

Open-Cell technologies and the potential of Phycocyanin for COVID-19 prevention and

treatment algorithm

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Introduction



The purpose of this communication is to improve disease prevention and ensure better disease management in the early stages of the disease by reducing demand for hospitalization.

I have been hesitant for a while to share this information being unsure whether it will constitute a breach of the principles of medical ethics. But when my husband's physician colleagues were diagnosed with COVID-19, I decided that failure to share this information would be a much greater crime than sharing it. Please consider this information through a critical lens. It is not to be construed as an advertisement, propaganda or undisputable facts. The information presented herein is intended for physicians only as they are able to evaluate each statement drawing on their expertise and experience as well as to adequately assess research publications or treatment algorithms.

I am not sure whether the old government or the new one that will soon take charge or the Health Expert Council (under the President's Office) will give any response to the letter addressed to them on this topic, thus I leave the decision-making to the sole discretion of each person who has been diagnosed with COVID-19 or who does not want to become infected. Knowledge will not make you fall ill, on the contrary, knowledge may even help you prevent getting sick. Thus this information is in line with the "do no harm" principle.

The information I will share with you is collected from the sources listed below and presented in a summary manner:

- COVID-19 treatment protocol published on the EVMS portal (which is similar to other publicly available protocols thus I use it for referential purposes)
- Publications available on medical research portals (a list of links is provided at the end of this presentation)
- Information provided by the laboratory that has invented Open-Cell technology and applied it to S.platensis.
- Information provided by the company that represents the first product to contain spirulina treated with Open-Cell technology.



COVID-19 treatment algorithm, Quercetin and other food supplements





EVMS CRITICAL CARE COVID-19 MANAGEMENT PROTOCOL

Developed and updated by Paul Marik, MD Chief of Pulmonary and Critical Care Medicine Eastern Virginia Medical School, Norfolk, VA November 2nd, 2020

Vitamin C and Vitamin D as well as a Vitamin B complex and trace elements zinc and magnesium are recommended for all stages of the disease (you can access the information by clicking on the link and viewing the protocols for all the stages of the disease).

Quercetin is recommended for all stages; however, its administration is limited in case of intubation, as it is taken orally.

The anti-viral, immunomodulatory and anti-microbial activity of Quercetin has been mostly established during in vitro studies; there are some results from in vivo studies as well but there have been virtually no studies involving human subjects.

General treatment diagram

The course of COVID-19 and General Approach to treatment



https://www.evms.edu/media/evms_public/departments/internal_medicine/EVMS_Critical_Care_COVID-19_Protocol.p







I-MASK+

Prophylaxis & Early Outpatient Treatment Protocol for COVID-19

PROPHYLAXIS PROTOCOL

Ivermectin Prophylaxis for high risk individuals 150-200 mcg/kg once weekly

Post COVID-19 exposure prophylaxis* 200 mcg/kg x1 dose, repeat in 72 hours

- Vitamin D3 1,000-3,000 IU/day
- Vitamin C 1,000 mg twice daily and Quercetin 250 mg/day
- Melatonin 6 mg before bedtime (causes drowsiness)
- Zinc 100 mg/day
- Aspirin 80-100 mg/day (unless contraindicated)

EARLY OUTPATIENT PROTOCOL**

Ivermectin	200 mcg/kg	daily fo	or two days
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- Vitamin D3 4,000 IU/day
- Vitamin C 2,000 mg 2-3 times daily and Quercetin 250 mg twice a day
- Melatonin 10 mg before bedtime
- Zinc 200 mg/day
- Aspirin 325 mg/day (unless contraindicated)

The treatment algorithms for more advanced stages of COVID-19 are not included here due to their size, as the goal of this communication is to improve prevention and ensure better disease management in the early stages of the disease by reducing demand for hospitalization.

