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Covid-19 and DHA: A Hypothesis of Immune Cell Mechanism and Response

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Preface

Unlike antibiotics that "kill" bacteria, and terminate infections, there is no medicine that is "toxic" to viruses. Another approach against viruses is suggested here to materially reduce the effect of viruses, and in particular, the coronavirus that causes Covid-19. The hypothesis is based on boosting the immune system by supplementing it with DHA in phospholipid form (PL-DHA).

Potential remedies to protect against viruses should address the functioning of the immune system. The approach suggested here is intended to be a tool to assist the body's natural immune response without adding complications.

A recent study[1] has documented that DHA plays a role in reducing inflammation within the human and mammalian immune responses in a number of ways. This paper advances the hypothesis that PL-DHA may provide an effective boost to immune cell functioning that may play a role in recovery from the coronavirus. This boost derives from the anti-inflammatory properties of PL-DHA and how they interact with the immune response.

DHA's Remarkable Capability

DHA molecules initiate channels within cell membranes. These channels work as gateway switches in many cell signal transduction pathways. For example, the DHA molecule is located at the very tip of the Spermatozoon where it attaches to the egg cell wall. The molecule functions, in part, to punch a hole in the cell wall and thereby creates channels to transfer DNA coding into the egg cell. Without DHA, the egg's cell membrane will not be opened to prepare the protein transfer channels for fertilization.

The cell membranes of all living organisms, as well as viruses including coronaviruses, are made of phospholipid bilayers, PL-bilayers for short. The outer surface of these PL-bilayers is hydrophilic, while the inside is hydrophobic and functions to bind the two layers together. The unique structure of DHA allows for penetration into this PL-bilayer. This cell membrane structure is so prevalent in nature that all cells, including cancer cells, bacteria, and coronaviruses are structured similarly.

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[1] "Omega-3 Fatty Acids and Inflammatory Processes", Philip C. Calder. Nutrients 2010, 2, 355-374; dot:10.3390/nu2030355.

Reactive Oxidative Species

ROS (Reactive Oxidative Species) are oxygen atoms that hold unpaired free electrons (e-), comprised of a negative ion of oxygen (O-), or hydroxyl ion (OH-) in the body, that functions as a kind of disinfectant that our immune cells use to destroy foreign cells. When a macrophage, mast cell, or phagocyte (immune system cells) engulf an invading pathogen, the cell(s) employ this ROS weapon to internally destroy any pathogens present. This process is called a "respiratory burst" and serves to change the RNA folding, and thereby destroys the pathogen from within. Also used in this effort is protease which are protein hydrolyzing enzymes found inside the cells that function to break down the pathogen's protein.

While not all immune cells conduct phagocytosis, the phagocytes, and/or macrophages, that do function to destroy invading pathogens may die in the process; the incapacitated pathogens remain contained inside the body, and the entirety of the "dead cells" are excreted as "puss" and "phlegm" from the body.

It is suggested here that eosinophil cells may use the internal respiratory burst as a weapon against nearby viruses. If Phospholipid DHA (PL-DHA) attaches to the virus PL-bilayer it could create a channel initiator and allow for respiratory burst to enter the virus cell. Although a far greater understanding of this process is needed, we do know that the DHA molecules in the PL-bilayer act as an electron conductor and can neutralize the pathogen.

The body's immune cells' weapon of choice is ROS, but ROS should not be present everywhere in the body. Uncontrolled ROS damages healthy organs, joints, and potentially every part of the body including immune cells themselves. ROS may be the main culprit in uncontrolled immune overreaction that results in chronic inflammation, and as is the case with disinfectants, an ROS overdose will result in an agonizing death. In other words, exogenous ROS in the body is a toxin.

Danger of Oxidation to Extracted PUFA

Current manufacturing methods to produce PUFA (polyunsaturated fatty acid) supplements involve extracting the oil from the host making the extracted oil susceptible to damaging oxidation. Oxidized PUFA such as EPA, ALA, ARA, and DHA become toxic ROS in the body once they oxidize. Each double bond (covalent bond) of carbon carries a free electron. Peroxidized double bonds cause what is known as a "peroxidation chain reaction" which further damages the PUFA. Elevated doses of these supposed antioxidants will oxidize in the body and destroy healthy and immune cells alike, and can ultimately accelerate aging and encourage premature death.

