The evolution of the global COVID-19 epidemic in Morocco and understanding the different therapeutic approaches of chitosan in the control of the pandemic

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Abstract
In 2020, Coronavirus disease (COVID-19), a new viral respiratory disease caused by a virus that belongs to Coronaviridae family, has been identified. It is a very severe flu that negatively affects the functions of the lung and other respiratory organs. COVID-19 virus can be transmitted between people either by touching an infected person or by direct contact with their respiratory droplets. Therefore, the COVID-19 virus has become a global concern due to its rapid spread and severity. Based on the World Health Organization report from 2 March 2020 to 24 October 2022, the total infected cases and deaths in Morocco are around 1,265,389 (3.46%) and 16,280 (0.04%), respectively. Recently, some scientists have found that chitosan, a polymer existed in nature, can inhibit COVID-19 infection and repair damaged tissue. Therefore, understanding chitosan mechanisms in controlling COVID-19, might lead to innovative strategies in the medical field, such as developing drugs against SARS-CoV-2, and replacing vaccines, which have negative side effects. This review aims to show the evolution of the COVID-19 pandemic worldwide, specifically in Morocco, its pathophysiology, and its ability to silence the immune system. This review also provides an overview of the treatments and measures applied to protect human beings and how chitosan acts and controls COVID-19.

Keywords Coronavirus · Aminopolysaccharide · Health · Death · Recovery · Vaccines

Abbreviations
GlcNAc Acetyl-d-glucosamine
AAT Alanine amino transferase
AL-GC Alginate and galactosylated chitosan

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Introduction

On November 16, 2020, Morocco declared the highest number of coronavirus disease 2019 (COVID-19) cases. At the onset of the COVID-19 pandemic, Morocco had several strategies to circumvent the difficulties in controlling the virus. The spread of the severe acute respiratory syndrome coronavirus (SARS-CoV-2) pathogen in 2019 has prompted the Moroccan scientific community to find therapeutic solutions to deal with the COVID-19 pandemic in a definitive way. Although scientific trials have been conducted to characterize the effects of SARS-CoV-2 and new information on the pathogen has been developed, there are still outstanding questions that need to be addressed regarding the pathophysiology of COVID-19, its intelligence, and its long-term side effects. COVID-19 can present with multi-organ...
involvement, including cardiovascular [1], neurological [2], and renal [3], which is largely due to a disruption of the host immune response [4]. Structurally, SARS-CoV-2 has four major proteins, namely spike glycoproteins (S), small envelope glycoproteins (E), membrane glycoproteins (M), and nucleocapsid proteins (N), and others, which have different functions [5]. For instance, the spike glycoprotein is a trimeric transmembrane glycoprotein that facilitates binding and invasion of virus into the host cell [6]. This host binding is mediated through angiotensin converting enzyme 2 (ACE2) receptors, which are carbopeptidases of mainly pulmonary origin, responsible for the hydrolysis of angiotensin I into the vasoconstrictor angiotensin II [6, 7].

Although much attention has not been covered concerning natural resources as potential therapeutic molecules, some reports show that a natural and biocompatible polymer, mainly derived from the exoskeleton of crustaceans, such as chitosan, can be used to combat COVID-19 [8]. Chitosan has attracted many attention in several fields, especially in chemistry and environmental science, because of its unique features and properties that allow the production of new formulations, especially biocomposites [9–17], nanoparticles [18], nanocomposites [19–21] and others [22, 23]. Moreover, the bibliometric study done by Chiari et al. [24] showed that the top countries that used polymers, to carry either anti-SARS-CoV2 or COVID-19 vaccines, were the USA, China, and India. All in all, the present review shows whether applying chitosan without other components would be the best strategy to treat COVID-19 and will encourage the low middle-income countries, like Morocco, to valorize the waste of marine sources and produce chitosan. Thus, this review summarizes the application of chitosan-based biomaterials in treating complications from COVID-19. By analyzing its design considerations and application, new ideas for therapy should be proposed by exploiting natural resources.

**Evolution of COVID-19 in Morocco**

Since the World Health Organization (WHO) announced how dangerous COVID-19 is, it has spread and settled in all earth’s corners before humans consider this issue seriously and take a countermeasure to deal with it. The SARS-CoV-2 surprised the world due to its rapid transmission and strong offensive action, which robbed many people’s lives daily.

The causes and origin of this virus have not been identified, but it has been linked to the wholesale seafood market in Wuhan because it was the only common thing between the first four cases. After careful tests and analysis, the Chinese government announced this virus was new. Its gene sequence was similar to those belonging to the coronavirus family, especially severe acute respiratory syndrome coronavirus (SARS-CoV, recorded in November 2002) as well as middle east respiratory syndrome coronavirus (MERS-CoV, recorded in September 2012), which was transmitted to humans through animals, such as pigs and dromedary camels. It caused the respiratory failure with a high mortality rate [25–27].

