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Review

Will curcumin nanosystems be the next promising antiviral alternatives in COVID-19 treatment trials?

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ABSTRACT

The COVID-19 has become of striking interest since the number of deaths is constantly rising all over the globe, and the search for an efficient treatment is more urgent. In light of this worrisome scenario, this opinion review aimed to discuss the current knowledge about the potential role of curcumin and its nanostructured systems on the SARS-CoV-2 targets. From this perspective, this work demonstrated that curcumin urges as a potential antiviral key for the treatment of SARS-CoV-2 based on its relation to the infection pathways. Moreover, the use of curcumin-loaded nanocarriers for increasing its bioavailability and therapeutic efficiency was highlighted. Additionally, the potential of the nanostructured systems by themselves and their synergic action with curcumin on molecular targets for viral infections have been explored. Finally, a viewpoint of the studies that need to be carried out to implant curcumin as a treatment for COVID-19 was addressed.

1. Introduction

COVID-19 is a viral disease that triggers Severe Acute Respiratory Syndrome (SARS). This disease emerged in December 2019 in Wuhan, China, and spread worldwide, becoming one of the most worrisome pandemic outbreaks of the 21st century [1].

In order to better characterize this infection, the elucidation of the virus's genome was performed, revealing a similarity of 79% to coronaviruses. Hence, this new strain was named a type 2 coronavirus, known as SARS-CoV-2 [2]. According to the World Health Organization (WHO), the number of COVID-19-confirmed cases has surpassed 120 million, and more than 2.7 million deaths have been reported worldwide (to date) [3]. The absence of an effective pharmacological treatment able to reduce the viral load and minimize the disease progression to the Acute Respiratory Distress Syndrome (ARDS) is one of the main factors that leads to the high mortality rate of this disease [4].

In light of this situation, marketed drugs have been tested to elucidate the COVID-19 biological pathways and identify the SARS-CoV-2 biological target in order to provide a specific and, by consequence, more effective alternative to treat the disease [5]. One of the targets of the drugs selected to treat COVID-19 is the main protease (M^{pro} also known as $3CL^{pro}$), which acts in the coronavirus RNA replication [6]. Besides the aforementioned biological route, another important site is the angiotensin-converting enzyme 2 receptor (ACE II), since it facilitates the entry of the SARS-CoV-2 into the host cell [7]. The latter has encouraged the hypothesis that drugs with suitable ACE II inhibitory activity may become a feasible alternative to be explored.

Indeed, these therapeutic approaches are supported by the SARS-CoV-2 similarity to other viruses from the same family that have infected people before; however, there is still no robust therapeutic evidence for COVID-19 [4]. In this context, some studies have demonstrated the potential of natural product-derived compounds, such as curcumin, against SARS-CoV-2 [8].

Curcumin (Fig. 1a), a polyphenol obtained from the *Curcuma longa* rhizome [9], is the major curcuminoid presented in this plant (77%), along with 17% of demetoxicurcumin (curcumin II) and 3% of bisdemetoxicurcumin (curcumin III) [10].

