Microalgae-based approaches to overcome the effects of the COVID-19 pandemic

Enfoques basados en microalgas para superar los efectos de la pandemia por COVID-19

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Keywords

Economic recovery; aquaculture; genetic engineering; biomolecules; oral vaccines.

Abstract

At the end of 2019, a new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began to spread rapidly worldwide, to the point of becoming a pandemic by early 2020. After almost two years of living with this new disease, humanity continues to face one of its greatest crises, not only health-wise but also environmentally and economically. To alleviate some of the effects suffered worldwide by the pandemic, it is necessary to integrate new strategies in medical therapies and economic strengthening. Under this scenario, the present review presents the functionalities of microalgae that could be exploited to boost the areas most affected by the pandemic. Among the most promising benefits are the various biomolecules derived from microalgae that could be adjuvant therapies or preventive agents and their potential to become biofactories of antibodies or vaccines through genetic engineering. Finally, the development of microalgae-based industries could become a driver of the economy and a source of local employment generation. In this way, the positive impact of microalgae-derived products in pharmacological, environmental, and industrial fields that could be exploited to counteract the consequences of two years of the pandemic is presented.

Palabras clave

Reactivación económica; acuicultura; ingeniería genética; biomoléculas; vacunas orales.

Resumen

A finales del 2019 un nuevo coronavirus llamado coronavirus de tipo 2 causante del síndrome respiratorio agudo severo (SARS-CoV-2) empezó a propagarse rápidamente a nivel mundial, al punto de convertirse en una pandemia para inicios del 2020. Después de casi dos años de vivir con esta nueva enfermedad, la humanidad sigue enfrentado una de sus mayores crisis, no solamente a nivel de salud, sino también ambiental y económico. Para poder alivianar algunos de los efectos sufridos mundialmente por la pandemia es necesario la integración de estrategias novedades en terapias médicas y fortalecimiento económico. Bajo este escenario, la presente revisión presenta las funcionalidades de las microalgas que podrían ser explotadas para impulsar las áreas más afectadas por la pandemia. Entre los beneficios más promisorios se destacan las diversas biomoléculas derivadas de microalgas que podrían ser terapias adyuvantes o agentes preventivos, así como su potencial para convertirse en biofábricas de anticuerpos o vacunas a través de ingeniería genética. Finalmente, el desarrollo de industrias a base de microalgas podría convertirse en un impulsor de la economía y una fuente de generación de empleos locales. De esta forma se expone el impacto positivo de los productos derivados de microalgas en ámbitos farmacológicos, ambientales e industriales que podrían explotarse para contrarrestar las consecuencias de dos años en pandemia.

Introduction

Coronaviruses are a diverse group of viruses belonging to the Coronaviridae family. These viruses can cause respiratory infections in several mammals -bats, camels, civets- and avian species. However, the symptoms of the coronavirus-associated disease vary across the different host species. In humans, coronavirus infections may be asymptomatic or accompanied by mild to severe respiratory infections, fever, cough, shortness of breath, and gastrointestinal irritation. In the worst scenario, especially in immunocompromised individuals, coronavirus infections may lead to severe pneumonia and, subsequently, the patient's death [1], [2]. In 2019, a novel coronavirus, now known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), emerged with a new disease - Coronavirus disease 2019 (COVID-19)- causing an outbreak that has rapidly extended globally within a short period. Based on the severity of the disease and its rapid spread worldwide, the World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020 [3].

The COVID-19 pandemic has hit humanity in an unprecedented way. By the end of June 2021 nearly four million lives had been lost worldwide. It threatens millions of people's lives all over the world every day. [4]. In turn, the effects of two years of the pandemic have been genuinely challenging in different spheres of life on earth. Human physiological and psychological effects are still being quantified [5]–[7]. COVID contamination, especially from plastic products, is alarming; millions of discarded single-use plastics (masks, gloves, aprons, and bottles of sanitizers) have been added to the terrestrial environment [8]. Moreover, as if that were not enough, the pandemic has had an unprecedented impact on the global economy, with entrepreneurs and small businesses generally being the most affected [4].