The virus COVID-19 appeared for the first time in Asia, especially in Wuhan city of China in December 2019. After approximately 18 to 45 days, the virus reached
the continent of Oceania, America, Europe, and, lately, Africa (Table 1). The first patient in Africa was recorded in lower-middle-income countries such as Egypt on February 14, 2020 (Table 1). After a short period, almost all countries of the African continent become carriers of the virus. For instance, Morocco declared the first patient, who is a Moroccan national coming from Italy, on March 2, 2020 [28], and the highest number of COVID-19 cases was 6195 infected people and 64 deaths on November 16, 2020.

Up to now, the virus of COVID-19 has changed over time. It has resulted in the emergence of new strains, Alpha (from United Kingdom), Beta (from South Africa), Gamma (from Brazil), Delta (from India), Epsilon (from United States), Zeta (from Brazil), Eta (from India), Theta (from Philippines), Iota (from United States), Kappa (from India), Lambda (from Peru), and Omicron (from different countries), with different characteristics, such as their ease of spreading and their severity. The variant Delta and Omicron are the most contagious COVID-19 variants than the original one because of their high transmissibility, high severity (increased N° of infected

Table 1 Emergence time of novel coronavirus disease (COVID-19) in different continents

| Continents | Countries | Emergence time | References |
|------------|-----------|----------------|------------|
| Asia       | China     | December 2019  | [26]       |
|            | Japan     | January 15, 2020 | [32]      |
|            | South Korea | January 20, 2020 | [33]     |
|            | India     | January 27, 2020 | [34]     |
|            | Iran      | February 18, 2020 | [35]    |
| Europe     | France    | January 24, 2020 | [36]     |
|            | Spain     | January 31, 2020 | [37]     |
|            | Italy     | February 21, 2020 | [38]   |
|            | Germany   | February 21, 2020 | [39]    |
|            | United Kingdom | February 21, 2020 | [40] |
| America    | United States of America | January 20, 2020 | [39] |
|            | Canada    | January 27, 2020 | [40]     |
|            | Mexico    | February 27, 2020 | [41]    |
|            | Argentina | March 3, 2020   | [42]      |
|            | Brazil    | March 5, 2020   | [43]      |
| Oceania    | New Zealand | January 18, 2020 | [44] |
|            | Australia | January 22, 2020 | [45]     |
|            | French Polynsia | March 10, 2020 | [46] |
|            | Fiji      | March 19, 2020  | [47]      |
|            | Papua New Guinea | March 23, 2020 | [48] |
| Africa     | Egypt     | February 14, 2020 | [9]     |
|            | Algeria   | February 25, 2020 | [50] |
|            | Nigeria   | February 27, 2020 | [51] |
|            | Morocco   | March 2, 2020   | [52]      |
|            | Tunisia   | March 2, 2020   | [50]      |
people and deaths), and their ability to decrease the effectiveness of vaccines [29]. Additionally, the severity of the Omicron variant was 100-fold higher than that of the Delta variant.

At the early stage of the COVID-19 pandemic, Morocco faced difficulties controlling the virus. Among them are convincing people to avoid crowded places, wear masks in public spaces, etc. [30]. Nevertheless, the Moroccan government devised multiple measures to clarify the seriousness of the COVID-19 pandemic. To improve the medical infrastructure and to absorb the economic shock in all sectors of the state, the Moroccan king created mutual funds, starting with 10 billion dirhams, then the total budget was increased three times due to the contribution of companies and citizens. Also, the king imposed a curfew, created several health centers to receive patients and detect cases early, and assigned a group of national and local bodies to make society aware. Nevertheless, since April, 22nd 2021, it was confirmed that two patients coming from India are infected by the Delta variant (B.1.617.2) and Kappa variant (B.1.617.1). On December 15, 2021, one case was infected by the Omicron variant [31]. Due to the spread of new COVID-19 variants, cases (12,039 and 3177) and deaths (72 and 18) were recorded on August 5, 2021, and January 17, 2022, respectively.

**Pathophysiology of COVID-19**

The pathophysiology of COVID-19 is not yet fully understood. Cells in the body expressing the ACE2 receptor can be infected by SARS-CoV-2, including lung cells. Binding occurs between the S1 subunit of the spike (S) protein of the virus via the receptor-binding domain (RBD) and the ACE2 receptor, allowing endocytosis of the virus and subsequent release of the viral material into the cytoplasm of the infected cell [53]. After entering the host cells, the virus exploits the cellular machinery to replicate and spread in the host [54, 55]. SARS-CoV-2 causes severe pneumonia in the respiratory tract [46]. In general, the virus alters its behavior and disrupts its normal function by entering the host cell using its endogenous transcriptional machinery. When SARS-CoV-2 infection occurs, it triggers the host’s major innate and adaptive immune responses to activate in the body [57]. The immune system first activates the first line of defense, innate immunity, which relies on immune cells capable of destroying viruses in a non-specific manner, and then adaptive immunity, which is set up in a second phase to eliminate the virus [58]. The antiviral immune response involves both the innate and the adaptive immune response, which are presented in Fig. 1.

