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Immunomodulatory agents as potential therapeutic or preventive strategies for COVID-19

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Abstract. – Currently, the COVID-19 pandemic, caused by the novel SARS-CoV-2 coronavirus, represents the greatest global health threat. Most people infected by the virus present mild to moderate respiratory symptoms and recover with supportive treatments. However, certain susceptible hosts develop an acute respiratory distress syndrome (ARDS), associated with an inflammatory "cytokine storm", leading to lung damage. Despite the current availability of different COVID-19 vaccines, the new emerging SARS-CoV-2 genetic variants represent a major concern worldwide, due to their increased transmissibility and rapid spread. Indeed, it seems that some mutations or combinations of mutations might confer selective advantages to the virus, such as the ability to evade the host immune responses elicited by COVID-19 vaccines. Several therapeutic approaches have been investigated but, to date, a unique and fully effective therapeutic protocol has not yet been achieved. In addition, steroid-based therapies, aimed to reduce inflammation in patients with severe COVID-19 disease, may increase the risk of opportunistic infections, increasing the hospitalization time and mortality rate of these patients. Hence, there is an unmet need to develop more effective therapeutic options. Here, we discuss the potential use of natural immunomodulators such as Thymosin α1 (Tα1), all-trans retinoic acid (ATRA), and lactoferrin (LF), as adjunctive or preventive treatment of severe COVID-19 disease. These agents are considered to be multifunctional molecules because of their ability to enhance antiviral host immunity and restore the immune balance, depending on the host immune status. Furthermore, they are able to exert a broad-spectrum antimicrobial activity by means of direct interactions with cellular or molecular targets of pathogens or indirectly by increasing the host immune response. Thus, due to the aforementioned properties, these agents might have a great potential in a clinical setting, not only to counteract SARS-CoV-2 infection, but also to prevent opportunistic infections in critically ill COVID-19 patients.

Key Words:
COVID-19, Immunomodulatory agents, Thymosin α1, All-trans retinoic acid, Lactoferrin, Anti-inflammatory activity, Antimicrobial activity.

Introduction

COVID-19 is a disease caused by the new coronavirus SARS-CoV-2[1]. Most infected people experience mild to moderate respiratory illness and recover without receiving a specific treatment. However, elderly individuals or those with comorbidities such as cardiovascular disease, obesity, diabetes, chronic respiratory disease, and cancer are more susceptible to develop serious illness. The severe COVID-19 disease is characterized by an imbalance between inflammatory and regulatory T immune responses to the virus, leading to an excessive production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, and to a lesser extent, interleukin (IL)-1β, and IL-6. This excessive inflammatory immune response contributes to the lung damage and correlates with the severity of COVID-19 pneumonia[2,3]. In a physiological setting, the inflammatory immune response is regulated by $CD4^+$ regulatory T cells (Tregs). The detailed analysis led to the identification of two subpopulations of Tregs, i.e., the IL-10-producing T-regulatory cell type 1 (Tr1), and the transforming growth factor-β (TGF-β)-secreting T-helper cell type 3 (Th3)[4,5]. These cells play a crucial role in maintaining both local and systemic immune homeostasis. A complex molecular interaction between innate and adaptive immunity governs the development of Tregs. Particularly, the indoleamine 2,3-dioxygenase (IDO)-expressing plasmacytoid DCs (pDCs), *via* the release of TGF-β, is essential in promoting