In this scenario, it is possible to observe that curcumin is one of the

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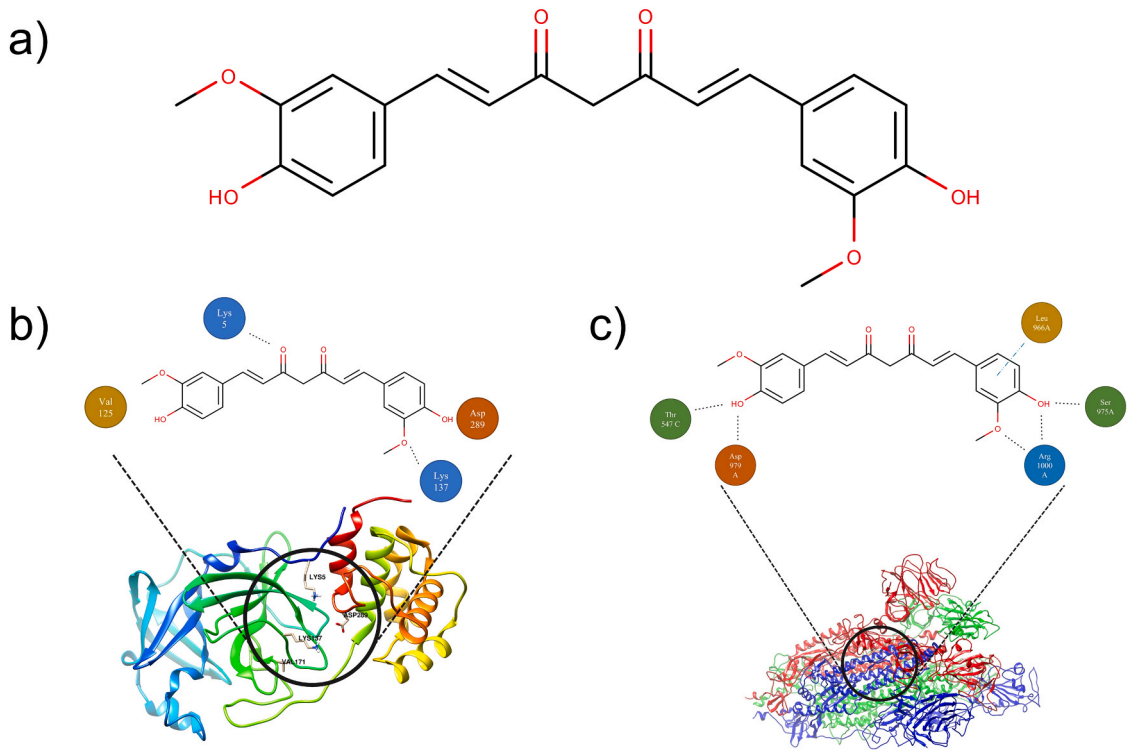

Fig. 1. Chemical structure of a) curcumin, and its b) interaction with SARS-CoV-2–3CL^{pro} and c) SARS-CoV-2-S. Dotted lines show hydrogen bonding (black) and pi-sigma interaction (blue). Amino acids are shown according to their side-chain classification: polar (yellow), non-polar (green), acid (orange), and basic (blue). (*In silico* analysis performed according to the rationale of Dandapat, Jena, Kanungo, Nayak and Chainy [8], Gonzalez-Paz, Lossada, Moncayo, Romero, Paz, Vera-Villalobos, Pérez, San-Blas and Alvarado [11]).
Source: Own authorship.

most thoroughly investigated and promising dietary natural product-derived molecules. Approximately 3000 preclinical investigations have been carried out, from which the potential beneficial effects and safety (tolerated up to 12 g/day) of curcumin have been reported [10,12]. Regarding its biological properties, scientific reports have described its use as anti-inflammatory [13], anticancer [14], antioxidant [13], and antidepressant [15]. Additionally, curcumin is an antiviral [16] agent, which also displays potential effects in the treatment of COVID-19, as demonstrated by Zahedipour et al. [17]. These authors suggested that curcumin may act by viral inhibition, inflammatory modulation and/or immunological responses, with the potential to reverse the pulmonary edema and pathways associated to the fibrosis in COVID-19 infection [17].

Indeed, the approach used by Zahedipour and colleagues [17] highlighted curcumin's promising potential in COVID-19 infection. However, the authors did not properly consider curcumin's biopharmaceutical limitations and its effect on the biological response. In this perspective, this review discusses not only relevant aspects of the investigation of curcumin against COVID-19 and its mechanisms of antiviral action against SARS-CoV-2, but also highlights the nanotechnological approach as the means to overcome curcumin's drawbacks and to enable a favorable drug response against SARS-CoV-2.

2. Curcumin as an antiviral alternative against SARS-CoV-2

Curcumin has shown itself as an effective molecule to treat viral infections due to its ability to modulate a great number of molecular targets that contribute to the infection process. Among those, the following could be mentioned: (i) transcription and replication regulation [18], (ii) inhibition of proteases [19,20], (iii) inhibition of attachment and entry of the virus to the cells [21] and (iv) inactivation and attack of the virus's structures [22].