However, when the immune response becomes ineffective, the virus spreads and causes massive destruction of affected tissues, generating new uncontrolled inflammation. In patients infected with COVID-19, significant increases in blood levels of chemokines and pro-inflammatory cytokines have been observed [59]. It has been hypothesized that the virus spreads through the respiratory mucosa and infects other cells, leading to a cytokine storm that induces T-cell necrosis or apoptosis and the generation of multiple immune responses [49]. In several acute cases, patients with
acute respiratory distress and septic shock have succumbed to multi-organ failure [60].

COVID-19 infection leads to severe acute inflammation [61, 62], in the inflammatory response may include the so-called cytokine storm, where levels of interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) are extremely high. The high degree of inflammation creates a high potential for multi-organ damage, involving not only the lungs, which leads to interstitial pneumonia and severe respiratory failure, but also the gut, central nervous system, cardiovascular system, kidneys, and muscle [62, 63].

Similarly, as possible direct mediators of inflammation, ACE2 and differentiation cluster 6 (CD6) are possible mediators [58, 64]. In addition, acute inflammation, such as that associated with COVID-19, is a powerful, harmful stimulus for sarcopenia development, manifested by elevated C-reactive protein (CRP), Interleukin-6 and TNF-α, which are also the strongest correlates of frailty [65]. The severity and pathogenesis of COVID-19, with a high potential to induce sarcopenia, generate mitochondrial damage. Ferritin, the acute phase reactant and a key player in iron homeostasis, may interact directly with mitochondrial energy production [66, 67], stimulating energy production from aerobic to anaerobic modes, generating reactive oxygen species (ROS), and increasing cellular sensitivity to damage and apoptosis.

**Intelligence of SARS-CoV-2**

The ability of SARS-CoV-2 to adapt to the host immune system was rapidly observed in clinical settings where an immunocompromised COVID-19 patient, after 154 days of infection, exhibited different variants of the virus, including the E484K substitution [68]. Neutralizing SARS-CoV-2 antibodies acquired during infection almost entirely target NTD and RBD. In RBD, the ability to escape is limited, and the E484K mutation is one of the most common mutations to escape monoclonal antibodies [69]. Researchers mapped the escape mutations of the ten
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antibodies and determined the effect of each mutation on antibody escape. All ten antibodies bind to SARS-CoV-2 RBD with high affinity but differ in their neutralization potencies, the extent to which they compete with CEA2 for RBD binding, and cross-reactivity with SARS-CoV-1 [70]. Other investigators report that authentic SARS-CoV-2, if constantly under pressure, can escape even a strong polyclonal serum targeting multiple neutralizing epitopes. Their study reports that three mutations allowed SARS-CoV-2 to escape the polyclonal antibody response of a highly neutralizing COVID-19 convalescent plasma. After injecting the initial strain of SARS-CoV-2 coronavirus into the plasma of a convalescent patient to see how the virus reacted, they first noticed that during the first 38 days, the plasma neutralized the virus without any problem even when diluted 640 times. At the end of the 45 day, the first mutation that escaped the antibodies appeared on the peak protein. At 80 days, a second mutation appeared and concerned the terrible E484K mutation, present notably in the South African and Brazilian variants and recently detected in the English variant. The third change between days 80 and 90 was accompanied by "complete abrogation of neutralization activity by the plasma sample" (Fig. 2). Computer modeling predicted that deletion and insertion into the N3 and N5 loops prevent neutralizing antibody binding [71].

Fig. 2 Successive mutations neutralize antibodies in less than 90 days
The COVID-19 pandemic has 4 phases: the first phase is characterized by chest wall infection, fever, muscle weakness, and nausea; the second phase is characterized by hard breathing; the third phase is designated by hyper inflammatory syndrome and damage of lung and cardiac muscle cells; while the last phase is referred by loss of life or healing [72, 73]. Thus, providing an effective vaccine is the best means of protecting humans and controlling COVID-19. Vaccines are products made from a mixture of molecules, living organisms to kill or to construct COVID-19, and their toxins [75]. These products can increase the immune system by stimulating the production of immunoglobulins to remove foreign substances from the body [75]. At the beginning of the COVID-19 pandemic, no efficient treatment was available against this virus because of its different impact on human being depending on their age, their gender, their immune system state, whether they have an allergy to some drugs or components of the vaccine, as well as the stage of infection. Many treatments have been applied during the emergency period to reduce COVID-19 risks.