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the differentiation of naïve TCD4$^+$ into Treg CD4$^+$CD25$^+$ lymphocytes[6]. An altered generation of Tregs induces initiation and perpetuation of an inflammatory response towards different harmful stimuli, including microorganisms, leading to extensive tissue injury[7]. Although in critical COVID-19 patients pulmonary failure is due to uncontrolled inflammation, other factors such as neurological mechanisms, thromboembolism, and super-infections might also play an important pathogenic role[8-10]. As a matter of fact, secondary bacterial and fungal infections represent important complications of viral pneumonia, especially in severely ill patients[11]. Alterations in airway mucociliary clearance, induced by respiratory viruses, may favor pulmonary colonization by exogenous or endogenous bacteria of the upper respiratory tract. Particularly, *Streptococcus pneumoniae*, *Staphylococcus aureus,* and *Haemophilus influenzae* are the most common pathogens responsible for secondary bacterial pneumonia that is generally associated with more severe clinical outcome[12]. Furthermore, in acute respiratory failure, many patients with COVID-19 require admission to intensive care units (ICU) for mechanical ventilation, which increases their risk of ICU-acquired bacterial and fungal opportunistic infections[13,14]. Notably, invasive pulmonary aspergillosis (IPA) is more common and severe in ICU patients with COVID-19 than in those without COVID-19[13,15]. Systemic *Aspergillus* infections have also been associated with other coronavirus diseases, such as the 2003 outbreak of severe acute respiratory syndrome-coronavirus (SARS-CoV 2003) and Middle East Respiratory Syndrome-coronavirus (MERS)[16,17]. Furthermore, during the 2009 influenza A (H1A1) pandemic, cases of IPA were documented in patients with ARDS, in the absence of the known factors that predispose to opportunistic mycoses[18]. The risk of developing opportunistic infections in critically ill patients with COVID-19 is increased by the use of steroid immunosuppressive therapy[18]. Corticosteroids have a good inhibitory effect on inflammatory response and are often used as an auxiliary therapy for the treatment of viral pneumonia. However, to date, the real efficacy of these drugs in patients with severe SARS-Cov-2 infection remains controversial. From this perspective, a meta-analysis study showed that corticosteroid treatment was associated with a higher mortality rate and bacterial super-infection in COVID-19 patients[19]. Corticosteroids can increase the risk of developing fungal infections by inhibiting the IL-2 and interferon (IFN)-γ production by T lymphocytes, as well as by inducing the shift of T cell responses from Th1 to Th2[20]. In this respect, IFN-γ plays a key role in host defenses against fungi through the activation of macrophages and DCs, which are crucial for a successful clearance of such pathogens[21-23]. Moreover, there is evidence that a shift in Th1/Th2 immune response is associated with an increased susceptibility to pulmonary fungal infections[24]. So far, despite a huge effort to counteract the current pandemic, no therapy has been shown to be highly effective in the control of COVID-19 pneumonia. In this context, although COVID-19 vaccine represents the most powerful weapon to fight the virus, the rapid emergence of the new SARS-CoV-2 variants urgently requires new therapeutic approaches. Here, we discuss the therapeutic potential of natural immunomodulatory agents such as Tα1, ATRA, and LF to treat, manage, and prevent severe COVID-19. The rationale for the use of these agents as adjunctive therapies would be to enhance the host immune response to fight SARS-CoV-2 replication more efficiently. Additionally, they might prevent the progression to severe forms of COVID-19 pneumonia by restoring the immune homeostasis and hindering hyperinflammation. Also, their use could counteract the steroid-induced immunosuppression, thus protecting patients against opportunistic infections. In this context, it is worth noting that ATRA and LF can also exert a direct antimicrobial activity against a broad spectrum of pathogens[25-30]. Due to these features that are summarized in Figure 1, Tα1, ATRA and LF might be very promising candidates in the prophylaxis and/or therapy of the most severe clinical forms of COVID-19, especially in highly vulnerable patients.

