Bioactive lipids-based therapeutic approach to COVID-19 and other similar infections

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Abstract

It is suggested that COVID-19 (coronavirus) and other enveloped viruses can be inactivated by bioactive lipids.

Bioactive lipids (BALs) AA, gamma-linolenic acid (GLA), dihomo-GLA (DGLA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) are precursors to anti-inflammatory metabolites prostaglandin E1, lipoxin A4, resolvins, protectins and maresins that enhance phagocytosis of macrophages and leukocytes to clear debris, enhance microbial clearance and wound healing to restore homeostasis. BALs influence cell membrane fluidity and thus, prevent SARS-CoV-2, influenza, and Arboviruses (such as Chikungunya, Dengue, Zika) to infect the target cells. BALs modulate the generation of M1 and M2 macrophages. Mesenchymal and adipose tissue-derived stem cells secrete LXA4 and other BALs to bring about their beneficial actions in COVID-19. Prostaglandin E2 (PGE2), derived from arachidonic acid, triggers generation of anti-inflammatory lipoxin A4 and thus, modulates pathogenesis of COVID-19. AA, the precursor to both PGE2 and LXA4, and thus, is suited to prevent and ameliorate COVID-19.

Bioactive lipids-based therapeutic approach to COVID-19 and other similar infections

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Abstract

Background: COVID-19 is a pandemic caused by SARS-CoV-2 infection. Development of specific anti-viral compounds and effective vaccine(s) is likely to take considerable time and efforts. But more fundamental issue is how under physiological conditions, several microbial infections are effectively controlled by the immune and non-immune system(s) of the body. Evidence suggests that epithelial and other cells and T, NK, and other immunocytes release bioactive lipids especially arachidonic acid (AA) in response to microbial infections to inactivate them and upregulate the immune system.

Hypothesis: It is suggested that COVID-19 (coronavirus) and other enveloped viruses **including** severe acute respiratory syndrome (SARS-CoV-1 of 2002-2003) and Middle East respiratory syndrome (MERS; 2012-ongoing) and hepatitis B and C (HBV and HCV) can be inactivated by bioactive lipids.

Discussion: The released bioactive lipids such as AA, gamma-linolenic acid (GLA, dihomo-GLA (DGLA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) are precursors to anti-inflammatory metabolites prostaglandin E1, lipoxin A4, resolvins, protectins and maresins that enhance phagocytosis of macrophages and leukocytes to clear debris from the site(s) of infection and injury, enhance microbial clearance and wound healing to restore homeostasis. The positive and negative feedback regulation among pro- and anti-inflammatory cytokines and bioactive lipids is essential in the recovery from COVID-19 and other similar illnesses. Bioactive lipids influence cell membrane fluidity and thus, prevent SARS-CoV-2, influenza, and Arboviruses

(such as Chikungunya, Dengue, Zika) to infect the target cells. Bioactive lipids modulate the generation of M1 and M2 macrophages and activity of other immunocytes. Mesenchymal and adipose tissue-derived stem cells secrete LXA4 and other bioactive lipids to bring about their beneficial actions in COVID-19. Prostaglandin E2 (PGE2), derived from arachidonic acid, an important bioactive lipid, modulates inflammatory events, triggers generation of anti-inflammatory lipoxin A4 and other similar compounds and thus, modulates pathogenesis of COVID-19. AA, the precursor to both PGE2 and LXA4, and thus, is more suited to prevent and ameliorate COVID-19. Bioactive lipids regulate vasomotor tone, inflammation, thrombosis, immune response, inactivate enveloped viruses, regulate T cell proliferation and secretion of cytokines, stem cell survival, proliferation and differentiation, and leukocyte and macrophage functions, JAK kinase activity and neutrophil extracellular traps, events that attest to their critical role in COVID-19.

Conclusions: Hence, it is proposed that studies **need to be performed to explore the anti-viral actions of** various bioactive lipids against SARS-CoV-2, SARS, MERS, HCV, and HBV. **Based on the current evidence, it is suggested that oral and/or** parenteral administration of bioactive lipids especially AA **could be exploited as a potential therapeutic** approach in the prevention and management of COVID-19 and other similar infections.

Keywords: Bioactive lipids, essential fatty acids, prostaglandins, polyunsaturated fatty acids, lipoxin A4, resolvins, protectins, maresins, inflammation, macrophages, COVID-19, SARS-CoV-2.

Abbreviations:

BALs = Bioactive lipids

LXA4 = lipoxin A4

PGs = Prostaglandins

LTs = Leukotrienes

TXs =Thromboxanes

RBD = Receptor binding domain

SARS = Severe acute respiratory syndrome

COVID-19 = Coronavirus disease 2019

ACE = Angiotensin converting enzyme

ACE2 = Angiotensin converting enzyme 2

ARDS = Acute respiratory distress syndrome

TMPRSS2 = Transmembrane protease serine 2

IL = Interleukin

TNF = Tumor necrosis factor

ROS = Reactive oxygen species

NO = Nitric oxide

MERS = Middle East respiratory syndrome

HBV = Hepatitis B virus

HCV = Hepatitis C virus

CNS = Central nervous system

AngII = Angiotensin II

LGE = Late-gadolinium enhancement

RV = Right ventricle

LV = Left ventricle

ECMO = Extracorporeal membrane oxygenation

MRI = Magnetic resonance imaging

CRP =C-reactive protein

PLA2 = Phospholipase A2

PLC =Phospholipase C

PLD = Phospholipase D

COX = Cyclo-oxygenase

LOX = Lipoxygenase

PGDH = Prostaglandin dehydrogenase

AA = Arachidonic acid

GLA =Gamma-linolenic acid

DGLA = Dihomo-gamma-linolenic acid

EPA =Eicosapentaenoic acid

DHA =Docosahexaenoic acid

LA =Linoleic acid

ALA =Alpha-linolenic acid

CO = Carbon monoxide

H₂S = Hydrogen sulfide

MSCs =Mesenchymal stem cells

MIF =Macrophage inhibitory factor

HMGB1 = High mobility group box 1

NK =Natural killer

PMNs = polymorphonuclear cells

IFN = Interferon

HETE = Hydroxyeicosatetraenoic acid

HPETE = Hydroperoxyeicosatetraenoic acid

Introduction

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), the etiologic agent of the current outbreak of coronavirus disease 2019 (COVID-19), presents great similarity to the other coronaviruses SARS-CoV-1 and MERS-CoV, which caused the severe acute respiratory syndrome (SARS in 2002-2003) and Middle East respiratory syndrome (MERS from 2012-ongoing) outbreaks, respectively. These are enveloped viruses and share a great homology in their structures [1].

SARS-CoV-2 virus particles contain proteins known as spikes protruding from their surface. These spike proteins bind to human cells to enable the viral membrane to fuse with the cell membrane that facilitate the viral genes to enter the host cell to produce its actions (see Figure 1 for structure of SARS-CoV-2). Even though the sequences and structures of the spikes of SARS-CoV-2 and SARS-CoV-1 are similar, antibodies directed against SARS-CoV-1 do not bind to the SARS-CoV-2 spike protein [2, 3] though some amount of limited cross reactivity has been reported [4-6]. This indicates that more specific antibodies need to be generated for their potential use in humans.

Current strategies that are being employed against COVID-19 include inhibitors of viral entry into cells, viral replication, and RNA synthesis. SARS-CoV-2 utilizes angiotensin-converting enzyme 2 (ACE2) and the cellular protease transmembrane protease serine 2 (TMPRSS2) to enter target cells. Hence, chemicals that act on these two ligands are under development. But these strategies take considerable time to come to the clinic. SARS-CoV-2 spike glycoprotein (S protein) is cleaved into S1 and S2 subunits at the time of infection. S1 contains the receptor binding domain (RBD) that binds to the peptidase domain (PD) of ACE2, while S2 is needed for membrane fusion. When S1 binds to the ACE2, another cleavage site on S2 is exposed that is cleaved by host proteases to facilitate viral infection. It is noteworthy that the S protein of SARS-CoV-2 exploits ACE2 for host infection [7]. ACE2 is expressed in many tissues including but not limited to lungs, heart, kidney, and intestines which are the targets of the SARS-CoV-2. ACE2 is needed for the maturation of angiotensin to control vasoconstriction and blood pressure. A reduced expression of ACE2 is associated with cardiovascular diseases that explains why many with COVID-19 may develop myocardia damage and heart failure (see Figure 1 for the structure of SARS-CoV-2; and similarities and differences between Swine flu

A/Mexico/09 (H1N1) virus and SARS-CoV-2; Table 1 for similarities and differences between influenza and corona viruses and Figure 2 for the role of ACE2 in humans).

Historical aspects of influenza

Influenza, or flu, attacks principally the respiratory system and is highly contagious. The infection can spread from one person to the other through droplets generated during cough, sneeze or talk. These droplets can travel into the air and eventually be inhaled by others leading to spread of the disease. In addition, the virus can spread by touch when one person touches any infected surface with the virus and then touches his or her mouth, eyes, or nose. In the USA, during the flu season more than 200,000 are hospitalized for flu-related complications. Young children, elderly (> 65yrs), pregnant women and people with asthma, diabetes mellitus and/or heart disease are particularly vulnerable to risk of flu-related complications, including but not limited to pneumonia, myocarditis, central nervous system (CNS), eye, ear and sinus infections and bronchitis. Recent studies suggested that SARS-CoV-2 can infect neuronal cells that can result in encephalitis-like clinical presentation, produce thrombosis of the cerebral veins and arteries leading to stroke and other complications. It needs to be noted that post-COVID-19 manifestations include persistent headache, memory loss, confusion, inability to concentrate, breathlessness, cough, low grade fever, muscle pains and unexplained weakness [8-13].

It is noteworthy that there have been several influenza pandemics. The first flu pandemic recorded in 1918 termed as “Spanish flu” (this is a misnomer as it did not originate in Spain and is more aptly termed as “1918 influenza pandemic,” or the “1918 flu pandemic,”) in which the death toll is estimated ~ 20 million to 50 million worldwide. The flu pandemic of 1957-1958 killed ~ 2 million people worldwide. The pandemic of 1968-1969 killed ~1 million, whereas >12,000 Americans died during the H1N1 (or “swine flu”) pandemic of 2009-2010. The current pandemic of COVID-19 is spreading rapidly across all nations and its final impact is yet to be gauged as the pandemic is still continuing. The current COVID-19 pandemic is particularly deadly since many carriers are asymptomatic. It is estimated that ~40% of those infected with SARS-CoV-2 are asymptomatic and are responsible for spreading the infection.

In general, most influenza outbreaks seem to be disproportionately lethal to the very young and elderly. The surprisingly higher than expected mortality during the flu pandemic of 1918 in young adults has been attributed to the triggering of a cytokine storm. Another explanation offered for the higher mortality in the young during this pandemic is to the superadded bacterial infection [14-16]. It is rather paradoxical to think that the strong immune reaction is harmful, whereas limited immune response of children and middle-aged adults is much less lethal.

Structure of influenza virus

The structure of the influenza virion is similar to SARS-CoV-2 and both are enveloped viruses (see Figure 2). It is important to understand the similarities and differences in the structure of influenza and SARS-CoV-2 viruses as given Table 1. These differences may underlie the variations seen between influenza-induced illness and SARS-CoV-2-induced severe illness in the form of ARDS (acute respiratory distress syndrome), cytokine storm and thrombosis of the lung capillaries and vessels, stroke, myocarditis and other features.

COVID-19 and ACE2

Even though COVID-19 is primarily a respiratory infection, it is now known that its manifestations may be seen in almost all systems of the body including cardiovascular and immune systems. Those who have pre-existing cardiovascular conditions are particularly vulnerable to disproportionately worse outcomes with almost 5-10-fold increase in mortality [17-18].

