


## REVIEW

## Lipid-based therapies against SARS-CoV-2 infection

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## Summary

Viruses have evolved to manipulate host lipid metabolism to benefit their replication cycle. Enveloped viruses, including coronaviruses, use host lipids in various stages of the viral life cycle, particularly in the formation of replication compartments and envelopes. Host lipids are utilised by the virus in receptor binding, viral fusion and entry, as well as viral replication. Association of dyslipidaemia with the pathological development of Covid-19 raises the possibility that exploitation of host lipid metabolism might have therapeutic benefit against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In this review, promising host lipid targets are discussed along with potential inhibitors. In addition, specific host lipids are involved in the inflammatory responses due to viral infection, so lipid supplementation represents another potential strategy to counteract the severity of viral infection. Furthermore, switching the lipid metabolism through a ketogenic diet is another potential way of limiting the effects of viral infection. Taken together, restricting the access of host lipids to the virus, either by using lipid inhibitors or supplementation with exogenous lipids, might significantly limit SARS-CoV-2 infection and/or severity.

## KEYWORDS

Covid-19, inflammation, lipids inhibitors, lipids supplementation, SARS-CoV-2

**Abbreviations:** AA, arachidonic acid; ACAT, Acyl-CoA cholesterol acyltransferase; ACC, acetyl CoA carboxylase; ACE2, angiotensin-converting enzyme 2; AM, alveolar macrophage; ATII, alveolar type II; CerS, ceramide synthase; CERT, ceramide transfer protein; cPLA2 $\alpha$ , cytosolic phospholipase A2 $\alpha$  enzyme; DAG, diacylglycerol; DGAT, diacylglycerol acyltransferase; DHA, docosahexaenoic acid; DHET, dihydroxyeicosatrienoic acid; DMV, double membrane vesicle; DPPC, dipalmitoyl-phosphatidylcholine; EET, epoxyeicosatrienoic acid; EPA, eicosapentaenoic acid; FASN, fatty acid synthetase enzyme; FFA, free fatty acid; HDL, high-density lipoprotein; HE, hemagglutinin-esterase; HMGR, 3-hydroxy-3-methyl-glutaryl-Coenzyme A reductase; IL-6, interleukin-6; LA, linoleic acid; LD, lipid droplet; LDL, low-density lipoprotein; LE/L, late endosomes/ lysosomes; LPA, lysophosphatidic acid; LPC, lysophosphatidylcholine; LPCAT, lysophosphatidylcholine acyl transferase; LPE, lysophosphatidylethanolamine; LPLs, lysophospholipids; LPS, lysophosphatidylserine; LTPs, lipid transfer proteins; MBCD, methyl-B-cyclodextrin; MCTs, medium chain triglycerides; MUFA, monounsaturated fatty acid; NF-KB, nuclear factor kappa-light-chain-enhancer of activated B cells; NPC, Niemann-Pick C; OA, oleic acid; OEA, oleoylethanolamide; OSBP, oxysterol binding protein; PA, palmitic acid; PC, phosphatidyl choline; PCSK9, proprotein convertase subtilisin/kexin type 9; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PI3P, phosphatidylinositol-3-phosphate; PI4P, phosphatidylinositol-4-phosphate; Pls, phospholipids; PS, phosphatidylserine; PUFA, polyunsaturated fatty acid; S1P1, sphingosine-1-phosphate receptor 1; SCD1, stearoyl-CoA desaturase 1; SP, surfactant protein; SPT, serine palmitoyl transferase; SREBP, sterol regulatory element-binding protein; TG, triglycerides; TLR, Toll like receptor; TNF- $\alpha$ , tumour necrosis factor alpha; VLDL, very low-density lipoprotein.

Eman Humaid Alketbi and Rania Hamdy contributed equally to this study.

## 1 | INTRODUCTION

Coronaviruses including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are family of enveloped viruses<sup>1</sup> (Figure 1). The virion production involves major changes in the host cellular lipidome.<sup>2,3</sup> Since coronaviruses lack the basic metabolic processes,<sup>4,5</sup> they manipulate the host lipid metabolism in various stages of the life cycle.<sup>6</sup> Viral infections modify the host lipid synthesis, transportation and metabolism for its replication and to get the lipids required for the formation of their envelopes and double membrane vesicles (DMV).<sup>5</sup> The lipids are critically required for virus invasion, attachment, fusion and replication.<sup>7</sup> Lipids play crucial role as source of energy and signalling in SARS-CoV-2 life cycle.<sup>8</sup> Therefore, we aimed to study the importance of host lipids in SARS-CoV-2 infection in order to explore novel therapeutic host lipid targets for the development of effective, broad spectrum and safe antiviral therapies and to avoid the evolved drug resistance by the virus.

## 2 | SARS-CoV-2 INFECTION ALTERED THE HOST LIPID METABOLISM

A significant elevated lipogenesis has been observed as a sign of SARS-CoV-2-infection.<sup>2</sup> Lipidomics changes associated with Covid-19 disease give mechanistic insight about the optimal lipid

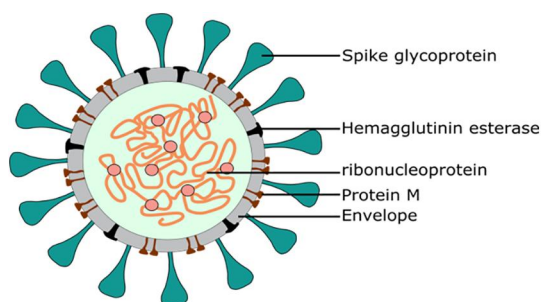


FIGURE 1 Structural features SARS-CoV-2

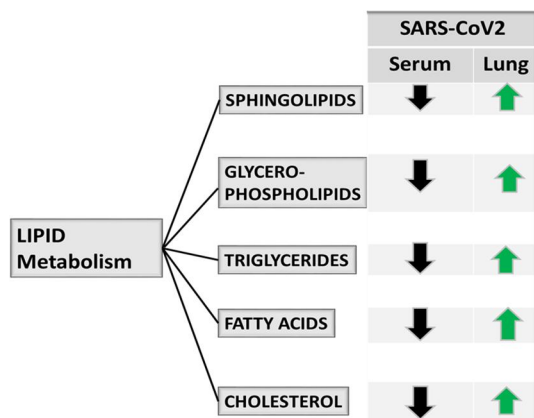


FIGURE 2 SARS-CoV-2 infection altered the host lipid metabolism

microenvironment required during the viral infection. Shen et al.<sup>9</sup> reported a significant alteration in the serum lipid levels of SARS-CoV-2-infected patients when compared to healthy individuals (Figure 2). They reported a significant decrease in over 100 lipids including sphingolipids, glycerophospholipids and fatty acids in the serum of SARS-CoV-2-infected patients.<sup>9</sup> Similarly, Hu et al.<sup>10</sup> showed that total cholesterol (TC), high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol levels were sharply decreased in the serum of infected patient when compared to healthy control. On the other hand, lipidomics analysis of virus-infected alveolar cells showed significant increase in multiple lipid pathways (Figure 2) and lipid modifying enzymes.<sup>11</sup>