Accordingly, curcumin has presented effectiveness against a wide number of viruses, such as the Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), Human Cytomegalovirus (HCMV), Epstein-Barr Virus (EBV), Bovine Herpesvirus 1 (BHV 1), Chikungunya Virus, Ebola Virus, Enterovirus 71 (EV71), Rift Valley Fever Virus (RVFV), Human Norovirus (HuNoV), Respiratory Syncytial Virus (RSV), Fish Viral Hemorrhagic Septicemia Virus (VHSV), and Influenza A Virus (IAV) [23].

Additionally, studies also related curcumin activity to SARS-CoV, a coronavirus, identified in 2003. This molecule inhibited the 3C-like protease (3CL^{pro}) with half-maximum inhibitory concentration (IC_{50}) of 40.0 μM. Such activity represents greater inhibitory potential when compared to other natural product-derived compounds as (i) Hesperetin (*Isatis indigotica*) IC_{50} = 60.0 μM, (ii) Quercetin (*Allium cepa*) IC50 = 52.7 μM, (iii) Broussochalcone A (*Broussonetia papyrifera*) IC_{50} = 88.1 μM, (iv) Betulonic acid (*Juniperus formosana*) $IC_{50} > 100$ μM, and (v) Hinokinin (*Chamaecyparis obtusa*) $IC_{50} > 100$ μM [24,25].

Furthermore, this molecule was also able to inhibit papain-like protease (PL^{pro}), whose IC_{50} value (5.7 ± 0.3 μM) was more expressive than the natural product-derived compounds, (i) Broussochalcone A (*Broussonetia papyrifera*) IC_{50} = 9.2 μM, (ii) Kaempeferol (*Zingiber officinale*) IC_{50} = 16.3 μM, and (iii) Quercetin (*Allium cepa*) IC_{50} = 16.3 μM [26,27]. Hence, (i) the large antiviral spectrum due to multiple biological targets, (ii) the expressive *in vitro* inhibitory activity reported above and (iii) the high *in vivo* tolerability and, by consequence, the US Food and Drug Administration (FDA) approval [28], make this compound a natural product with high potential to be used against coronaviruses.

Moreover, preliminary computational studies predict curcumin's ability to inhibit proteases and to interact with S and ACE 2 proteins [28,29]. Such aspects will be further discussed.

2.1. SARS-CoV-2 protease inhibitor

Proteases play an essential role in viral replication and can represent potential targets for the COVID-19 treatment [30,31]. Indeed, the protein sequences of the SARS-CoV M^{pro} and the SARS-CoV-2 M^{pro} are 96% identical and their active sites, in both proteins, remain free from mutations [32].

In silico preliminary studies have been performed to evaluate different medicinal plant compounds as potential inhibitors of SARS-CoV-2 M^{pro} [33]. In this perspective, Ibrahim and collaborators [34] evaluated the inhibitory effect of curcumin, quercetin, piperine, kaempferol, capsaicin, carnosol, acetyl eugenol and other natural compounds (32 total) against the main protease of SARS-CoV-2 (M^{pro}). Curcumin revealed a high potency as M^{pro} inhibitor, displaying binding energy of - 9.2 kcal/mol. Such affinity is attributed to its ability to form multiple hydrogen bonds, van der Waals interactions, and hydrophobic and pi (π)-based interactions with the key amino acids within the active site [34].

Accordingly, Gonzalez-Paz et al. [11] also performed a molecular docking study to compare capsaicin, piperine, and curcumin with chloroquine and hydroxychloroquine. The authors showed that curcumin was able to promote higher inhibition of $3CL^{pro}$ of SARS-CoV-2 than the tested control drugs (chloroquine and hydroxychloroquine). The scheme showing the interaction between curcumin and the SARS-CoV-2–$3CL^{pro}$ is shown in Fig. 1b. Based on this rationale, it is expected that curcumin would reduce the viral load in human cells in a shorter treatment time when compared to other drugs with minor inhibitory action, which could prevent the disease from worsening into stages such as ARDS.