Mildly Symptomatic patients (on floor/ward in hospital):

- Vitamin C and Quercetin
- Zinc
- Melatonin
- Vitamin D3 or Calcifediol
- Ivermectin. Highly recommended
- B complex vitamins
- Enoxaparin
- Methylprednisolone
- Famotidine (in renal impairment).
- Vascepa or Lovaza alternative DHA/EPA 4g daily.
- Remdesivir. Optional (not recommended): Considering the high cost of this agent and the lack of benefit on patient centered outcomes the role of this drug seems very limited.
- N/C 2L /min if required

https://www.evms.edu/internal_medicine/EVMS_Critical_Care_COVID-19_Protocol.pd



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FRONT LINE COVID-19 CRITICAL CARE ALLIANCE PROPHYLAXIS & EARLY OUTPATIENT TREATMENT PROTOCOL FOR COVID-19

There is no **specific drug** or a "miracle pill" for the prophylaxis or treatment of COVID-19 available. However, a number of medicinal products (food supplements or medicines) have recently demonstrated some potential for both prophylaxis and treatment of COVID-19 cases.

- Ivermectin,
- Vitamin D,
- Quercetin,
- corticosteroids

Moreover, it is likely that not one single medicine will be effective in treating this complex disease and that **multiple medicines will be required with different action mechanisms** and administered in particular stages of the disease.

https://www.evms.edu/internal_medicine/EVMS_Critical_Care_COVID-19_Protocol.pdf

Quercetin is a plant pigment (flavonoid). It is found in various plants and food products, such as red wine, onions, green tea, apples, berries, ginkgo biloba and St. John's-wort. Quercetin is mostly taken orally for treating cardiovascular diseases and cancer prevention. It is also used to treat arthritis, bladder infections and diabetes.

Quercetin possesses antioxidant and anti-inflammatory properties which can help reduce inflammation, kill cancer cells, manage blood sugar levels and prevent heart diseases.

However, there are only a handful of studies supporting this data.

Despite this, Quercetin was included in the algorithm without conducting any additional studies. Quercetin is listed in a number of protocols for the treatment and prophylaxis of COVID-19.

It is recommended to combine Quercetin (plant polyphenol) with Vitamin C and zinc for prophylaxis and for treating the symptoms of the early stages of the disease. This is supported by the following interesting basic scientific findings which suggest that:

- Zinc is essential for both innate and acquired immunity. Moreover, zinc inhibits in vitro SARS-CoV-2 RNA-dependent RNA polymerase.
- Quercetin exhibits direct virucidal action against different viruses including SARS-CoV-2. It is a powerful antioxidant with anti-inflammatory properties.
- Vitamin C improves the effect of Quercetin and possesses anti-viral and anti-inflammatory properties. <u>https://www.evms.edu/</u>

Spirulina platensis (due to the phycocyanins (and other phycobilins), beta-carotenes, omega acids, zinc, magnesium, Vitamin D, Vitamin B complex and other components found in it) possesses the same properties as the above agents. *Open-Cell* technology further stimulates

the resorption processes of the components in the human body (in the mucosa of the oral cavity or the respiratory mucosa) as all components are released from the membranes limiting their intake. When administered through the mucosa of the oral cavity, the effect occurs

within 1 hour (based on the empirical data). The product can be made available in an inhaled form. In this way, both local and systemic effect would be achieved.

The effects of S.Platensis vs desirable effects for COVID-19 management

Desirable effects of drugs for treating COVID-19 (before cytokine storm develops):

- 1. Antiviral. To prevent the virus from replicating.
- 2. Immunomodulating. Depending on the situation at hand, during the infection stage, the non-specific immune system plays a crucial role: timely and adequate response can prevent the development of the disease at the early stage and ameliorate the course of the disease.
- 3. Anti-inflammatory. Both in the early stages and when the diseases progresses.
- 4. Prevention of hypomagnesemia, hypercoagulation, thrombosis and other conditions (that may increase the risk of cytokine storm).
- 5. Anti-microbial. Prevention of secondary infection.
- 6. Saturation of blood with oxygen, effective delivery of oxygen to body tissues.

