, biliverdin and free iron [25]. This enzyme has anti-inflammatory and antioxidant properties, which modulate innate and adaptive immune responses. In addition, recent studies have reported that HO-1 may exert significant antiviral activity against a wide variety of viruses, including HIV, hepatitis C virus, hepatitis B virus, enterovirus 71, influenza virus, respiratory syncytial virus, dengue virus, and Ebola virus, among others [31]. The activation of HO-1 by its substrate hemin ensured the protection against HIV infection. Treatments against viral infections that enhance HO-1 include various anesthetics (isoflurane or sevoflurane), hemin, estrogen, statins, curcumin, resveratrol, and melatonin [32]. Therefore, HO-1 expression can be strongly induced by heme analogues, such as hemin and curcumin derivatives, such as boron–curcumin complexes [33, 34].

Lymphocytopenia is a common feature of SARS-Cov-2 infection, which can be used as an early marker in patients with SARS-CoV-2 infections, and is more pronounced in patients infected with SARS-CoV-2. Current data show that hemin can ameliorate lung damage resulting from virus infection. In addition, reports indicate that hemin may alleviate lung damage caused by other factors, such as lipopolysaccharide, mechanical ventilation, complement activation, and transfusion. All these results suggest that the effect of hemin in protecting the lungs has a broad spectrum and potentially involves against several diseases in the clinical setting [35].

Do rosocyanine (boron–curcumin) and hemin [iron(III)–porphyrin chloride] act against SARS-CoV-2? The following candidate molecules could be able to ensure very good blood protection against SARS-CoV-2:

(i) Rosocyanine is a promising and inexpensive alternative used in the photodynamic inactivation of viruses. Rosocyanine has been shown to be an extremely effective inhibitor of viral proteases (HIV-1 and HIV-2) and in addition a potent chelator of free iron. Taking into consideration the above-presented scientific arguments and also the capacity of curcumin to form boron adducts, several boron-based curcumin nutraceuticals could be prepared for viral disease (COVID-19) prevention [36].

(ii) Hemin, a commercial heme compound, used as an inducer of HO-1 has been shown to have antiviral activity. Hemin has been approved as a drug by the *Food and Drug Administration* (FDA) for use in patients with acute porphyria since the 1970s. Scientific data show that protoporphyrin, hemin and other natural porphyrins, as well as related

metalloporphyrins, have activity against ribonucleic acid (RNA) viruses through an inhibition mechanism of viral enveloped proteases. In addition, it is also known that porphyrins can be a remarkable viral trap (for SARS-CoV-2 too), as they can be intercalated in the host cell membranes affecting the fusion of the virus with the human body. Considering the present demand of medication, it could be worth testing the antiviral properties and safety of hemin against COVID-19 [37]. Various compelling evidence indicate a possible role for hemin-induced HO-1 as a therapy strategy against the SARS-CoV-2-induced cytokine storm syndrome. Hemin-induced HO-1 might be a harmless, novel, and promising approach for controlling SARS-CoV-2 infection and limiting cytokine [38].

Recently, it has been hypothesized that heterozygous patients with HBT would develop resistance against SARS-CoV-2 due to the absence of the beta chain in hemoglobin (potential target of the virus). This hypothesis has been studied starting from the high percentages of the beta-thalassemia population present in four areas of Italy: Sardinia, Sicily, Puglia, and Emilia Romagna [39, 40]. To this end, there are two classes of natural compounds suitable for protecting the blood against SARS-CoV-2: exogenous porphyrins [41] and boron–curcumin compounds [3]. Our current approaches for prophylaxis and treatment for COVID-19, based on HBT model and on using iron as a “bargaining chip” for blood protection and boron–curcumin complex as well, should be taken into consideration by specialized agencies – FDA, *World Health Organization* (WHO), *European Medicines Agency* (EMA). We believe that new decisions for COVID-19 prophylaxis and treatment are being actually imperative due to the spread of SARS-CoV-2 infections at the present moment.

#### Conflict of interests

The authors declare that they have no conflict of interests.

#### Ethics approval

This article did not contain human participants or animals.

#### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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### Corresponding author

Ion Romulus Scorei, Professor, Biochem, PhD, BioBoron Research Institute, S.C. Natural Research S.R.L., 31B Dunării Street, 207465 Podari, Dolj County, Romania; Phone +40351–407 543, e-mail: romulus\_ion@yahoo.com