There are many similarities between SARS-CoV-2 and SARS-CoV. SARS-CoV-2 and SARS-CoV spike proteins share 76.5% identity in amino acid sequences and their spike proteins have a high degree of homology [19-22]. It has been shown that residue 394 (glutamine) in the SARS-CoV-2 receptor-binding domain (RBD), corresponding to residue 479 in SARS-CoV, is recognized by the critical lysine 31 on the human ACE2 receptor [23]. SARS-CoV-2 recognizes and binds to human ACE2 more avidly compared to SARS-CoV [24-26]. It is known that blocking the renin-angiotensin pathway attenuates or at last reduces the severity of the lung

damage due to SARS-CoV-2. This suggests that ACE2 is needed not only the virus to enter the target cell but also protects from lung injury.

ACE and its homologue ACE2 regulate the renin–angiotensin system. ACE cleaves the decapeptide angiotensin (Ang)I into the octapeptide AngII, whereas ACE2 cleaves a single residue from AngI to generate Ang1–9 and a residue from AngII to generate Ang1–7. Thus, ACE2 has a negative regulatory control on the renin–angiotensin system by inactivating AngII (see Figure 2). It is known that in ARDS (acute respiratory distress syndrome) there is a marked downregulation of ACE2 protein while ACE levels remained constant. ARDS can be improved by catalytically active ACE2. AngII levels in lungs and plasma are markedly increased in ARDS with a concomitant decreased ACE2 expression. Thus, ACE promotes ARDS through increased AngII production whereas ACE2 protects against ARDS [27]. In other words, inhibition of ACE activity may lead to decrease in the activity and receptor number of ACE-2 due to the feedback regulation that exists between ACE and ACE-2. The host cell entry of SARS-CoV-2 depends on the ACE2 receptor and can be blocked by inhibiting the cellular serine protease TMPRSS2 that is employed by SARS-CoV-2 for S protein priming.

Clinical picture of COVID-19

The most prominent and hallmark symptoms of COVID-19 are cough, fever, muscle aches, headaches and difficulty breathing that may lead to the development of ARDS necessitating some of these patients to be put on ventilator and ECMO (extracorporeal membrane oxygenation). It is estimated that about 20-30% of the patients put on ventilators eventually succumb to the disease [28-30]. In addition, some patients may have headache, dizziness, abdominal pain, diarrhea, nausea, and vomiting. With the onset of alveolar damage, these patients will have progressive respiratory failure that may lead to death (see Table 2 for common clinical features of COVID-19).

Since ACE2 is needed for host cell entry and subsequent viral replication, efforts have been made to study its expression and distribution in human body to know the potential infection routes of SARS-CoV-2. High ACE2 expression is seen in type II alveolar cells (AT2) of lung, esophagus upper and stratified epithelial cells, enterocytes from ileum and colon, cholangiocytes,

myocardial cells, kidney proximal tubule cells, and bladder urothelial cells [31-33]. It is remarkable that ACE2 protein is present in various human organs including oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain. The expression of ACE2 protein on lung alveolar epithelial cells and enterocytes of the small intestine, vascular endothelial cells, and arterial smooth muscle cells of several organs may account for damage to these tissues during COVID-19. This, in turn, may lead to the development of ARDS, thromboembolic manifestations and gastrointestinal disorders. The wide distribution of ACE2 in several human organs provides a clue as to the COVID-19 disease manifestations especially regarding the vascular complications such as thrombosis seen in peripheral blood vessels and in the smaller blood vessels of lungs.

Since several tissues contain high ACE2-expressing cells, they are potential sources through which SARS-CoV-2 can enter the body to produce its infection. In addition to these cells/tissues, another potential source of entry for the SARS-CoV-2 virus is the mucosa of oral cavity which has been shown to express ACE2 and are highly enriched in epithelial cells. Among different oral sites, ACE2 expression is highest in tongue than buccal and gingival tissues [33]. This observation lends support to the observation that SARS-CoV-2 can be shed by oral droplets and saliva and mucosa of oral cavity is a potential route of infection. Since many organs/tissues have the ACE2 receptor and SARS-CoV-2 is able to infect almost all tissues in the body, it is likely that SARS-CoV-2 can be found in the saliva, urine, feces, and other secretions. This is supported by the recent report that SARS-CoV-2 has been found in the sewage of several cities [34-37]. Hence, it is imperative that efforts should be made to see whether SARS-CoV-2 is present in all the urine, feces, and saliva in those who have been suspected to have the disease. This is important to know the source and route of infection to take suitable preventive measures to stop the spread of COVID-19. It is important to note that SARS-CoV-2 has been detected in municipal water supply and in sewage water, a possible source of infection. This assumes significance especially for third world countries (such as India) where the sewage and drinking water supply systems are not adequate. Since housing is inadequate and more than 5-6 persons live under one roof and washroom facilities are limited, the possibility of water source spread of COVID-19 is highly likely. This coupled with the lack of adequate facilities for testing (both RT-PR and antibody) further aggravates the spread of COVID-19 in these countries. This is supported by the belief that in India with a population of almost 1.3 billion for one detected

COVID-19 case there could be almost 300-400 undetected cases implying that there could be almost 300 million infected with SARS-CoV-2.

Some of the unusual manifestation of COVID-19 include anosmia and dysgeusia, skin rashes, diarrhea, kidney abnormalities and potentially life-threatening blood clots.

Anosmia (loss of sense of smell) and dysgeusia (alteration of sense of taste) are the most common early manifestation of COVID-19 that may go unnoticed, especially in the elderly. It was reported that anosmia could be present in ~73% of patients much before COVID-19 diagnosis. Improvement in anosmia may occur in ~27% of patients. The mean time to improvement was reported to be ~7.2 days whereas 85% showed improvement within 10 days [38]. These observations indicate that anosmia can be a presenting symptom of COVID-19. Anosmia may be critical to identify individuals infected with SARS-CoV2.

Skin rashes and COVID toes

Similar to many viral infections such as chicken pox or herpes, patients with COVID-19 also may show skin rashes that could be due to either direct invasion of the skin by the virus or as a result of immune reaction to the virus as seen in Epstein Barr Virus or West Nile infections. Some patients of COVID-19, especially children, show head-to-toe red rashes, hive-like eruptions, blister-like bubbles and even lacy, purple rashes spreading across larger patches of skin, and some are red, tender bumps that appear around the toes and heels—dubbed “COVID toes.” It is suspected that those with lacy purple rashes are more likely to develop blood clots. Though it is not clear whether SARS-CoV-2 itself can cause rashes it is likely that the manifestations are as a result of an inert particle reaction in the skin, initiating an inflammatory process in response to circulating antibodies and sensitized lymphocytes. It is noteworthy that histological examination of the skin biopsy of these rashes showed that the findings are very much similar to hand-foot-and mouth disease and the RT-PCR for SARS-CoV-2 from the vesicles was negative. This negative reaction could be due to low viral load or absence of the virus itself. This suggests that contact with the skin rashes may not be infective [39].

Gut manifestations

Since intestinal epithelial cells are rich in ACE2, it is no wonder that gut is also a major target of SARS-CoV-2. Some of the gastrointestinal manifestations of COVID-19 include diarrhea, nausea and vomiting. It appears that those who had gastrointestinal symptoms tend to be diagnosed later and endure longer infections (partly because they are misdiagnosed with the mistaken belief that gut symptoms are unlikely due to COVID-19). It needs to be emphasized that gut is a massive immune organ and so when they are infected it takes a long time to clear the virus from such a large organ. Since gut can get involved in COVID-19, it stands to reason that SARS-CoV-2 can be excreted in feces that itself could form a source of infection. Under normal conditions, the acid in the stomach is expected to inactivate the virus. Hence, use of antacids or proton pump inhibitors that suppress acid production may create a fertile ground for SARS-CoV-2 to proliferate and travel to the other parts of the gut. In contrast to this, it was reported that H₂ blockers could be of benefit in COVID-19 [40, 41]. It has been proposed that SARS-CoV-2 may induce differentiation and activate mast cells. Such activated mast cells release histamine, proteases, cytokines, chemokines, and arachidonic acid derived prostaglandins (PGs) and leukotrienes (LTs) that have a role in inflammation. Histamine is known to be involved in the expression of chemokine IL-8 and cytokine IL-6, an effect that can be inhibited by H₂ blockers. Alveolar macrophages activated by SARS-CoV-2 release IL-1 that, in turn, stimulates mast cells to produce IL-6. Both IL-1 and IL-6 can work together to produce excessive inflammation as seen in COVID-19. Furthermore, histamine enhances IL-1-induced IL-6 gene expression and protein synthesis via H₂ receptors in peripheral monocytes. Thus, histamine released by mast cells during inflammatory reaction as seen in COVID-19 can increase production of IL-1 to amplify inflammatory process in the lung infected with SARS-CoV-2 [40]. This work is supported by the in silico work that showed that famotidine could interact with the catalytic site of the three proteases associated with SARS-CoV-2 and suggested that its intravenous administration could be of significant benefit in COVID-19 [41]. This proposal is supported by the observation that famotidine use was associated with a better outcome in those with COVID-19 [42-44]. These initial observations need to be confirmed in a large-scale double-blind placebo controlled clinical trials.

Renovascular system

The function of ACE in the kidney is to convert Ang I to Ang II to regulate blood pressure and salt and water balance (through aldosterone secretion modulation). Pulmonary epithelium is the main source of ACE. Intrarenal ACE production in the human kidney is about five times higher compared to ACE found in the human lung [45, 46]. A remarkably high concentration of ACE is present in the brush border of the proximal tubule, glomerular endothelium, mesangial cells, podocytes, and distal nephron [47-51]. The purpose of ACE2 enzyme is to counteracts many functions of the ACE (see Figure 2). ACE2 is needed to convert Ang II into the vasodilator and antiproliferative Ang 1-7 and Ang I into the inactive Ang 1-9. Ang 1-7 is an antioxidant, anti-fibrotic, and anti-inflammatory molecule, and acts through its receptor Mas (MasR) [52, 53]. ACE2 expression is also seen in heart, liver, lung, and neurons [54-56]. ACE2 expression is present in significant amounts in tubular and glomerular epithelium, vascular smooth muscle cells, the endothelium of interlobular arteries, and glomerular mesangial cells [57, 58]. SARS-CoV-2 infection is seen in the kidney due to the presence of ACE2. SARS-CoV-2 can be detected in the urine of the infected people. Acute kidney injury among COVID-19 patients is seen in almost ~ 36.6% of the patients admitted and some of them need dialysis [59, 60]. What is more important is the fact that those with renal injury due to COVID-19 could be correlated with severity of the respiratory symptoms. It is likely that SARS-CoV-2 can directly affect the kidneys and the resultant inflammatory response may worsen not only the respiratory involvement but also if there is any previous renal disease. The cytokines that are released as a result of SARS-CoV-2 infection can affect the blood vessels leading to renal ischemia that may worsen renal function necessitating appropriate interventions in the form of dialysis. This suggests that all those who have been diagnosed to have COVID-19 need to be assessed for their renal status and look for hematuria and urinary albumin presence, an indication of renal damage. But it is not yet clear whether COVID-19 can cause any long-lasting renal damage and if so, what that could be.

Hepatobiliary system

Hepatocytes have ACE2 receptor and so are also target of SARS-CoV-2 infection. Further, more than half of the patients admitted for COVID-19 show alterations (higher

or lower) in the levels of liver enzymes indicating that liver has been affected. But it is apparent that liver cell failure is unlikely and so hepatic functions are likely to reverse to normal over a period of time. The alterations seen in hepatic enzymes in COVID-19 could be due to either direct infection of hepatocytes by SARS-CoV-2 or secondary to inflammatory response seen in these patients. Lymphocytic infiltration associated with sinusoidal dilatation, steatosis, and multifocal hepatic necrosis can be seen in COVID-19 [61]. In the event these patients have pre-existing liver disease, it is likely to be exaggerated and may lead to further damage to liver in view of the inflammatory events associated with COVID-19.