## 3 | LIPIDS MIGRATE FROM SERUM TO ALVEOLAR SPACE TO SUPPORT SARS-CoV-2 INFECTION

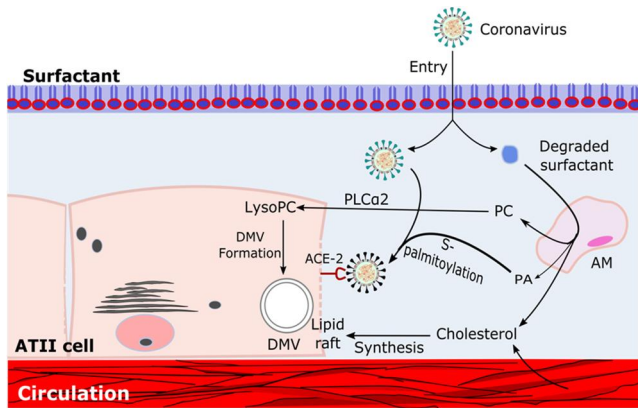
A significant reduction in the serum lipid levels of Covid-19 patients was observed, which is dramatically associated with the severity of the disease symptoms.<sup>12</sup> The progression in SARS-CoV2 infection is associated with the leaking of plasma lipids and cholesterol into the alveolar space.<sup>12</sup> However, the signal leading to the transport of lipids from blood to alveolar space is not yet identified. The occupancy of angiotensin-converting enzyme 2 (ACE2) receptor by the viral glycoprotein may be a major signal, particularly that the increase in lung cholesterol can result in increasing the ACE2 trafficking to the infection site.<sup>13</sup> Although the intra-alveolar microenvironment is separated from the systemic circulation, it is believed that neutral fat, cholesterol (free and esterified forms) and phospholipids (PLs) are transported in the circulation combined with one another and with lipoproteins as macromolecular complexes.<sup>14</sup> Alveolar type II (ATII) cells have long been known to bind and take up lipoproteins, including HDL, LDL and very LDL (VLDL), and to resecret PLs and cholesterol,<sup>15-17</sup> which are mostly used up to support the viral infection at the alveolar cells.

The increase in lipid metabolism following viral infection indicated that the virus hijacks the host cells to utilize the host lipids for their own propagation. The aforementioned data indicated the importance of host lipids and their relocation to the site of viral infection. Further, viral binding may signal the transportation of lipids from the circulation to the alveolar space. Here, we are proposing that viral binding, entry and replication disrupt the lipids balance at the alveolar space, site of infection, leading to transportation of lipids from the circulation to the alveolar space. In order to explain this mechanism, the importance of host lipids to the virus is highlighted.

## 4 | HOST LIPIDS MANIPULATION DURING VIRUS INVASION

### 4.1 | At the surfactant

Surfactant is the major component within the lung defence system that has unique properties displaying both lung stabilizing and



**FIGURE 3** Role of host lipids in viral entry and invasion. ACE-2; Angiotensin-converting enzyme 2, AM; Alveolar macrophage, ATII; Alveolar type II cells, DMV; Double membrane vesicle, PLC $\alpha$ 2; Cellular phospholipase, PA; Palmitic acid, PC; Phosphatidyl choline

antimicrobial properties.<sup>18</sup> Surfactant is synthesised within the ATII epithelial cells.<sup>19</sup> Surfactant is actively being secreted and its materials are constantly being exchanged and recycled into the ATII cells to maintain constant surfactant pool size,<sup>20,21</sup> while some materials can be degraded by alveolar macrophages (AM) to lipids that can support the viral infection (Figure 3). These lipids include palmitic acid (PA), phosphatidyl choline (PC) and cholesterol.

Pulmonary surfactant is a complex mixture of lipids and proteins that forms a film lines the alveolar air-surface interface and protect the lungs from pathogen invasion.<sup>21</sup> Disruption of surfactant lipids can disturb the surface tension lowering ability and allow the pathogens entry.<sup>22</sup> However, the process by which the virus penetrates the surfactant and reaches the ATII cells is not known. Several studies demonstrate that human viruses including SARS-CoV-2 can significantly alter surfactant phospholipids composition and causing loss of surfactant and hence promote the viral penetration.<sup>23</sup> On the other hand, binding of surfactant proteins (SP), which importantly contribute to the surfactant behaviour as a defence system,<sup>24,25</sup> to the virus occurs by recognition of hemagglutinin and neuraminidase glycans on the surface of the virus, thereby hindering the ability of the virus to enter the cell.<sup>26</sup> However, the hemagglutinins found on SARS-CoV-2 exhibit antigenic variations that resulted in reduced binding, leading to greater virulence and subsequent high mortality and morbidity in patients.<sup>26</sup> SARS-CoV-2 hemagglutinin-esterase (HE) provides classical glycan-binding lectin activity, while exhibiting hemagglutination and destruction of the surfactant proteins<sup>27</sup> (Figure 1).

## 4.2 | At the alveolar cell

### 4.2.1 | Host lipids potentiate the viral attachment and entry to ATII cells

Viral attachment to the host cell receptor is lipid-dependent.<sup>28</sup> The entry of SARS-CoV-2 is mediated by the binding of viral spike (S)

protein to ACE2 receptor, which is localised in cholesterol-rich microdomains within the lipid rafts<sup>29</sup> (Figure 3). Lipid rafts are regions of the plasma membrane characterised by high concentrations of sphingolipids (sphingomyelin and sphingoglycolipids) and cholesterol.<sup>30</sup> Therefore, cholesterol increases the expression of ACE2 receptor and hence facilitates the interaction between the S protein and ACE2 receptor.<sup>28</sup> S-palmitoylation is a unique protein lipidation process essential for viral invasion.<sup>31</sup> S-palmitoylation of SARS-CoV-2 S protein has been reported to facilitate its anchor and fusion with the host cellular membrane receptor (Figure 3). Furthermore, it has been reported that the HDL scavenger receptor B type 1 (SR-B1) facilitates ACE2-dependent uptake of SARS-CoV-2 by augmenting the virus attachment to ATII cells.<sup>32</sup> Viral internalisation process occurs by the fusion of the envelope lipid with the plasma membrane, which is mediated by endocytosis. Inhibition of viral endocytosis by cholesterol depletion indicates the importance of raft-mediated endocytosis for the viral entry.<sup>33</sup>