Before the appearance of the use of anti-COVID vaccines, most of the therapeutic strategies used to deal with this virus were derived from the work of previous epidemics of SARS and other influenza viruses (Table 2). Such as antiviral therapies, adjuvant therapies by combining antivirals with antibiotics or immunostimulants, and several other therapies to be used depending on the region [73]. The most widely used treatments are antiviral drugs (i.e., remdesivir), anti-inflammatory agents (i.e., carbohydrate-free flavonoid), antirheumatic drugs (i.e., chloroquine), JAK-inhibitors (i.e., ruxolitinib), and low molecular weight heparin (i.e., thromboprophylaxis) [76–79].

In addition, a big effort has been made by a group of high-income countries to create a vaccine. As of February 2020, China came up with several technical ways to develop COVID-19 vaccines, especially using the inactivated vaccine, which consists of virus particles incapable of causing disease; however, they can increase the defense of the body against future contact with COVID-19 [80]. Afterward, China successfully developed different vaccines, and the most effective vaccines were made by Sinopharm biotechnology (Chinese state) and Sinovac Biotechnology (a

| Table 2 | Treatments used before the appearance of the vaccine for SARS-CoV-2 [73] |
|---------|---------------------------------------------------------------------|
| **Antiviral therapies** | **Adjuvant therapies** |
| Chloroquine (CQ) & hydroxychloroquine (HCQ) | Antibacterial therapy |
| Remdesivir | Immunomodulators |
| Lopinavir/ritonavir | Anticoagulants |
| Umifenovir | Vitamins and micronutrients |
| Favipiravir et ribavirine | |
| Oseltamivir | |
private company) [81]. At the end of August 2020, American pharmaceutical company Janssen/Johnson & Johnson and an England University/AstraZeneca company produced vaccines against COVID-19 using a recombinant adenovirus vector responsible for the expressing of severe acute respiratory syndrome coronavirus two spike proteins [82]. As of December 2020, an American pharmaceutical company called Moderna and a German biotechnology company (BioNTech) collaborated with American pharmaceutical giant Pfizer were successfully rollout vaccines against COVID-19 [83], which are composed of lipid nanoparticles containing a messenger ribonucleic acid (mRNA) of severe acute respiratory syndrome coronavirus 2 [84].

Although the development of a new vaccine requires many trials and takes several years to complete clinical research as well as to prove its safety and its effectiveness, some vaccines, such as those produced by Pfizer vaccines/BioNTech, Moderna, Johnson & Johnson, and Sinopharm have been authorized to be used in humans by the WHO [78]. As of January 2021, vaccines were distributed across the globe and initially authorized to be taken by the elderly (aged > 65) and those who have an essential role in society, such as health workers, teachers, and military and police forces [86].

Since January 2021, Morocco, a low-middle income country, has ordered more than 60 million vaccine doses from Sinopharm, Sinovac, and AstraZeneca companies to achieve pandemic control [86, 88]. Afterward, according to Moroccan Ministry, it received approximately 300,000 and 600,000 doses of vaccines from Johnson & Johnson and Pfizer-BioNTech companies, respectively. These vaccines were applied two times to treat citizens aged 18 years and over, except those from Johnson & Johnson were applied only once [88, 89]. At the beginning of the vaccination campaign, only 60% of citizens were willing to take the vaccines [90]. However, the vaccine acceptance rate increased when the government announced that access to public spaces and traveling, inside and outside Morocco, would be without restrictions only if the citizen has the vaccine pass. As of February 11, 2022, 4%, 49%, and 14% of the Moroccan population have received the first, second, and third vaccine doses.

Although many reports demonstrated that vaccines are 60 to 80% effective against COVID-19, they have short- and long-term side effects (Fig. 3). Therefore, it may be essential to provide drugs from naturally occurring substances to protect the health of individuals.

**Treatments with biomaterials based on chitosan**

**Chitin and chitosan**

Chitin (β-1,4-linked 2-acetamido-2-deoxy-D-glucose) is the second most abundant polymer in the world after cellulose. Its production is estimated at $10^{10}$ to $10^{12}$ tons per year. The main sources of this polymer are marine and terrestrial animals, insects, and microorganisms [91]. Chitin can be found in the shells of crustaceans (crabs and shrimps), cell wall of insects and scorpions, cuttlefish bones, cephalopod
beaks, and the scales of fish and lissamphibians (Fig. 4). Several marine sources of chitin have been explored [92] and thus the annual amount of chitin-based waste discarded in northern Morocco is estimated at 21,120,000 tons [93]. The partial or complete de-N-acetylation of chitin produces chitosan, which contains varying amounts of N-acetyl-D-glucosamine (GlcNAc) and D-Glucosamine (GlcN). Due to quaternary ammonium salt groups, chitosan has positive charges [94]. These molecules from marine and even terrestrial resources are nonetheless potent antivirals in this respect. In addition, studies have shown that chitin and chitosan are effective against viruses. It is suggested that chitin and chitosan polymers have the ability to fight viral infections through two approaches: direct antiviral activity and induction of antiviral immune responses (Fig. 5).

