Targeting arachidonic acid–related metabolites in COVID-19 patients: potential use of drug-loaded nanoparticles

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Abstract

In March 2020, The World Health Organization (WHO) has declared that the coronavirus disease 2019 (COVID-19) is characterized as a global pandemic. As of September 2020, infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread to 213 countries and territories around the world, affected more than 31.5 million people, and caused more than 970,000 deaths worldwide. Although COVID-19 is a respiratory illness that mainly targets the lungs, it is currently well established that it is a multifactorial disease that affects other extra-pulmonary systems and strongly associated with a detrimental inflammatory response. Evidence has shown that SARS-CoV-2 causes perturbation in the arachidonic acid (AA) metabolic pathways; this disruption could lead to an imbalance between the pro-inflammatory metabolites of AA including mid-chain HETEs and terminal HETE (20-HETE) and the anti-inflammatory metabolites such as EETs and subterminal HETEs. Therefore, we propose novel therapeutic strategies to modulate the level of endogenous anti-inflammatory metabolites of AA and induce the patient's endogenous resolution mechanisms that will ameliorate the virus-associated systemic inflammation and enhance the primary outcomes in COVID-19 patients. Also, we propose that using nanoencapsulation of AA and its associated metabolites will contribute to the development of safer and more efficacious treatments for the management of COVID-19.

Keywords COVID-19 · Arachidonic acid · Nanoparticles · SARS-CoV-2 · Cytochrome P450 · EETs · Subterminal HETEs

1 Introduction

Coronavirus disease 2019 (COVID-19) has been declared by The World Health Organization (WHO) to be the cause of a global pandemic in March 2020 [1]. As of September 2020, infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected more than 31.5 million people, 23 million of whom have recovered. It also caused more than 970,000 deaths worldwide [2]. The first cohort of infections was identified in Wuhan, the capital city of Hubei province in mainland China. Patients with severe outcomes were initially diagnosed with pneumonia of unknown cause; the causative pathogen was later identified as a novel

enveloped RNA member of β coronaviruses belonging to the Coronaviridae family [3]. Members of this family are known to result in mild infections. Nevertheless, the outbreaks caused by the Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) had significant health outcomes in terms of severity and mortality [4].

COVID-19 is a respiratory infectious illness, the major transmission route of SARS-CoV-2 from human to human is the close contact with infected individuals through respiratory droplets [5]. Other probable routes of transmission involve aerosol and oral-fecal transmission as well as touching surfaces or objects that are contaminated with the virus and then touching mucus membranes found mainly in the mouth, nose, or eyes [6, 7]. COVID-19 has an approximate incubation period of up to 14 days starting from the time of exposure to the virus; however, the majority of patients develop symptoms in the fourth or the fifth day of infection [8, 9]. The disease has a wide range of non-specific symptoms; some infected individuals have no or mild flu-like symptoms while others could develop life-threatening outcomes including severe

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pneumonia with acute respiratory distress syndrome (ARDS) leading to death [10].

Although COVID-19 is a respiratory illness that mainly targets the lungs; it also appears to affect other extra-pulmonary systems such as the cardiovascular, renal, gastrointestinal, immune, and nervous systems [11]. The progression pace of the disease is vastly influenced by the existence of multiple patient comorbidities. Not all COVID-19 patients respond in the same manner to the virus. Elderly patients and those with numerous comorbidities such as cardiovascular disease, metabolic syndrome, cancer, renal, or immunosuppressive diseases are at a greater risk of contracting the virus and developing more severe outcomes to the infection [12, 13]. Some countries have implemented more successful measures in fighting the pandemic than others. For instance, South Korea, Hong Kong, and Taiwan curbed community transmission of the virus earlier than other countries such as Italy, France, Spain, and the USA. These measures include rapid expansion of the PCR testing capacity, quarantine of suspected cases, mass masking strategy, early suspension of non-essential travel, and social distancing [14].

Cytochrome P450 (CYP) enzymes are a superfamily of enzymes that are involved in the metabolism of endobiotics such as steroids, arachidonic acid (AA), and bile acids as well as xenobiotics including drugs and carcinogens. The family comprises 57 human CYP enzymes that are responsible for the metabolism of approximately three-fourths of marketed drugs [15, 16]. AA, a part of the membrane phospholipid pool, is engaged in several pathways of metabolism and most of its generated metabolites have a specific biological activity [17]. AA is metabolized by CYP enzymes through three distinct metabolic pathways; the first one is allylic oxidation to generate midchain hydroxyeicosatetraenoic acids (HETEs), and the second pathway is olefinic epoxidation, by CYP epoxigenases, to produce epoxyeicosatrienoic acids (EETs) typified as 5,6-, 8,9-, 11,12-, and 14,15-EET. The third group of metabolites is generated through terminal/subterminal hydroxylation reaction to form terminal 20-HETE and subterminal HETEs (Fig. 1) [18–20].