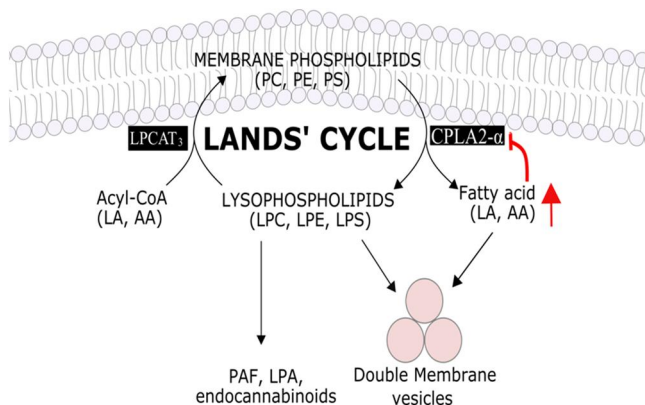
### 4.2.2 | Virus hijacks the host lipids for viral replication and envelope formation

#### *Lipids manipulation for the formation of DMVs and envelopes*

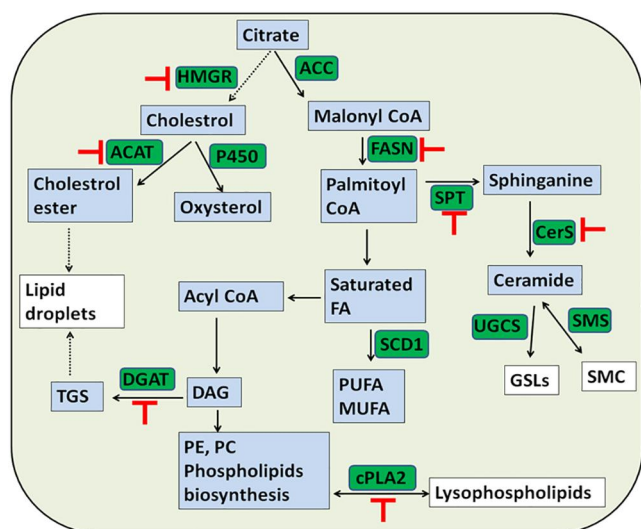
Coronaviruses hijack the host cells for the formation of replication and transcription complex, the double membrane vesicles (DMVs).<sup>34,35</sup> Formation of DMVs is a key factor for viral replication that provides a favourable barrier to protect the viral replication compartments from the host innate immune responses.<sup>36</sup> DMVs formation requires specific lipid compositions, the unsaturated lysophospholipids (Figure 3).<sup>37</sup> Coronaviruses manipulate the host cellular pathways particularly the lipid metabolism and lipid trafficking to ensure the availability of required lipids for DMVs formation (Figure 3).<sup>38</sup>

DMVs biogenesis is a complex process that critically requires modification of lipid composition either via lipid transfer proteins sterol regulatory element-binding proteins (SREBP) or lipid biosynthesis via cellular cytosolic phospholipase A2 $\alpha$  enzyme (cPLA2 $\alpha$ ).<sup>39</sup> SREBPs play essential role in the formation of DMVs, viral protein palmitoylation and viral replication.<sup>40</sup> cPLA2 $\alpha$  is a crucial lipid processing enzyme that plays a critical role in the formation of DMVs (Figure 3).<sup>41</sup> Inhibition of SREBPs and cPLA2 $\alpha$  can be employed as potential strategy to eradicate coronavirus. Furthermore, viruses stimulate the synthesis of lipid components including in particular lysophospholipids (LPLs) to support the rapid DMVs biogenesis. Therefore, inhibition of LPL synthesis resulted in loss of DMVs and dramatic reduction in viral replication (Figures 3 and 4).<sup>42</sup>

Viruses access the energy required for their replication and assembly via lipid droplets. Lipid droplet serve as storage of neutral lipid including triglycerides and cholesterol esters, which can be employed for energy production, signalling and cell immune response.<sup>43</sup> Monocytes from SARS-CoV-2-infected patients showed accumulated level of triglycerides and cholesterol ester with increased level of diacylglycerol acyltransferase (DGAT) enzyme required for TGs synthesis.<sup>44</sup> This indicates the utilisation of lipid



**FIGURE 4** Land's cycle showing the importance of cPLA2- $\alpha$ , LA and AA in the formation of lysophospholipids, critically important in virus DMV and envelope formation. Red arrows indicated the negative feedback mechanism following exogenous supplementation of AA



**FIGURE 5** Intracellular host lipids metabolism. Important lipids to the virus are indicated in white color, critical biosynthetic enzymes are indicated in green color, and their potential inhibition is indicated in red color

stores from the lipid droplets during viral infection. Utilisation of lipid stores serve to provide energy and substrates for the virus replication and to dampen the host antiviral responses.<sup>45</sup>

Viral envelopes are made of lipid bilayer, which can supply the required protection from environmental stresses including the effect of host defensive systems. SARS-CoV-2 lipid bilayer is rich in fatty acids such as linoleic acid (LA), arachidonic acid (AA), PA and oleic acid (OA), while LA and AA play protective role during the virus entry.<sup>46</sup> Furthermore, several studies confirmed that enveloped viruses including coronaviruses are developed or bud from the lipid rafts.<sup>30,47</sup>

#### *Virus enhances the intracellular transportation of host lipids*

A quick process for the intracellular lipids transportation is required to support the process of viral replication, which is achieved by

nonvesicular lipid transfer proteins (LTPs). Viruses hijack the LTPs to mobilize the lipids required for the formation of replication organelles. Cholesterol is transported by oxysterol binding protein (OSBP),<sup>48</sup> while ceramide transportation occurs by ceramide transfer protein (CERT).<sup>49</sup> Both are significantly required in viral replication. Furthermore, Niemann-pick C (NPC) is required to carry and transfer the free and recycled cholesterol to the site of replication.

#### *Virus manipulates the intracellular host lipid biosynthesis*

Biosynthesis of fatty acids is initiated by the carboxylation of citrate with acetyl CoA carboxylase to malonyl-CoA, which is then converted to PA by FASN (Figure 5). PA is then elongated and converted to diacylglycerols and then TAGs by DGAT1. PA serves as precursor for the biosynthesis of phospholipids and sphingolipids.<sup>45</sup> Furthermore, PA plays important role in the palmitoylation of viral protein (Figure 3). Cholesterol biosynthesis is catalysed by HMGR from acetyl CoA.<sup>50</sup> Cholesterol is then esterified by acyl-CoA cholesterol acyltransferase and employed in lipid droplets formation. Viral infection induced the lipids hydrolysis to yield necessary lipid metabolites such as lysophospholipid and FFAs that are required for viral infection (Figure 3–5).