Among the advantages of using natural resources, including chitosan, are the reduced side effects of the therapy and its high safety. In the last year, several publications have indicated the possibility of using biopolymers to prevent and to treat infections caused by the latest beta-coronavirus [95], and its effect can be linked to its diverse characteristics (Table 3).

**Immunostimulatory action of chitosan against SARS-COV-2**

Chitin and its derivative chitosan have the power to increase antiviral immune responses. Depending on their size, purity, molecular weight (MW), morphology, degree of deacetylation (DD), viscosity, and concentration, these polysaccharides are greatly interested in immunology. These polymers create protective responses against pathogenic challenges by stimulating innate immune cells (such as macrophages (MQ) and natural killer (NK) cells) [96]. As a natural cationic polysaccharide, chitosan has attracted much attention due to its antimicrobial, antioxidant, anti-inflammatory, and immunostimulatory properties [78]. The
N-acetyl-glucosamine moieties in chitosan have been shown to stimulate ROS production, nitric oxide (NO) secretion, and myeloperoxidase activity in phagocytes. Phagocytosis of chitosan by macrophages and ROS production generate interferon-gamma (IFN-γ) synthesis in spleen cells. IFN-γ exerts its antiviral effect by preventing the translation of viral mRNAs [79]. In addition, chitosan can promote the levels of systemic (IgG) and mucosal (IgA) humoral responses, but it is also the migration of neutrophils [80] (Fig. 6A).

Some studies have shown that chitosan, by inducing mitochondrial stress and the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway, can promote the production of type I IFN that promotes dendritic cell maturation [78]. On the other hand, it has also been shown that chitosan, by inducing ROS production and lysosomal disruption, activates the inmmunmasome NLRP3 ("NOD-like receptor family, pyrin domain containing 3" or CIAS1) in a phagocytosis-dependent manner stimulating the release of pro-inflammatory factors such as IL-1, IL-6, IL-8, TNF-α [78, 79]. Consequently, induction of Type 1

**Fig. 4 Sources of chitin and chitosan.** Marine animals: Crustaceans, Coelenterates, Annelids, Mollusks, Lobsters, Shrimp, Krill, Crabs, Cuttlefish Bones, Fish Scales; Insects: Scorpion, Brachiopod, Beetle, Diptera, Cockroach, Spider, Beetle, Ant; Microorganisms: green algae, yeasts, fungi (cell wall), mycelia penicillium, brown algae, Chytridiaceae, Ascomycetes, Blastocladiaae
Table 3  Advantages of using chitosan as a delivery system for the treatment of respiratory viral diseases

| Characteristics       | Description                                                                                                                                 |
|-----------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Biocompatibility      | Biocompatible in nature and does not possess any toxicity profiles. It also did not trigger any inflammatory reaction                           |
| Structure             | Strong hydrogen bonding groups (i.e., -OH, -COOH, and -NH₂) are present in the chitosan structure. It also has sufficient chain flexibility, and its molecular weight can be altered using various strong organic acids |
| Mucoadhesive property | Surface energy properties favor spreading into mucus                                                                                       |
| Stability             | The presence of surface charge makes the chitosan stable                                                                                   |
| Loading capacity      | Capable of loading a large concentration of drugs of various pharmacological categories                                                   |
| Release kinetics      | Shows good release of drugs within a suitable period                                                                                       |
| Nature                | It is biologically active and can possess a large number of pharmacological activities                                                     |
| Mechanical property   | A high-absorbing property characterizes it                                                                                                  |
| Porosity              | Highly permeable. It can interact with the mucosal cell of the respiratory tract, opening the tight junction and increasing the drug’s permeation |
| Biodegradability      | Biodegradable in nature. Its degraded product does not show any toxicity and can easily be eliminated from the body                            |
T helper (Th1) cell responses and an isotype shift of IgG2 as effective immune responses against viral infections [78].