At the time of EET discovery, they were initially characterized as vascular endothelium-derived hyperpolarizing factors (EDHFs) that mainly affect the cardiovascular and renal physiology through strong vasodilatory action [21, 22]. Nevertheless, the biosynthesis of EETs is not exclusively limited to the endothelial tissue; EETs could be produced in any type of cells that express CYP epoxigenases [23]. The pharmacokinetic profile of EETs indicates that these endogenously biosynthesized compounds have short half-lives due to rapid hydrolysis by the catalytic action of soluble epoxide hydrolase (sEH) enzymes. These are a group of enzymes found in the cytosol and peroxisomes, they specifically bind to certain epoxides and transform them into the less active corresponding diols dihydroxyeicosatrienoic acids (DHETs) [24, 25].

Strategies to enhance the biological activity of EETs include chemical inhibition of sEH and genetic techniques to knock out the expression of sEH gene, leading to stabilization of the levels of EETs and improvement of their pharmacokinetic instability [26, 27].

Another group of AA metabolites is the subterminal HETEs, they are lipid mediators that are biosynthesized by the catalytic action of CYP monooxygenases such as CYP1A1, CYP2E1, and CYP4F2 [16]. This group of metabolites comprises four members namely 16-, 17-, 18- and 19-HETE; their physiological and pathophysiological roles are not fully elucidated to date. However, some of them have shown significant anti-inflammatory effects. Interestingly, their biological activity tends to be more significant in some body systems, such as the renal and cardiovascular systems [18, 28]. Strategies to boost the level of subterminal HETEs include enzyme induction such as using isoniazid, a well-known CYP2E1 inducer, to increase the level of 19-HETE and using synthetic analogs such as 19-HETE and 16-HETE lab-generated analogs that have longer half-lives and a better pharmacokinetic profile than the endogenously produced sub-terminal HETEs [29–31].

In the meantime, there is no FDA-approved drug that improves the primary outcomes such as hospitalization and mortality rates in COVID-19 patients. Interestingly, several active clinical trials are being conducted for different possible treatments for COVID-19 such as lopinavir-ritonavir, low-dose corticosteroids, favipiravir, and remdesivir. The most recent update from the RECOVERY trial, which included more than 6400 patients in the UK, shows that the cheap and widely available dexamethasone was able to decrease mortality rate by one-third among patients severely ill with COVID-19 [32, 33]. However, some patients especially those who are hypertensive, diabetic, or immunocompromised may experience serious side effects upon administration of this drug. This highlights the role that AA metabolites can play in the case of COVID-19 patients who cannot tolerate the use of glucocorticoids. Moreover, there are no clinically approved prophylactic agents for the disease [34]. Due to the seriousness and the huge impact of the pandemic, there is an increasing interest in repositioning of current clinically approved drugs and finding novel therapeutic modalities that can enhance the primary clinical outcome in COVID-19 patients.

2 Statement of the hypothesis

We hypothesize that infection with SARS-CoV-2 causes perturbation in the AA metabolic pathways leading to an imbalance between the pro-inflammatory metabolites of AA and its anti-inflammatory metabolites such as EETs and subterminal HETEs. In this regard, augmentation of COVID-19 patients' active resolution processes against inflammation induced by

Fig. 1 Different pathways involved in cytochrome P450-mediated arachidonic acid metabolism. Arachidonic acid undergoes metabolism by

different P450 families into mid-chain HETEs, terminal/subterminal HETEs, and EETs

SARS-CoV-2 infection would be a perfect supplement to the current anti-inflammatory therapeutic approaches. Here, we propose novel strategies to balance the level of endogenous anti-inflammatory metabolites of AA and induce the patient's endogenous resolution mechanisms. Also, we propose that using nanoencapsulation of AA and its associated metabolites will contribute to the development of safer and more efficacious treatments for the management of COVID-19.