Thrombosis and its consequences in COVID-19

Vascular endothelial cells carry the ACE2 receptor, which implies that SARS-CoV-2 can directly attack the blood vessels, especially of the lungs resulting in thrombosis in the pulmonary blood vessels (both venous and arterial) due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis that contributes to ARDS seen in these patients. It is noteworthy that some patients with COVID-19, especially those who have severe disease, may have vascular thrombosis (due to endothelialitis) in the legs and lungs and sometimes these patients develop disseminated intravascular coagulation. This led to the suggestion that anti-thrombotic therapy may be of significant benefit to these patients.

These presumptions are supported by a recent study which showed that those who died from COVID-19 or influenza-associated respiratory failure showed diffuse alveolar damage with perivascular T-cell infiltration. COVID-19 specimens also showed severe endothelial injury with intracellular virus and disrupted cell membranes, whereas the pulmonary vessels revealed extensive thrombosis with microangiopathy and alveolar capillary microthrombi with an extremely high prevalence of intussusceptive angiogenesis compared to those with influenza. These results suggest that vascular angiogenesis pulmonary pathology of COVID-19 is distinctly different from that of equally severe influenza infection [62].

It has been reported that a remarkably high numbers of ACE2-positive cells are present in the lungs of those with Covid-19 compared to uninfected controls. Vascular endothelial cells are the main target of SARS-CoV-2 that can lead to disruption of intercellular junctions, cell swelling, and a loss of contact with the basal membrane. SARS-CoV-2 virus has been demonstrated within the endothelial cells suggesting that the virus has a direct effect on these cells (endothelial cells) that may be exaggerated by the perivascular inflammation noted [62]. Since many patients of COVID-19 recover completely even after ventilatory therapy, it can be assumed that several features described [62] are reversible though the time needed for this reversal to normal remains to be determined. It is also equally true that we still do not know whether all those who have recovered from COVID-19 have any residual pulmonary damage and if so, what are their long-term consequences. Nevertheless, the presence extensive capillary microthrombi in those with COVID-19 suggests that early institution of anti-coagulant therapy is warranted. Thrombosis of cerebral vessels leading to stroke is more common in young people suggesting that stroke in the young need to be assessed for the presence of SARS-CoV-2 infection. The big question is-does many, if not all, cases of stroke in the young need to be investigated for SARS-CoV-2 even during non-epidemic or non-pandemic period. One investigation that may help is the measurement of D-dimer in these patients. Similarly, coronary heart disease in the young with no known risk factors also need to be investigated for the presence of silent COVID-19 infection. This aspect needs special attention as almost ~80% of the patients with SARS-CoV-2 infection are asymptomatic.

Another peculiar manifestation seen in COVID-19 is the complete lack of clot lysis at 30 minutes on a thromboelastogram (TEG) assay coupled with a D-dimer value above 2600 ng/ml, indication that these patients need aggressive anticoagulation and many of them require mechanical ventilation, had acute renal failure requiring dialysis and some had thrombotic stroke. Other important abnormal laboratory investigations include elevated fibrinogen with normal platelet count, elevated prothrombin time and partial thromboplastin time. Many of these patients may also present cardiac abnormalities in the form of right heart failure, right ventricle dilatation, pulmonary thromboembolism and even after recovery from COVID-19. Some of these patients may continue to have palpitations and chest pain and MRI shows diffuse myocardial edema and fibrosis by late-gadolinium enhancement (LGE), or both along with impaired RV

cardiac index and ejection fraction, despite preserved LV function. How long these abnormalities persist and whether it has any life-long consequences remain to be determined.

Neurological manifestations

In a retrospective study performed in 214 COVID-19 hospitalized patients in Wuhan, China it was reported that ~37% showed some central neurological manifestations. Some of these include headache, dizziness, impaired consciousness, ataxia, epilepsy, and stroke. Of all, the most common manifestations have been headache and dizziness. Other manifestations include loss of taste and smell, neuralgia, and muscle pains, Guillain-Barre syndrome and some of these patients showed increase in plasma creatine kinase implying pathological involvement of muscles. Some patients even had stroke. It is not clear how many of these neurological manifestations are truly due to nervous system involvement or because of hypoxia. Nevertheless, they need to be considered as a part of the COVID-19 manifestations. These reported neurological manifestations reported from China have been confirmed from a study done in France. In order to document properly the possible involvement of nervous system in patients with COVID-19, detailed clinical, neurological and electrophysiological studies of these patients and efforts need to be made to isolate SARS-CoV-2 from cerebrospinal fluid, and autopsies of the COVID-19 patients need be carried out.

COVID-19 in children

Some disturbing findings reported in children needs special attention. It has been reported that children are uniquely susceptible to develop an acute cardiac decompensation due to severe inflammation following SARS-CoV-2 infection, termed multisystem inflammatory syndrome in children (MIS-C) [63-66]. Treatment with immunoglobulin seem to benefit these subjects with recovery of left ventricular systolic function. MIS-C has remarkably close similarities with Kawasaki disease. The data obtained so far indicates that these children present with cardiogenic shock, left ventricular dysfunction and severe inflammatory state. The mean ages of these patients is about 10 years, all had fever, 80% had gastrointestinal symptoms such as pain abdomen, vomiting and diarrhea and comorbidities such as higher body mass index (17%), asthma (9%), and lupus (3%), and overweight. Only 17% presented with chest pain.

Many of these patients had left ventricular ejection fraction that was less than 30%, and 80% required inotropic support with 28% treated with extracorporeal membrane oxygenation (ECMO). All had severe inflammatory state as evidenced by elevated C-reactive protein and [d-dimer](#), higher plasma IL-6 elevated troponin, and NT-proBNP or BNP elevation. These patients are in need of IV inotropic support, IV immunoglobulin, anticoagulation with [heparin](#), and received IV steroids.

Current therapeutic approaches to COVID-19

Several clinical trials are underway to know the efficacy of several drugs that could be useful either alone or in combination for COVID-19. Some of these include interferons, guanosine-analog RNA synthesis inhibitors, reverse transcriptase inhibitors or influenza drugs, Remdesivir, an antiviral. Some drugs are being investigated for their potential to block viral entry into the host cell (umifenovir, chloroquine or interferon), viral replication (lopinavir and ritonavir, ASC09 or darunavir/cobicistat) and viral RNA synthesis (inhibitors or influenza drugs, like remdesivir, favipiravir, emtricitabine/tenofovir alafenamide or ribavirin).

Since SARS-CoV-2 employs ACE2 and TMPRSS2 to enter target cells, attempts are being made to develop drugs that inhibit TMPRSS2. Janus-associated kinase (JAK) inhibitors that suppress inflammation are also being tested for their efficacy against COVID-19. Clinical trials are underway to use these drugs along with mesenchymal stem cells for COVID-19. These efforts will take time to know which of the strategies are likely to be successful. Several vaccines are under development for SARS-CoV-2 and are likely to take considerable time before they become available for the world's population. Furthermore, initial studies showed that those who developed COVID-19 do develop protective antibodies but whose titer seems to decline in about 3-6 months raising the possibility that even vaccine induced antibodies may not last long. It was also noted that some of the patients who recovered from COVID-19 have anti-interferon antibodies that may interfere with the anti-viral action of IFN (interferon) that seems to be more common in those who had severe COVID-19.

In view of these uncertainties and increasing incidence of mutations it is important to look at other novel and out of box methods of inactivating SARS-CoV-2 by understanding the

natural mechanisms by which human body fights such infections. In the current **narrative** review, the potential role of bioactive lipids (BALs) in the pathobiology of COVID-19 is discussed based on their actions in the regulation of inflammation and immune response. Thus, the current study does not need ethical approval as it did not involve any interventions or studies in experimental animals or patients.

Bioactive lipids inactivate enveloped viruses

It is noteworthy that one of the unappreciated mechanisms by which many microbes can be inactivated by the human innate immune system is by elaboration of polyunsaturated fatty acids (PUFAs) and their metabolites (termed as bioactive lipids). Several bioactive lipids especially linoleic acid (LA), gamma-linolenic acid (GLA), dihomogamma-LA (DGLA), arachidonic acid (AA), alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can inactivate Streptococci, Staphylococci, both gram-positive and gram-negative bacteria, fungi and enveloped viruses, including influenza, HCV, HBV and HIV [67-75]. These fatty acids disrupt the microbial cell membranes, interfere with the cellular metabolic processes including inhibition of respiratory activity, transportation of amino acids, and uncoupling of oxidative phosphorylation. Based on these evidences [67-75], it is reasonable to propose that alveolar macrophages, leukocytes, T and B cells, NK cells and other immunocytes release AA and other unsaturated fatty acids to inactivate various microbes including SARS-CoV-2, SARS, and MERS. It is possible that human body protects itself from various microbes using these unsaturated fatty acids. Based on these observations, it can be suggested that a deficiency of AA and other unsaturated fatty acids can predispose an individual susceptible to various infections including SARS-CoV-2, SARS, and MERS. Alveolar macrophages can secrete AA and other unsaturated fatty acids into the alveolar fluid to inactivate SARS-CoV-2, SARS and MERS and several other bacteria and fungi [76-92]. This implies that administration of these fatty acids could be of significant benefit against SARS-CoV-2, SARS, and MERS.

Phospholipase A2 (PLA2) is microbicidal in nature

Type-IIA secreted phospholipase A2 (sPLA₂-IIA) releases AA and other unsaturated fatty acids from the cell membrane phospholipid pool, a mechanism developed by various cells

including immunocytes to fight against microbes. It is noteworthy that sPLA₂-IIA present in animal and human biological fluids is sufficient to bring about its antimicrobial action. Human recombinant sPLA₂-IIA induced release of PUFAs in response to several bacteria and viruses at concentrations ~ 1.1 ng/ml that prefers anionic phospholipids such as phosphatidylglycerol, which is the main phospholipid component of bacterial membranes. In contrast to this, higher concentrations of sPLA₂-IIA are needed to act on the host cell membranes and surfactant both of which are mainly composed of phosphatidylcholine that is a poor substrate for sPLA₂-IIA. It is noteworthy that over-expression of human sPLA₂-IIA renders cells resistant to *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus anthracis* infections. Furthermore, intranasal administration of sPLA₂-IIA protects mice from microbial infections including pulmonary anthrax, implying that this mode of administration of sPLA₂-IIA and PUFAs could be employed to protect against SARS-CoV-2, SARS, and MERS [93-96]. In a similar fashion, even bioactive lipids can be administered intranasally to prevent various microbial infections including SARS-CoV-2, SARS, and MERS.

Bioactive lipids (BALs) including AA mediate the antimicrobial action of macrophages

Humans are constantly exposed to various microbes through inhaled air that calls for an efficient and simple mechanism(s) to prevent and protect lungs from various infections. In other words, alveolar macrophages need to possess an efficient mechanism to prevent microbial infections. Inhaled staphylococci can be eliminated by alveolar macrophages utilizing AA and other bioactive lipids derived from the extracellular fluid and thus, protect lungs from the invading microbes. Even immunocytes may protect various tissues from microbial infections in the same fashion [72, 93, 94, 98-108] (see Figures 3A and 3B for metabolism of essential fatty acids and their role in inflammation and restoration of homeostasis and their role in COVID-19). This is supported by the observation that lymphokine-activated macrophages release bioactive lipids to induce apoptosis of tumor cells [107]. Thus, alveolar lining material interacts with alveolar macrophages, whereas tumor cells interact with microenvironment that is tuned to the benefit of the body. Proliferation of tumor cells can be inhibited by the immunocytes present in the tumor microenvironment by secreting bioactive lipids. Even normal cells surrounding the tumor cells can secrete bioactive lipids in order to restrain tumor cell growth. At the same time, it is possible that tumor cells may take advantage of the secreted bioactive lipids especially GLA,

DGLA, AA, EPA and DHA to form PGE₂/PGE₃ and leukotrienes that possess immunosuppressive actions. Thus, there may be an intense competition between normal cells/immunocytes and tumor cells for the secreted bioactive lipids. The outcome (tumor cell growth or tumor cell apoptosis) of this competition depends on the way the released GLA/DGLA/AA/EPA/DHA (by the normal cells) are metabolized by normal and tumor cells. If the normal cells are able to dominate and produce lipoxins, resolvins, protectins and maresins by utilizing these fatty acids (GLA/DGLA/AA/EPA/DHA) and enhance NO and ROS generation then the tumor cells are induced to undergo apoptosis or remain dormant for a long time. In contrast, if tumor cells are able to uptake these fatty acids to convert them to PGE₂/PGE₃/LTs and inhibit or decrease the formation/production of lipoxins, resolvins, protectins and maresins by normal cells (since the surrounding immunocytes or normal cells are unable to have access to AA/EPA/DHA), then the tumor cells will be able to induce immunosuppression and proliferate (see Figure 4).