Immunomodulatory Agents

Thymosin Alpha1

Thymosin α1, a small peptide hormone consisting of 28 amino acids produced by the thymus gland, is well known for its immunomodulatory properties, being it able to affect both innate and adaptive immunity[31,32]. Indeed, Tα1 exerts beneficial effects in various pathological conditions, such as cancer, cystic fibrosis, and sepsis[33-35]. The peptide has the capability to antagonize the dexamethasone (DEX)-induced apoptosis of CD4$^+$CD8$^+$ thymocytes, as well as to counteract the decrease of thymus and spleen indices in

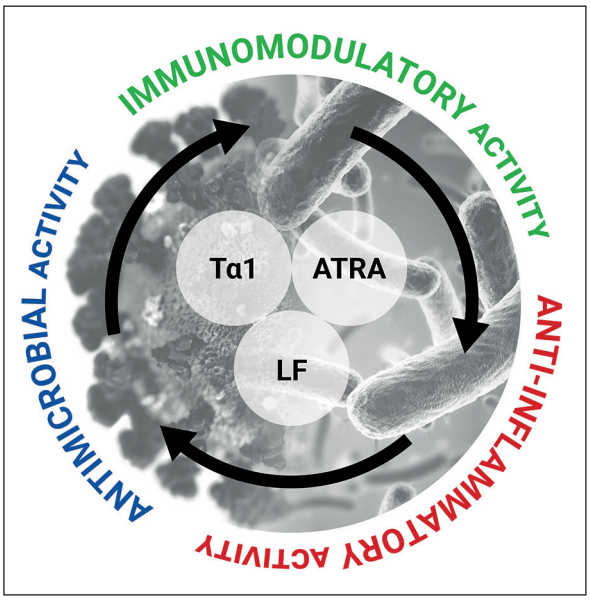

Figure 1. Immune-based novel potential strategies for the treatment and management of COVID-19. Tα1, ATRA and LF are three natural and multifaceted molecules shearing some common features. Firstly, being able to modulate innate and adaptive immune responses, they may have therapeutic efficacy against SARS-CoV-2 infection. Secondly, they can mitigate the cytokine storm that represents the crucial event in ARDS pathogenesis associated with severe COVID-19 pneumonia. Finally, they may protect critically ill patients against opportunistic infections, by exerting a direct antimicrobial activity, or indirectly by boosting the immune system. Therefore, due to their immunological and antimicrobial properties, alongside a good safety profile, these agents may be relevant in the treatment and control of the most severe forms of SARS-CoV-2 infection. Tα1, Thymosin α1; ATRA, all-trans retinoic acid; LF, lactoferrin.

hydrocortisone (HC)-treated mice[31,36]. *In vitro* Tα1 has been shown to be capable of activating myeloid dendritic cells (mDCs) in response to *Aspergillus* conidia by modulating the expression of specific Toll-like receptors (TLRs), i.e., TLR-2, TLR-4, and TLR-9, through the p38 mitogen-activated protein kinase/nuclear factor (NF)-*k*B-dependent pathway[37]. A preclinical study on pulmonary aspergillosis also showed that Tα1 induces activation and expansion of tolerogenic Tregs by targeting the immunoregulatory IDO pathway in pDC cells at the early stage of infection. Interestingly, the early but not late activation of Tregs, induced by Tα1, was associated with suppression of polymorphonuclear (PMN) functional activities, including the production of inflammatory cytokines such as TNF-α[38]. A recent *in vitro* study has also shown that Tα1 mitigates the inflammatory cytokine expression in peripheral blood cells from COVID-19 and decreases the levels of the $CD38^{+}HLA\text{-}Dr^{+}$ marker