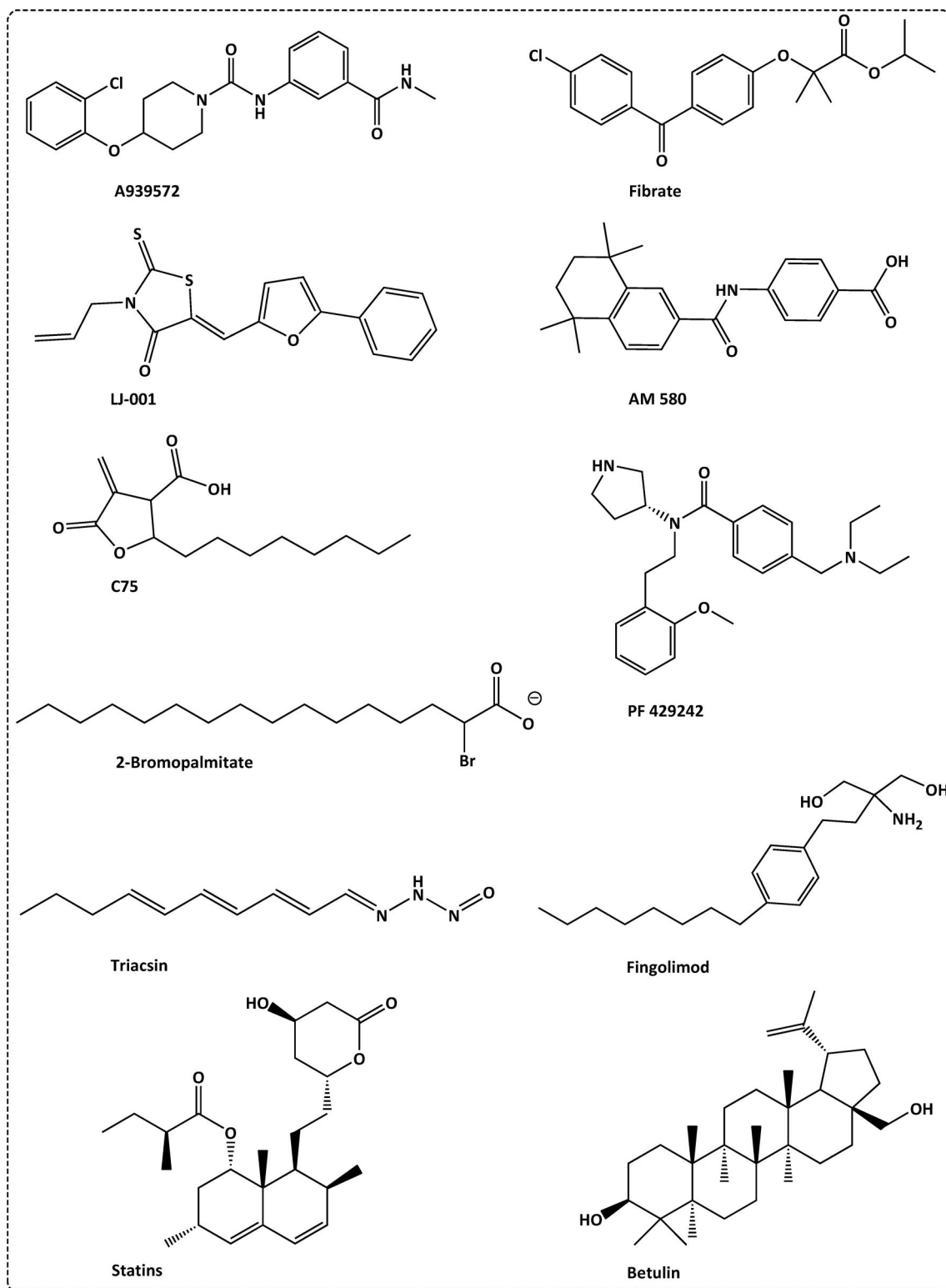
## 5 | HOST LIPIDS AS THERAPEUTIC TARGETS FOR THE DEVELOPMENT OF ANTIVIRAL DRUGS

The significant changes of host lipidomics due to viral infection and the importance of host lipids to the viral pathogenicity indicated that targeting the host lipids can offer excellent potential to counteract the SARS-CoV-2 infection. The aforementioned data indicated that host lipid biosynthesis, metabolism, transfer and lipid modifying enzymes can serve as excellent targets for the development of anti-SARS-CoV-2 drugs. Host-targeting strategies can avoid the impact of antiviral drug resistance when compared to viral-targeting strategies. Careful selection of a target with less side effects on the host, while providing broad-spectrum antiviral activity can serve as excellent opportunity to overcome this pandemic life-threatening disease. Here, we have identified most promising host lipid targets and their potential inhibitors (Figures 6 and 7 and Tables 1 and 2).

### 5.1 | Targeting the host lipids, employed during viral invasion

#### 5.1.1 | Targeting the host lipid raft and viral fusion

Cholesterol-lowering agents can inhibit the optimum lipid microenvironment required for viral infection (Figure 6 and Table 1). Methyl- $\beta$ -cyclodextrin interacts with the lipid raft via its lipophilic core, and hence competes with the viral binding site<sup>51</sup> (Figure 7 and Table 1). On the other hand, statins inhibit HMGR enzyme, the rate-limiting



**FIGURE 6** Identified inhibitors that can be employed to target the host lipids, utilized in the invasion and pathogenesis of SARS-CoV-2

enzyme in cholesterol biosynthesis and hence reduce the available cholesterol.<sup>28,52</sup> Consequently, it lowers the expression of membrane ACE2 receptors and blocks the viral entry.<sup>53</sup>

Plant phytosterols such as betulinic acid are lipophilic compounds with cholesterol-like structures, which can interact with the

lipid rafts, decrease the membrane cholesterol and hence can inhibit the viral attachment to the host cell<sup>51,54</sup> (Table 2). Interestingly, phytosterols are synthesised naturally with high levels in oilseed plants such as rapeseed, corn and wheat, and nuts such as pine nuts and pistachios.<sup>55</sup>