3 Supporting evidence for the hypothesis

3.1 Coronavirus-associated perturbation in the arachidonic acid metabolic fate

Coronaviruses are a group of enveloped viruses characterized by possessing a large single-stranded RNA. Currently, they comprise a total of seven coronaviruses that have the ability to

infect humans, including the most recently emerging virus SARS-CoV-2 [5, 35, 36]. The SARS-CoV-2 life cycle involves lipids at different levels, ranging from serving as entry co-factors for the virus at the cell surface, representing an essential component in the process of viral replication, to the important role as an energy source that could be utilized to aid in the viral replication process [37–39]. Additionally, lipids contribute to the distribution of viral proteins, the maturation of virus particles, and the adhesion and release of the virions [40]. Therefore, the biosynthetic pathways of the host lipids represent a major determinant of the viral virulence as well as infectivity and it plays a vital role in the host defense mechanisms.

AA is a polyunsaturated fatty acid that is formed by the action of the phospholipase-A2 (PLA2) enzyme on the cell membrane phospholipids in the case of inflammatory conditions [41]. It has been suggested that AA and some of its metabolites could exert antiviral action and may be involved in the inactivation of enveloped viruses, such as influenza virus, MERS-CoV, or SARS-CoV-2. Additionally, the perturbation in AA and its associated metabolites may serve as a contributing factor that increases the susceptibility of humans to infection with these viruses [42]. Antimicrobial effects of AA have been previously reported as it has the ability to cause leakage in cell membranes or lead to uncoupling of the oxidative phosphorylation in some microorganisms [43].

SARS-CoV-2 infection causes an excessively widespread immune response in the body, a condition known as a cytokine storm. It is considered as one of the main causes of ARDS, multiple-organ failure, and even death in a brief period of time [44]. A cytokine storm causes a significant release of a number of inflammatory mediators including pro-inflammatory cytokines such as interleukin 6 (IL-6), IL-1 β , tumor necrosis factor- α (TNF- α), and eicosanoids such as AA and its associated metabolites [45].

It has been suggested that infection with SARS-CoV-2 will stimulate the immune system components such as T cells, B cells, leukocytes, and macrophages to release AA to aid in the process of inactivation of the invading pathogen. Yan et al. have performed an experiment on human coronavirus 229E (HCoV-229E) as a model of coronavirus infection. They infected the hepatocyte-derived carcinoma cell line (Huh-7) with the virus and analyzed the virus-mediated host cell lipid response using ultra-high-performance liquid chromatography-mass spectrometry (UPLC-MS). In this study, they showed that infection with the virus caused significant perturbation of fatty acids downstream of cytosolic PLA2 activation including AA. The results suggested that infection with coronaviruses did not disturb the composition of the cellular lipid components in a random way. Conversely, the virus modulates the infected host lipidomic and metabolomic profiles in a very accurate way to reach a sophisticated environment that is suitable and optimal for the viral invasion [45]. As

an integral part of the perturbation in AA and its metabolic fate, we speculate that infection with SARS-CoV-2 will lead to an imbalance between the pro-inflammatory metabolites of AA including mid-chain HETEs and terminal HETE (20-HETE) and the anti-inflammatory ones such as EETs and subterminal HETEs.

3.2 The potential role of arachidonic acid-derived epoxyeicosatrienoic acids in the resolution of the hyperinflammatory state in COVID-19 patients

EETs are a group of metabolites that are generated from arachidonic acid by CYP epoxygenases such as CYP2J2, CYP2C8, and CYP2C9 in different types of cells in the human body [46]. As mentioned earlier, they exert their action through hyperpolarization and subsequent relaxation of vascular smooth muscle cells by enhancing the activity of calcium-sensitive potassium (K_{Ca}) channels [21, 47]. EETs' biological actions are not limited to the vasodilatory effects; they have been reported to be involved in the process of resolution of inflammation in the human body. EETs have been reported to possess a non-vasodilatory property which is distinguished from their membrane-hyperpolarizing effect. EETs have the ability to inhibit NF- κ B suggesting that they could be beneficial for treating vascular and nonvascular inflammatory disorders [48]. They act as special mediators that aid in promoting the removal of cellular debris and triggering the anti-inflammatory programs to prohibit multiple major pro-inflammatory cytokines [49].