Crosstalk between microbes and host cells/tissues

Similarly, there could occur a crosstalk between the invading microorganisms and the host tissue/cells to utilize GLA/DGLA/AA/EPA/DHA secreted by normal cells/target cells (including T cells and NK cells) and the microbes. Microbes are known to influence the metabolism of GLA/DGLA/AA/EPA/DHA by target cells to form PGE₂/PGE₃/LTs to produce local inflammation and immunosuppression. On the other hand, the host tissues/cells and immunocytes utilize these fatty acids to inactivate microbes by producing lipid peroxides, NO, and regulating the production of IL-6, TNF- α and IFN and other anti-microbial cytokines/products. This is supported by the observation that (i) some bacteria can induce activation of the inflammatory signalling pathway [109]; (ii) COX-2 expression was increased in macrophages infected with the wild-type colon cancer-associated E. coli 11G5 strain but not by a clbQ mutant, indicating that tumor- infiltrating bacteria induce the expression of COX-2 to enable the tumor cells and tumor infiltrating macrophages to produce PGE₂, a immunosuppressor [110]; (iii) heat-killed Mycobacterium can downregulate MMP-9 in murine peritoneal macrophages through COX-2 and independent of TNF- α [111] suggesting that immunosuppression seen in the host during tuberculosis infection is due to local production of PGE₂; and finally, (iv) COX-2 can be induced by CMV (cytomegalovirus) in human RPE cells that can lead to translocation of the induced NF-kB from the cytoplasm to the nucleus associated

with an increase in the production of PGE1 and PGE2 in these cells that significantly increased CMV proliferation [112]. Since, under physiological conditions, there is a balance maintained between pro-inflammatory PGE2 and anti-inflammatory lipoxins, resolvins, protectins and maresins it is reasonable to suggest that these anti-inflammatory bioactive lipids inhibit viral replication (similar to GLA/DGLA/AA/EPA/DHA). These studies lend support to the concept that microbes (and in a similar fashion tumor cells) enhance the expression of COX-2 and other enzymes of the PG pathway in the host cell and thus, alter the balance between pro-inflammatory and anti-inflammatory bioactive lipids at the site of infection or tumor invasion. This, in turn, alters the host response to tumor cells or infection by the invading microbes (including viruses such as SARS-CoV-2). It is possible, but yet to be verified, that tumor cells can upsurge the COX-2-LOX pathway of the normal cells in the tumor microenvironment for their benefit. In a similar fashion, certain bacteria (such as Lactobacilli) may support the host tissues to overcome microbial resistance by modulating host COX-LOX enzymes [113, 114].

Immunocytes release bioactive lipids (BALs)

Immunocytes (NK cells, cytotoxic tumor lymphocytes: CTL cells, lymphokine activated killer cells, dendritic cells, leukocytes, etc.,) release perforin and granzyme, cytokines IL-6, TNF- α , and IFN- γ to eliminate tumor and infected cells. Surprisingly, NK cells and CTLs induce tumor cell apoptosis even in the absence of perforin and granzyme by enhancing the expression of soluble PLA2 (sPLA2) [115]. PLD (phospholipase D) activation that leads to release of AA is needed for the CD16-triggered signaling cascade to induce exocytosis of the NK cytotoxic granules [116, 117]. It is noteworthy that lipids form a constitutive component of cytolytic granules of CTL, NK and $\gamma\delta$ T cells [118] and cytokine-activated macrophages (and probably other immunocytes) can release bioactive lipids to induce apoptosis of tumor cells [107, 119-121]. These results emphasize the importance of PLA2/PLD and release of bioactive lipids for the cytolytic action and release of cytolytic granules by immunocytes.

It is noteworthy that macrophages and tissue-resident memory CD8+ T cells cooperate with each other to sense pathogens and protect the barrier tissues [122]. This is somewhat akin to the crosstalk/interaction seen between alveolar lining material and macrophages to eliminate invading microbes and tumor cells [100]. A close cooperation/interaction exists between epithelial cells and macrophages that is similar to the interaction between tissue resident memory

T cells and their surrounding milieu. The resident memory T cells are dependent on fatty acids for their survival and function. These much-needed fatty acids are transported to the T cells by the specific fatty acid binding protein (FABP). The type of FABP expressed by the T cells depends on the tissue in which they are resident implying that the tissue resident memory T cells show varying patterns of FABP isoform usage that, in turn, is determined by tissue-derived factors. To meet the fatty acid demands of the tissue resident memory T cells (and other immunocytes including macrophages), these cells modify their FABP expression depending on the tissue in which they are located or relocated [123]. This suggests that each tissue and their resident memory T cells (and macrophages and other immunocytes) need to get a specific type(s) of bioactive lipid(s) not only for their survival but also to bring about their specific action(s) that is tailored to their location as dictated by the local milieu. In an extension of this argument, it can be postulated that to inactivate a specific type of invading microbes (including viruses) a specific type or types of bioactive lipid(s) is needed that, in turn, depends on the target tissue.

Macrophages can be either M1 or M2 type. M1 type macrophages have pro-inflammatory actions whereas M2 is anti-inflammatory in nature (see Figure 5). M1 are needed to kill the invading microbes including SARS-CoV2 and clear the debris. Once the much-needed inflammatory process is completed and invading microbes are cleared, M2 are needed to induce resolution of inflammation and restore homeostasis. PGE2 and leukotrienes are needed for the generation of M1 macrophages and they (M1) generate these pro-inflammatory PGE2 and leukotrienes. In contrast, anti-inflammatory cytokines and lipoxin A4 (LXA4) from AA, resolvins from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and protectins and maresins from DHA facilitate generation of M2 macrophages and induce resolution of inflammation restore homeostasis [73, 124-136]. But there is one caveat for this process of inflammation to anti-inflammation or resolution of inflammation to occur in a coordinated, smooth and orderly fashion, which is the availability of GLA/DGLA/AA/EPA/DHA in adequate amounts at the right time and at the right place. Any discrepancy in this sequence of events may result in acute inflammatory process to become chronic and failure of resolution. For this smooth transition from pro-inflammatory events to resolution of inflammation and restoration of homeostasis needs adequate activity of desaturases, COX and LOX enzymes (including soluble epoxy hydrolase: sEH), PGDH, an appropriate balance between pro- and anti-inflammatory cytokines, generation of adequate amounts of ROS, NO, CO, H2S and sufficient activity of various anti-oxidants. These enzymes, free radicals and antioxidants are needed to regulate oxidative and

mitochondrial stress and to regulate the actions of leukocytes, macrophages, T cells, NK cells and CT cells and to process a smooth and timely communication(s) between various immunocytes, host cells/tissues and the invading microbes (including SARS-CoV-2). Any hindrance in any one of these process will result in exacerbation of the clinical picture of COVID-19 and lead to the onset of its complications.

In this context, the relationship between pro-inflammatory cytokines and EFA metabolism needs a closer look. Both TNF- α and IL-6 can block the activities of desaturases which are needed for the conversion of dietary linoleic acid (LA) and alpha-linolenic acid (ALA) to their respective long-chain metabolites namely AA and EPA and DHA respectively [137]. This could be the reason as to why patients with rheumatoid arthritis, lupus, and sepsis have low plasma concentrations of AA, EPA and DHA [138-141]. As a consequence of this precursor (GLA, DGLA, AA, EPA and DHA) deficiency, the generation of LXA4, resolvins, protectins and maresins that are potent inhibitors of IL-6 and TNF- α formation is insufficient. Hence it is predicted that patients with COVID-19 will have deficiency of GLA/DGLA/AA/EPA/DHA and LXA4/maresins, resolvins/protectins. These results indicate that administration of GLA/DGLA/AA/EPA/DHA/PGE1/LXA4, resolvins, protectins and maresins will be of significant benefit in COVID-19 by (i) suppressing inappropriate production of IL-6 and TNF- α , (ii) ameliorating inflammation and excess pro-inflammatory cytokine storm, (iii) protecting normal cells (especially bone marrow cells, myocardial cells, hepatic and renal tissues) and thus, initiate recovery [142-155].

Bioactive lipids and M1 and M2 macrophages

Once the inflammatory process has achieved its function of eliminating the invading microbes (including SARS-CoV-2) and debris removal is completed by the M1 type, macrophages change their phenotype to M2 type to initiate resolution of inflammatory process by producing anti-inflammatory cytokines and anti-inflammatory bioactive lipids such as lipoxin A4 (LXA4) from AA, resolvins from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and protectins and maresins from DHA [156-169]. These results imply that pro-inflammatory bioactive lipids induce the M1 phenotype whereas anti-inflammatory bioactive lipids trigger the generation of M2 macrophage phenotype. These studies suggest that the way GLA/DGLA/AA/EPA/DHA are metabolized by the macrophages and their modulation by the

pro- and anti-inflammatory cytokines, changes in the activities of desaturases, cyclo-oxygenase-2 (COX-2) and LOX (5-, 12-, and 15-lipoxygenases) determines the shift in the balance between M1 and M2 macrophages [156-169]. Thus, generation of adequate concentrations of GLA/DGLA/AA/EPA/DHA and their conversion to PGE₁, LXA₄, resolvins, protectins and maresins by the appropriate concentrations and action of desaturases, COX-2, 5-, 12-, and 15-LOX and 15-PGDH results in the generation of M1 and M2 macrophages as the situation demands. When the adequate amounts of IL-6 and TNF- α and other pro-inflammatory cytokines are generated in the initial stages of infection due to SARS-CoV-2 (and other enveloped viruses and microbes) and formation of PGE₂ occurs in adequate amounts it leads to the generation of M1 macrophages, whereas generation of M2 type occurs when PGE₁/LXA₄/resolvins/protectins/maresins are formed in appropriate amounts at the time of resolution of inflammation [156-169]. Though this argument looks apparently simple and straight forward, it is not known how exactly this shift of balance from pro- to anti-inflammatory pathway and M1 to M2 phenotype occurs is not clear. In this shift of balance from pro- to anti-inflammatory pathway and maintenance of balance between M1 and M2 macrophages, there seems to be a critical role for NO/CO/H₂S (nitric oxide/carbon monoxide/hydrogen sulfide) that have an important role in the acceleration of resolution of inflammation and tissue regeneration. This balance between pro- and anti-inflammatory status and M1 and M2 macrophages and factors that could be involved in their formation and action are critical for fighting viral infections HCV, HBV, SARS-CoV-2, SARS and MERS and restore homeostasis by inducing necessary tissue repair and regeneration and resolution of inflammation (see Figures 3B, 4, 5, and 6A).