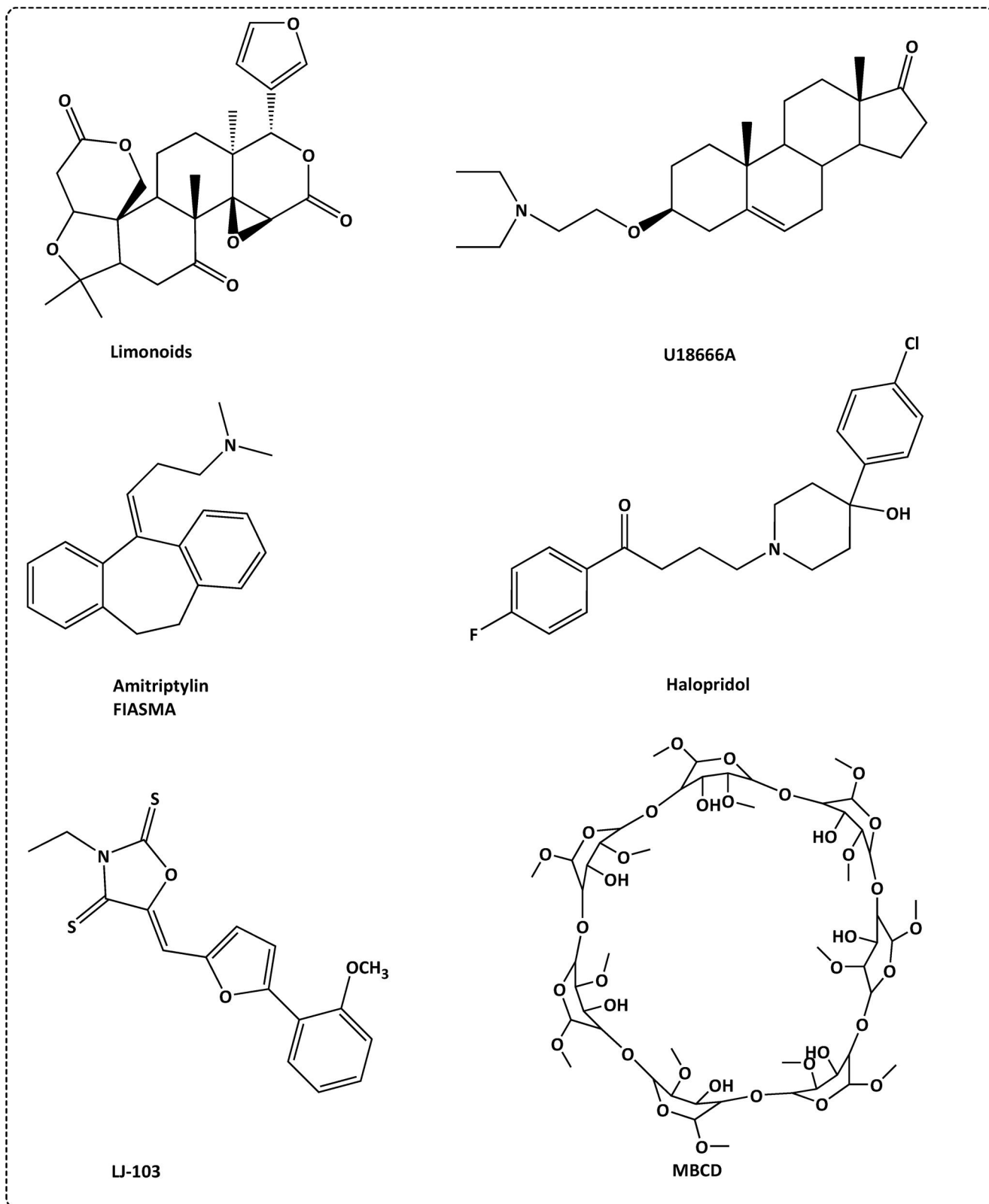


FIGURE 7 Lipids inhibitors that interfere with SARS-CoV-2 entry

TABLE 1 Host lipids as targets to inhibit SARS-CoV-2 infection

| Host lipid                                 | Effect of viral infection   | Role in viral pathogenesis   | Strategy of lipid target therapy  | Inhibitor  | FDA-approved drugs  |
|--|---|--|---|--|---|
| Lipid raft (cholesterol and sphingolipids) | <ul style="list-style-type: none"> <li>Increased to mediate the viral</li> <li>Entry</li> <li>Endocytosis</li> <li>Inflammation and immune response</li> <li>Cell transmission</li> </ul> | <ul style="list-style-type: none"> <li>Expression of lipid raft mediates the presence of ACE2 and TMPRSS2 in high levels</li> <li>Required for SARS-CoV-2 main protease activity<sup>76</sup></li> </ul> | <ul style="list-style-type: none"> <li>Disrupt the lipid raft stability by depleting cholesterol</li> <li>Inhibition of HMGR</li> </ul> | <ul style="list-style-type: none"> <li>MBCD</li> <li>Statin</li> <li>Fibrates</li> </ul>   | <ul style="list-style-type: none"> <li>Yes</li> <li>Yes</li> <li>Yes</li> </ul>                     |
| Sphingomyelin                              | <ul style="list-style-type: none"> <li>Decreased during viral infection</li> <li>It has a protective action</li> </ul>  | <ul style="list-style-type: none"> <li>Acid sphingomyelinase break down sphingomyelin to ceramide, which is required for viral entry</li> </ul>  | <ul style="list-style-type: none"> <li>Inhibit acid sphingomyelinase</li> </ul>   | <ul style="list-style-type: none"> <li>FIASMA</li> </ul>                                   | <ul style="list-style-type: none"> <li>Various drugs act as FIASMA such as Amitriptyline</li> </ul> |
| Cholesterol regulator                      | <ul style="list-style-type: none"> <li>Cholesterol hemostasis regulator</li> </ul>  | <ul style="list-style-type: none"> <li>PCSK9 as lipoprotein haemostasis</li> </ul>   | <ul style="list-style-type: none"> <li>Inhibition of PCSK9</li> </ul>   | <ul style="list-style-type: none"> <li>Annexin 2</li> </ul>                                | <ul style="list-style-type: none"> <li>Transduction regulatory protein</li> </ul>                   |
| Palmitic acid (S-palmitoylation)           | <ul style="list-style-type: none"> <li>Palmitoylation of S protein, which is required for viral entry.</li> </ul>   | <ul style="list-style-type: none"> <li>ZDHH5 allows protein palmitoylation and membrane interaction</li> </ul>   | <ul style="list-style-type: none"> <li>Inhibition of ZDHH5</li> </ul>   | <ul style="list-style-type: none"> <li>2-Bromopalmitate</li> </ul>                         | <ul style="list-style-type: none"> <li>No</li> </ul>  |
| LPLs                                       | <ul style="list-style-type: none"> <li>Increased during the viral infection.</li> <li>Play critical role in DMVs formation and viral replication.</li> </ul>                              | <ul style="list-style-type: none"> <li>Activation of cPLA2<math>\alpha</math> release LPLs from PL, which is critical for viral envelope formation</li> </ul>  | <ul style="list-style-type: none"> <li>Inhibition of cPLA2<math>\alpha</math></li> </ul>  | <ul style="list-style-type: none"> <li>Pyrrolidine-2</li> </ul>                            | <ul style="list-style-type: none"> <li>Synthetic compound not licensed yet</li> </ul>               |
| PI3P                                       | <ul style="list-style-type: none"> <li>PI3P is a lipid signalling mediator that activates membrane remodelling.</li> <li>PVS34 converts PI to PI3P.</li> </ul>                            | <ul style="list-style-type: none"> <li>Employed as platform of autophagosome and phagocytosis required in viral replication<sup>77</sup></li> </ul>  | <ul style="list-style-type: none"> <li>Inhibition of PVS34 can block viral infection</li> </ul>   | <ul style="list-style-type: none"> <li>SAR405 inhibits PI3P<sup>78</sup></li> </ul>        | <ul style="list-style-type: none"> <li>Not licensed yet</li> </ul>                                  |
| Fatty acid                                 | <ul style="list-style-type: none"> <li>Its synthesis is increased during viral infection.</li> </ul>  | <ul style="list-style-type: none"> <li>It is the main component of membrane</li> </ul>   | <ul style="list-style-type: none"> <li>Inhibition of fatty acid synthesis via inhibition of FANS</li> </ul>                             | <ul style="list-style-type: none"> <li>Cerulenin</li> <li>C75</li> <li>Fibrates</li> </ul> | <ul style="list-style-type: none"> <li>Yes</li> <li>Yes</li> <li>Yes</li> </ul>                     |
| TGs  | <ul style="list-style-type: none"> <li>Component in the lipid droplet.</li> </ul>   | <ul style="list-style-type: none"> <li>As source of energy</li> </ul>  | <ul style="list-style-type: none"> <li>Inhibition of DGAT</li> </ul>  | <ul style="list-style-type: none"> <li>A922500</li> </ul>                                  | <ul style="list-style-type: none"> <li>Clinical study</li> </ul>                                    |
| Unsaturated fatty acid                     | <ul style="list-style-type: none"> <li>Important role in viral attachment with ACE2.</li> </ul>   | <ul style="list-style-type: none"> <li>SCD1 enzyme required for the synthesis of unsaturated fatty acid</li> </ul>   | <ul style="list-style-type: none"> <li>Inhibit SCD1</li> </ul>  | <ul style="list-style-type: none"> <li>A939572</li> </ul>                                  | <ul style="list-style-type: none"> <li>Clinical study</li> </ul>                                    |
| Lipid droplet                              | <ul style="list-style-type: none"> <li>Contain cholesterol ester and TGs.</li> </ul>  | <ul style="list-style-type: none"> <li>LD required for anabolism as energy source</li> </ul>   | <ul style="list-style-type: none"> <li>Inhibit LD</li> </ul>  | <ul style="list-style-type: none"> <li>Triacin c</li> </ul>                                | <ul style="list-style-type: none"> <li>Yes</li> </ul>   |
| Sterol                                     | <ul style="list-style-type: none"> <li>Regulate sterol biosynthesis</li> </ul>  | <ul style="list-style-type: none"> <li>Transcriptional factor SERBP regulate cholesterol synthesis and uptake of fatty acid</li> </ul>   | <ul style="list-style-type: none"> <li>Inhibition of SERBP</li> </ul>   | <ul style="list-style-type: none"> <li>AM580</li> </ul>                                    | <ul style="list-style-type: none"> <li>Yes</li> </ul>   |
| Sphingolipid                               | <ul style="list-style-type: none"> <li>Protective role</li> </ul>   | <ul style="list-style-type: none"> <li>Important role in signalling pathway</li> </ul>   | <ul style="list-style-type: none"> <li>Sphingo-mimetics</li> </ul>  | <ul style="list-style-type: none"> <li>Fingolimod</li> </ul>                               | <ul style="list-style-type: none"> <li>Yes</li> </ul>   |
| Lipid transfer                             | <ul style="list-style-type: none"> <li>OSBP</li> <li>CERT</li> </ul>  | <ul style="list-style-type: none"> <li>Inhibit lipid transfer will block the microenvironment required for viral infection</li> </ul>  | <ul style="list-style-type: none"> <li>Inhibition of the hijack of lipid transfer by virus</li> </ul>                                   | <ul style="list-style-type: none"> <li>HPA-12</li> <li>TTP-8307</li> </ul>                 | <ul style="list-style-type: none"> <li>No</li> <li>No</li> </ul>                                    |