Therefore, it is imperative to propose comprehensive alternative solutions to impact the sectors most affected by the pandemic. The intervention to reduce the impact and spread of COVID-19 requires the development of policies and guidance through a collaborative effort among government, academia, medicine, and citizens [9]. The importance of interdisciplinary cooperation and bringing together the world's scientists to find appropriate solutions for controlling and managing the COVID-19 pandemic could positively alleviate the main effects, manage the pandemic more stably and prevent future pandemics such as the one we are experiencing [10].

In this scenario, in need of prompt and practical solutions, microalgae could emerge as a promising model to partially fight the effects of COVID 19. The bioeconomy that revolves around microalgae is widely known. Microalgae contribute to the economy by producing valuable biomass for human-related applications (pharmaceuticals, cosmetics, food, and feed). However, microalgae can contribute much more to the bioeconomy by increasing the current production capacity and developing new applications [11], including employment generation in this path. In this Mini-Review, the potential of microalgae to alleviate the effects of the COVID-19 pandemic is investigated from three approaches: production of natural compounds, impact on economic reactivation, and genetic engineering.

Microalgae cultures

Microalgae comprise a diverse polyphyletic group of microorganisms (eukaryotes and prokaryotes) characterized by photosynthesis. The wide range of biomolecules they synthesize (carbohydrates, lipids, proteins, and pigments) has made them commercially attractive organisms. It is estimated that about 44000 species of microalgae have been described worldwide, isolated from diverse environments such as freshwater, marine water, and hydrothermal sources [12]. Microalgae are unicellular organisms that generally inhabit aquatic environments; they can grow as individual cells or associated in chains or small colonies; and are found in many shapes and sizes, ranging from three to ten micrometers [13].

In recent years, microalgae have become a viable platform for numerous biotechnological applications such as the production of biofuels, vitamins, carotenoids, enzymes, pharmaceuticals, and recombinant proteins. In addition, their adaptive ability to grow fast in photobioreactors or open ponds, producing high yields of usable biomass for industrial applications, has attracted the attention of the research and development (R&D) sector [14], [15]. As a result, microalgae biomass production increased worldwide and reached 32.67 Mt [Fresh weight (FW)] in 2016. Algae biomass is supplied mainly by aquaculture [16]. In human consumption (nutraceuticals), China is the primary producer of microalgal biomass globally. There are four main microalgae grown commercially. Among them, Spirulina (*Arthrospira* sp.) is the most extensive microalgal product by tonnage and value, followed by *Chlorella* sp., *Dunaliella* sp., and *Haematococcus* sp. [17].

The two most common methods of microalgae cultivation are open cultivation systems, such as open ponds, tanks, and raceway ponds, and controlled closed cultivation systems using different types of bioreactors [18]. The raceway ponds are one of the most frequently used and energy-efficient open pond types for microalgae cultivation. It consists of closed-loop channels around 30-cm deep and paddlewheel, enabling microalgae biomass recirculation [19]. On the other hand, closed cultivation systems are more efficient in quality. Although they present important challenges such as bio-fouling, overheating, cleaning issues, and very high capital costs for designing and operating [19], these systems can be operated in highly controlled conditions overcoming the disadvantages of an open cultivation system.

Microalgal value-added products against COVID 19

The biologically active compounds from microalgae as pharmaceuticals and nutraceuticals have received much attention recently. The biomedical applications of microalgae are widely recognized, and their extracts have been proven as antineoplastic, antimicrobial, antiviral, and antifungal. In addition, as being considered as GRAS (generally recognized as safe), their consumption by humans makes them feasible for health applications [20], [21].

Even though research involving metabolites from microalgae in several implicated immune-related pathways is still relatively few, several novel studies have been carried out to map the auxiliary effects of these metabolites on the immune response pathways using both *in vivo* and *in vitro* methods [22]. Furthermore, immunomodulation by microalgal metabolites might be important in the fight against COVID-19 since patients suffer from immunopathological damage brought upon by a reactive cytokine storm. This situation results from hyperactive inflammatory responses resulting in cytokine release syndrome (CRS). Herein we describe the main types of microalgal explored-metabolites and their promising effects on COVID-19 prevention and treatment.