Some observational studies have reported that severe cases of COVID-19 infections are closely associated with older age and whether the affected person has comorbidities such as hypertension or diabetes mellitus. However, it is obvious now that severe disease and even death could also happen in youthful patients who are otherwise healthy and have no pre-existing medical conditions [50, 51]. COVID-19 severity and mortality have been associated with elevated levels of inflammatory markers in plasma such as C-reactive protein and ferritin as well as the fibrin degradation product, D-dimers [52]. Additionally, COVID-19 patients with severe outcomes have shown a high neutrophil-to-lymphocyte ratio and elevated pro-inflammatory cytokines and chemokines that resemble other cases that involve cytokine storm [53]. In addition to the high levels of IL-6, IL-7, and TNF- α , severe cases of COVID-19 patients have elevated production of inflammatory chemokines such as CC-chemokine ligand 2 (CCL2), CCL3, and CXC-chemokine ligand 10 (CXCL10) [54, 55].

The hyperinflammatory status is widely accepted as an essential component of severe SARS-CoV-2 infection [56]. Therefore, a comprehensive understanding of the human body measures for proper control of the heightened inflammatory state is encouraged for better treatment modalities. Lipid mediators including AA and its associated metabolites are crucial

players in the initiation of the inflammatory response in addition to their role in the process of resolution [57, 58]. The resolution of inflammation has been previously considered as a passive process. Nevertheless, current research has characterized the resolution of inflammation as an active and greatly sophisticated cellular and biochemical process [59, 60]. Currently, multiple endogenous bioactive lipid molecules are described to act as specialized pro-resolving mediators (SPMs) including resolvins, lipoxins, and protectins, they are highly responsible for operating the controlled resolution process that will lead eventually to the cessation of the inflammatory status [61–64].

Other key lipid mediators that participate in the effective resolution of inflammation include the AA-derived EETs. Along with other epoxy fatty acids, EETs stimulate the formation of SPMs through redirecting the metabolic pathways of AA to enhance the process of resolution of inflammation [65, 66]. Analysis of bronchoalveolar fluid obtained from severe COVID-19 patients has demonstrated that it has high levels of CCL2 and CCL7 chemokines. Both are strong recruiters of CC-chemokine receptor 2–positive (CCR2+) monocytes, a key component of the hyperinflammatory state [67, 68]. It has been shown that human monocytes express CYP epoxygenases such CYP2J and CYP2C enzymes. CYP2J2 and EETs have been previously demonstrated to possess strong anti-inflammatory effects through inhibition of nuclear factor-kappa B (NF- κ B) [69]. Additionally, mice treated with epoxygenase inhibitor (SKF525A) have shown a significant decrease in arachidonic acid–derived EETs and resulted in a dramatic increase in the recruitment of monocytes. On the other hand, sEH^{−/−} mice showed completely opposite phenotype to epoxygenase-inhibited mice in the course of inflammation resolution. Epoxygenase inhibition has led to recruitment of CCR2+ and CCL2^{hi} monocytes in addition to substantial levels of CCL2 peptide [49].

It is well established that EETs are swiftly hydrolyzed by the sEH enzyme. For this reason, using sEH inhibitors is representing a successful strategy to stabilize EET levels. Another strategy to boost the level of EETs is to use epoxygenase product mimetics (EETs synthetic analogs) [70–72]. While most of the ongoing clinical trials on COVID-19 patients are examining either antiviral or anti-inflammatory agents in order to treat the disease, potentiation of the endogenous inflammation resolution pathways represents a novel therapeutic modality for the treatment of COVID-19 [73–75]. Interestingly, several reports have shown that EETs, CYP epoxygenases, and sEH are also widely spread in both central and peripheral nervous systems. EETs have evident neuroprotective effects on the central nervous system, they modulate the neuronal excitability, increase the cerebral blood flow, and, most importantly, reduce neuroinflammation [76–78]. Given the complexity of the hyperinflammatory status in COVID-19 patients as well as virus-induced acute

disseminated encephalomyelitis, it is now widely accepted that targeting a single pro-inflammatory mediator might not be sufficient to attenuate COVID-19 progression [79, 80]. Therefore, we postulate that using sEH inhibitors or EETs synthetic analogs could offer new therapeutic interventions that aid in the management of COVID-19.