2.2. Angiotensin-converting enzyme II as a target for SARS-CoV-2 inhibition

ACE II is a cell receptor extensively present in the human body, mostly in the capillary blood vessels and lung tissue [35]. This receptor is associated to respiratory viral disorders such as SARS [36]. The virus's ability to bind with ACE II is due to its spike protein (S), which was first described for SARS-CoV [7]. Therefore, since SARS-CoV-S shares ~76% similarity in amino acid sequences with SARS-CoV-2-S, the affinity of the protein S from the new strain to the ACE II was investigated [37]. The study revealed that SARS-CoV-2 displays the most efficient binding to ACE II when compared to the SARS-CoV, which could explain the current increase in human-human transmission ability of this new strain of coronavirus [38].

The virus entry into the cell occurs from a sequence of events. The host cell presents on its membrane the type 2 transmembrane serine protease (TMPRSS2), which cleaves the ACE II and promotes the binding by the SARS-CoV-2-S protein [39]. Subsequently, cellular proteases mediate the virus and cell membrane fusion, leading to the virus replication in the cytosol [37]. Hence, the angiotensin-converting enzyme proved to be a potent *in vivo* binding site for drugs that acted against SARS-CoV [40]. Recently, Zhou et al. [41] evaluated the infectivity of SARS-CoV-2 on HeLa cells expressing or not the ACE II receptors from humans, Chinese horseshoe bats, civets, pigs, and mice. They observed that SARS-CoV-2 was able to use all ACE II receptors, except for the mice ACE II, and did not use other coronavirus receptors, such as aminopeptidase N and dipeptidyl peptidase 4.

Furthermore, in view of the pursuit of new drug candidates for SARS-CoV-2 inhibition, *in silico* studies have demonstrated that curcumin has a dual inhibitory action at this target site: (i) inhibition of SARS-CoV-2-S (Fig. 1c) and (ii) inhibition of cell ACE II receptor [8]. Therefore, based on the role of ACE II on the SARS-CoV-2 replication cycle, curcumin emerges as a promising dual-inhibitor (directly and/or indirectly) of this target, which would disrupt the aforementioned viral pathway.

3. Nanotechnological approaches to improve curcumin properties against SARS-CoV-2

Notwithstanding its many biological benefits and potential as a candidate to treat COVID-19 due to its inhibition of SARS-CoV-2 viral pathways, curcumin has physicochemical properties that reduce its bioavailability. Among those, its poor water-solubility (11 ng/ml) and low stability in aqueous media, especially in alkaline pH, are worth to mention [42]. Furthermore, after oral administration, curcumin is

Table 1
Different nanosystems eligible to be used as curcumin carrier and their advantages and disadvantages.

Nanosystem	Advantages	Disadvantages	Reference
Nanoemulsions	• Biocompatibility • Increased permeability and biodistribution • Great versatility of use	• High surfactant/co-surfactant concentration • High production cost • High storage cost	[45]
Microemulsions	• Biocompatibility • Increased permeability and biodistribution • Great versatility of use • Reduces drug degradation • Form spontaneously	• Remarkably high surfactant/co-surfactant concentration • May present toxicity due to surfactant concentration • Sensitive to temperature and salinity changes	[46]
Liposomes	• Biocompatibility and biodegradability • Good permeability • Increased drug efficacy	• High production cost • Drug leakage • Phospholipids may undergo oxidation and hydrolysis • Sensitive to osmosis • Inadequate stability	[47]
Nanogels	• Tunable Size • Ease of Preparation • Swelling • Biocompatibility • Stimuli responsiveness (temperature, pH, light, biological agent, *etc.*)	• Partial drug load and suboptimal kinetic release • Immunogenic when interact with serum proteins • Adverse effects may occur due to the presence of surfactant and/or monomers in the matrix	[48]
Micelles	• Increased drug solubility • Low toxicity • Prolonged drug circulation	• Low stability in the blood stream • Drug leakage	[49]
Nanoparticles	• Versatility • Easy customization and functionalization • Easy cell uptake • Great permeability • Controlled release	• Safety[a] • Stability[a] • Preparation procedures[a]	[50,51]

[a] Nanoparticles represent a large group of nanocarrier. Those characteristics may change depending upon the type of particle and its composition material.

rapidly metabolized, *i.e.*, the drug is reduced (Phase I) and conjugated (Phase II) by the gastrointestinal tract and liver metabolism, respectively, before its elimination [42]. To overcome these drawbacks, nanostructured carriers (nanosystems) have been used, since they can protect drugs from chemical and metabolic degradation, enhance their solubility and modify their transport through biological membranes [43].