Studies conducted around the world have shown that spirulina has multiple beneficial properties with the following ones being relevant in the treatment of COVID-19:

- kills a large number of viruses;
- acts as an effective immunomodulatory agent;
- suppresses inflammation (phycocyanins and beta-carotenes are strong anti-oxidants);
- alleviates pain (phycocyanin effectively blocks COX-2 receptors);
- kills pathogenic microbes resistant to most commonly used antibiotics;
- possesses anti-allergic properties (blocks the release of histamine);
- accelerates the wound healing process (and reduces the development of fibrosis);
- stimulates cell regeneration (including lung tissue);
- normalizes metabolic processes;
- compensates for the deficiency of vitamins and minerals; contains significant amounts of B12, B1, B6, B9, iron, magnesium and zinc;
- reduces lipid levels in blood (MTG);
- helps prevent atherosclerosis and coronary diseases (normalizes glucose levels + dyslipidemia management + antioxidant activity).



Open-Cell technology



Open-Cell technology takes the potential applications of spirulina to new heights



All elements are covered by the outer membrane of spirulina and the membranes of bacteria

Spirulina powder

"Released" spirulina elements as seen through a microscope (at the same magnification as the photograph on the left)

Open-Cell Spirulina

Separation of different groups of substances into layers in a liquid medium

Open-Cell Spirulina

Open-Cell technology takes the potential applications of spirulina to new heights

Limitations of the use of spirulina powder

Spirulina is a biomass of cyanobacteria surrounded by a strong multi-layer membrane in the shape of a spiral coil. Its blue-green color comes from the pigment phycocyanin, one of the most valuable elements of spirulina which is beneficial for human health.

As you can see, the cells of the cyanobacteria are arranged one after the other within a tube-shaped spirulina membrane. It resembles a long stuffed "sausage".





Non-digestible membrane

The multi-layered spiral-shaped membrane cannot be broken down (digested) by monogastric organisms, including humans. In terms of its composition, the membrane of the spirulina is similar to the membranes of the beneficial bacteria found in humans. If we had enzymes capable of digesting the spirulina membrane, we would end up digesting our own beneficial bacteria.

Open-Cell technology has solved this problem: it has unlocked the "safe" of the spirulina so that all the components can easily be absorbed through the oral or respiratory mucosa.



Open-Cell technology takes the potential applications of spirulina to new heights







Source: the archive UNERA Luxembourg Laboratory

https://www.fortivitum.lt/pages/open-cell-spirulina

The UNERA *Open-Cell* technology allows breaking down the spirulina membrane and the membrane of the bacteria. All the nutrients contained in the cell enter a special liquid medium and are ready for human consumption. Various forms of consumption are available: it can be inhaled, delivered by a spray on the buccal mucosa using a multi-dispenser (the fastest route of administration is through the mucosal layer) or it can be used in other form.

UNERA Open-Cell Spirulina



Benefits of Spirulina Platensis in medicine





Nutritional and therapeutic benefits of S.Platensis

Besides usual minerals, trace elements and vitamins, spirulina is rich in: **Pigments:**

- phycocyanin, a strong antioxidant that binds heavy metals and radionuclides, alleviates inflammation and prevents the growth of tumor cells; stimulates the immune system and has antiviral and anti-microbial properties;
- chlorophyll improves oxygen saturation in the body tissues, boosts energy levels and exhibits detoxifying effect;
- beta-carotenes have strong antioxidant properties important for the prevention of oncological and cardiovascular diseases; betacarotenes are also important for maintaining good eyesight;

All essential amino acids which are the fundamental building blocks for the human body, as well as polyunsaturated fatty acids;

A high amount of iron which is vital for blood production; spirulina contains a greater amount of iron than meat, liver or spinach.