Any amount of peroxide inside the PUFA is an unwanted toxin. PUFA supplements, once extracted, do not have the antioxidant enzymes that normal cells possess, such as superoxide dismutase (SOD) and catalase that function to clean and remove the ROS inside the cells. PUFA supplements often add tocopherols (synthetic Vitamin E) as an antioxidant to protect against such damaging oxidation. However, tocopherols function as an absorbent, and once saturated with the oxidants, lose their protective nature. Delivering PUFA supplements in the form of gel capsules offer inadequate protection against oxidation. Packaging that includes the use of a pump bottle to deliver each serving (the packaging common for animal Omega 3 supplements) actually "pump" additional oxygen into the bottle once opened, thereby negating the package's stated shelf life.

Within a few weeks of use, peroxide builds up inside as more PUFA molecules continue to oxidize and can remain undetected even in the absence of a rancid smell. Ingesting oxidized PUFA supplements can lead to many illnesses.

PL-DHA's known ability to attach to the membrane surface and then penetrate inside the PL-bilayers is due to its unique three dimensional structure that is not evident in other Omega 3 PUFAs such as EPA and ALA. This penetration property of DHA is the critically important feature of its functionality in our body.[2]

SARS-CoV-2

The structure of the SARS-CoV-2 virus consists of a PL-bilayer envelope surrounding the core RNA. The structure has a crown-like spike protein receptor, that is probably formed from the center of the bilayer clusters attached to it. It is reported that this spike protein is oriented to attach to the human ACE2 enzyme protein, whose function is to regulate blood pressure in the body.[3]

SARS-CoV—2 viruses are about 120 nm in diameter and may be less than 1/millionth of the volume size of phagocytes or macrophages. Due to this minute size it may not be possible for immune cells to consume all the viruses by phagocytosis. However, normal cells that are infected and start transmitting the danger signal protein (which causes the phagocytic "first-responder" cells to react) may get contained by the phagocytes before bursting the replicated SARS-CoV-2 viruses and spreading them through the body. Viruses that are external to these infected cells need to be engulfed as well in order to be destroyed by phagocytes. One of the "weapons of choice" by the immune cells in this regard is the "respiratory burst" of the ROS that is mentioned above.

PL-DHA and SARS-CoV-2 Virus

PL-DHA has the ability to attach and penetrate SARS-CoV-2 virus envelopes.[4] This penetration functions to increase the so called membrane fluidity of the virus cell, to create a channel for the electron burst through the membrane to the inside of the cell. The effectiveness of the respiratory burst is enhanced if it reaches the RNA that is protected inside the PL-bilayers, leading to incapacitation of the virus.

The proposed immune boost created by this action is the increased supplementation level of PL-DHA in the fluid throughout the body to potentially heal the damaged cells' signaling capability. And for defense against the SARS-CoV-2 virus, PL-DHA may amplify immune cell effectiveness.

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[2] "Eicosapentaenoic acid and docosahexaenoic acid (EPA and DHA) have distinct membrane locations and lipid interactions as determined by X-ray diffraction". Sherratt, et. al. *Chemistry and Physics of Lipids 212 (2018) 73–79.*

Author's Note: In this article, Sheratt et al describe the EPA inside the arbitrarily enlarged bilayers. There is no known mechanism by which EPA can fatten the bilayers. A different explanation is that EPA did not have the ability to penetrate into the bilayers. This author believes it is the geometry of the molecules that prohibit EPA's penetration, while allowing DHA's penetration into the bilayers.