Respiratory syncytial virus (RSV) is another serious respiratory system virus that causes severe and intense illness in newborns, the elderly and immunocompromised individuals. Studies have shown that intranasal immunization with chitosan and DNA-based vaccines that encode RSV epitopes can increase the production of serum IgG and mucosal IgA antibodies and increase the number of IFN-γ-secreting T cells and effective cytotoxic T lymphocyte (CTL) responses, associated with a remarkable decrease in viral load. Therefore, using chitosan with DNA can reduce and significantly lower the inflammation of lung tissue and improve antiviral responses [85, 86]. This could be a solution to counteract the inflammatory lung tissue damage caused by SARS-CoV-2. Based on their physical and chemical properties, there are several chitosan forms, including solutions, powders, micro/nano-particles, and hydrogels. The use of chitosan as an antigen carrier and/or adjuvant in mucosal vaccines has been shown to induce cellular and humoral immune responses [75]. Ghendon et al., showed that the use of chitosan as a solution in combination with attenuated influenza vaccines could increase the immunogenicity of these vaccines and stimulate humoral immune responses against different influenza virus variants [102]. Sui and colleagues also demonstrated that intranasal administration of a chitosan solution with the matrix proteins influenza 1 and 2 (M1 and M2), can induce the production of IgG and IgA antibodies via increasing the immunogenicity of M1 and M2 proteins [103, 104]. Therefore, they concluded that using chitosan...
solutions provides good protection against influenza viruses while increasing the production of antigen-specific antibodies and the population of IFN-γ-secreting T cells [104]. In addition, chitosan derivatives have attracted significant immunological interest. Trimethylated chitosan (TMC), a water-soluble chitosan derivative, has a higher positive charge than chitosan. Administration of TMC with inactivated whole influenza virus [105, 106] and H3N2 subunit antigen intranasally resulted in increased mucosal uptake of an antigen across the nasal epithelium, leading to systemic and local immune responses with significantly higher levels of influenza-specific antibodies [107]. These derivatives may have potent immunostimulatory properties concerning the treatment of SARS-CoV-2. In addition, numerous studies have shown that the use of chitosan nanoparticles with viral antigens such as hepatitis B surface antigen (HBsAg) [108], recombinant influenza A H1N1 virus [109], avian infectious bronchitis virus (IBV) [110], and recombinant HA influenza antigen [111] elicit both, elevated humoral (systemic and mucosal) immune responses, and cell-mediated immune responses and IFNγ production.

**Potential antiviral effects of chitosan against SARS-COV-2**

As a contagious disease, COVID-19 has a high transmission rate. An infected individual can produce numerous aerosol particles (containing SARS-CoV-2 viruses) by breathing or speaking, posing a threat of infection if these particles are inhaled by nearby individuals near the COVID-19 patient [112].

Since SARS-CoV-2 is considered a particle, and more specifically, a nanoparticle, it has a zeta potential that is generally positive due to its capsid having the spike protein [113]. Based on this, an interesting view has been suggested, aimed at conferring protection against this pandemic virus involving the exploitation of chitosan to prepare nanofibers capable of being incorporated into the clothing of health care providers. In this way, the repulsive electrostatic forces between the fabric surface and SARS-CoV-2 particles could lower the viral load around these individuals and thus result in less transmissibility of the virus [114] (Fig. 6C).

Milewska et al. developed chitosan-based anti-coronavirus compounds shown to effectively inhibit the infection of all low pathogenic human coronaviruses in vitro and ex vivo. The chitosan binding explains this inhibition to the coronavirus spike protein (polymer-protein), which prevents the latter’s interaction with the cellular receptor [115], on a cell culture model of the airways infected with a virus, which the same group developed in 2020. Therefore, they concluded that chitosan could also effectively inhibit SARS-CoV-2 and MERS-CoV in this model [116].

The uses of chitosan with DNA can significantly decrease the inflammation of lung tissue and improve antiviral responses and, thus, immune system enhancement against SARS-CoV [78]. Applying chitosan nanoparticles as a vaccine adjuvant or as a vehicle for intranasal drug (Fig. 6-B), siRNA, and peptide delivery could be a promising approach to combat SARS-CoV-2 [117]. Bioavanta-Bosti, in 2020, showed the potential of its chitosan nanoparticle technology for the formulation of anti-COVID-19 drug aerosols. Aerosols formed from Novochizol™ nanoparticles can be used to deliver any anti-COVID-19 drug to the lungs of severely affected
patients. Nevertheless, the source material for the production of Novochizol™ is chitosan. The Novochizol™ technology generates spherical chitosan nanoparticles with unique and customizable physicochemical characteristics, capable of being administered at all stages of the disease, for example, in ventilators, and in the airways. These Novochizol™ nanoparticles adhere to the mucous membranes, and the active material gradually releases Novochizol™ [78]. All trials using chitosan were summarized in Table 4.

**Chitosan for tissue repair in COVID-19**

Following the COVID-19 infection, the study of tissue damage caused by SARS-CoV-2 has become an important area of biomedical research. As shown in Fig. 7, COVID-19 causes tissue damage and multi-organ failure, ultimately leading to patient death. Given the tissue damage observed in patients with COVID-19, a promising approach to promote tissue repair is to use natural Scaffold biomaterials. These biomaterials have been used as components in engineering a wide range of tissues, including vital organs [112], such as the use of chitosan scaffold in the regeneration of tissues such as lungs, brain and liver by 3D printing (Fig. 8).

**Action on the lungs**

Lung diseases are one of the leading causes of illness and death worldwide. Patients with severe lung problems, such as lung cancers, cystic fibrosis, and pulmonary hypertension, are at high risk due to their health status [113].