Therapeutic effects of S.Platensis



Studies conducted around the world have shown that spirulina possesses unique properties:

- kills a large number of viruses;
- acts as an effective immunomodulatory agent;
- suppresses inflammation (phycocyanins and betacarotenes are strong anti-oxidants);
- alleviates pain (phycocyanin effectively blocks COX-2 receptors);
- kills pathogenic microbes resistant to most commonly used antibiotics;
- prevents growth of cancer cells (in G0/G1);
- possesses anti-allergic properties;
- reduces lipid levels in blood (MTG);
- prevents atherosclerosis and coronary diseases;
- accelerates the wound healing process;
- stimulates cell regeneration;
- normalizes metabolic processes;
- compensates for the deficiency of vitamins and minerals; contains significant amounts of B12, B1, B6, B9, iron, magnesium and zinc;
- flush heavy metals, toxins and radionuclides from the body.

Most of the effects below are achieved thanks to the bluecolored pigment **phycocyanin**. It turns purple when exposed to light.



Source: the archive of the UNERA Luxembourg Laboratory

UNERA *Open-Cell* technology allows purification of different substances. Solutions containing phycocyanin (blue and red, fat (yellow), chlorophyll (green), polysaccharides (greenish) are seen in the photo above. The desired fraction of components may be purified and mixed with other desired components. **This opens up great potential for application in medicine.**

Source: the archive of the UNERA Luxembourg Laboratory

Potential applications of Spirulina platensis derived Phycocyaninum elements

FORTIVITUM





Phycocyanin and its applications in medicine





Studies suggest the following indications for phycocyanin



1. Infections:

- Anti-microbial activity (a particularly large number of studies focus on antibioticresistant strains)
- Anti-viral activity

2. Inflammation:

- Suppresses inflammation by blocking COX-2 receptors
- Suppresses inflammation by targeting inflammatory cytokines (TNF-α, interleukin-6 MMP-3, (IL-6), glycosaminoglycans)
- Analgesic effect

3. Immunomodulatory effect:

- Indirect stimulation of hematopoiesis in the bone marrow
- Positive effect on the antibody-producing system
- May enhance situational proliferation of immune cells and organs of the immune system
- 4. Oncology (more than one route of action):
 - Anti-oxidant effect
 - Blocks COX-2 receptors (indicated as an important route in oncology)
 - Initiates apoptosis of cancer cells, prevents their growth in G0/G1
 - Other MOA: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5687155/
 - Improves treatment results in combination with all conventional treatment methods
- 5. Managing blood lipid levels, prevention of cardiovascular diseases and atherosclerosis due to anti-oxidant effect (neutralizing free radicals) and anti-inflammatory activity mechanism
- 6. Protects against effects of radiation

The list of the sources used is provided at the end of the presentation

MMP-3, NO, and sulfated

Potential dosage of phycocyanin



Provisional daily dosage suggestions for nutraceuticals that might aid control of RNA viruses including influenza and coronavirus

Prophylactic dose Anti-viral dose For oncology patients

or Spirulina-bound pigment exist for either rodents or humans.

1 0 0 m g / p / d a y 100-250mg/p/day 1g/p/day

Ferulic acid	500-1,000 mg	- https://examine.com/spirulina/research/#interactions-with-cancer-metabolism_immunological-interactions
Lipoic acid	1,200-1,800 mg (in place of ferulic acid)	100 mg of phycocyanin (from Spirulina powder) is likely to have anti-viral effect and this dose is equivalent to the prophylactic dose. However, individual
Spirulina	15 g (or 100 mg PCB)	effect may vary greatly due to individual intestinal characteristics (absorption coefficient).
N-Acetylcysteine	1,200–1,800 mg	More detailed information:
Selenium	50-100 mcg	 Estimated upper bound CEDI for phycocyanins from all GRAS notified uses of spirulina extract in food is 1,140 mg/p/day or 19 milligrams
Glucosamine	3,000 mg or more	per kilogram body weight per day (mg/kg bw/d) for a 60 kg individual based on uses addressed in GRN 000424 (Ref. 3)
Zinc	30-50 mg	 Desert Lake Technologies, LLC got GRAS notification in 2012 for its CyaninPlus[™] product. It is a water extract of the Spirulina platensis or
Yeast Beta-Glucan	250-500 mg	Spirulina maxima intended for use as an ingredient in food at levels of up to 250 mg per serving, equivalent to approximately 125 mg of C-PC.
Elderberry	600–1,500 mg	 C-PC-enriched aqueous extract from Spirulina platensis, equivalent to ~1 g phycocyanin per day is confirmed as safe.
J Med Food. 2007 Dec;10(Spirulina as a source of ph https://pdfs.semanticscho https://www.federalregister https://www.govinfo.gov/	lar.org/	The suitable clinical dose of PCB remains to be defined. Without mass-produced pigment derived from commercially available PCB- enriched <i>Spirulina</i> extracts, bioengineered organisms, or chemically synthesized pigment, ingestion of whole <i>Spirulina</i> is still the least expensive way to benefit from this phytonutrient. A tablespoon of <i>Spirulina</i> powder (about 15 g) contains approximately 100 mg of PCB, daily dose that might be effective [https://pubmed.ncbi.nlm.nih.gov/ 18158824/]. Interestingly, no relevant data about relative absorption and bioefficacy of free PCB