Interaction between PGE₂ and LXA₄

Despite the fact that, in general, PGE₂ is considered as a pro-inflammatory bioactive lipid, studies did suggest that this prostaglandin can also have anti-inflammatory and immunosuppressive actions [170-176], especially, by altering macrophage polarization by MSCs (mesenchymal stem cells) [177-179]. This pro- and anti-inflammatory actions of PGE₂ seem to depend on its binding to different types of PGE₂ receptors (EPs) that is concentration dependent. At low concentrations, PGE₂ binds to the high-affinity EP₄ receptor and enhances IL-23 production [180], whereas high PGE₂ amounts bind to EP₂ receptor and suppresses IL-23 release [181, 182]. These results account for the dual pro and anti-inflammatory actions of PGE₂

[183]. Furthermore, PGE₂ can induce LXA₄ and suppress LTB₄ production by modulating 5- and 15-lipoxygenase expression and thus, enable pro-inflammatory status to be switched over to anti-inflammatory pathway (see Figure 7). This switchover from pro-inflammatory (LTB₄) pathway to the anti-inflammatory pathway (LXA₄) enables the removal of neutrophils from the site of inflammation and help in the resolution of inflammation [182-184]. This crosstalk between macrophages and neutrophil on one hand and PGE₂ and LXA₄ on the other enables induction of resolution of inflammation that is critical to dampen inflammation. This redirection of the formation of PGE₂ from AA to LXA₄ to induce resolution of inflammation seems to depend on the biphasic release of AA from the cell membrane lipid pool. The first pulse of release of AA occurs due to the activation of iPLA₂ (calcium independent phospholipase A₂) that is utilized for the formation of PGE₂ whereas the second phase of release of AA due to the activation of cPLA₂ (cytosolic phospholipase A₂) and sPLA₂ (**secreted phospholipase A₂**) is utilized for the formation of LXA₄ (see Figures 5-7). This implies that the cell has the unique ability to direct AA released by iPLA₂ to form PGE₂ and cPLA₂ and sPLA₂ induced release of AA for the formation of LXA₄. It is not clear whether other PGEs also have actions similar to PGE₂. For instance, PGE₁, derived from DGLA, is an anti-inflammatory, vasodilator, and platelet anti-aggregator, whose actions are remarkably similar to those of LXA₄. It is likely that PGE₁ may also enhance the formation of LXA₄. But this needs to be confirmed.

PGE₂ augments tissue regeneration

It is evident from these results [161-184] that once the inflammation and the concentrations of PGE₂ reach a peak, AA released from the cell membrane lipid pool is redirected to form LXA₄ instead of PGE₂ (see Figures 3B, 4 and 7). This redirection of AA metabolism from PGE₂ to LXA₄ is an essential step needed to induce resolution of inflammation [156, 183-185]. This attainment of PGE₂ concentration to peak not only initiates LXA₄ synthesis but also triggers simultaneously tissue regeneration. This is supported by the report that 15-PGDH-(15-prostaglandin dehydrogenase, a prostaglandin degrading enzyme) deficient mice not only have a twofold increase in bone marrow, colon, and liver PGE₂ levels but also showed increased fitness of these tissues with augmented hematopoietic capacity. These 15-PGDH deficient animals showed a rapid liver regeneration after partial hepatectomy and enhanced recovery of neutrophils, platelets, and erythrocytes [185]. Several other studies are in support of this observation that PGE₂ promotes hematopoiesis [186-189]. Thus, administration of PGE₂,

LXA4, AA, EPA and DHA, resolvins, protectins and maresins, which are potent inhibitors of IL-6, TNF- α and other pro-inflammatory cytokines [154–156, 182, 183] are expected to be of significant benefit in COVID-19. It is predicted that administration of appropriate amounts and in a timely manner of AA/PGE2/LXA4 and other bioactive lipids not only inactivate SARS-CoV-2 virus [117, 133, 135, 156, 163, 190, 191] but can prevent or even reverse inappropriate activation of coagulation, microvascular thrombosis and consumption of coagulation factors seen in those with severe COVID-19 and suppress cytokine storm [183, 191].

LXA4 mediates MSCs (mesenchymal stem cells) resolution of inflammation

It has been demonstrated that bone marrow derived MSCs can reduce the severity of acute lung injury by secreting LXA4, whereas blocking LXA4 receptor reversed this protective action. Furthermore, LXA4 by itself has been shown to suppress LPS-induced acute lung injury in experimental animals by decreasing the production of TNF- α and MIP-2. Both human alveolar epithelial type II cells and MSCs express biosynthetic enzymes and receptors for LXA4 [192, 193]. These results coupled with the observation that MSCs are effective in the treatment of diabetic nephropathy by secreting LXA4 that, in turn, downregulates TNF- α , IL-6, IL-8, and IFN- γ [194]. This may explain the beneficial action of MSCs reported in COVID-19 [195].

In addition, targeted PGE2 suppression has been shown to significantly improve survival against lethal influenza infection, whereas PGE2 administration enhanced mortality [196]. These results can be interpreted to indicate that when PGE2 synthesis is blocked in a specific fashion, there will be an increase in LXA4 synthesis since both PGE2 and LXA4 are derived from the same precursor AA that, in turn, is responsible for the beneficial action of inhibition of PGE2 pathway and thus, an increase in LXA4 formation is of benefit in the influenza and COVID-19 (see Figures 3B, 4, 6, 7). It is noteworthy that AA can also be metabolized by cytochrome P450 set of enzymes to form a variety of epoxyeicosatrienoic acids (EETs) that are also known to possess anti-inflammatory action. EETs are degraded by soluble epoxy hydrolase (sEH) and hence, inhibition of sEH will enhance their half-life and thus, their beneficial actions can be augmented. It is interesting to note that LXA4 inhibits the activity of sEH and supplementation of ALA (and possibly other fatty acids such as AA/EPA/DHA) has been shown to inhibit the activity of sEH [197, 198]. These results suggest that AA/EPA/DHA/LXA4/resolvins/protectins and maresins inhibit sEH activity and ultimately

enhance the concentrations of LXA4/resolvins/protectins/maresins and possibly, inhibit excess production of PGE2 and thus suppress inflammatory events seen in COVID-19 (see Figures 3B, 4, 6, 7).

Increased mortality due to COVID-19 in those with co-morbid conditions and BALs

It is known that those who have obesity, type 2 diabetes mellitus, hypertension, and coronary heart disease and even otherwise elderly have a degree of mortality if they get COVID-19. The exact cause of this is not clear. Previously, we showed that plasma levels of AA/EPA/DHA are low in these diseases suggesting that the activities of desaturases are defective or decreased leading to a deficiency of AA/EPA/DHA in them [199]. In addition, these fatty acids are needed to maintain normal cell membrane fluidity and integrity. Hence, AA/EPA/DHA deficiency will lead to alterations in the expression of ACE2 and SARS-CoV-2 cannot be inactivated by BALs (since their concentrations are below the physiological optimum levels) leading to an increase in the virulence of the virus. AA/EPA/DHA deficiency induced alterations in the cell membrane fluidity may enhance the binding of SARS-CoV-2 to ACE-2. This is supported by the recent report that SARS-CoV-2 spike (S) receptor binding domains (RBDs) tightly bind the essential free fatty acid (EFA) linoleic acid (LA) in three composite binding pockets. LA binding appears to stabilize a locked S conformation that results in reduced ACE2 interaction in vitro. In human cells, LA supplementation synergized with the COVID-19 drug remdesivir and suppressed SARS-CoV-2 replication [200]. It is likely that other PUFAs such as GLA, DGLA, AA, EPA and DHA may have similar properties and thus, selectively inhibit the binding of SARS-CoV-2 to ACE2 and inhibit viral replication as suggested previously [156, 183, 190, 191]. In such a scenario, deficiency of AA/EPA/DHA will also result in decreased formation of LXA4/resolvins/protectins/maresins and as a result the inflammatory process triggered by SARS-CoV-2 will flourish leading to cytokine storm.

Several studies suggested that children are unlikely to have severe COVID-19 and even if they develop the disease it is rather mild unlike in elderly who may have cytokine storm and consequently higher degree of mortality. This discrepancy in the clinical picture and mortality due to COVID-19 remains unexplained that can also be attributed to BALs. It is known that with increasing age there is a decrease in the activity of desaturases. Thus, elderly will have low activity of delta-6-desaturase and delta-5desaturase and so have a decrease in the plasma levels

of GLA/DGLA/AA/EPA/DHA. In addition, with increasing age there is a fall in the plasma circulating levels of LXA₄ [201]. Thus, deficiencies of AA/EPA/DHA and LXA₄ and low activities of desaturases may account for severe COVID-19 seen in the elderly and those with other co-morbid conditions. This could be rectified to a large extent by supplementation of AA/EPA/DHA. This is supported by the observation that supplementation/administration of AA does not increase the formation of PGE₂ and inflammatory process and in fact, may suppress inflammation [202-204]. AA can be given both orally and intravenously without any significant side effects and is safe to normal healthy subjects [205].

Young children are unlikely to have significant COVID-19 disease since they have high activity of desaturases and are able to form significant amounts of AA/EPA/DHA/LXA₄ when needed (see Figure 6). The robustness of the desaturase-PLA₂-BALs pathway in the children may render them less susceptible to the cytokine storm and COVID-19 infection and when this system fails, they may develop systemic multi-system inflammatory syndrome characterized by myocarditis, ARDS, and other features described in them.

Conclusions and therapeutic implications

It is evident from the preceding discussion that AA and other PUFAs can potentially inactivate SARS-CoV-2, SARS, MERS, HCV, HBV, and influenza viruses. Of all the unsaturated fatty acids, perhaps AA (AA > EPA = DHA) is the most potent in this ability. Studies suggested that AA need to undergo peroxidation to inactivate HCV and HBV since vitamin E that interferes with its (AA) peroxidation abrogated its (AA) anti-viral action [73-75, 157, 182].

Inflammatory events triggered by microbes including SARS-CoV-2 results in excess production of IL-6 and TNF- α and PGE₂ and LTs by leukocytes, macrophages, T cells and the target tissues that can be suppressed by BALs GLA/DGLA/AA/EPA/DHA and their metabolites LXA₄, resolvins, protectins and maresins. Thus, both inactivation of enveloped viruses and suppressing the associated inflammatory events is achieved by these BALs in association with anti-inflammatory cytokines. This implies that a delicate balance normally exists between pro and anti-inflammatory events and molecules involved in these processes that ultimately determines recovery and restoration of homeostasis. In addition, BALs also can regulate the plasticity of macrophages to enable them to switch from M1 to M2 phenotype (or

vice versa) (see Figure 5). Based on these evidences, it is reasonable to propose that administration of AA/EPA/DHA could be of significant benefit in SARS-CoV-2, SARS, and MERS (and in HCV and HBV and influenza) infections. These PUFAs could be administered orally and/or intravenously without any significant side effects. It is not unreasonable to suggest that suitable preparations of PUFAs could be prepared for their intranasal administration.

Recent studies did suggest that formation of neutrophil extracellular traps (NETs)-may contribute to organ damage and mortality in COVID-19 [206]. It is noteworthy that NETs formation can be modulated (enhance or suppress their formation as the situation demands) by LXA4/resolvins/protectins/maresins [207-210], yet another mechanism by which BALs are of potential therapeutic benefit in COVID-19. BALs are also capable of inhibiting janus kinase (JAK) and thus, may bring about their beneficial action in COVID-19 [211-214]. Thus, BALs have several actions that attest to the fact that they are of benefit in COVID-19. In addition, corticosteroids are known to inhibit the activities of PLA2, desaturases, COX-2 and LOX enzymes and thus, may bring about their immunosuppressive action, at least, in part by inhibiting the formation of PGE2. It is paradoxical that corticosteroids inhibit the formation of LXA4 > LTB4 that may explain why steroids interfere with the resolution of inflammation and wound healing process. Thus, continued use of corticosteroids results in an EFA deficiency state and leads to decreased formation of LXA4, resolvins, protectins and maresins. This may explain why dexamethasone is beneficial only in mild to moderately severe COVID-19 but not those who are critically ill. The more critically ill with COVID-19 are expected to have an EFA deficiency state and hence, are unlikely to respond since they do not have adequate cellular/plasma content of AA/EPA/DHA to form appropriate amounts of PGE2 and LXA4 to resolve inflammation and augment wound healing [117, 133-136]. This may explain as to why those with COVID-19 who have high levels of cortisol on admission to hospital have a substantially increased risk of dying [215] since they are more likely to have high degree of EFA deficiency state. Hence, if these patients are supplemented with BALs along with other treatment options are expected to respond favorably.

