Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Can complementary and alternative medicines be beneficial in the treatment of COVID-19 through improving immune system function?

Dear Editor

Emerging in China in late 2019, the coronavirus disease-2019 (COVID-19) infection epidemic is growing rapidly and new cases are reported around the world [1]. The first cases were linked to a wet market, and subsequently, the virus has spread rapidly in China through human-to-human transmission, and the universal impact of the COVID-19 virus is now spreading worldwide [2]. The disease originated from COVID19 is a type of viral pneumonia that is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Currently, no clinically approved antiviral drugs have been introduced for SARS-CoV-2 infection [3]. Identifying the mechanism of action of the virus and its interaction with the immune system will help prevent and treat the disease. In other hand, according to Ref. [4], a specific adaptive immune response in the incubation and non-severe stages is required to eliminate the virus and to preclude disease progression to severe stages.

Protecting the body against infection, the immune system prevents death by producing protein molecules called antibodies that bind to the antigens of infectious agents [5,6]. Through frequently interacting innate and adaptive mechanisms, the immune system defends against bacterial infection. The immune system assesses the amino acid sequence space of potential antibodies for identifying invader pathogens. According to Ref. [5], a hierarchical strategy is evolved by the immune system for recognizing the effective antibodies in the infinite protein sequence space.The two components of the innate immune system and the adaptive immune system form the pervasive immune system [7]. The innate system consists of exterior defenses (e.g. mucous membranes and the skin), serum proteins, and nonspecific phagocytic leukocytes [7,8]. This system is a more primitive one built formerly into cells that are located on the front line of defense against bacterial invasions, including epithelial cells in the lung, gut, skin, and periodontium as well as neutrophils and macrophages [9]. However, the adaptive immune system, which develops in a longer time, responds specifically. In fact, after evolvement, it provides a more specific response against invader organisms. Several investigations have shown that the virus has some effects on immune system operations [10–13]. According to the literature, different parameters of immune function are influenced by viruses including antibody generation, immunoglobulin levels, induction of immunological tolerance, graft-versus-host reaction, graft rejection, delayed-type skin reaction, lymphocyte transformation, and phagocytosis. In Ref. [10], the authors have examined these parameters comprehensively.

Recognizing the disease and its consequences on the immune system will support its better management providing preferred treatment strategies and more effective prevention [14]. The complexity of the disease becomes more apparent when it is revealed that certain segments of the population are more susceptible to severe infection and subsequently to death [14]. The responses of innate and adaptive immune systems make the base of the host anti-microbial defense. In order to quickly control and effectively deal with the viral infection, the innate immune system operates and simultaneously triggers the adaptive immune system. The innate immune system distinguishes influenza viruses through multiple mechanisms [15]. This system, which is programmed genetically for meeting the similar features of attacking microbes, acts rapidly and protects the body against infection early.

Among phagocytic cells, macrophages, neutrophils, and Dendritic Cells (DCs) play a major role in the innate immune response to influenza [14]. Influenza virus targets airway epithelial cells lining the respiratory mucosa. After infecting and lysing these cells, the virus of influenza A can infect alveolar macrophages and DCs residing in the airway [15]. As soon as sensing infection, DCs taking up viral antigens operate the main function in priming effector T cell responses [15,16]. After activation, influenza virus-specified CD4 and CD8 T cells operate together with antibody-generating B cells to elevate viral release in the lung [15,17]. T cells are principal moderators of the immune response and handle their performances by modulating the functions of other immune cells and modifying the behavior of parenchymal and endothelial cells [18]. In the case of COVID-19, after entering cells, the virus's antigen will be introduced to the antigen presentation cells, which are among the main parts of the body's antiviral immunity [19].

More than 80% of the world's population uses Complementary and Alternative Medicines (CAMs). In the US health care system, CAM is becoming an increasing component, with 70% of the population using that at least once and costing $34 billion annually [20]. Since the establishment of the National CAM-Center, the number of basic science and treatment-based clinical trials about CAM has increased significantly [20]. It is estimated that the worldwide market for herbal remedies, including herbal products and raw materials, will grow 5 and 15% annually. The worldwide herbal drug market is estimated at $62 billion, which is estimated to grow to $5 trillion by 2050. The global pharmaceutical market in 2004 was worth $550 billion and in 2008 it was up to $900 billion [21]. Herbal sources of immune-boosting materials are consumed in many countries to raise health, to promote the body's normal resistance against infectious agents and to prohibit as well as to cure various diseases [22].