### 5.1.2 | Lipid hinders the viral entry

Elovanoids are polyunsaturated fatty acids (PUFA) with prohomeostatic lipid mediator activity (Figure 6 and Table 2). Elovanoids

downregulate the expression of ACE2 and enhance the expression of a set of protective proteins including acid sphingomyelinase that hinder the viral binding to ACE2 receptor.<sup>56</sup> Viral entry is associated with the activation of acid sphingomyelinase and creation of ceramide-rich

TABLE 2 Supplementation of bioactive lipids to inhibit SARS-CoV-2 infection

| Lipid  | Role in Covid-19   | Mechanism  | Example  |
|--|--|--|--|
| Phytosterol  | <ul style="list-style-type: none"> <li>Interfere with lipid raft and regulate lipid synthesis</li> </ul> | <ul style="list-style-type: none"> <li>Inhibit viral attachment</li> <li>Inhibit SERBP</li> </ul>  | <ul style="list-style-type: none"> <li>Betulinic acid</li> </ul>                       |
| Elovanoids   | <ul style="list-style-type: none"> <li>Inhibit viral entry</li> </ul>                                    | <ul style="list-style-type: none"> <li>Lipid mediator</li> </ul>   | <ul style="list-style-type: none"> <li>Exogenous supply</li> </ul>                     |
| Bioactive lipids (PUFAs) including LA, AA, DHA and EPA | <ul style="list-style-type: none"> <li>Protective lipids that can inhibit viral infection</li> </ul>     | <ul style="list-style-type: none"> <li>Inhibit viral infection and modulate the inflammation response</li> <li>Bioactive lipid deficiency will decrease ACE2 expression<sup>83</sup></li> <li>LA leakage of viral envelope can cause destabilisation of its bilayer</li> </ul> | <ul style="list-style-type: none"> <li>Exogenous supply of balanced Omega-6</li> </ul> |

patches on the plasma membrane. Therefore, inhibition of acid sphingomyelinase can block SARS-CoV-2 infection.<sup>57</sup>

### 5.1.3 | Targeting the S-palmitoylation process

Since ZDHHC5 S-palmitoyltransferase is important for viral S protein attachment. It can be a potential therapeutic target for the inhibition of SARS-CoV-2 infection.<sup>31</sup> 2-Bromopalmitate was confirmed as a candidate compound to inhibit S-palmitoylation<sup>58</sup> (Figure 6 and Table 1).

### 5.1.4 | Targeting viral endocytosis

Endocytosis is a pH-dependent process, which is facilitated by cysteine proteases, such as cathepsin B or L, allowing the release of viral nucleocapsid into the cytoplasm. Chloroquine neutralizes the endosome-lysosomal acidic pH and thus blocks the protease activity and viral internalisation.<sup>50</sup> On the other hand, PVS34 perturbs the structure of viral membrane (Figure 6 and Table 1). PVS34 inhibits the phosphoinositide (PI) 3-kinase centres, which functions in autophagy, and endocytosis. VPS34 inhibits the required membranes components needed for the formation of SARS-CoV-2 particles.<sup>59</sup>

### 5.1.5 | Targeting the lipid droplets

Triacsin C blocks the lipid droplet formation through the inhibition of triglycerides-modulating enzymes particularly the long chain fatty acyl CoA synthetase.<sup>60</sup> A922500 is a potent DGAT inhibitor that can inhibit the lipid droplet formation and hence can stop the production of infectious progeny from SARS-CoV-2-infected cells<sup>60</sup> (Figure 6 and Table 1).