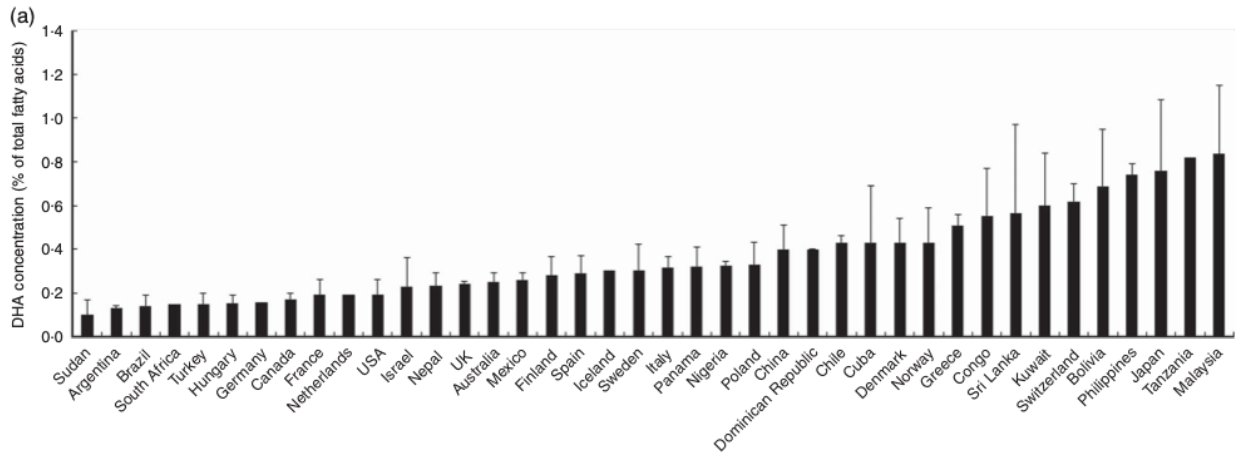
[3] https://www.wired.com/story/meet-ace2-the-enzyme-at-the-center-of-the-covid-19-mystery/.6/1/2020.

[4]"Eicosapentaenoic acid and docosahexaenoic acid (EPA and DHA) have distinct membrane locations and lipid interactions as determined by X-ray diffraction". Sherratt, et. al. *Chemistry and Physics of Lipids 212 (2018) 73–79.*

Supporting Evidence[5]

Strong correlations exist between DHA levels in the populations of different countries and the control of Covid-19 spread. DHA levels in the world's populations are compared between DHA levels in lactating mother's breast milk compared to that from the average US lactating woman. Malaysia, Tanzania, The Philippines, and Japan contain more than five times the DHA than found in the average US lactating woman have been reported to have a remarkably lower number of per capita SARS-CoV-2 infection.

DHA Concentration by Population as Represented in Lactating Mothers' Milk



Source: Footnote 6.

Lower infection rates in Japan have largely been attributed to better tracking and societal behavior to contain the virus.[6] However, considering Japan's much closer proximity and contact with China, its very dense population centers encourage quickly accelerating community spread of disease.

Unlike China, information from these countries are not withheld. Japan has 10 times the population density than that of the US, while S. Korea has about 15 times the population density of the US, while Malaysia and Tanzania are equally populous as S. Korea. The very low death rates per capita (less than 1/100 of the US infection rate) of these countries even compared to their surrounding countries cannot be explained by so called "more effective tracking"[7] nor by the "mutation theory

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[5] "An updated review of worldwide levels of docosahexaenoic and" arachidonic acid in human breast milk by region", Fu et. al, *Public Health Nutrition: 19(15), 2675–2687*

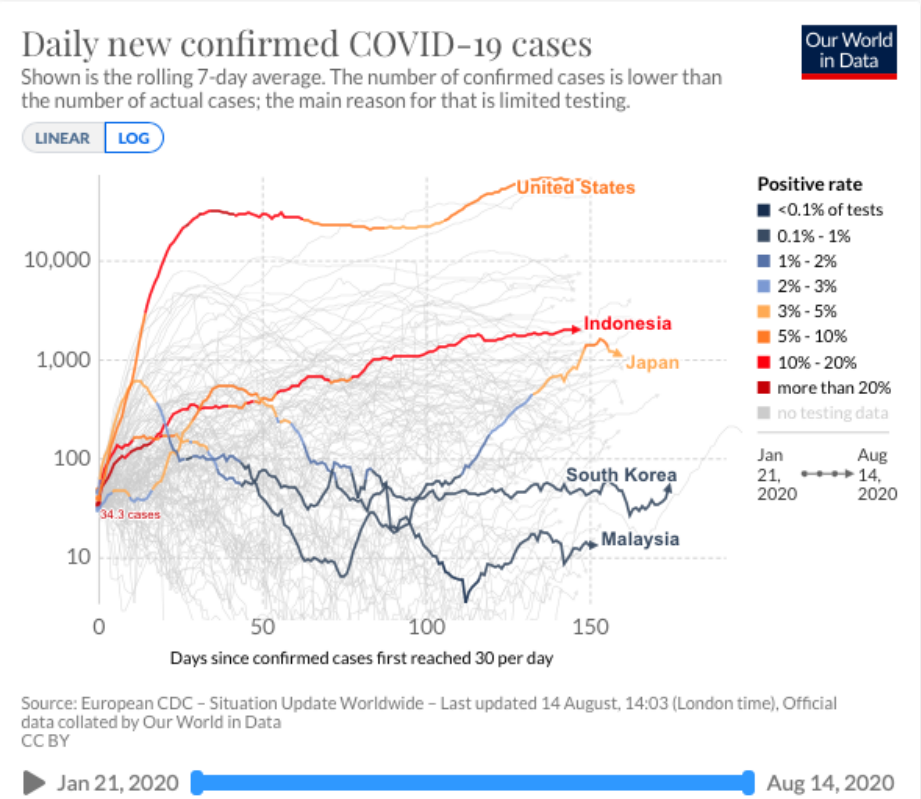
Author's Note: Although S. Korean data is specifically missing from this report, S. Korea is reported to also experience a very low per capita covid-19 infection rate.