in $CD8^{+}$ T cells, which is up-regulated by an array of inflammatory conditions[39]. This regulatory mechanism, exerted by Tα1 in the control of inflammation, suggests its possible effectiveness in the treatment of critically ill COVID-19 patients[40]. The low Tα1 serum levels of individuals with inflammatory/autoimmune diseases like psoriatic arthritis, multiple sclerosis or sepsis, reinforce the concept of the pivotal role played by the hormone in maintaining immune homeostasis in physiological conditions[41]. Moreover, when used in chemo-immunotherapy protocols, Tα1 has beneficial effects in B16 melanoma tumor-bearing mice, as well as in patients with metastatic melanoma, by enhancing natural killer activity (NK) and effector T cell responses[42,43]. Considering the central role of NK and cytotoxic $CD8^{+}$ T lymphocytes in the control of viral infections, the protective effect of Tα1, in severe COVID-19, could be mediated by the recovery of lymphocytopenia, which has been associated with the worst prognosis in these patients[44]. Furthermore, Tα1 could counteract the virus not only by increasing the number and function of T lymphocytes, but also by enhancing the efficiency of antigen presentation to the effector T cells. In this regard, it has been reported that Tα1 increases the expression of major histocompatibility complex (MHC) class I and class II on DCs, which play a key role in the antigen presentation process[37,45]. Notably, MHC class I is implicated in the innate antiviral immune responses by triggering cytotoxic $CD8^{+}$ T lymphocytes. Besides its effectiveness against COVID-19, the antiviral activity of Tα1 has also been documented in chronic hepatitis B and C, either alone or in combination with IFN-α and in HIV/AIDS[46-49]. In a murine model of cytomegalovirus (CMV) infection, Tα1 has been shown to exert a protective role by inducing the production of antiviral mediators, such as IFN-α and IFN-γ in pDCs, *via* the TLR9/MyD88/IRF7-dependent pathway[50]. Also, it has been demonstrated that Tα1 improves the efficacy of influenza vaccine in elderly and immunocompromised patients by increasing the antibody immune response to influenza virus, and for this reason, it can be used as a vaccine adjuvant[51]. Besides its protective effect against viruses, Tα1 also exerts a remarkable antifungal activity against systemic *Candida albicans* infection, both in *in vivo* and *in vitro* experimental models, *via* the enhancement of the fungal intracellular killing by polymorphonuclear