### 5.1.6 | Targeting the viral DMVs formation

AM580, a stable retinobenzoic acid derivative, exhibits potent antiviral activity by blocking the activation of SREBP pathway and hence

inhibits DMVs formation<sup>4</sup> (Figure 6 and Table 1). Betulin inhibits SREBP cleavage and maturation.<sup>61</sup> cPLA2 $\alpha$  inhibitor such as pyrrolidine-2 significantly decreases the formation of DMVs<sup>41</sup> (Figure 6 and Table 1). Phosphatidylinositol-4-phosphate is a potent membrane modifiers that can interfere with the formation of DMVs.<sup>42</sup>

### 5.1.7 | Targeting the intracellular lipid transportation

OSBP inhibitors such as TTP-8307, OSW-1 and itraconazole are potent antiviral drugs.<sup>48</sup> HPA-12 and limonoids are CERT<sup>62</sup> and sphingomyelin synthesis inhibitors,<sup>63</sup> respectively (Figure 7 and Table 1). Inhibition or loss of NPC can block cholesterol transport and hence impairs the infectivity of SARS-CoV-2. U18666A is NPC inhibitor that blocks the movement of cholesterol out of lysosomes and hence impairs the viral pathogenicity.<sup>29</sup> Haloperidol is an anti-SARS-CoV-2 candidate, since it hinders the viral entry and replication by inhibiting cholesterol trafficking from the late endosomes/lysosomes (LE/L)<sup>29</sup> (Figure 7 and Table 1).

## 5.2 | Targeting the host lipid biosynthetic pathways

Lipidomics profile of coronavirus-infected patients showed significant increase in fatty acid synthesis with the upregulation of AA, LA (the metabolic precursor of AA), PA and OA metabolism, in addition to significant elevated levels of lysophospholipids (LPC, LPE). Both, LA and AA play important role in the regulation of cPLA2 $\alpha$ , and hence the level of lysophospholipids that are required in viral envelope and DMV formation (Figure 4). Therefore, exogenous supplementation of LA and AA can suppress viral infection via negative feedback inhibition mechanism of cPLA2 $\alpha$ , thus reducing the production of lysophospholipids (Figure 4).<sup>64</sup> Coronavirus infection is associated with the selective upregulation of key lipid-modifying enzyme, cPLA2 $\alpha$  and the high production of glycerophospholipids, LPL, fatty acids<sup>41,64</sup> and the long-chain PUFA.<sup>65</sup> Lysophospholipids is required by SARS-CoV for the optimal formation of replicative organelles (Figure 4).<sup>66</sup> LPL is a crucial component required in the formation of DMVs.<sup>41</sup> cPLA2 inhibition can significantly suppress the formation of virus progeny.<sup>41</sup> Plant-based natural supplements could be a good



source of LA, which accounts for more than 50% of the lipid content in plant seed oil such as nuts.<sup>67</sup>

SARS-CoV-2-infection is associated with an increase in the levels of lipid-modifying enzymes including the fatty acid synthetase enzyme (FASN),<sup>45</sup> and HMGR, the rate-limiting enzyme in cholesterol synthesis and the activation of transcriptional factor SERBP, which regulates the synthesis of cholesterol.<sup>68</sup> SARS-CoV-2 infection also caused an increase in the production of inositol (PI), ceramide sphingolipid, phosphatidyl choline, lysophosphatidyl inositol and lysophatidylcholine.<sup>69,70</sup> Collectively, disruption of the aforementioned lipid microenvironments can significantly inhibit SARS-CoV-2 infection.

Lipid-lowering agents such as statins can inhibit HMGR, and hence inhibit cholesterol biosynthesis, leading to disturbance in lipid raft formation, inhibition of viral replication and immunomodulation activity.<sup>71</sup> Fibrates are triglyceride-lowering agents that target the fatty acid synthesis and showed potent antiviral activity (Figure 6 and Table 1). Annexin A2 is a natural inhibitor of PCSK9, a cholesterol homeostasis regulator, which was recommended with statin in the treatment of Covid-19 patients.<sup>72</sup>

Viral nsp3 activates fatty acid synthesis.<sup>73</sup> Therefore, the use of FASN inhibitors such as the natural product cerulenin and the synthetic inhibitor C75 can be employed as potential anti-SARS-CoV-2 drugs (Figure 6 and Table 1).<sup>74</sup> Stearoyl-CoA desaturase1 (SCD1) is the rate-limiting step in MUFA and PUFA biosynthesis. The piperazine derivative A939572 is SCD1 inhibitor, suggesting its potential antiviral activity (Figure 6 and Table 1).<sup>75</sup> Fingolimod (Figure 6) is a sphingomimetics drug employed in clinical trial for the treatment of Covid-19 due to its selective inhibition activity of S1P1 (sphingosine-1-phosphate-1) and its immunosuppressive activity in the late severe infection via the inhibition of TLR-mediated immune response (Table 1).<sup>50</sup>

### 5.3 | Targeting the viral lipid to inhibit SARS-CoV-2 fusion and invasion

LJ001 is a membrane-binding compound that is selectively targets the viral unsaturated phospholipids and inhibits viral entry.<sup>50</sup> Unfortunately, LJ001 shows poor physiological stability, and hence used as lead compound for the development of more effective and stable antiviral drugs such as LJ103 (Figure 7).

## 6 | LIPIDS SUPPLEMENTATION AS INHIBITORY MECHANISM TO SARS-CoV-2

PUFAs including docosahexaenoic acids (AA, DHA, omega-3 fatty acid), and eicosapentaenoic acid were consistently upregulated in cells infected with the virus.<sup>79</sup> It has been shown that PUFAs can inactivate SARS-CoV-2 by blocking the viral proliferation and by inducing the leakage and lysis of viral envelope.<sup>80</sup> Therefore, PUFAs supplementation can help in reducing the susceptibility of SARS-CoV-2 infection. Eicosanoids are

proinflammatory mediators and signalling molecules that elevated in SARS-CoV-2 infected cells (Table 2).<sup>81</sup> Further, AA is an endogenous antiviral compound released by the immune cells in response to viral infection in order to inactivate SARS-CoV2.<sup>82</sup> Therefore, its exogenous supplementation can provide an inhibition activity to SARS-CoV-2 (Table 2).