S.Platensis and Phycocyanin. Safety profile



- Numerous toxicological studies, such as acute, sub-chronic, chronic, mutagenic, teratogenic/developmental toxicity, carcinogenic, and multiple generational/reproduction tests, have confirmed excellent safety profile of Arthrospira platensis and Arthrospira maxima (Class A rating by the dietary supplements information expert committee of the US pharmacopeial convention). They were of paramount importance in the determination that water extracts of Spirulina or C-PC are safe as well.
- In animal models, C-PC possesses low toxicity and lack of adverse effects. For example, in acute oral toxicity study, the measured LD₅₀ values were estimated to be greater than 3 g/kg for rats and mice, without mortality even at the highest dose of C-PC from Arthrospira maxima tested (3 g/kg o.p.). No changes in behavior or histopathology, or effect on body weight were observed [31].
- Furthermore, acute and sub-chronic oral toxicity study revealed that C-PC (isolated from Spirulina platensis) at high concentrations
 [0.25–5.0 g/kg body weight (w/w)] did not induce any symptoms of toxicity nor mortality of the albino rats [32].
- In human randomized, double-blind, placebo-controlled study, high dose of C-PC-enriched aqueous extract from Spirulina platensis, equivalent to

~1 g phycocyanin per day (the highest dose generally recognized as safe by the US FDA), after 2 weeks showed safety regarding anticoagulant activity and platelet activation status markers, but reduced levels of aspartate transaminase and alanine transaminase in conjunction with rapid and robust relief of chronic pain [33].

- Unlike cancer cells, C-PC is non-toxic to normal cells, for example, platelets and erythrocytes [34].
- Based on the comparison of the known amino acid sequences of phycocyanins with the sequences of known protein allergens, we determined that there is a low probability that phycocyanins are protein allergens. There is concluded that the spirulina phycocyanins present an insignificant allergy risk
- Spirulina also has not exhibited neither acute nor chronic toxicities, making it safe for human consumption.

To conclude, animal and clinical scientific studies support that *Spirulina* and C-PC, its most abundant organic component, are safe for human consumption, in agreement by their more than 1000 years use in diet.

- <u>https://www.nature.com/</u>
- https://www.govinfo.gov/
- <u>https://www.accessdata.fda.gov/scripts</u>
- · https://www.researchgate.Nutritional and toxicological aspects of Spirulina Arthrospira
- https://www.intechopen.com/spirulina-phycobiliproteins-as-food



Open-Cell Spirulina and COVID-19 pandemic



Niche application of phycocyanin and other S.Platensis components

The clinical studies accumulated and analyzed by the EVMS have shown that even expensive medicines are not 100% effective in treating COVID-19. Thus, our non-specific immune response remains the main "weapon" and the rest are just additional measures supporting it.

The components found in spirulina that have been purified with *Open-Cell* technology can be ideal substances for a unique "mix" for treating COVID-19. It would further enhance the effect of the currently used medicines and would complement the existing treatment algorithm. The full spirulina formula could be used for prophylaxis in the early stages of the disease.