Currently, lung transplantation is considered to be a favorable treatment. However, the shortage of donors has hampered organ transplants, and immunosuppression would then be required for life. In addition, the alternative therapeutic options are limited to mechanical support systems such as ventilators and extracorporeal membrane oxygenators [114, 115]. Although these systems provide support for the majority of patients, in some cases, they cannot be used. Advances in tissue engineering and regenerative medicine appear to offer a promising alternative for treating lung defects [116].

Biomaterials have the potential to provide the same niche and microenvironment for lung tissue regeneration [117]. Indeed, these biomaterials must have biocompatibility, porosity, biodegradability, and mechanical properties that match native, healthy lung tissue [118]. Polymers are widely used biomaterials to promote tissue repair and regeneration [119, 120]. Among the natural polymers that are used for lung tissue regeneration is chitosan. As a natural biomaterial, chitosan has shown immunocompatibility with gelatin in hydrogel form. As a result, this material has allowed the growth of human respiratory epithelial cells [121]. Recently, a biologically and mechanically adapted 3D-printed scaffold using chitosan/polycaprolactone was tested for lung tissue engineering [122]. The scaffold showed excellent potential in swelling, degradation, and mechanical behavior, although it could be modified by adjusting the polycaprolactone content. This scaffold also revealed notable cell adhesion, non-toxicity, low apoptosis, high proliferation, and cell biocompatibility.
| Biomaterial | Use                        | In vivo/in vitro | Effects                                                                 | References |
|-------------|----------------------------|------------------|-------------------------------------------------------------------------|------------|
| Chitosan nanofibers | Bibs/clothing               | In vitro         | The electrostatic repulsion between chitosan nanofibers and positively charged SARS-CoV-2 | [114]      |
| $N$-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride (HTCC) | Drug                       | In vitro         | Interaction of the drugs with protein S recombinant ectodomain blocking cellular protein S-host interaction and subsequent viral infection | [114]      |
| Chitosan nanoparticles (Novochizol™) | Aerosol spray               | In vitro         | Adhesion of nanoparticles of Novochizol™ to the respiratory system. Then, the delivery of anti-COVID-19 substances | [88]       |
| $N$-Palmitoyl-$N$-monomethyl-$N,N$-dimethyl-$N,N,N$-trimethyl-6-O-glycolchitosan | Drug (10–100 µg mL)       | In vitro & In vivo | Low concentration of the drug reduces SARS-CoV-2 Infection in A549ACE2+human lung cells and Vero E6 cells | [111]      |
| Chitosan/DNA | Vaccine                     | In vitro         | Decrease in the inflammation of lung tissue and the improvement of the immune system against SARS-CoV | [88]       |
In sum, the chitosan/polycaprolactone scaffold with a 4:1 ratio revealed better activity for the MRC-5 cell culture. Thus, this scaffold may be a good candidate for lung tissue engineering and can be used for further studies on COVID-19[122].

In addition, Oudadesse et al. have shown that combined chitosan and bioceramics have positive properties on bone tissue restoration [123]. Bioceramics are also used for the reconstruction and repair of bone tissue. However, bioceramics have recently been used to repair soft tissues such as skin, lungs, and
nerves [124]. Bioceramics can promote cell proliferation and differentiation, enhance angiogenesis and exhibit antibacterial and anti-inflammatory activity. The efficacy of bioceramics in skin wound healing has been confirmed by pre-clinical trials [125]. Bioactive glass (BG) used in flexible tissue engineering, has shown interesting and promising results in supporting cell growth in vital organs such as the heart and lungs [126, 127]. The combination of chitosan with BG in a lung tissue engineering context could yield promising and expected results. Because in the study on the use of BG 58S (58 SiO2-36 CaO-6 P2O5) for lung tissue repair showed that it promotes the proliferation and growth of lung epithelial cells in a mouse model (MLE-12) [128]. In addition, the porous BG composite consisting of poly(DL-lactic acid) (PDLLA) and Bioglass® 45S5 has been shown to stimulate lung cell proliferation, confirming its cytocompatibility [129]. In the same sense, the porous composite of PDLLA and Bioglass® 45S5 stimulated the proliferation of the lung carcinoma cell line A549, increasing Bioglass® content (0.5 and 40 wt%) and with an increase in cell adhesion observed [130].

**Action on the liver**

In addition to its effect on the pulmonary tract, SARS-CoV-2 carries its action to the liver. Recent reports and case studies have shown that approximately 2–11% of patients with COVID-19 also develop chronic liver disease. Currently, liver dysfunction has been observed in 14–53% of patients with severe COVID-19. The cases of acute liver injury were confirmed by liver function markers of COVID-19 patients, which showed increased levels of alkaline phosphatase (ALP), aspartate, alanine aminotransferase (AAT), total bilirubin, and gamma-glutamyl transferase (GGT) [131, 132]. The severe and prolonged hepatic effects observed in post-COVID-19 patients could be attributed to the direct cytopathic effect of the virus on liver cells. Also, hypoxia associated with pneumonia, sepsis, or drug-induced hepatotoxicity, could contribute to chronic liver injury [133]. The ability of SARS-CoV-2 to infect the liver due to the expression of angiotensin-converting enzyme 2, or ACE2, receptors present in liver cholangiocytes [134], indicating that the virus could bind directly to cholangiocytes and disrupt liver function [135].