Peptides and proteins

Although not yet tested against COVID 19, peptides and proteins derived from microalgae could be promising for adjuvant therapies due to their history as solid antivirals. These compounds include the Cyanovirin-N, a lectin protein extracted from the cyanobacteria *Nostoc ellipsosporum*. This molecule exhibited antiviral activities against human immunodeficiency virus (HIV), influenza, and the Ebola virus. Other lectins, such as microvirin, griffithsin, scytovirin, and phlorotannins, have also been tested to counteract several viruses, including HIV [23]. Furthermore, a novel microalgae peptide named griffithsin demonstrated the inhibition of viral entry for the cases of HIV, SARS-CoV-1, and MERS-CoV [23].

In 2020, Chen et al. [24] discovered a peptide from *Isochrysis zhanjiangenesis* capable of blocking the angiotensin-I-converting enzyme (ACE); this enzyme is highly expressed in lungs and participates in vascular functions. During COVID-19 infection, the activity of this enzyme is altered, leading to an increase in cytokines in the blood. Therefore, the utilization of ACE inhibitor drugs has been proposed to mediate cytokine storms in COVID-19 patients, in the same way as would the peptide from *I. zhanjiangenesis* [22]. Furthermore, *in silico* studies using bioinformatics tools such as molecular docking has identified promising active microalgal peptides against spike protein of COVID-19. For example, the peptide LDAVNR from *S. platensis* showed a strong inhibition interaction with the SARS-CoV-2 spike protein [25].

Pigments

Astaxanthin (3, 3′-dihydroxy-β, β'-carotene-4, 4′-dione) is a natural pigment, a carotenoid with anti-inflammatory, immunomodulatory, and antioxidative properties. It is currently found to have the strongest antioxidant capacity, which is 1,000 times of Vitamin E, 200 times of tea polyphenols, 100 times of α-tocopherol, 65 times of vitamin C, 17 times of grape seed [26]. It is produced mainly by the microalgae *Haematococcus pluvialis*. Preliminary reports have indicated that the administration of this carotenoid to COVID-19 patients could alleviate cytokine storm, thereby preventing acute respiratory distress syndrome (ARDS) and acute lung injury (ALI). This evidence may suggest a likely beneficial implication of microalgae sourced natural astaxanthin in SARS-CoV-2 infected individuals [27], [28]. In animal models, astaxanthin has been demonstrated to alleviate ALI/ARDS by offsetting the cytokine storm, inhibiting subsequent fibrosis, and increasing survival rates. Additionally, human clinical trials have proven its safety for human consumption with no noticeable side effects [29].

Phycocyanin, a blue pigment-protein obtained from Spirulina, is a potent inhibitor of NADPH oxidase, with anti-inflammatory, antioxidation, and anti-tumor activity [28]. Moreover, C-phycocyanin is an indispensable component of the cyanobacteria photosynthetic machinery, making it an abundant pigment in the cells [30]. In this sense, C-phycocyanin was proved to reduce the secretion levels of a protein, which causes cytokine storms in COVID-19 patients [23], [31]. In addition, *in silico* analyses have shown a great potential of phycocyanobilins (blue phycobilins) to inhibit SARS-CoV-2 polymerase [32].

Carbohydrates

Carrageenan is a sulfated polysaccharide of microalgae origin, inhibiting the attachment, transcription, and replication of viruses in host cells. It has been tested with a nasal spray containing zanamivir (antiviral drug) and carrageenan reported to exert synergistic effects on the influenza virus [28]. Calcium spirulan is another polysaccharide derived from Spirulina, which inhibits the replication of several viruses, such as influenza, mumps, and HIV [28], [33]. Other promissory carbohydrates include microalgae polysaccharides such as fucans, nostoflan, naviculan, alginates, galactans, and laminarin. These molecules have been tested in terms of their antiviral efficacy toward viruses such as dengue (DENV), HIV, hepatitis A virus (Hep A) virus, and herpes simplex virus-1 and −2 (HSV-1 and HSV-2) [23].