3.3 Could the modulation of subterminal hydroxyeicosatetraenoic acid levels be effective for the treatment of COVID-19?

Subterminal (ω -n)-hydroxylation is described as an oxidation reaction mediated by CYP monooxygenases enzymes that transform the methylene (−CH₂−) group number 16 to 19 found in the hydrophobic long chain of AA into more polar alcohol products known as subterminal hydroxyeicosatetraenoic acids (HETEs) [16, 81]. Subterminal HETEs comprise a group of bioactive lipid mediators that are involved in a wide array of physiological and pathophysiological processes [82]. They are endogenously formed through the metabolic action of some CYP enzymes including CYP1A1 which transform AA into different metabolites namely 19-HETE > 18-HETE > 17-HETE = 16-HETE. In addition, human CYP1A2, CYP2C19, CYP2E1, CYP4A11, and CYP4F2 have been also reported to be involved in the formation of subterminal HETEs especially 16- and 19-HETE [83–87].

A considerable number of patients infected with SARS-CoV-2 develop ARDS that is significantly associated with a very high mortality rate. One prominent characteristic of the ARDS is the recruitment of neutrophils into the extravascular compartments of the lungs [52, 88–90]. The process of neutrophil migration involves neutrophil priming leading to decreased deformability and confinement within the pulmonary capillary bed. Then, neutrophils migrate through endothelium reaching the airspaces, where they get transformed into phagocytes that attack the virus by releasing oxidants and proteases [91, 92]. In human blood, neutrophils represent the predominant phagocytic cell type, comprising nearly 50–60% of all leukocytes [93]. Neutrophils as well as their toxic metabolites represent the major cause of tissue injury in the case of ARDS. They are responsible for the elevated lung epithelial and endothelial permeability that eventually lead to alveolar edema and arterial hypoxemia. Indeed, ARDS-associated death is strongly correlated with the degree of neutrophilia in the lung [94–96].

Incubation of human polymorphonuclear neutrophils (PMNs) with a sub-stimulatory concentration of AA led to the formation of 16-HETE which is believed to be involved in the unstimulated status of the neutrophils. 16-HETE has been reported to act as a natural inhibitor of PMNs through hormone-like reaction. The mechanism of inhibition is through deactivation of recruitment, aggregation, and

adhesion of PMNs. Additionally, esterified 16-HETE has a potent effect on the affinity of PMNs adhesion receptors towards endothelial cells since it alters the composition and physical characteristics of the cell membrane of PMNs [97, 98]. Moreover, 16-HETE has been demonstrated to act as a potent and specific inhibitor of PMNs function *in vitro* and has been capable of decreasing elevated intracranial pressure in an experimental model of thromboembolic stroke. Consequently, the anti-neutrophil effect of 16-HETE could be considered as a novel anti-inflammatory approach in the case of COVID-19 patients where neutrophil activation represents a major cause of tissue injury [99, 100].

Another member of subterminal HETEs is 19-HETE; it has been also reported to possess anti-inflammatory effects. It is protected against angiotensin II-induced cellular hypertrophy by reducing the level of pro-inflammatory midchain HETEs. Also, it noncompetitively inhibited the catalytic activity of CYP1B1, decreased the levels of lipoxygenase and cyclooxygenase-2 enzymes, and decreased the levels of IL-6 and IL-8 [18, 101]. Strategies to enhance the levels of subterminal HETEs in the body include using specific CYP modulators such as isoniazid, a well-established inducer of hepatic CYP2E1, that increase the production of endogenous 19-HETE levels as well as using subterminal HETE synthetic analogs [29, 30, 102]. Table 1 shows a number of clinically approved drugs that we suggest could be included in the ongoing search for a treatment or adjuvant treatment of COVID-19 as well as their potential mechanism of action.

The clinical and experimental usage of subterminal HETE metabolites is facing a real challenge of the poor pharmacokinetic profile of these compounds. Therefore, this necessitates the need for the development of pharmacological agents that have enhanced bioavailability and possessing a metabolically stable pharmacokinetic properties. For the purpose of designing robust 19-HETE analogs, Falck et al. have used the carbon backbone of 20-hydroxyeicosa-5(Z),14(Z)-dienoic acid (20-

5,14-HEDE) for the synthesis of 19-HETE synthetic analogs after incorporation of hydroxyl group at C(19) [30]. Likewise, some 16-HETE synthetic analogs have been invented and proved to maintain the biological activity of 16-HETE but with higher stability and longer half-lives. These analogs are protected from the auto-oxidation process and metabolism by lipoxygenase and cyclooxygenase branches of the AA pathway [109].