cells[52,53]. An important protective effect of Tα1 against *Aspergillus fumigatus* was also observed in an experimental murine model of bone marrow transplantation due to an increased Th1 immune response against the fungus and a rapid myeloid recovery in neutropenic mice[37]. Based on the aforementioned pleiotropic activities, Tα1 might have great potential in a clinical setting as a complementary therapeutic option for COVID-19 disease. By affecting the Th1/Th2 balance, and thus orienting T helper cells toward anti-inflammatory or pro-inflammatory responses, depending on the immune microenvironment[54], Tα1 could be effective against SARS-CoV-2 and its variants. Furthermore, by boosting both innate and adaptive immunity, it could also prevent the occurrence of secondary fungal infections, improving the clinical outcome of critically ill COVID-19 patients. Likewise, Tα1 due to its ability to enhance immune responses, counteracting hyperinflammation, deserves special attention in preventing severe COVID-19 in frail patients, such as the elderly and those with comorbidities as cancer[55]. Finally, it could also act as a COVID-19 vaccine adjuvant, particularly in these categories of patients.

All-Trans Retinoic Acid

The retinoic acid (RA), a metabolically active vitamin A metabolite, possesses various biological activities on embryonic development, hormone function, and modulation of immune responses due to its ability to interact with different cells types[56,57]. RA deficiency, especially in childhood, is associated with increased morbidity and mortality risk from infectious diseases, particularly gastrointestinal and pulmonary infections, and with impaired immune response to vaccine[58-60]. RA plays a pivotal role in maintaining the intestinal immune homeostasis, by inducing the differentiation of Foxp3 regulatory T cells and immunoglobulin IgA production and by its ability to modulate the homing of innate lymphoid cells (ILC) at mucosal sites[61-64]. As a matter of fact, the above-mentioned T cell sub-population plays a pivotal role in regulating inflammatory responses and repairing tissue damage at the level of the skin, airway, and intestinal barrier[64,65]. RA induces the differentiation of effector T lymphocytes by promoting the cytokine production by DCs during infection, thus exerting a protective effect on intestinal mucosa against invading pathogens[63,66]. Furthermore, RA is able to modulate the macrophage activity, which is induced by bacterial lipopolysaccharide (LPS) or IFN-γ, *via* the inhibition of the production of nitric oxide (NO) and pro-inflammatory cytokines such as TNF-α and IL-12[67]. Studies in a murine model showed that in combination with TGF-β and prostaglandin E2 (PGE2), RA works in synergy with IL-4 in promoting the anti-inflammatory (M2) macrophage polarization[68]. Recent evidence that macrophages are the main actors in acute lung injury (ALI) and ARDS pathogenesis has been reported[69]. Therefore, the retinoid displays a key role in the maintenance of immune homeostasis by promoting immunological tolerance in different pathophysiological conditions. From this perspective, RA might represent a very promising tool in therapeutic strategies against inflammatory diseases, including ARDS associated with COVID-19. Recent studies support the hypothesis that a defective metabolism of RA may be associated with the cytokine storm syndrome in patients with COVID-19. Other hyperinflammatory conditions, such as sepsis and chronic autoimmune disorders, have been associated with retinoic acid deficiency, opening new perspectives for the treatment of such diseases[70]. RA may also exert an important antiviral activity by modulating the production of type-I IFN (IFN-α-IFN-β), the most powerful orchestrator in the host defense mechanism against viral infections[71]. In addition to the antiviral activity, ATRA also exerts antimicrobial activity against bacterial and fungal pathogens. Particularly, it is able to reduce bacterial burden by promoting autophagy in primary human and murine macrophages infected with *Mycobacterium tuberculosis* and *Bordetella pertussis*[72]. In previous works, for the first time, we highlighted another aspect of ATRA as a fungistatic drug by demonstrating that it can inhibit *in vitro* the growth of *Candida albicans* and *Aspergillus fumigatus.* Our results also showed a synergistic interaction between ATRA and conventional antifungal drugs such as amphotericin B and posaconazole[25,73]. Interestingly, *in vivo* in a rat model of IPA, ATRA has been proven to exert a remarkable protective antifungal effect comparable to that of posaconazole[73]. In line with the results of other authors, our *in vitro* studies also showed that the antifungal activity of ATRA might be due not only to a direct fungistatic action but also to its capability of potentiating macrophage phagocytosis against fungi[73,74]. Using a molecular docking approach, we hypothesized that the mechanism underlying the fungistatic effect of ATRA might be due to its interaction

with the fungal heath shock protein (HSP)-90, a key virulence regulator in many fungal species[73]. ATRA has been approved for systemic therapy in humans and has a well-documented safety profile. Notably, the use of the retinoid as differentiation inducer, combined with other chemotherapeutic agents, represents the current standard therapy for the treatment of Acute Promyelocytic Leukemia (APL) in adults and of Neuroblastoma (NB) in children[75,76]. In leukemic patients treated with ATRA in association with chemotherapy, a rapid differentiation of leukemic cells and a lower occurrence of systemic mycosis have been observed[77,78]. Therefore, the safety profile, alongside the immunomodulatory/anti-inflammatory and antimicrobial properties, suggests the possible use of RA as supportive treatment in the control of the most severe COVID-19 disease, as well as in the prevention of the development of opportunistic infections in other categories of critically ill patients.