Crude extracts and other molecules

Different microalgae extracts have been proven to exhibit anti-inflammatory properties by acting on the NF-κB pathway. This pathway is altered in COVID-19 patients, promoting CRS induction. Metabolites presented in microalgae extracts such as carotenoids and peptides have reported effective down-regulation on NF-κB related pro-inflammatory cytokines. For example, peptides and violaxanthin from *Chlorella* sp., and crude carotenoid extracts, were able to reduce cytokine production in treated cells [22]. Furthermore, oxylipins isolated from *Chlamydomonas debaryana* and *Nannochloropsis gaditana* were able to reduce the dependent inflammatory generation of cytokines [22]. Furthermore, *S. platensis* could enhance the immune system response against viruses by activating immune cells and inducing the production of interferon-gamma, an important cytokine with antiviral activity [28], [33]. Other metabolites derived from microalgae such as diterpenes, bromophenol, the sulfated polysaccharide polymannuroguluronate, and the fatty acids monogalactosyl diacylglycerol have shown viral inhibitions properties against different viruses [34].

Genetic Engineering: Biofactory of pharmaceutical compounds

Due to their low-cost and advantageous ecological production, microalgae can be used as biofactories for medical therapies while exploiting the most cutting-edge technologies on genetic modification. Molecular manipulation of microorganisms allows the heterologous expression of proteins, known as the introduction of genetic material encoding a protein from one species into the cell of another different species to produce it, which means the production of foreign proteins at desirable yields in controlled environments. This resource has provided the opportunity for custom-made microalgae-based drugs and therapies. In this sense, microalgae offer exceptional molecular machinery for producing highly complex molecules [35].

Oral vaccines based on microalgae biomass have been proposed using genetic modification for heterologous protein expression. Oral and other non-invasive administration routes represent low production costs for vaccines. In addition, due to their higher acceptance among the population, it is expected that oral vaccines improve immunization coverage and minimize the need for trained healthcare personnel due to the possibility of self-administration [36].

Hence oral microalgae-based vaccines allow the expression of complex heterologous proteins in a short time under controlled conditions in a low-cost culture media; and then some advances have been made on this technology. For example, an oral microalgae-based vaccine against Zika significantly elicited specific IgG and IgA immune response [37]. In this case, the authors produce 365 µg/g of the ZK protein in *Schizochytrium* sp. [37]. One of the main difficulties of this approach is the low expression yields and unstable production. However, an inducible geminiviral vector was developed recently (called Algevir), allowing the production of antigenic proteins from viral proteins and bacterial toxins at high levels [38]. Other microalgae-based vaccines have been tested at the pre-clinical level [39], including candidates against the Human papillomavirus [40] and Malaria parasitemia [41], both by protein expression on the model algae *C. reinhardtii;* and nuclear HIV antigen expression in the same species [42]. Hence, apart from the potential discovery of novel antiviral compound on microalgae, the advances in molecular manipulation on these microorganisms also offers the opportunity to create new vaccines against COVID-19.

The antibodies and cytokines are another relevant example of biopharmaceuticals for therapy produced in modified microalgae. Promising effects have been reported by antibodies integrated on the chloroplast of *C. reinhardtii* to fight cancer [35] and against Botulinum neurotoxin [43]. Other authors have shown a significant effect on malignant progression by microalgae-produced cytokines such as IFN-α, which prevent chronic viral diseases and some cancers [44]. The ability of some microalgae species to secrete antibodies highlights their potential for producing glycosylated antigens, providing valuable premise to design strategies for the production of SARS-CoV-2 S protein, RBD, and anti-SARS-CoV-2 antibodies [45]. Moreover, the studies on the oral delivery of nanoantibodies are promising [43], [45].

Finally, an innovative approach recently reported for modified microalgae is their use as delivery vehicles interference RNA (RNAi) [46]. The development of this technology for human therapies needs important advances on the ethical issues regarding genic therapies. However, notable innovations are expected regarding coronaviruses therapy since promising results preventing the replication of this type of virus have been made using the RNAi technology [47], and some authors have already proposed specific RNAi to fight SARS-CoV-2 [48].

