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## OPINION

## Oleoylethanolamide, A Bioactive Lipid Amide, as A Promising Treatment Strategy for Coronavirus/COVID-19

Samad Ghaffari,<sup>a</sup> Neda Roshanravan,<sup>a</sup> Helda Tutunchi,<sup>b</sup> Alireza Ostadrahimi,<sup>b</sup> Mahboub Pouraghaei,<sup>c</sup> and Behnam Kafil<sup>b</sup><sup>a</sup>Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran<sup>b</sup>Nutrition Research Center, Department of Clinical Nutrition, School of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran<sup>c</sup>Emergency Medicine Research Team, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

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The current outbreak of COVID-19 (coronavirus) has been identified by World Health Organization (WHO) as a global pandemic. With the emergence of the COVID-19 virus and considering the lack of effective pharmaceutical treatment for it, there is an urgent need to identify safe and effective drugs or potential adjuvant therapy in this regard. Bioactive lipids with an array of known health-promoting properties can be suggested as effective agents in alleviating acute respiratory stress induced by virus. The bioactive lipid amide, oleoylethanolamide (OEA), due to several distinctive homeostatic properties, including anti-inflammatory activities, modulation of immune response, and anti-oxidant effects can be considered as a novel potential pharmacological alternative for the management of COVID-19. © 2020 IMSS. Published by Elsevier Inc.

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**Introduction***SARS-CoV-2: Prevalence, Phylogenetics, Taxonomy and Structural Biology*

The novel coronavirus (COVID-19) has led to the economic disruptions and global health concerns due to its sustained human-to-human transmission and rapid spread (1). As of 1 April 2020, this severe acute respiratory syndrome (SARS-CoV-2) has affected a total of 867,922 confirmed cases with 43,152 deaths in 200 countries and territories (2). The acute respiratory distress syndrome (ARDS), which results in multiple organ failure and sepsis, remains the most common cause of death in these patients. Older adults, subjects with underlying chronic illnesses including cancer, hypertension and diabetes are the most seriously affected groups (3). There is currently no known treatment for SARS-CoV-2 infection, and investigators in many countries around the world have undertaken several clinical trials to solve the problem.

This highly transmittable and pathogenic viral belongs to the subfamily Orthocoronavirinae in the family of Coronaviridae, in the order Nidovirales (4). The subfamily of coronaviruses family includes alpha ( $\alpha$ ), beta ( $\beta$ ), gamma ( $\gamma$ ) and delta ( $\delta$ ) coronavirus (5). Coronaviruses were initially thought to infect only animals, but evidences from the last decade indicate that the disease is capable of infecting humans as well. SARS outbreak caused by SARS-CoV in 2002 in Guangdong, China, and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) prevalence in 2012 in Saudi Arabia, were approval for the possibility of the virus spread in humans and the witness for the lethality of coronaviruses (6,7).

Genetic recombination event at S protein in the receptor binding domain (RBD) region of SARS-CoV-2 is thought to be the most important reason for the higher transmission rate of SARS-CoV-2 regarding to SARS-CoV. The SARS-CoV-2, a large sized virus (approximately 120 nanometers in diameter), is a positive-sense single-stranded RNA (+ssRNA) virus, and contains an outer lipid (fatty) membrane. Its RNA sequence is approximately 30,000 bases in length (8). An analysis of genome sequence data from SARS-CoV-2 revealed that SARS-CoV-2 was approximately 79% similar to SARS-CoV at the nucleotide sequence. Interestingly, new evidence suggests that the

Address reprint requests to: Neda Roshanravan, Cardiovascular Research Center, Tabriz University of Medical Sciences, 5166615573 Tabriz, Iran; Phone/FAX: (0098) (41) 33373919; E-mail: [Neda.roshanravan10@gmail.com](mailto:Neda.roshanravan10@gmail.com)

SARS-CoV-2 RBD is well suited for binding to the human angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed in the membranes of various cells in the body, such as type II alveolar epithelial cells of the lungs. In fact, binding of the SARS-CoV to the ACE2 (9) receptors, disrupts the function of it (10). Intestine, kidney and blood vessels are the other main cells for ACE2 expression, and this fact may explain why some patients with Covid-19 experience gastrointestinal symptoms (11). The virus binds to the host-cell ACE2 receptor via a particular surface glycoprotein called a “spike” (peplomer), and enters the host cell. It is supposed that the entry of the virus to human cells increases the inflammatory activity through various mechanisms with consequent release of pro-inflammatory cytokines, which cause serious damage, specially to the respiratory tract (12). Theoretically, it is assumed that a decrease in the activity of ACE2 in cell membranes may reduce the ability of SARS-CoV-2 to penetrate cells (13).

Along with other endemic human coronaviruses, it seems that the SARS-CoV-2 will become the fifth endemic coronavirus in the human population. Nowadays, discovering therapeutic options from currently available agents appear to be essential for the treatment and prophylaxis of this pandemic. In this manuscript, we aimed to introduce oleylethanolamide (OEA), a bioactive lipid mediator, as a novel potential pharmacological alternative for the management of COVID-19.