Lactoferrin

Lactoferrin (LF) is a multifunctional glycoprotein present in milk and, to a lesser extent, in exocrine body fluids such as bile, tears, seminal fluid, and uterine secretions[79]. At first, LF was extracted from bovine milk and, subsequently, added into many commercial products, such as nutritional supplements, infant formula, and cosmetics[80]. This protein displays many biological properties, including antioxidant, anti-inflammatory, and immunomodulatory activities[81,82]. Due to the propensity of its basic N-terminal domain to interact with a variety of pathogens and host cell targets, LF also possesses a wide spectrum of antimicrobial activity[83]. It is considered an important component of host defense mechanisms for its role in the activation of T and B lymphocytes, and of NK cell cytotoxicity against microbial pathogens[82]. As an immunomodulator, LF shares with Tα1 and ATRA the ability to up- or down-regulate several immune cell functions, depending on the microenvironment and the host immune status[83]. It has been reported that LF is able to modulate innate immunity by a direct interaction with pro-inflammatory pathogen-associated microbial patterns (PAMPs) that are recognized by the Toll-like receptors expressed by natural immune cells[84,85]. Also, it has been shown that by binding the LPS of Gram-negative bacteria, or the soluble CD14 (sCD14), which is a TLR-4 co-receptor, LF is able to prevent the LPS-induced immune cell activation, thus inhibiting the production of pro-inflammatory cytokines[85]. Due to its ability to mitigate inflammatory responses, LF might play an important role in reducing tissue injury caused by uncontrolled inflammation. Moreover, through its binding to free iron, LF is involved in the regulation of iron homeostasis, counteracting the oxidative stress, and thus re-establishing the normal levels of various proteins that are altered in inflammation, such as ferroportin, ceruloplasmin, transferrin receptor 1, and ferritin[86]. Owing to its iron-binding property, LF also exerts a bacteriostatic activity through a mechanism of competition with bacteria for the free mineral that is essential for bacterial cell growth[87]. The presence of LF in neutrophils and its release at high concentration, as a component of neutrophil extracellular traps, during inflammation, further support its role in phagocytic killing and in other immune responses to infections[88]. LF also exerts a direct bactericidal action because of its ability to bind microbial targets, i.e., LPS, porin, and other outer membranes (OM) proteins in Gram-negative bacteria, as well as teichoic acid in Gram-positive bacteria, leading to the disruption of the bacterial cell wall[89]. Interestingly, a combination of lactoperoxidase (Lpo) and LF exhibits bactericidal activity against multi-drug resistant *Acinetobacter baumannii* strains both in *in vitro* and *in vivo,* in a murine model of acute *Acinetobacter baumannii* pneumonia[26]. Furthermore, *in vitro* studies also showed that LF can inhibit biofilm production by *Pseudomonas aeruginosa*[27]. In this regard, it is worth mentioning that *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are the most common opportunistic and multidrug-resistant (MDR) bacteria related to ventilator-associated and hospital-acquired pneumonia. The occurrence of such pulmonary infections in hospitalized patients, especially in those with impaired immune response, is associated with poor clinical outcomes and could increase the complexity of the treatment of COVID-19 pneumonia[90]. An additional mechanism by which LF exerts its antibacterial activity is related to the induction of the pathogen's opsonization. In fact, by acting as an opsonin-like molecule, LF promotes the clearance of microbes by professional phagocytic cells[91]. Owing to its ability to sequester iron, LF is also capable to exert a strong antifungal activity against opportunistic fungi, such as various species of *Candida*, including *Candida tropicalis*, *Candida krusei*, and *Candida albicans*[92], as well as against *Aspergillus fumigatus*[93]. Although iron sequestration may play a role in the antifungal