[6] Ibid

[7] https://www.telegraph.co.uk/news/2020/07/22/infectious-covid-19-mutation-dominant-globally-fueling-faster/?yptr=yahoo

that says the virus mutated after coming to Europe to become more contagious".[8] These anomalies are beyond coincidence. Despite these high population densities with so few cases per capita compared to countries such as the US, perhaps many more people in these four countries might have been equally infected, but not become symptomatic enough to merit testing. This may have occurred because of their high levels of internal DHA molecules that combat the early virus symptoms.[9] These countries may have had hundreds of times more cases than reported, and because their populations have more DHA in their bodies, the symptoms did not manifest enough to require testing. The correlation suggests that with increased levels of PL-DHA supplementation to boost the immune system, Covid-19 can become a more manageable health crisis.

Coronavirus symptoms occur not when the virus initially enters the body, but rather when the virus invades healthy cells to start replicating (signaling infection). Innate immune cells are supposed to respond and "sweep" throughout the body even before this happens. Depending on the surface affinity of foreign organisms, such as viruses, and pathogens, these innate immune cells attach and swallow them. Eosinophils for acidic, basophils for basic, and neutrophils for neutral substances. Depending on the surface affinity of the virus, they will be internalized by these cells, and cleansed by respiratory burst, and/or broken down by its protease digestion. With the help of PL-DHA, some people may rid themselves of these virus cells without developing symptoms. When the virus starts to multiply themselves inside the infected cells, symptoms such as fever, difficulty breathing,



etc. manifest. At this point, the larger immune cells that rely on memory antibodies will be activated. Most of the vaccines rely on adoptive immune response, the antibodies, B, and T cells,

[8]Case Investigation and Contact Tracing Part of Multi-pronged Approach to Fight Covid-19 Pandemic. CDC 4/29/2020.

[9] https://ourworldindata.org/coronavirus./Daily New Confirmed Covid-19 Cases.8/14/2020.

and phagocytes, which work after the cell infection, and cytokine burst stage. Viruses that PL-DHA is attached to are considerably easier to be deactivated even inside the infected cells that are swallowed by larger phagocytes. Those larger cells and antibodies that lead them may not be efficient in locating viruses that are less than one millionth in size and could be much more numerous than the immune cells at this stage. The author suggests treating patients at this stage of infection using vaccine alternatives such as PL-DHA.

PL-DHA is not the sole solution against virus attacks like Covid-19 either, however. While DHA molecules help the innate immune cells and probably other immune cells to destroy and terminate the RNA inside the virus cells and to prevent replication, there must be symptom relieving measures that prevent severe respiratory difficulty symptoms which could lead to patient deaths, especially among seniors. These innate immune cells do not have long lifespans. They engulf contaminated cells to “clean" the viruses that become captured, then they die to prevent what’s inside from getting out to spread in a process called necroptosis. When they die, they pass through the cell membrane, skin and other surfaces to be excreted as phlegm, puss, or other bodily waste products. However, in the case of SARS-COV2 viruses that cause serious difficulty in lung function, it is conceivable that it is the waste product (phlegm) that inhibits the lung’s oxygen transfer function. And further that mortality is greater among elderly patients could be explained by the fact that they may have developed overactive immune response that results in increased dead cells (phlegm) which may be the direct cause of their severe respiratory difficulty and resulting deaths.

The reported positive effect of the steroid Dexamethasone may be the indication that this remedy to relieve deadly symptoms may be to control the excessive immune response in the lungs. It is this author’s suggestion that the supplementation of PL-DHA may help remedy such post infectious complications and expedite recovery especially in elderly people who have pre-existing respiratory issues.