Microalgae in economic reactivation: the aquaculture example

The COVID 19 pandemic circumstances offer new opportunities to create new jobs, technologies, and infrastructure to engineer a climate-friendly and sustainable future economy [49]. The pandemic has driven unemployment to its highest levels since the Great Depression in several parts of the world. For example, from March to April 2020 unemployment rate in the United States increased from 4.4% to over 14.7% [50]. Therefore, there is a global need to revive the economy and generate new quality jobs. Microalgal biotechnology is presented as an opportunity to generate a productive industry that meets the needs of developing countries, contributing to the economic, social, and environmental areas. Furthermore, it can be integrated into various agro-industrial processes to obtain high value-added products from waste sources that have not been used [51].

Rumin et al. (2020) identified the top six driving microalgae market opportunities in Europe. These six significant market opportunities were biofuels, bioplastics, biofertilizers, nutraceuticals, pharmaceuticals, and cosmetics. They also pointed out two areas that were making good progress, such as harvesting and extraction technologies and advances in the development of genetically modified microalgae [52]. Other interesting report concluded that the main promising markets for microalgae in the coming decades are the production of proteins for food and health applications (including vaccines and recombinant proteins), the production of polysaccharides and antibiotics, and the use of microalgae for bioremediation and biofertilization [53].

This versatility of economic opportunities offered by microalgae opens the door to new cutting-edge applications and markets. For example, expanding the activities of growing microalgae in developing countries to derive and sell products may be a strategy that could help eradicate poverty by creating local jobs and generating new sources of income for the population [54].

As an example of an economic reactivation model, microalgae could positively impact the local aquaculture business. Fisheries and aquaculture are two systems that are highly vulnerable to the effects associated with COVID-19. According to Food and Agriculture Organization, each stage in the chain of fisheries and aquaculture processes is susceptible to being disrupted or stopped by impacts from COVID-19. For example, suppose one of these links (buyer-seller) is broken by the disease. In that case, the result will be a cascading chain of disruptions affecting livelihoods (of fishers) and food security [55].

Feed inputs for aquaculture production represent between 40 and 75% of production costs [56]. In this sense, microalgae have several attractive characteristics, widely validated, to be a sustainable fish food and feed solution [57]. Therefore, aquaculture is a promising sector and market of high global importance for protein production, which could exploit the potential offered by microalgal crops to grow the fish industry, and by side effects, the economy.

Finally, in a context where it is necessary to generate sustainable industries with low environmental impact, the diverse microalgae applications could be considered one of the foremost players in the clean energy market and hold future promise for developing countries in creating more jobs and opportunities [58]. Moreover, microalgae could contribute to sustainable development thanks to their capacity to mitigate CO_2, supply energy and food security, treat wastewater, combat malnutrition, create jobs, and stimulate economic growth [54].

Challenges and future perspectives

In the present review, we addressed three approaches where microalgae could help overcome several of the effects generated by the COVID 19 pandemic. Based on the evaluated reports, it could be deduced that although it will not replace SARS-CoV-2 vaccinations, microalgae biomolecules may be effective candidates for the adjuvant therapy of COVID-19 patients, mainly to prevent cytokine storms once the patients are diagnosed. Of course, these promising algal molecules must go through the regulatory and testing processes, but they are an alternative to consider because of their bioactivity advantages and low-cost production. Moreover, new genetic engineering tools could take microalgae to a new level, turning them into biofactories to produce numerous biomolecules such as antibodies or cytokines. Also, their GRAS quality could make them great candidates for future oral vaccines, which would help control the delivery of vaccines in isolated and developing regions.

Although microalgae have been the panacea for various global problems for several years, the lack of support and investment in technologies (e.g., harvesting and packaging) has slowed progress in generating solutions. COVID-19 ravages highlight the need to invest and exploit the true potential of microalgae and might represent the beginning of laboratory results translation to products that can be accessed and used by the entire population.

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