Different nanotechnological carriers for curcumin have been developed, such as (i) nanoemulsions, (ii) microemulsions, (iii) liposomes, (iv) nanogels, (v) micelles, and (vi) nanoparticles [44]. Table 1 summarizes the main advantages and disadvantages of these nanosystems.

Indeed, in light of the current pandemic of COVID-19, it is noteworthy that at least three nanotechnological curcumin-based products are available on the market in the form of polymeric nanoparticles (Nanocurc™), liposomes (Lipocurc™) and nanomicelles (Sinacurcumin®) [52,53]. To date, only three studies have evaluated the *in vivo* efficacy of curcumin-loaded nanosystems against COVID-19. Saber-Moghaddam and collaborators [53] conducted an open, non-randomized clinical trial of the effectiveness of an oral curcumin nanosystem (Sinacurcumin®, a soft gel capsules containing 40 mg of curcuminoids in nanomicelles, two capsules twice a day for 2 weeks). The study involved patients hospitalized with COVID-19 classified as mild to moderate. The authors observed that most of the symptoms quickly reduced in the group treated with Sinacurcumin®. They concluded that the curcumin-loaded nanosystem can improve the recovery time in hospitalized patients with COVID-19. However, because these findings are preliminary and could not be statistically representative, the authors recommended other randomized, placebo-controlled clinical trials with larger groups.

Moreover, Valizadeh et al. [54] conducted a randomized, double-blind, placebo-controlled study to evaluate not the antiviral activity, but rather the effects of Sinacurcumin® 40 mg (4 capsules daily for 14 days) on the modulation of inflammatory cytokines in patients with COVID-19. mRNA expression and levels of cytokine secretion were assessed by real-time PCR and ELISA. Sinacurcumin® was able to modulate the increase rate of inflammatory cytokines, especially the expression of IL-1β and IL-6 mRNA, and the secretion of cytokines, in patients with COVID-19, which may increase clinical outcomes and general recovery.

Another study highlighting the anti-inflammatory response of the same formulation in patients with COVID-19 was carried out by Tahmasebi et al. [55]. Indeed, they investigated the therapeutic effects of Sinacurcumin® on the frequency and responses of Th17 cells (T helper cells) in patients with mild and severe COVID-19. They concluded that Sinacurcumin® was able to reduce the frequency of Th17 cells and the related inflammatory factors in patients with mild and severe COVID-19. Therefore, Sinacurcumin® can be considered a potential modulator in improving the patient's inflammatory condition.

In addition to these studies, there is a registered protocol [56] for a prospective placebo-controlled clinical trial with a parallel group, randomized in a single center, in patients with COVID-19. This study will evaluate the effectiveness of nanomicelles containing curcumin and their effects on the patient's immune responses after treatment.

Despite the positive outcomes from the *in vivo* studies of Sinacurcumin® in the treatment of COVID-19, this formulation focuses on reducing symptoms and mediating inflammatory responses generated by the disease. However, it is important to emphasize that other nanosystems have advantages (Table 1) that may provide additional features and outcomes in treatment options based on curcumin.

Finally, no *in vitro* nor *in vivo* studies have evaluated the response of free and/or entrapped curcumin and its antiviral potential and possible mechanisms against SARS-CoV-2. In view of the potential mechanisms from which curcumin nanosystems could inhibit the activity of SARS-CoV-2, a proposed summary of the aforementioned mechanisms is presented in Fig. 2.