It is still an open question as to when the *Open-Cell* spirulina will be available in spray form or even when phycocyanin will be purified and whether this will be done in Lithuania. However, *Open-Cell* spirulina with "released" phycocyanin and other components preserved in honey are already available as a food supplement in USA, Ireland, Luxemburg. Table 1. Pharmacological therapy for COVID by stage of illness: What has worked and what has failed*

	Pre-exposure/ Post-Exposure/ Incubation	Symptomatic Phase	Pulmonary/ inflammatory phase
Hydroxychloroquine	Unclear benefit	No benefit	?Trend to harm
Remdesivir	n/a	?? Reduced time to recovery No mortality benefit	No benefit
Lopivinar-Ritonavir	n/a	No benefit	No benefit
Interferon $\boldsymbol{\alpha}/\boldsymbol{\beta}$	Inhaled ? Benefit	No benefit	?Trend harm
Tocilizumab	n/a	n/a	No Benefit
Convalescent Serum	n/a	Unlikely	No Benefit
Corticosteroids	n/a	Trend to harm	BENEFIT
Ivermectin	BENEFIT	BENEFIT	BENEFIT

https://www.evms.edu/media/evms_public/nternal_medicine/EVM

*based on randomized controlled trials (see supporting information below)

The list of used resources :



- 1. <u>The antioxidant, immunomodulatory, and anti-inflammatory activities of Spirulina: an https://www.researchgate.net/publication/</u> 303798959 The antioxidant immunomodulatory and anti- inflammatory activities of Spirulina an overview
- 2. C-Phycocyanin: A Biliprotein with Antioxidant, Anti-Inflammatory and Neuroprotective Effects, PDF at https://www.researchgate.net/publication/10740146 C-Phycocyanin A Biliprotein with Antioxidant Anti-Inflammatory and Neuroprotective Effects
- 3. Nutraceuticals have potential for boosting the type 1 interferon response or RNA viruses including influenza and coronavirushttps://www.researchgate.net/ publication/Nutraceuticals have potential for boosting the type 1 interferon response to RNA viruses including influenza and coronavirus
- 4. Therapeutic and Nutritional Potential of Spirulina in Combating COVID-19 Infection; paskutine versija https://preprints.aijr.org/index.php/ap/preprint/view/49
- 5. Activation of the human innate immune system by Spirulina https://www.researchgate.net/publication/ 11404492 Activation of the human innate immune system by Spirulina Augmentation of interferon production and NK cytotoxicity by oral administration
- 6. The effects of Spirulina on anemia and immune function in senior citizens; PDF from: https://www.researchgate.net/
- The effects of Spirulina on anemia and immune function in senior citizens
- 7. https://www.researchgate.net/publication/302982832 Medical Application of Spirulina platensis Derived C- Phycocyanin
- 8. Anti-Inflammatory publications summary : https://pdfs.semanticscholar.org/dfea
- 9. www.researchgate.net/Phycocyanin_attenuates_pulmonary_fibrosis_via_the_TLR2-MyD88-NF-kB_signaling_pathway
- 10. Effects of phycocyanin on pulmonary and gut microbiota in a radiation-induced pulmonary fibrosis model:
- 11.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7556228
- 12.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5687155/
- 13.<u>https://link.springer.com/article/10.1186/s12935-018-0511-5</u>
- 14.https://www.nature.com/articles/s41598-019-55605-w
- 15.https://pubmed.ncbi.nlm.nih.gov/31844085/
- 16.<u>https://link.springer.com/article/10.1007/s11274-010-0516-2</u>
- 17.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7130854/
- 18. https://www.researchgate.net/publication/281815052 Nutritional and toxicological aspects of Spirulina Arthrospira
- 19.https://europepmc.org/article/cba/295843
- 20.https://pubmed.ncbi.nlm.nih.gov/19914399/
- 21.<u>https://www.e-algae.org/m/journal/view.php?number=2817</u>
- 22.http://www.spirulinasource.com
- 23.https://www.x-mol.com/paper/1306772809090043904
- 24.http://www.spirulinasource.com/library/health-library/

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