Taken together, here, we speculate that modulating the levels of specific subterminal HETEs could serve as a potential therapeutic modality to limit the inflammatory lung injury associated with SARS-CoV-2 infection, without having a negative effect on the patient's own defense mechanisms. In addition, we also suggest that inhibition of the pro-inflammatory AA metabolites such as mid-chain HETEs and 20-HETE could be also considered as a possible target in COVID-19 patients. Illustration diagram (Fig. 2) summarizes the suggested imbalance between pro-inflammatory and anti-inflammatory AA metabolites in COVID-19 patients and modulating their levels as a potential therapeutic target.

3.4 Promising role of drug-loaded nanoparticles in the treatment of COVID-19

Scarce information is known about subterminal HETEs pharmacokinetic profile and their specific catabolic pathways. Nevertheless, because of the great similarity between their structures and 20-HETE, it is reasonable that they share identical catabolic pathways with this terminal HETE. For instance, they could be metabolized by β -oxidation, esterification, alcohol dehydrogenase oxidation, cyclooxygenase/lipoxygenase metabolism, and auto-oxidation. Also, one study has shown that a large portion of the urinary excreted HETEs are conjugated to glucuronide and are of hepatic origin [110]. Therefore, this instability represents a challenging limitation against their use as a research tool and hinders their

Table 1 List of clinically approved drugs and other agents that are known as CYP modulators and suggested to be used as potential candidates in the ongoing search for effective treatment or adjuvant therapy for COVID-19

Drug	Mechanism of action	References
Aspirin	Low-dose aspirin (50 mg daily) has been clinically reported to induce the activity of CYP2C19 in both 7-day and 14-day time course.	[16, 142]
Fenofibrate	Antihyperlipidemic drug that has been shown to significantly increase the formation of 14,15-EET, 11,12-EET, and 8,9-EET, and decrease the formation of 20-HETE.	[143]
Fluconazole	Antifungal agent that has been shown to act as a specific inhibitor for the production of the pro-inflammatory metabolites of AA (mid-chain HETEs).	[87, 144]
Isoniazid	Anti-bacterial agent that is a well-known inducer of hepatic CYP2E1, it has been reported to result in a consequent increase in 19-HETE formation rate.	[29]
Resveratrol	Nutritional supplement that has been recently demonstrated to directly inhibit CYP1B1 and decrease its associated mid-chain HETEs.	[87, 145]
2-methoxyestradiol	A biologically active metabolite of estradiol that has been reported to act as a selective CYP1B1 inhibitor and as a strong anti-inflammatory agent.	[146, 147]

Fig. 2 Illustration diagram summarizes the perturbation in arachidonic acid metabolic fate characterizing the imbalance between pro-inflammatory and anti-inflammatory metabolites in COVID-19 patients

and how could modulating their levels serve as a potential therapeutic target. EETs, epoxyeicosatrienoic acids; sEH, soluble epoxide hydrolase

benefits in pharmacotherapy [30, 111, 112]. Consequently, the application of a drug delivery system in this case would have a significant superiority.

Currently, massive attention has been paid to nanomedicine, defined as the medical application of nanotechnology for diagnosis, prophylaxis, and treatment of diseases, as it plays an important role in hastening the development of potential clinically translatable treatments against SARS-CoV-2 [113, 114]. Previously, nanomedicine has already shown its promising effectiveness against multiple viral infections such as influenza virus [115], hepatitis B virus (HBV), hepatitis C virus (HCV)[116], HIV [117], and respiratory syncytial virus [118]. COVID-19 adds a considerable global health burden to the already existing challenge represented by other viral infections; it has an unfavorable influence on both health and socioeconomic status [119]. In some diseases, effective treatment of the infection is curbed by the emergence of drug resistance that will eventually lead to increased public health burden, and elevation of morbidity and mortality rates [120, 121]. Therefore, there is an urgent need for the development of new approaches to treat COVID-19. In this regard, the development of drug-loaded nanoparticles that encompass some molecules which are known to target AA metabolites in COVID-19 patients represents a possible therapeutic approach in the ongoing search for COVID-19 treatment.