Beyond the array of advantages of nanosystems on the delivery of burdensome molecules, nanoparticles (NPs) exhibit the advantage of easy customization and functionalization (Table 1) [50]. Moreover, there are a countless number of particles of distinct materials and structural organizations to be explored, such as (i) lipid-based nanoparticles, (ii) polymeric nanoparticles, and (iii) inorganic nanoparticles [57]. On that matter, nanoparticle features can be engineered to

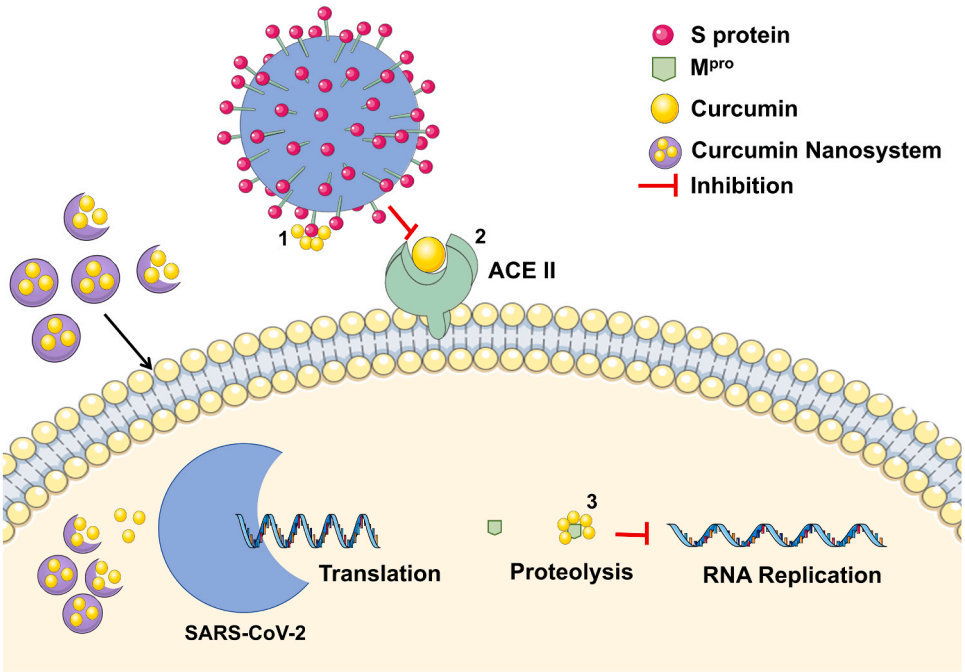

Fig. 2. Proposed rationale for curcumin nanosystems inhibition mechanisms according to the literature findings. 1) Curcumin inhibition by binding on SARS-CoV-2 S protein. 2) Curcumin inhibition by binding on ACE II receptor on the human cell membrane. 3) Curcumin inhibiting viral RNA replication by binding to SARS-CoV-2 M^{pro}.
Source: Own authorship.

strategically target extracellular and intracellular viruses [58,59]. Indeed, functionalization of NPs may be achieved by linking antibodies [60], carbohydrates [61], heparin [62], polyanionic molecules [63], among other compounds, to their surface. Furthermore, these changes on the particle surface may lead to an extended antiviral spectrum based on the blank-nanoparticle itself [64].

Those nanoparticles mechanisms of action are achieved through different pathways, such as (1) viral inactivation (directly or indirectly), (2) fixation of viruses in host cells, (3) viral penetration, and (4) viral replication, which are mainly dependent on the nature of the nanoparticles used and their functionalization [65]. In this way, nanoparticles are able to block these steps and modify the structure of the capsid protein, reducing viral load, either by physical or chemical means [66].

Therefore, a viral inactivation can occur through interactions between the nanoparticles and the viral surface protein (S-protein) by Kazimir interactions and Van der Waals forces. In fact, this phenomenon was already observed in metallic nanoparticles due to their shape, size, structure, and local field enhancement of action [67]. Since the S-protein can be found on the novel coronavirus surface [68], it is possible that nanoparticles could interact with the SARS-CoV-2 protein.

Additionally, the SARS-CoV-2-S protein is responsible for fixation (subunit 1) and entry (subunit 2) of viruses [37,69]. The subunit 1 bonds specifically with the receptor of the angiotensin-converting enzyme II (ACE II) on human surface cells. On the other hand, the subunit 2 is related to the fusion of the attached virus to the membrane, which is internalized mostly by endocytosis mechanisms [69–71]. These mechanisms can also be blocked by electrostatic interactions, expressed by zeta potential readings, between the nanoparticles with different charges and the virus, which neutralizes the effective charge on the virus particles. This leads to viral aggregation, as observed for cationic nanoparticles developed by Ting and colleagues [72].