### *Oleylethanolamide*

The bioactive lipid amide OEA is synthesized in the gastrointestinal tract, and is related to several distinctive homeostatic properties, including anti-inflammatory activities, immune response, stimulation of lipolysis and fatty acid oxidation (14). OEA, a member of the N-acylethanolamine (NAE) family, is derived from the omega-9 monounsaturated fatty acid, oleic acid. Previous studies have indicated that the down-regulation of OEA levels arises in situation such as exposure to stress, which contributes to the increase in inflammatory markers and the NAE catabolism (15,16). In the current epidemiological studies on inflammatory-related diseases, OEA is considered an endocannabinoid-like lipid, which interacts with the peroxisome proliferator-activated receptor- $\alpha$  (PPAR- $\alpha$ ) and mediates the anti-inflammatory processes (17). It is generally accepted that the endocannabinoid system (ECS) consists of the membrane cannabinoid receptors (cannabinoid receptor type 1 [CB1R] and type 2 [CB2R]), endogenous ligands (endocannabinoids), and enzymes responsible for the synthesis and degradation of ligands (18). The collaboration of the ECS in the management and elimination of infectious agents such as viruses, bacteria, and some protozoa is indicated previously (19). Scientific researchers recently showed that the activation of the ECS relieves pain and reduces inflammation in the lungs. Based on their evidence,

endogenous and exogenous cannabinoids can be considered as therapeutic potential agents for respiratory pathogen clearance (20).

### *Oleylethanolamide and SARS-CoV-2 Infection*

Based on previous studies, angiotensin receptors can be inhibited by several unsaturated fatty acids and their metabolites such as oleic acid. Emerging evidence suggests that these fatty acids can decrease the affinity of angiotensin receptors (21). Recent evidences also indicate that some unsaturated fatty acids can be served as endogenous anti-viral compounds, and their deficiency make humans more susceptible to certain viral infections including SARS-CoV-2, SARS and MERS (22).

In view of the fact that SARS-CoV-2 infection leads to increased release of the pro-inflammatory cytokines, including interleukin-6 (IL-6) and IL-1 $\beta$  in COVID-19 patients via binding to the Toll Like Receptors (TLRs) (12), it is assumed that OEA inhibits this pathway through its anti-inflammatory properties. In fact, OEA binds with high affinity to PPAR- $\alpha$  receptors and initiates a cascade of events, which can eventually attenuate the inflammatory responses.

TLRs, important components of the innate immune system, are distinct classes of pattern-recognition receptors (PRRs), and are localized in the cell surface or in the intracellular compartments such as endolysosome, endoplasmic reticulum, endosome, and lysosomes. They can detect viral danger signals in the extracellular milieu and endosomes by leucine rich repeat-containing trans membrane proteins in their structure (23). The initiation of this downstream signaling, culminates in the activation of transcription nuclear factor kappa B (NF- $\kappa$ B), and leads to the over expression of inflammatory cytokines adhesion molecules and chemokines (24,25).

Peroxisome proliferator-activated receptors (PPARs) are other classes of transcriptional factors involved in modulation of inflammatory pathways. These nuclear receptor proteins consist of three subtypes including PPAR- $\alpha$ , PPAR- $\gamma$ , and PPAR- $\beta/\delta$  (25). PPARs can alleviate the expression of inflammatory mediators via inducing I $\kappa$ B $\alpha$  as the main inhibitor of NF- $\kappa$ B signaling pathway (26). Previously, it has been indicated that the activation of TLRs pathways can attenuate the expression level of PPARs, and intensify the expression level of pro-inflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (27).

Interestingly, OEA may modulate cross-talk between PPAR- $\alpha$  and TLRs and regulates the inflammatory responses in COVID-19. In other words, OEA may have a beneficial synergistic effect against SARS-CoV-2 infection. OEA, a high affinity endogenous ligand of PPAR- $\alpha$  (28), binds to PPAR- $\alpha$  receptors, and increases the expression level of anti-inflammatory cytokine such as IL-10. In addition, it attenuates the inflammatory responses and decreases the expression of TLR4, and interfering with the ERK1/2/AP-1/STAT3 signaling cascade (29–31). In a recent

clinical trial, OEA supplementation could decrease inflammation in obese patients via reducing serum concentrations of inflammatory markers including IL-6 and TNF- $\alpha$  (32). On the whole, the results found in previous studies demonstrate that the activation of PPAR- $\alpha$  by OEA can prevent the expression of genes coding for several inflammatory cytokines. It is well established that OEA can also significantly reduce lipopolysaccharide-induced oxidative/nitrosative stress and prevents endothelial cell damage. By increasing the activity of the anti-oxidative enzymes, these beneficial effects of OEA can be justified (33,34). It has been suggested that excessive inflammation, oxidation and an increased immune response are the main contributors to COVID-19 pathology. OEA through the antioxidant and anti-inflammatory effects may be effective in the attenuation of inflammation and oxidation in coronavirus infected subjects.

### OEA and Safety

The utmost concern about OEA supplementation in COVID-19 patients is its safety. In previous clinical trials, doses of 250 mg/d of OEA oral intake by participants exhibited satisfactory safety when compared to placebo. Also, even when OEA was given to humans at a dose of 250 mg/d for 3 months, no side effects were reported (28,32).

### Conclusion

Based on available evidences, exogenous administration of OEA appears to be a homeostatic signal to counter COVID-19 infection and alleviate patients' inflammatory status. At present, we have decided to conduct a clinical trial on COVID-19 patients in Iran to evaluate this hypothesis. We hope that the results of this trial provide new insight for researchers to tackle the virus.

### Conflict of Interest

No potential conflict of interest disclosed.

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