It is worth noting that glucocorticoids in addition to inhibiting the expression of PLA2, COX-2, LOX, and desaturases enhance the expression of annexin-1 also called as lipocortin 1. Annexin-1 shows all the actions of glucocorticoids and induces anti-inflammatory cytokine IL-10. Annexin-1 suppresses the expression of TNF- α , IL-6, and other cytokines [216]. For the

anti-inflammatory action of annexin-1, there is an essential role for LXA4. Both LXA4 and/or annexin-1 seem to enhance the production of IL-10, which suppresses TNF- α action and the consequent tissue injury and lethality [217]. Thus, there is a complex and inter-dependent interaction among PLA2, COX-2, desaturases, annexin-1 and LXA4 in the anti-inflammatory action of corticosteroids.

The recent observation that patients who took statins are likely to have much reduced mortality rate [218, 219] can be related to their action on EFA metabolism [220- 223]. Statins are known to enhance the formation of AA and LXA4 and thus, bring about their beneficial actions. This action of statins on the bioactive lipids is one of the reasons for their anti-inflammatory action. Similarly, the less frequent and mild disease seen in children and decreased incidence of COVID-19 in women can also be ascribed to BALs. For instance, the activity of desaturases decreases with age (see Figure 6B), whereas estrogen stimulates LXA4 synthesis [224, 225]. Thus, it is anticipated that children have a higher capacity to generate GLA, DGLA, AA, EPA and DHA that can be converted to form beneficial LXA4, resolvins, protectins and maresins to fight SARS-CoV-2. On the other hand, pre-menopausal women generate significantly higher amounts of LXA4 due to the stimulatory action of estrogen and thus, are resistant and less likely to develop severe COVID-19. Similarly, even the beneficial action of blocking GM-CSF and administration of colchicine in COVID-19 can be related to their ability to modulate BALs [226-230]. The property of colchicine to potentiate the actions of PGE1 is especially interesting since both PGE1 and LXA4 have similar actions.

A recent study reported that circulating levels of IL-2, IL-4, TNF- α , IFN- γ and C-reactive protein are not associated with severity of COVID-19 symptoms. This indicates that there could be two phases in the pathobiology of COVID-19, one phase characterized by hyperinflammation in the beginning of the disease and another phase of immunosuppression with little or no changes in the pro-inflammatory cytokines as seen in sepsis [231-233]. If this is true, then it will be hazardous to administer dexamethasone, anti-cytokine and other immunosuppressive therapies during the immunosuppressive phase of COVID-19. Hence, one needs to exercise caution in rushing to administer immunosuppressive therapies without measuring plasma cytokines levels and viral load (see Figures 8 and 9).

It was reported that H₂ blockers such as famotidine could be of significant benefit in those who are admitted with COVID-19 [234, 235]. Those who have taken famotidine were found to have better outcome. The exact cause for this benefit is not clear. Famotidine could inhibit 3-chymotrypsin-like protease, the enzyme that processes proteins essential for viral replication. At this juncture, it is noteworthy that famotidine enhances AA formation and thus, augments duodenal ulcer healing. Patients with peptic ulcer have low plasma concentrations of AA that reverted to normal following famotidine, fish oil and ARASCO oil (AA rich oil) treatments [236-238]. These results emphasize the importance of AA and other BALs in the pathobiology of peptic ulcer disease and their role in wound healing. It is also significant to know that *Helicobacter Pylori*, the organism that is responsible for peptic ulceration, can be inhibited by BALs [239-240] that is in tune with the anti-microbial action of BALs.

Impaired interferon (IFN) type I response in the form of no IFN- β and low IFN- α production and activity was described in those with severe COVID-19 associated with a persistent blood viral load (SARS-CoV-2) and an exacerbated inflammatory response. In these patients, inflammation was found to be driven by upregulation of NF- κ B and enhanced production of TNF- α and IL-6 [241, 242]. These data imply that type I IFN deficiency could be a hallmark of severe COVID-19 suggesting that IFN therapy is indicated in these patients. This is supported by the observation that severe COVID-19 is associated with impaired T cell responses in the form of lymphopenia and functional exhaustion of CD4⁺ and CD8⁺ T cells possibly, due to deficient IFN production. Furthermore, deficient, or dysregulated IFN responses observed in SARS-CoV-2 infection may influence the generation of T_{reg} cells during the recovery phase of COVID-19.

TNF- α and IL-6 enhance PGE₂ and thus, may indirectly suppress LXA₄ concentrations, whereas both PGE₂ and LXA₄ and their precursor AA decrease TNF- α , IL-6 and IFN production [154, 155, 243-245]. IFN seems to bring about its actions by activating phospholipase C, D and A₂ to induce the release of AA (and possibly GLA, DGLA, EPA and DHA) that can be converted to PGE₂ and LXA₄ [246-248]. PGE₂, LXA₄, AA, EPA and DHA are potent inhibitors of IFN production [249-254] and IFN can both enhance and decrease PGE₂ synthesis depending on the context [255, 256]. These results could be interpreted to imply that if the production of IFN is optimum it leads to synthesis and release of adequate

amounts of PGE₂ to induce the required degree of inflammation. This optimal action of IFN, PGE₂ production and inflammatory reaction results in the initiation of inflammation resolution process such that homeostasis is restored. In the event the levels of IFN is inadequate as seen in severe COVID-19, the production of PGE₂ will be suboptimal and so the inflammatory process is not adequate to initiate resolution of inflammation that results in persistence of inflammation as seen in severe COVID-19. This altered PGE₂ production can result in inadequate LXA₄ production and failure of wound healing. Furthermore, both PGE₂ and LXA₄ inhibit IFN and TNF- α production, whereas IFN and TNF- α are inducers of PGE₂ production. Similar interaction between EPA/DHA and their eicosanoids is expected on IFN and TNF- α . IFN (IFN- γ but not IFN- α and IFN- β) can enhance the production of TNF- α [257-259]. This positive and negative feedback among AA/EPA/DHA/GLA/DGLA/PGE₂, LXA₄, resolvins, protectins and maresins and IFN and TNF- α is needed to effectively eliminate SARS-CoV-2 and other microbes and eventually restore homeostasis. Thus, inadequate production of IFN- α in those with COVID-19 (that may in part be due to inadequate tissue content of GLA, DGLA, AA, EPA, DHA) leads to relatively low (but more than normal) levels of PGE₂ [260] and excess of LXA₄ (this ratio between PGE₂ and LXA₄ is relative). As a result of this relative deficiency of PGE₂, excess production of TNF- α and IL-6 occurs leading to cytokine storm seen in severe COVID-19. Excess TNF- α causes decreased formation of AA/EPA/DHA due to its inhibitory action on desaturases [137]. This further aggravates deficiency of AA/EPA/DHA that can result in persistent excess production of TNF- α and IL-6 due to the absence of negative feedback regulation of these fatty acids on cytokines. In this scenario, administration of GLA/DGLA/AA/EPA/DHA may be of significant benefit to suppress excess production of TNF- α and IL-6 and restore LXA₄ levels to normal and halt this vicious circle of events. This implies that use of IFN alone will not be of benefit in COVID-19 unless and otherwise it is co-administered with BALs.

This imbalance in the immune response, cytokines and BALs is supported by the observation that in those with severe COVID-19 the germinal centers (where B and T cells are formed meet the demands of infections for adequate immune response) in the thoracic lymph nodes and spleens are absent that seems to be associated with high plasma levels of TNF- α implying that this cytokine is suppressing the immune system [261, 262]. These results are interesting in the light of the observation that 15-PGDH deficient animals not only have a

twofold increase in bone marrow, colon, and liver PGE₂ levels but also showed augmented hematopoietic capacity [185]. This implies that AA/EPA/DHA, IFN, TNF- α and PGE₂ dysregulation results in inadequate immune response in COVID-19 (see Figure 10).

The recent report that bradykinin may have a critical role in cytokine storm seen in COVID-19 [263] can also be explained in terms of BALs. For instance, it is known that GLA, EPA and DHA (and possibly AA, PGE₂, LXA₄) can alter cell membrane fluidity and thus, alter the binding characteristics of bradykinin receptor (B₂R) to bradykinin [264]. In addition, bradykinin stimulates PLA₂ and enhances PGE₂ formation [265-267]. PGE₂ restrains mast cell activity and LXA₄ can resolve inflammation induced by mast cell degranulation [268-270]. These results imply that the actions of bradykinin can be regulated and inhibited by LXA₄ and other similar compounds resolvins, protectins and maresins (see Figure 11). Based on the concepts proposed here, we successfully treated 10 consecutive patients of COVID-19 by the administration of oral BALs, oral and inhalation of corticosteroids and heparin, oral B1, B6, B12 and vitamin C (that form co-factors of EFA metabolism), and insulin (for hyperglycemia and incidentally it has anti-inflammatory action and enhances the activities of desaturases). In this open label study, 5 were asymptomatic, 3 had mild disease and 2 had moderately severe disease with co-morbid conditions type 2 diabetes mellitus, hypertension, and coronary heart disease. All have recovered completely without any side effects. **In addition, these patients were on statins that are known to be of benefit in COVID-19 [271, 272].**

Future research strategies and therapeutic implications

The concepts presented here can be verified by studying the effect of BALs (especially AA, EPA, DHA, LXA₄, resolvins, protectin and maresins) on the survival and proliferation of SARS-CoV-2, SARS, and MERS in vitro and in vivo. It is predicted that BALs, especially LA and AA inactivate SARS-CoV-2, SARS, and MERS. Studies need to be performed to know whether PUFAs and their metabolites can influence the plasticity of macrophages to form M1 and M2 phenotypes. It is important to evaluate the role of desaturases, COX-2 and 5-, 12-, and 15-LOX enzymes and different types of phospholipases in COVID-19. It is predicted that those who have severe COVID-19 will show exaggerated expression of PLA₂ and COX-2, whereas those who recover from COVID-19 are likely to show both COX-2 and 12-LOX and 15-LOX expression resulting in synthesis and release of adequate amounts of LXA₄ to result in resolution of

inflammation (see Figs. 5-8). This can be confirmed by measuring plasma levels of various BALs that will throw light whether a deficiency of LXA4, resolvins, protectins and maresins could be responsible for the severe COVID-19 and high degree mortality. It is predicted that timely production of PGE2 and LXA4 may fail to occur in these patients (see Figs. 5-8). Similarly, a close association between the plasma levels of IL-6, TNF- α and IFN and various BALs could be seen that could be correlated to the clinical picture.

Based on the evidence presented here, it is suggested that LA, GLA, DGLA, AA, EPA and DHA could be administered to prevent and manage COVID-19. Of all the BALs, it is likely that LA and AA may be of significant benefit in the treatment of COVID-19. The clinical implications of potential use of BALs in the prevention and treatment of COVID-19 lies in the fact that the antibodies developed against SARS-CoV-2 (either due to infection or immunization) may not last long enough to prevent a second infection. Alternatively, SARS-CoV-2 may undergo substantial mutation(s) such that the initial immunization against the current strain(s) may not work against the mutated viruses. In such a scenario, it is worthwhile to investigate whether a combination of vaccine against SARS-CoV-2 and BALs (especially LA and AA) will be of significant benefit in preventing COVID-19. Since BALs have the broad property of inactivating all types of enveloped viruses, it is likely that their (BALs, especially AA) administration may work in the prevention and treatment of all types of SARs viruses irrespective of changes in their genome.

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Dedication: This work is dedicated to my teacher Prof. E N B Sarma, guide, adviser, and philosopher.

Legends to figures and tables:

Legends to Figures and Tables:

Figure 1A. Structure of SARS-CoV-2 that causes COVID-19. Note the structural similarity with Swine flu virus given in Figure 1B.