activity of LF *in vivo*, more recently, it has been suggested that the main antifungal mechanism of LF is iron-independent. Indeed, LF can interact directly with the fungal cell surface, leading to cell membrane damage[28,29]. Another mechanism of the antifungal activity of LF might be linked to its ability to induce apoptosis-like processes in fungal pathogens. To support this hypothesis, studies carried out in *Saccharomyces cerevisiae* have shown that lactoferrin-induced cell death is mitochondrial and caspase-dependent[30]. More interesting, LF also exhibits a powerful antiviral activity against a wide range of enveloped and naked viruses, acting at the early phases of infection by interfering with the virus-host cell interaction. Indeed, the LF ability to bind to heparan sulphate glycosaminoglycan (HSPGs) cell receptors, or viral particles or both, prevents the virus entry into the host cells[94]. In this regard, it has been demonstrated that by binding to HSPGs, LF blocks the host cell invasion by a variety of viruses, among which Herpes simplex virus, human papillomavirus, human immunodeficiency virus (HIV), rotavirus, and coronavirus, including the novel coronavirus SARS-CoV-2[95-99]. Consistently, not only ACE2, but also HSPGs cell receptors are involved in SARS-CoV-2 entry into the cells, representing one of the preliminary viral docking sites on the host cell surface[100]. Thus, LF by blocking the interaction SARS-CoV-2/host could play a protective role against SARS-CoV-2 infection. *In vitro* studies have shown that LF inhibited infection and replication of SARS-CoV-2 virus in Caco-2 intestinal epithelial cells, suggesting its protective role as a natural defense barrier in the respiratory and gastrointestinal tracts[99,101]. Previous works also demonstrated an up-regulation of TLR3 and TLR7 that are implicated in the recognition of viral RNA, and an increased expression of the antiviral cytokine IFN-α/β in infected cells upon LF treatment[102,103]. Thus, with the mentioned premises, this pleiotropic molecule might be considered as a nutraceutical supplement, in combination with other drugs, particularly in the treatment and management of asymptomatic or mild symptomatic COVID-19 patients. By re-establishing immune homeostasis, LF might be able to counteract the cytokine storm, thus preventing the most severe COVID-19 progression. Studies performed in humans and in experimental animal models on various inflammatory diseases showed that LF oral administration has a good safety profile. Also, its intravenous administration or nebulization could represent very attractive therapeutic options. Bovine lactoferrin (bLF), which has a high homology with the human lactoferrin (hLF), is already commercially available in liposomal formulation optimized for nebulizer delivery[104]. Overall, the immunomodulatory and anti-inflammatory properties, besides the broad-spectrum antimicrobial activity, make LF an attractive molecule with great potential in a clinical setting, not only to fight SARS-CoV-2 infection but also to prevent possible opportunistic super-infections in patients with severe COVID-19 disease.

Conclusions

Despite many efforts to counteract the COVID-19 pandemic, so far, the current therapies still seem inadequate in the management of severe COVID-19 pneumonia. A growing body of evidence also suggests that the new SARS-CoV-2 variants, especially the UK variant, are associated with increased hospitalization and death rates, representing a serious public health threat[105]. Furthermore, the circulation of the new emerging viral variants raises questions about the efficacy of the antibody response elicited by vaccines, and the real effectiveness of monoclonal or serum-derived polyclonal antibodies. Moreover, how long the COVID-19 vaccines may confer protective immunity remains, to date, the major concern worldwide[106]. Finally, despite the global collaboration to accelerate the production of COVID-19 vaccines, their supply is still limited, thus delaying mass vaccination. Given all these issues, novel specific therapeutic strategies are urgently needed. To date, the pathophysiological mechanisms underlying the cytokine storm and pulmonary damage have not been fully identified. However, targeting the dysfunctional immune response by limiting hyperinflammation and enhancing the host antiviral immunity could represent a valid strategy to control severe complications in critically ill COVID-19 patients. From this perspective, here we hypothesize the possible effectiveness of some natural immunomodulators such as Tα1, ATRA, and LF, as either complementary therapy or prophylactic intervention, according to the phase of SARS-CoV-2 infection. In the early stage of COVID-19, when it is fundamental to control virus replication, they could be used as a prophylactic strategy to reduce disease severity. In the later phase of the infection, characterized by the cytokine storm, these agents might

also be useful, in combination with standard therapies, to arrest the hyperinflammatory loop and thus to prevent lung injury in highly vulnerable patients. Additionally, either indirectly by boosting the immune system or directly by interacting with cellular or molecular targets of pathogens, they might counteract the development of opportunistic infections in severe COVID-19 cases. Therefore, protecting from secondary infections, their employment may allow to avoid the preemptive use of broad-spectrum antimicrobial agents that could lead to the emergence of drug-resistant microorganisms. In conclusion, owing to their immunomodulatory and antimicrobial properties, alongside the safety profile, these multifaceted molecules might be optimal candidates for novel potential therapeutic or preventive strategies to improve the clinical outcomes in patients with COVID-19. Further research is needed to confirm these hypotheses and to develop effective combination therapy protocols.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

All authors contributed toward drafting and critically revising the manuscript, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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