It has been shown that LA can tightly bind with the three composite pockets present on S protein, forming a complex that interrupts the binding with ACE2 receptor.<sup>84</sup> Therefore, LA intake, alone or more likely when synergised with remdesivir, can lead to efficient suppression of SARS-CoV-2 replication.<sup>84</sup> LA is an essential "omega-6" fatty acid that must be obtained from the diet, since it cannot be synthesised in the human body (Table 2). Therefore, the proper intake of these PUFAs can result in significant reduction in the viral loads and hence can decrease the morbidity and mortality associated with SARS-CoV-2 infection.<sup>82</sup>

Glycerophospholipids are essential structural and functional components of the cellular membrane. Cellular phospholipase, cPLA2 $\alpha$ , releases lysophospholipids and free fatty acids from glycerophospholipids-based membranes.<sup>41</sup> The released small bioactive lipid molecules (LA and AA) are required together with the produced lysophospholipids to form the specialised DMVs, required in viral replication (Figure 4).<sup>41</sup> It has been reported that inhibition of cPLA2 $\alpha$  resulted in a significant reduction in lysophospholipids, DMV formation and viral replication in infected cells.<sup>41</sup>

Yan et al.<sup>64</sup> reported that lysophospholipids and FAs downstream of cPLA2 activation are upregulated following the HCoV-229E infection. Therefore, the upregulation of these lipid species including LA and AA were believed to promote the efficient coronavirus replication.<sup>64</sup> However, they have noticed a significant reduction in virus replication when they exogenously supplemented to HCoV-229E- or MERS-CoV-infected cells<sup>64</sup> (Figure 4). This indicated that exogenous supplementation of these FAs can disrupt the equilibrium between membrane phospholipids and lysophospholipids and hence interfere with the optimal replication of the virus. In addition, supplementation of LA and AA can disturb the LA-AA metabolism and can result in feedback reversion of lysophospholipids to phospholipids through Lands' cycle (Figure 4).<sup>85</sup>

### 6.1 | Plant sources of essential fatty acids (LA and AA)

LA (C18:3) and AA (C20:4) are among the essential fatty acids that must be provided in human's diets.<sup>86</sup> Plants have been recommended as source of these essential fatty acids. Higher concentration of AA was reported in *Sonchus oleraceus* (Sow-thistle), *Chenopodium album* (goosefoot) and *Parietaria diffusa* (pellitory-of-the-wall).<sup>87</sup> They all are edible wild plants that have been proposed for human consumption in the Mediterranean region.<sup>87,88</sup> On the other hand, plants rich in LA can include *Nigella sativa*,<sup>89</sup> *Artemisia* species<sup>90</sup> and *Brassica napus* (Rapeseed). However, the fatty acids contents in plants can be

TABLE 3 Role of lipids in inflammation due to SARS-CoV-2 infection and their anti-inflammatory activity

| Lipid                          | Function  | Treatment strategy   |
|--------------------------------|---|--|
| Epoxyeicosatrienoic acid (EET) | Shifts the AA metabolism towards the formation of protective pro-resolving lipid mediators.   | Inhibition of sEH will increase the EET level and subsequently decreases the IL-6 level and NF-Kb activation |
| Oleylethanolamide (OEA)        | <ul style="list-style-type: none"> <li>Decreases the TLR expression</li> <li>Its downregulation can increase the stress and inflammation response.</li> </ul> | Exogenous administration of OEA  |

affected by environmental conditions including drought,<sup>91</sup> temperature<sup>92</sup> and salinity.<sup>92</sup> Therefore, it is important to assess the precise amounts of fatty acids from different regions in order to administer the right dose at the right condition.

## 6.2 | Switching the host metabolism by lipids supplementation

Switching the host metabolism from carbohydrate-dependent glycolytic state to fat-dependent ketogenic state can significantly affect the viral replication.<sup>93</sup> Supplementation of medium-chain triglycerides such as lauric acid can result in significant reduction in viral envelope formation. Therefore, it can be employed as prophylactic strategy for normal people and adjunct therapy in case of infected individuals.<sup>93</sup>

## 6.3 | Surfactant-based therapeutics supplementation

SARS-CoV-2 infection is associated with depleted surfactant. Therefore, it has been suggested that supplementation with synthetic surfactant, KL4 (a mix of DPPC, palmitoyl-oleoyl phosphatidylglycerol, PA and 21-amino acid synthetic peptide) can play a protective role in Covid-19 pandemic.<sup>94</sup>

## 7 | CRITICAL ROLE OF LIPID SUPPLEMENTATION IN RESOLVING THE INFLAMMATION CAUSED BY SARS-CoV-2

The pathogenicity of SARS-CoV-2 is associated with excessive inflammation, oxidative stress and release of cytokines. Imbalance between proinflammatory, anti-inflammatory eicosanoids is initiated in Covid-19 disease.<sup>95</sup>

### 7.1 | Autacoids (eicosanoids)

AA-derived autacoids or eicosanoids are inflammatory lipid mediators.<sup>81</sup> AA is metabolised by epoxygenase to

epoxyeicosatrienoic acids (EET). EET is inflammatory regulator that reduces the stress-based cytokines release.<sup>81</sup> However, EET is mainly converted to dihydroxyeicosatrienoic acids by the soluble epoxide hydrolase (sEH), and hence increases the release of cytokines. Therefore, inhibition of sEH can increase the EET level, and hence can suppress the release of IL-6 and activation of NF-kB<sup>81</sup> (Table 3). EET can shift the AA metabolism to proresolving lipid mediators such as lipoxin, resolvin, protectins and meostasis. Proresolving lipids can restore the normal balance and protect the lung. Lipoxin controls the inflammation without imparting immunosuppression activity.<sup>96</sup> Omega-3 fatty acids are rich in EET that possess anti-inflammatory activity (Table 3).<sup>81</sup>

### 7.2 | Cannabinoids

Oleylethanolamide (OEA) is a cannabinoid derived from oleic acid. It has potential removal activity of respiratory pathogen and can attenuate the inflammatory responses due to SARS-CoV-2 infection (Table 3).<sup>97</sup> Further, OEA can decrease TLR expression; thus reducing IL-6 and TNF- $\alpha$  during SARS-CoV-2 infection. TLR can initiate the proinflammatory cytokines release.

## 8 | CONCLUSION

In summary, SARS-CoV-2 infection is associated with host lipids migration from the circulation to the alveolar space in order to support the viral invasion and pathogenicity. In response, host lipids biosynthesis and release are enhanced to cover the viral needs. Furthermore, lipids such as AA and LA are released to limit the inflammation at the initiation of infection. Therefore, restricting the viral access to the host lipids either by applying specific inhibitors or supplementation with specific lipids can be of great importance to limit the viral infection and severity of disease.

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### CONFLICT OF INTERESTS

The authors declared that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

Eman Humaid Alketbi helped in writing the lipid supplementation and data interpretation. Rania Hamdy helped in collecting the data, designing and writing the first draft in addition to data interpretation. Abdalla El-Kabalawy helped in drawings and analysis of the data. Viktorija Juric and Marc Pignitter helped in collecting data regarding host lipid inhibitors. Kareem Mosa helped in writing and analysing the lipid supplementation as therapy. Ahmed M. Almejdi helped in supervising and interpreting the data. Ali A. El-Keblawy helped in writing the lipid supplementation, environmental factors and analysing the data. Sameh S. M. Soliman developed the idea, collected the data, designed the manuscript, wrote the first and final drafts, supervised the process of writing and analysis and analysed and interpreted the manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available within this article.

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