Furthermore, in a context in which SARS-CoV-2 is already loaded into the cell, the infectant RNA acts as a messenger RNA (mRNA), which is translated by the host's ribosomes to produce replicative viral enzymes. Subsequently, new RNA and mRNA genomes are produced for the synthesis of necessary components to assemble new viral particles [73].

Briefly, the SARS-CoV-2 replication is a complex process that involves RNA synthesis, proofreading, and capping [73,74]. In this sense, the SARS-CoV-2 viral replication can be disrupted by nanoparticles, as described by Salleh et al. [71], who affirm that silver nanoparticles (AgNPs) are able to attach to the viral DNA or RNA, thus, inhibiting the replication or propagation of the virus inside the host's cells.

Considering this view, two approaches can be explored, (a) the increase in bioavailability of curcumin and, by consequence, its antiviral activity by delivery in NPs; and (b) a synergic combination of activities from curcumin and NPs themselves promoting a dual mechanism of action. Accordingly, curcumin could exhibit its inhibition on SARS-CoV-2 targets and the functionalized NPs could further block the virus entrance in the cell or display different mechanisms according to their functionalization.

Motivated by this perspective, some authors have already tested curcumin-nanoparticles against other viruses. Yang, Li and Huang [75] developed curcumin-loaded silver nanoparticles (AgNP) and showed that curcumin-AgNP improved the antiviral activity compared to curcumin and AgNP themselves against a syncytial virus. In another approach, Ting et al. [72] synthesized curcumin-carbon dots and proved their ability to suppress the virus-cell entry and the viral-RNA of porcine epidemic diarrhea virus (*Coronaviridae* family). These data reassure that nanotechnological approaches to delivery curcumin are viable and should be further investigated.

4. Conclusions

COVID-19 represents a global threat due to its difficulty in treatment once there is no current approved antiviral drug with proven efficacy and minor adverse effects. In this scenario, curcumin becomes a promising drug to be used as an antiviral agent due to its broad-spectrum, low toxicity, and potential pharmacological mechanism against SARS-CoV-2. The latter has been investigated using *in silico* studies which showed great activity in both target sites of inhibition of SARS-CoV-2. Henceforward, an investigation of the potential of curcumin must be performed to enlarge the possibilities of treatment for the COVID-19. Although this drug has limitations, nanostructured systems can be used as a tool to overcome such drawbacks. Furthermore, curcumin nanocarriers are already available in the market, allowing clinical studies, such as the few already carried out in patients with COVID-19 to reduce the anti-inflammatory process and symptoms associated to this disease. Despite the promising responses of curcumin nanomicelles (Sinacurcumin®) in the symptoms' management of COVID-19, the *in vivo* antiviral properties have not yet been investigated. Additionally, other nanosystems, such as nanoparticles, can be investigated due to further possibilities of functionalization and possible antiviral synergy between the particle and the drug. Further, since turmeric (*Curcuma longa* extract) has a low curcumin concentration, $< 7\%$, its food-grade use should not be encouraged and do not replace proper treatment for COVID-19 once it lacks FDA approval.

5. Perspective

It is noteworthy the aforementioned capability of curcumin as an antiviral agent. Notwithstanding the promising enhancement in curcumin bioavailability by NPs and their *in vitro* synergistic mechanism against different viruses, studies aiming to verify if these early findings on the *Coronaviridae* family transpose to SARS-CoV-2 should be further performed. Initially, these studies need to attest curcumin-NPs efficiency to suppress the SARS-CoV-2 viral infection *in vitro*. Then, since some drugs and nanoparticles fail to ensure *in vitro* antiviral activity, animal-infected models must be used for *in vivo* testing. This careful outline would ensure safety in further steps. Finally, after preclinical trials to attest drug efficiency and safety, curcumin nanoparticles, especially the already FDA-approved formulations, may be used on human clinical trials.

Conflict of interest statement

The authors declare no competing financial interest.

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