Figure 1B. Structure of the Swine flu A/Mexico/09 (H1N1) virus.

For comparison between influenza virus and the corona virus see Table 2.

Figure 2. Scheme showing the actions of ACE and ACE2 and their role in the regulation of blood pressure, humoral balance, inflammation, cell proliferation, hypertrophy, and fibrosis.

The ACE/AngII/AT1R axis and the ACE2 / Ang 1-7 / MAS axis balance each other. Ang 1-7 is known to restore polyunsaturated fatty acids content of cells to normal especially in diabetes mellitus. Thus implies that there is a close interaction between Ang 1-7 and BALs and possibly some of the beneficial actions of Ang 1-7 on vascular tissue could be due to its actions on EFA metabolism (see Singh K, Singh T, Sharma PL. J Exp Pharmacol 2010; 2: 163–168. DOI: 10.2147/JEP.S14342).

Figure 3A. Scheme showing the metabolism of essential fatty acids, their role in inflammation and cytoprotection of endothelial cells.

Note that corticosteroids block the activity of PLA₂, desaturases, COX-2 and LOX and thus, produce EFAs/PUFAs deficiency, inhibit the formation of PGE₂ and LTs and of LXA₄/resolvins, protectins and maresins. Statins enhance the activities of desaturases and increase the formation of GLA, DGLA, AA and of LXA₄/resolvins/protectin/maresins. TNF- α and IL-6 decrease the activity of desaturases and thus, decrease the formation of GLA, DGLA and AA but enhance the activity of COX-2 and thus, produce EFA/PUFAs deficiency but increase the formation of PGE₂. TNF- α and IL-6 stimulate PLA₂ and thus, increase the release of AA from the cell membrane lipid pool. Thus, both corticosteroids and TNF- α and IL-6 produce EFA/PUFAs deficiency state but have opposite actions on PLA₂, and PGE₂ formation.

Figure 3B. Scheme showing the relationship among SARS-CoV-2 and other enveloped viruses induced events on EFA metabolism, pro- and anti-inflammatory cytokines and their modulation by steroids and statins. For details see text. Modified from Das UN. J Inflammation Res 3: 143–170.

Figure 4. A. Scheme showing potential interaction(s) among invading microbes including SARS-CoV-2, host cell (target tissue/cell), immunocytes including macrophages and bioactive lipids including GLA/DGLA/AA/EPA/DHA, LXA4, PGE2, lipid peroxides (LP), activity of PLA2 COX-2 and LOX enzymes, CO, NO, H₂S, and soluble epoxide hydrolase (sEH) and their relationship to the ability of microbes to infect the host cell and the response of host cell to infection. **B.** Similarly, potential interaction between tumor host cell (refers to surrounding normal cells present in the microenvironment of tumor) and the role of COX-2, LOX enzymes and the formation of PGE2/LXA4 and their effect(s) on tumor cell.

Legend to figure 4:

(A) When a microbe (including SARS-CoV-2) invades a normal cell (host cell), it may increase the production of PGE₂ using its own (or host cell) COX-2. Microbe (using its LPS) or by activating host cell LOX enzymes leads to the formation of LXA₄ that negates the synthesis or action of PGE₂. Microbial infection activates immunocytes leading to release of IL-6, TNF- α that enhance the production of NO, CO, H₂S and other ROS that can kill the microbes. Microbes can also activate PLA₂ that induces the release of AA/EPA/DHA from the cell membrane lipid pool that are utilized for the formation of PGE₂, LXA₄ and lipid peroxides. Depending on the stage of the inflammation initially there will be activation of iPLA₂ (inducible phospholipase A₂) that induces the release of AA that is directed to form PGE₂ and activation of M1 resulting in inflammation. Once PGE₂ levels reach the peak it triggers the activation of soluble PLA₂ (sPLA₂) and cytosolic PLA₂ (cPLA₂) inducing the release of second wave of AA and simultaneously activation of LOX leading to the formation of LXA₄ and M₂. This results in suppression of inflammation and restoration of homeostasis. BALS especially AA/EPA/DHA/LXA₄ and lipid peroxides kill the microbes including SARS-CoA₂. Lipid peroxides, LXA₄ and AA/EPA/DHA may inhibit the activity of soluble epoxide hydrolase that leads to suppression of inflammation. Mesenchymal stem cells (MSCs) produce LXA₄ to bring about their beneficial actions.

(B) Similar set of events occur in the presence of tumor cell. There is a crosstalk between normal cells surrounding the tumor cell and immunocytes. Tumor cells have high COX-2 activity that may lead to increased formation of PGE₂ (COX-2 of tumor cells may act on normal cells or on exposure to tumor cells normal cells may enhance their COX-2 activity). On exposure to tumor cell, PLA₂ of normal cells/immunocytes is activated to induce the release of AA/EPA/DHA to produce PGE₂ or LXA₄. If the released AA/EPA/DHA are converted to form excess of lipid peroxides and/or LXA₄, then tumor cell growth is inhibited or undergoes apoptosis. If the activity of COX-2 dominates then AA is converted to PGE₂ that induce immunosuppression and enhances tumor cell growth. IL-6 and TNF- α released by immunocytes induce the release of ROS that can enhance the formation of lipid peroxides to induce apoptosis of tumor cells. But both IL-6 and TNF- α can induce deficiency of AA/EPA/DHA in the tumor cells and surrounding normal cells and immunocytes by inhibiting the activities of desaturases.

See text for further details.

Figure 5. Scheme showing M1 and M2 macrophages and various cytokines produced by them and their respective functions.

DGLA, AA, EPA and DHA have anti-inflammatory actions and inhibit the production of pro-inflammatory TNF- α , IL-2 and IL-1 and facilitate the generation of M2 macrophages.

PGE₁ formed from DGLA, LXA₄ from LXA₄ are anti-inflammatory in nature.

Resolvins (R), protectins (P), and maresins (M) formed from EPA and DHA are anti-inflammatory and block the production of TNF, IL-1, IL-2.

PGE₂, Leukotrienes B₄, D₄ and E₄ formed from AA are pro-inflammatory in nature.

LXA₄, resolvins, protectins and maresins inhibit the production of PGE₂ and LTs.

Leukotrienes (of 5 series) are also formed from EPA that have pro-inflammatory action but are much less potent compared to LTs formed from AA.

EPA and DHA inhibit the production of PGE₂.

Figure 6A. Scheme showing potential relationship among AA, PGE₂, LXA₄ and viral load in a COVID-19 patient who recovers. AA is released from the cell membrane in two phases, first

phase is used for PGE₂ synthesis, whereas the second phase is meant for LXA₄ synthesis. Once PGE₂ concentration reaches its peak, LXA₄ synthesis is triggered that induces resolution of inflammation. AA release is triggered by SARS-CoV-2 and other infections.

Figure 6B. Scheme showing potential relationship among AA, PGE₂, LXA₄ and viral load in a COVID-19 patient who succumbs to the disease. Absence of biphasic nature of AA release and failure of PGE₂ to reach its peak to trigger LXA₄ synthesis that results in failure of resolution of inflammation fails (compare with Fig 7A). DGLA, EPA and DHA (not shown in the figure) may have actions/functions like AA. Desaturases activities fall with age.

Figure 7. Scheme showing the metabolism of AA and how pro-inflammatory LTA₄ can be converted to anti-inflammatory LXA₄ by the action of PGE₂. Similar conversion of pro-inflammatory PGs, TXs and LTs to anti-inflammatory resolvins, protectins and maresins may occur.

Figure 8. Scheme of events that are likely to occur in SARS-CoV-2 infection and the two phases of cytokine response in COVID-19. Initially there will be hyperinflammation due to release of excess of pro-inflammatory cytokines. Subsequently there could occur diminished release of cytokines and immunosuppression. During the hyperinflammation phase dexamethasone and anti-TNF or anti-IL-6 and other cytokine antagonists will be helpful. Once immunosuppression sets in dexamethasone is not of significant help and inflammation resolution molecules are needed to enhance recovery process. In severe COVID-19 there will be persistently elevated PGE₂ and LXA₄ fails to rise to induce resolution of inflammation. In contrast, in mild COVID-19, initially there will be an elevation in PGE₂ that falls to the normal physiological level that is accompanied by increase in LXA₄ to induce resolution of inflammation as shown in the figure. Compare this with figure 9. This figure is modified from Das UN. Arch Med Sci 2014; 10: 325–335.

Figure 9. Viral and host factors influence IFN response. When the viral burden is low, IFN production will be adequate to clear the viral infection effectively that is probably accompanied by initial PGE₂ response and timely LXA₄ generation to resolve inflammation. When viral load is high, virus itself may suppress IFN production and stimulate strong PGE₂ and weak LXA₄ responses leading to severe COVID-19. Late onset IFN response may aggravate inflammation as seen in severe COVID-19. PGE₂ response may parallel IFN response. AA release will occur in both mild and severe SARS-CoV-2 infection, but the product formed, and their concentrations (PGE₂ and LXA₄) may differ as shown in the figure. Compare this with figures 5 and 6.

Figure 10. Scheme showing interaction among SARS-CoV-2, host cells, immunocytes, AA and cytokines. Similar interaction may exist among SARS-CoV-2, host cells/immunocytes, EPA/DHA and resolvins, protectins and maresins.

Figure 11. Scheme showing potential involvement of bradykinin in severe COVID-19 as proposed by Garvin et al (263) and how it could be modulated by BALs.

Table 1. Comparison between Influenza virus and coronavirus (see Figures 1A and 1B also).

Table 2. Clinical features of COVID-19.

Preprint

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Figure 1A. Structure of SARS-CoV-2 that causes COVID-19. Note the structural similarity with Swine flu virus given in Figure 1B.

Figure 1B. Structure of the Swine flu A/Mexico/09 (H1N1) virus.

For comparison between influenza virus and the corona virus see Table 2.

Table 1. Comparison between Influenza virus and coronavirus (see Figures 1A and 1B also).

S.No	Influenza Virus	Corona virus
a.	Family: Orthomyxoviridae	Coronaviridae
b.	Genetic material: ssRNA (mostly) dsRNA rarely	ssRNA
c.	Subtypes: A, B, C, D	Alpha, beta, gamma and delta coronavirus
d.	Influenza type A is most common with 12 serotypes	Beta corona virus is the most common subtype affecting humans
e.	Type B is less common and has 2-3 times slower mutation rates	
f.	Structure: Size: 80-120nm Envelope: Glycoproteins- Hemagglutinin responsible for binding to host cells Neuraminidase for release of progeny virus from infected cells Genome: Mostly Segmented negative sense RNA e.g: Type A has 11 genes on 8 pieces of negative RNA each coding for different gene Replication: RNA dependent RNA polymerase	Size: 125nm Envelope: Has lipid bilayer which has M: membrane E: envelope S: spike proteins are anchored E:S:M= 1:20:300 Also has short spike ptn: hemagglutinin esterase Genome: positive ss RNA as bead on strand formation Size: 26.4 o 31.7kb with 5'-mehylated cap and 3'-poly A tail 2/3 rd of genome codes for replicase/transcriptase non- structural protein. 4 structural proteins are: spike, envelope, membrane nucleocapsid
g.	Incubation time: Short incubation time	5-6 days, sometimes longer
h.	Secondary infections: less common	Highly prevalent
i.	Primary carriers: children	adults
j.	Mortality rate: <0.1%	3-4%

Table 2. Clinical features of COVID-19.