The antiviral activity of nanoparticles is attributed to several mechanisms. Nanoparticles possess peerless physicochemical properties that enable them to act as an effective antiviral therapy including a small particle size that enhances drug delivery into anatomically challenging sites [122, 123], a large surface area that allows for accommodation of high amounts of the drug [124], and the capability to modify the surface charge in order to enhance cellular entry through the

negatively charged cellular membrane [125, 126]. In addition, nanoparticles possess intrinsic antiviral activity as it could be produced to have biomimetic features. A well-known example of this property is silver nanoparticles that have been shown to possess antiviral activity against HBV, HIV, and influenza virus [127, 128]. Also, gold nanoparticles have demonstrated substantial virucidal activity against the measles virus presenting them as a possible candidate for the prevention and treatment of enveloped viruses [129]. Moreover, nanoparticles provide a platform for optimization of drug dosing and augmentation of drug delivery through enhanced stability and prolonged drug retention times [130, 131]. They also possess the advantage of being able to be targeted with enhanced specificity towards particular cell types, specific organs, or even cellular organelles on the molecular level [132].

On the other hand, nanoparticles cannot be assigned to the term flawless. The tiny size of nanoparticles may increase their rate of clearance from the body to an extent that could hinder their usage in drug delivery [133]. Also, once the phagocytic machinery in the liver comes in contact with some types of nanoparticles, the particles got recognized, entrapped, and instantly removed from the circulation leading to a significant challenge in their design [134]. Moreover, nanoparticles can possess cellular activities that do not exist with traditional pharmacotherapy. For instance, these particles could have the ability to reach certain cellular compartments such as the nucleus or the mitochondria and cause detrimental effects [135].

It has been suggested that some strategies could be used to target SARS-CoV-2 using nanoparticles. The virus entry to the target cell is initiated with spike (S) protein (entry protein). Entry starts with binding of the surface unit, S1, of the S protein to angiotensin-converting enzyme 2 (ACE2), hence initiating viral attachment to the outer part of target cells

[136–138]. Therefore, nanoparticles have been previously constructed to block S protein and prevent coronaviral entry into cells. For instance, based on docking-mediated virtual screening, a group of peptide inhibitors for heptad repeat 1 (HR1) has been developed. HR1 and HR2 are major domains in the S protein of coronavirus; their inhibition will lead to the suppression of HR1/HR2-mediated membrane binding between MERS-CoV and host cells. One of the tested peptides showed promising results; it is called pregnancy-induced hypertension (PIH) peptide; it demonstrated a significant inhibitory effect possessing IC₅₀ of 1.171 μM . Interestingly, the inhibitory effect of PIH has been further enhanced 10-fold by formulating the gold nanorod complex. Additionally, the nano-formula has shown improved pharmacokinetic profile and biocompatibility on both levels, in vitro and in vivo [139, 140].

Similarly, peptide inhibitors against SARS-CoV-2 have been designed and simulated. The inhibitors' design was extracted from the protease domain of ACE2, which associates with SARS-CoV-2 receptor binding domains. These peptides were conjugated to the surfaces of nanoparticle reservoirs to enhance the metabolic stability and effectiveness of these inhibitors [141]. Another example of nanostructures used against coronaviruses is the carbon quantum dots (CQDs); they are classified into the first generation of antiviral CQDs that are synthesized from ethylenediamine/citric acid as carbon precursors and then conjugated with boronic acid ligands and second-generation CODs that are derived from 4-aminophenylboronic acid. The EC₅₀ of the former was $52 \pm 8 \mu\text{g mL}^{-1}$, while the latter showed higher potency with EC₅₀ of $5.2 \pm 0.7 \mu\text{g mL}^{-1}$ against human coronavirus (229E) infection [142].

Several nanotechnology-based systems have been applied in the field of nanomedicine for the purpose of drug delivery. Examples include polymeric nanoparticles that are synthesized from diverse types of polymers, lipid-solid nanoparticles, liposomes, and surfactant-based nanoparticles such as nanoemulsions [143–146]. The major limitation of the available antiviral therapeutics is the nonspecificity leading to unfavorable cytotoxicity of the host cells [147]. Despite the substantial advances made in the field of nanotechnology-based drug delivery systems, its application for the development of antiviral therapies is still limited.

Unsaturated fatty acids and their related metabolites have been previously formulated using nanotechnology-based strategies for the prevention and treatment of several types of cancers and cardiovascular diseases [103]. Likewise, AA and its associated metabolites could be incorporated into nanotechnology-based drug delivery systems that allow for safer and more efficacious delivery of these lipid molecules to the target cells. Given the urgency and seriousness of the current pandemic as well as the reported antiviral activity of polyunsaturated fatty acids including AA [43], we propose

that nanoencapsulation of AA and its associated metabolites such as 16- and 19-HETE as well as their corresponding synthetic analogs will contribute to the development of novel interventions for the management of COVID-19.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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