The hepatoprotection by chitosan has been confirmed in several past studies, which showed its power to abolish the hepatic alterations caused by some antitubercular drugs [134] and to counteract the hepatotoxicity induced by acetaminophen and carbon tetrachloride [135]. As a result of these hepatoprotective properties of chitosan, it could be a good candidate to limit all the alterations that SARS-CoV-2. In addition, porous sponges composed of a combination of alginate and galactosylated chitosan (AL-GC) stimulated hepatocyte growth to a greater extent than alginate sponge due to the presence of the hepatocyte-specific ligand asialoglycoprotein receptor (ASGPR) [133]. Thus, scaffolds of galactosylated polycaprolactone-chitosan exhibited improved liver functionality over seven days [136].
Action on the central nervous system

COVID-19 is also associated with various neurologic disorders, including headache, anosmia, impaired consciousness, loss of smell and taste, and stroke [137, 138]. A growing number of case reports and brain imaging data describe a wide range of neurologic manifestations in patients with COVID-19 [139]. Common clinical features include anosmia, ageusia, ischemic stroke, intracranial hemorrhage, hypoxic-ischemic encephalopathy, encephalitis, and acute hemorrhagic necrotizing encephalopathy [140]. MRI scans showed that 47% of patients had acute neurologic abnormalities, which manifested as acute ischemic infarction (31%), intracranial hemorrhage (6%), multiple sclerosis (10%), cerebral venous thrombosis (12%), Guillain–Barre syndrome, nonspecific encephalopathy (10%), Miller-Fisher syndrome (10%), and posterior reversible encephalopathy syndrome (PRES) (5%) [140]. The study report showed that the virus can cause inflammation of the brain tissue and can induce cell damage, leading to several neurological disorders [141, 142]. Yet the marine environment is known to be a rich source of bioactive chemical structures with promising biological activities such as neuroprotection. According to several studies, chitosan, one of the bioactive compounds derived from the sea, has powerful neuroprotective properties such as suppression of beta-amyloid formation, anti-neuroinflammatory activity, apoptosis inhibitors, and anti-neuro-oxidants [145]. Natural polymers, such as chitosan and alginate, are the most effective type of polymer used in neuronal tissue engineering, and they have been studied preclinically in many animal models, including primates [146].

The use of injectable chitosan and hyaluronic acid hydrogel allowed the regeneration of a peripheral nerve injury [139]. Thus, in chitosan and agarose-based hydrogels, cell attachment and growth were increased 15-fold [148]. In addition, chitosan has been used to manufacture neural tissue, including Schwann cell attachment and neuron survival [149]. In the same sense, chitosan has been successfully used in neuronal tissue engineering, allowing cell attachment, cell interaction, cell survival, and neuronal outgrowth [150, 151]. Other research has shown that Poly (ε-caprolactone)/chitosan fibers stimulated the attachment and proliferation of adrenal pheochromocytoma (PC12) cells, promoting neurite extension along the fiber orientation. Scaffolds based on poly(lactic-co-glycolic acid) and chitosan showed neuronal differentiation regarding peripheral nerve regeneration in vitro and in vivo [152, 153]. Similarly, scaffolds composed of poly(3,4-ethylene dioxythiophene)/chitosan/gelatin improved neurogenesis and cell growth [154], and therefore, chitosan can prevent further damage to brain cells and thus avoid shock and other disorders from viral infections such as COVID-19.

Conclusion

In low-middle-income countries, such as Morocco, the current pandemic has caused significant mortality and has had a huge social, economic, and health impact on Moroccan society. At present, post-COVID-19 complications are taking hold, and researchers are looking for treatments that will be effective and have no side effects,
and that could correct all that COVID-19 has caused. However, in Morocco, various treatments, which have been used, did not seem to be effective and had harmful side effects (i.e., cardiogenic shock). Chitosan-based biomaterials can halt, reverse, and even correct the effects of virus-induced tissue damage in various ways. Chitosan can restrain viral infections by stimulating the key mediators of immunity (i.e., ROS, leukotriene B4), making changes in the structure of viral capsid proteins, and inhibiting the formation of new viruses. Besides its immunomodulatory effect and antiviral activity, it can be used in drug delivery and tissue engineering. Future studies should focus on the different aspects of the applicability of any kind of technology that uses materials of natural origin due to their high biocompatibility with the human organism against this pandemic infection. Finally, these biomaterials could be a powerful alternative to remedy this virus definitively; therefore, they should be used clinically against the current and future global epidemic.

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