<u>The Case for PL-DHA to Combat Covid-19 versus Use of Any Extracted Omega 3 Oil</u>

Among the Omega 3’s, PL-DHA is known to penetrate the PL-bilayers of a virus including SARS-CoV-2. Generally, commonly available extracted Omega 3 supplements come with concentrated amounts of EPA (Eicosapentaenoic acid) in addition to the DHA. EPA is not known to penetrate the PL-bilayers. EPA is a Omega 3 Fatty Acid that has five covalent bonds in its molecule and is equally prone to oxidation as DHA (which has six), but since the source of such supplements (fish oils) and many algal species have more EPA than DHA, the elevated amounts of covalent bonds provide additional potential sites for the peroxidation chain reaction with less proportion of beneficial DHA molecules. Peroxidized EPA/DHA is an oxidant that would act as ROS outside the immune cells that could damage the immune cells themselves along with any healthy cells present. Extracted Omega 3 has a standard acceptable amount of peroxide in the industry, however, peroxide grows rather quickly once the package seal is no longer intact. Gel capsules do not provide an adequate oxygen barrier that quickly cause peroxide to pass acceptable levels. Oxidized Omega 3 oil is not only rancid, but can cause acute side-effects in individuals after consumption.

The source of all DHA is micro-algae. Accordingly, the most natural food source for DHA is un-extracted and unprocessed whole food explaining why oily fish or other seafood (including crustaceans) should be consumed. These creatures all acquire their DHA by feeding on ocean algae, either directly, or through DHA’s movement up the food chain. However, in lieu of acquiring DHA nutrition from eating lots of fresh fish, PL-DHA that is neither extracted, nor dried with

damaging heat should prove valuable in the fight against the SARS-CoV-2 virus when properly added to the diet.

Summary

We know that DHA is able to penetrate the PL-bilayers increasing membrane fluidity. The DHA molecule is responsible for cell signaling, and possibly initiates cell signal channel self assembly. By creating a space in the PL bilayer with its free electrons, DHA allows ROS to enter the bilayer.

DHA's cell signaling ability might further allow immune cells to use "respiratory burst" through the channel created by the PL-DHA to alter the RNA inside the SARS-CoV-2 virus envelope, thereby incapacitating it from further replication. It is evidenced that a variety of immune cells use respiratory burst against SARS-CoV-2 either inside the cells by phagocytosis, or on nearby cells. If sufficient DHA molecules exist in the body that can attach to SARS-CoV-2 virus surfaces, the effectiveness of the "respiratory burst" to reach into RNA will be increased and thereby reduce the impact of the virus.

There is a strong correlation between DHA levels in the populations of countries that consume more DHA, as represented by DHA levels in the breast milk of their lactating mothers', and the control of Covid-19 spread. The infection rates of the countries whose population has significantly higher average DHA levels in their bodies, have remarkably lower levels of reported Covid-19 cases and mortality. Consequently this suggests the hypothesis that PL-DHA may provide an effective boost to immune cell functioning that may play a role in recovery from the coronavirus. Further investigation to prove the value of PL-DHA as an effective tool against the SARS-CoV-2 virus is merited.

ZipZyme™ Omega by PhytoSmart

ZipZyme™ Omega is made from *Crypthecodinium cohnii (C. cohnii)* biomass, a species of dinoflagellate which is a type of micro-algae (phytoplankton) that is known to have a very high DHA content in its fatty acid profile. Due to our low temperature process, the special anti-oxidation enzymes, Catalase and SOD, (Superoxide Dismutase), as well as the metabolic DHA Synthase enzymes and additional fatty acid enzymes including Palmitic Acid, Oleic Acid and Myristic Acid, in every cell of ZipZyme™ are preserved. It is the safest and most highly bioavailable fresh food source of DHA. ZipZyme™ contains PL-DHA, the same form of DHA that is found in brain and retina tissues. A ZipZyme™ pack contains 30 5ml pouches (150 ml total) for small animals (containing 690mg DHA) and large animals (containing 1380mg DHA). The metabolic enzymes inside each pack have been documented to produce more than an additional 1,000 mg of Net DHA under optimized conditions in 400 hours. Specific rates of productivity in the acquiring animal's liver tissues are subject to further investigation.