- A. Asymptomatic:** The vast majority of healthy younger people don't develop a critical form of COVID-19. Though, some young people are seriously affected. The risk appears to rise with age and other associated diseases. In persons above the age of 60 and those who have heart disease, lung diseases (including smokers), kidney disease or immune deficiency or had a transplant are more vulnerable and may develop severe disease. However, loss of sense of smell seems to occur in many and have no other symptoms. Currently, it is estimated that ~50-75% are asymptomatic.
- B. Mild COVID-19:** Most people below the age of 60 and as many as ~80% of symptomatic cases will have this form of mild illness that lasts about 7-10 days. These people may have:
- i. Fever in 90% of cases
 - ii. Dry cough (70%)
 - iii. Tiredness (40%)
 - iv. Feeling slightly breathless (20%)
 - v. Muscle pains (15%)
 - vi. Headache (15%)
 - vii. Sore throat (14%)
 - viii. Diarrhea (4%)
 - ix. Running nose, sore or red eyes and vomiting and low mood may also occur in some.
- C. Moderate COVID-19:** People with moderate illness that also lasts about 7-14 days are more breathless and have tachycardia, may have cough and increasing breathlessness. The features of moderate COVID-19 include:
- i. Temperature $> 37.8^{\circ}\text{C}$
 - ii. Feeling breathless even on moderate exercise such as walking upstairs.
 - iii. Soreness due to cough
 - iv. Moderate to persistent cough, several times an hour.
 - v. Headache

- vi. Tiredness even if they stay in bed
- vii. A dry mouth.

D. **Severe COVID-19:** These are the patients who have developed pneumonia. Features of this form of COVID-19 include:

- i. Extreme breathlessness-such as unable to speak
- ii. Pain in the chest, abdomen or back
- iii. A high temperature
- iv. Tightness in the chest
- v. Anorexia
- vi. Confusion
- vii. Rapid and shallow breathing
- viii. Tachycardia
- ix. Looking sick
- x. Low blood pressure (<90/60 mm Hg)

E. **Critical COVID-19:** These are the people who have developed severe pneumonia and are on the verge of developing ARDS or already have developed ARDS. These people may also have sepsis. These are the patients who may need O₂ therapy or ventilatory and other supportive care in a hospital setting.

F. **Post-COVID-19 likely complications:**

- (i) **CVS:** myocarditis, CHF, venous and arterial thrombosis.
- (ii) **Respiratory:** persistent dyspnea, cough, lung fibrosis, ?COPD.
- (iii) **CNS:** confusion, memory loss, lethargy, Parkinson's disease, speech defects, tremors, gait abnormalities, venous and arterial thrombosis.
- (iv) **Immune system:** immune complex disease-like picture, increased susceptibility to infections.
- (v) **Renal system:** Renal failure, nephrotic syndrome, nephritis.

- (vi) **Endocrine system:** Worsening of existing diabetes mellitus or development of diabetes mellitus in a non-diabetic; other endocrine abnormalities may occur but not yet documented.

G. COVID-19 and pregnancy: The impact of SARS-CoV-2 infection on pregnancy and its outcome are not clear. The current evidence indicates that COVID-19 does not have much adverse impact on pregnancy. Newborn to COVID-19 pregnant women do not seem to have any adverse effect. But long-term consequences of mother's SARS-CoV-2 infection on the growth and development of children remains to be established.

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Figure 2. Scheme showing the actions of ACE and ACE2 and their role in the regulation of blood pressure, humoral balance, inflammation, cell proliferation, hypertrophy, and fibrosis.

The ACE/AngII/AT1R axis and the ACE2 / Ang 1-7 / MAS axis balance each other. Ang 1-7 is known to restore polyunsaturated fatty acids content of cells to normal especially in diabetes mellitus. Thus implies that there is a close interaction between Ang 1-7 and BALs and possibly some of the beneficial actions of Ang 1-7 on vascular tissue could be due to its actions on EFA metabolism (see Singh K, Singh T, Sharma PL. J Exp Pharmacol 2010; 2: 163–168. DOI: 10.2147/JEP.S14342).

Figure 3A. Scheme showing the metabolism of essential fatty acids, their role in inflammation and cytoprotection of endothelial cells.

Note that corticosteroids block the activity of PLA₂, desaturases, COX-2 and LOX and thus, produce EFAs/PUFAs deficiency, inhibit the formation of PGE₂ and LTs and of LXA₄/resolvins, protectins and maresins. Statins enhance the activities of desaturases and increase the formation of GLA, DGLA, AA and of LXA₄/resolvins/protectin/maresins. TNF- α and IL-6 decrease the activity of desaturases and thus, decrease the formation of GLA, DGLA and AA but enhance the activity of COX-2 and thus, produce EFA/PUFAs deficiency but increase the formation of PGE₂. TNF- α and IL-6 stimulate PLA₂ and thus, increase the release of AA from the cell membrane lipid pool. Thus, both corticosteroids and TNF- α and IL-6 produce EFA/PUFAs deficiency state but have opposite actions on PLA₂, and PGE₂ formation.

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Figure 3B. Scheme showing the relationship among SARS-CoV-2 and other enveloped viruses induced events on EFA metabolism, pro- and anti-inflammatory cytokines and their modulation by steroids and statins. For details see text. Modified from Das UN. J Inflammation Res 3: 143–170.

Figure 4. A. Scheme showing potential interaction(s) among invading microbes including SARS-CoV-2, host cell (target tissue/cell), immunocytes including macrophages and bioactive lipids including GLA/DGLA/AA/EPA/DHA, LXA4, PGE2, lipid peroxides (LP), activity of PLA2 COX-2 and LOX enzymes, CO, NO, H2S, and soluble epoxide hydrolase (sEH) and their relationship to the ability of microbes to infect the host cell and the response of host cell to infection. **B.** Similarly, potential interaction between tumor host cell (refers to surrounding normal cells present in the microenvironment of tumor) and the role of COX-2, LOX enzymes and the formation of PGE2/LXA4 and their effect(s) on tumor cell.

Legend to figure 4:

- (C) When a microbe (including SARS-CoV-2) invades a normal cell (host cell), it may increase the production of PGE₂ using its own (or host cell) COX-2. Microbe (using its LPS) or by activating host cell LOX enzymes leads to the formation of LXA₄ that negates the synthesis or action of PGE₂. Microbial infection activates immunocytes leading to release of IL-6, TNF- α that enhance the production of NO, CO, H₂S and other ROS that can kill the microbes. Microbes can also activate PLA₂ that induces the release of AA/EPA/DHA from the cell membrane lipid pool that are utilized for the formation of PGE₂, LXA₄ and lipid peroxides. Depending on the stage of the inflammation initially there will be activation of iPLA₂ (inducible phospholipase A₂) that induces the release of AA that is directed to form PGE₂ and activation of M1 resulting in inflammation. Once PGE₂ levels reach the peak it triggers the activation of soluble PLA₂ (sPLA₂) and cytosolic PLA₂ (cPLA₂) inducing the release of second wave of AA and simultaneously activation of LOX leading to the formation of LXA₄ and M₂. This results in suppression of inflammation and restoration of homeostasis. BALS especially AA/EPA/DHA/LXA₄ and lipid peroxides kill the microbes including SARS-CoA₂. Lipid peroxides, LXA₄ and AA/EPA/DHA may inhibit the activity of soluble epoxide hydrolase that leads to suppression of inflammation. Mesenchymal stem cells (MSCs) produce LXA₄ to bring about their beneficial actions.
- (D) Similar set of events occur in the presence of tumor cell. There is a crosstalk between normal cells surrounding the tumor cell and immunocytes. Tumor cells have high COX-2 activity that may lead to increased formation of PGE₂ (COX-2 of tumor cells may act on normal cells or on exposure to tumor cells normal cells may enhance their COX-2 activity). On exposure to tumor cell, PLA₂ of normal cells/immunocytes is activated to induce the release of AA/EPA/DHA to produce PGE₂ or LXA₄. If the released AA/EPA/DHA are converted to form excess of lipid peroxides and/or LXA₄, then tumor cell growth is inhibited or undergoes apoptosis. If the activity of COX-2 dominates then AA is converted to PGE₂ that induce immunosuppression and enhances tumor cell growth. IL-6 and TNF- α released by immunocytes induce the release of ROS that can

enhance the formation of lipid peroxides to induce apoptosis of tumor cells. But both IL-6 and TNF- α can induce deficiency of AA/EPA/DHA in the tumor cells and surrounding normal cells and immunocytes by inhibiting the activities of desaturases.

See text for further details.

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Figure 5. Scheme showing M1 and M2 macrophages and various cytokines produced by them and their respective functions.

DGLA, AA, EPA and DHA have anti-inflammatory actions and inhibit the production of pro-inflammatory TNF- α , IL-2 and IL-1 and facilitate the generation of M2 macrophages.

PGE1 formed from DGLA, LXA4 from LXA4 are anti-inflammatory in nature.

Resolvins (R), protectins (P), and maresins (M) formed from EPA and DHA are anti-inflammatory and block the production of TNF, IL-1, IL-2.

PGE2, Leukotrienes B4, D4 and E4 formed from AA are pro-inflammatory in nature.

LXA4, resolvins, protectins and maresins inhibit the production of PGE2 and LTs.

Leukotrienes (of 5 series) are also formed from EPA that have pro-inflammatory action but are much less potent compared to LTs formed from AA.

EPA and DHA inhibit the production of PGE2.

Figure 6A. Scheme showing potential relationship among AA, PGE2, LXA4 and viral load in a COVID-19 patient who recovers. AA is released from the cell membrane in two phases, first

phase is used for PGE₂ synthesis, whereas the second phase is meant for LXA₄ synthesis. Once PGE₂ concentration reaches its peak, LXA₄ synthesis is triggered that induces resolution of inflammation. AA release is triggered by SARS-CoV-2 and other infections.

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Severe COVID-19 (SARS-CoV-2) with ARDS

Figure 6B. Scheme showing potential relationship among AA, PGE₂, LXA₄ and viral load in a COVID-19 patient who succumbs to the disease. Absence of biphasic nature of AA release and

failure of PGE₂ to reach its peak to trigger LXA₄ synthesis that results in failure of resolution of inflammation fails (compare with Fig 7A). DGLA, EPA and DHA (not shown in the figure) may have actions/functions like AA. Desaturases activities fall with age.

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Figure 7. Scheme showing the metabolism of AA and how pro-inflammatory LTA4 can be converted to anti-inflammatory LXA4 by the action of PGE2. Similar conversion of pro-inflammatory PGs, TXs and LTs to anti-inflammatory resolvins, protectins and maresins may occur.

Figure 8. Scheme of events that are likely to occur in SARS-CoV-2 infection and the two phases of cytokine response in COVID-19. Initially there will be hyperinflammation due to release of excess of pro-inflammatory cytokines. Subsequently there could occur diminished release of cytokines and immunosuppression. During the hyperinflammation phase dexamethasone and anti-TNF or anti-IL-6 and other cytokine antagonists will be helpful. Once immunosuppression sets in dexamethasone is not of significant help and inflammation resolution molecules are needed to enhance recovery process. In severe COVID-19 there will be persistently elevated PGE2 and LXA4 fails to rise to induce resolution of inflammation. In contrast, in mild COVID-19, initially there will be an elevation in PGE2 that falls to the normal physiological level that is accompanied by increase in LXA4 to induce resolution of inflammation as shown in the figure. Compare this with figure 9. This figure is modified from Das UN. Arch Med Sci 2014; 10: 325–335.

Figure 9. Viral and host factors influence IFN response. When the viral burden is low, IFN production will be adequate to clear the viral infection effectively that is probably accompanied by initial PGE2 response and timely LXA4 generation to resolve inflammation. When viral load is high, virus itself may suppress IFN production and stimulate strong PGE2 and weak LXA4 responses leading to severe COVID-19. Late onset IFN response may aggravate inflammation as seen in severe COVID-19. PGE2 response may parallel IFN response. AA release will occur in both mild and severe SARS-CoV-2 infection, but the product formed and their concentrations (PGE2 and LXA4) may differ as shown in the figure. Compare this with figures 5 and 6.

Figure 10. Scheme showing interaction among SARS-CoV-2, host cells, immunocytes, AA and cytokines. Similar interaction may exist among SARS-CoV-2, host cells/immunocytes, EPA/DHA and resolvins, protectins and maresins.