It is found that CAMs are effective in boosting immune response vs. diseases. Several cases of CAMs proposed for prohibiting and curing diseases are discussed in this section. It has been suggested that as a CAM, curcumin, a polyphenolic compound extracted from spice and common food colourant turmeric [23], can enhance the antibody response even if it takes at low doses [24]. In fact, the beneficial effects of curcumin in improving different diseases are

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attributed partly to its ability to modulate the immune system [24]. Furthermore, several surveys demonstrate that curcumin is able to modulate both the activation and the proliferation of T cells [25,26]. It has also been shown that curcumin has the potential of regulating the growth and response of different immune cells. It affects NK cells, T cells, B cells, DCs, neutrophils, and macrophages [24]. CAMs have also found to be effective in infectious diseases [27,23]. In Ref. [23], the authors investigated the synergic effect of curcumin and its structural analogue (Monoacetylcurcumin) on anti-influenza virus infection. They found that, as with curcumin, Monoacetylcurcumin effectively inhibited influenza virus infection (IVA). The anti-influenza activity of curcumin was evaluated by Ref. [28]. The results of this study demonstrated that treatment of curcumin reduces influenza A viruses replication, affects an early stage of virus infection, and blocks haemagglutinating activity of IAV virus particles. Overall, they recommend that curcumin has promising potential for using as an anti-influenza drug. According to the previous research on antiviral potential of curcumin, the effectiveness of curcumin at very early stage of viral infection has been proven in a non-enveloped virus, human norovirus (HuNoV) [29]. The study by Ref. [30] demonstrated that antiviral mechanisms such as viral entry, rather than RNA replication of HuNoV, can be found by treatment of curcumin at various doses and durations. In addition [31], found the effectiveness of curcumin on various enveloped viruses such as vaccinia virus, IAV, and pseudorabies virus.

Providing minerals, vitamins, amino acids, herbs, and nutritional supplements are used to enrich the diet. These are mostly accompanied with CAMs, which include a group of various medic and health care orders, actions, and supplies not classified as a part of conventional medicines. Nutritional supplements appear to strengthen the immune system profiting transient immunosuppression that results from intense training [32]. It has been demonstrated that vitamin C [33], vitamin D [34] and zinc [35] boost the immune system versus viruses. Two assays executed in South Africa have shown promising results about vitamin C supplementation [32,36]. Vitamin D has also considerable effect on immune system. It has been demonstrated that vitamin D modulates innate and adaptive immune systems [9,37]. Both immune systems are adjusted by vitamin D, which suppresses the adaptive immune system but potents the innate immune response [9]. In Ref. [38], it is stated that vitamin D has reinforcing and inhibitory effects for the innate and adaptive immune systems, respectively. In Ref. [39], it is also stated that vitamin D, which has anti-inflammatory properties and modulates immunity in different ways, is effective in physiology and autoimmunity, and its deficiency is associated with chronic inflammatory diseases. Epidemiological surveys have confirmed that poor vitamin D consumption adheres to the raised risk of multiple diseases including autoimmune drawbacks. It seems that the immune regulatory effect of vitamin D has a significant role in this adherence. Adaptive immune cells are direct targets of vitamin D metabolites [40]. In fact, as concluded in Ref. [41], vitamin D is part of a complex set of factors that influence the immune response. Therefore, it is necessary to evaluate the serum level of vitamin D in children and the elderly and to maintain it at optimum levels and micronutrients should be used for improving health and fighting diseases.

The coronavirus disease 2019 (COVID-19) has been spread in Asia and all over the world [42] and has created a universal health emergency case [43]. As of 21 April 2010, this virus has infected more than 2,397,216 people with 162,956 deaths worldwide [44]. The radiological, clinical, laboratory, and epidemiological features as well as the clinical consequences and treatment of patients with laboratory-confirmed COVID-19 pneumonia were discussed in the recent study. This is not the first severe respiratory disease that has been spread by the coronavirus type. During the past two decades, different strains of this virus have created three epidemic diseases including the Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS), and COVID-19 [19,45].

The behavior of new coronavirus 2019 is similar to SARS-CoV so that it called SARS-CoV-2. Continuing by Acute Respiratory Distress Syndrome (ARDS) and septic shock, it eventually causes multiple organs to fail by the virus-induced cytokine storm in the body [46]. Similar to SARS-CoV and MERS-CoV, no clinically confirmed antiviral drug has been introduced for SARS-CoV-2 infection yet [19]. According to Ref. [47], down-regulation of gene expression related to antigen presentation due to MERS-CoV infection demonstrates that coronavirus can affect on the antigen presentation. Therefore, in order to produce a drug and to treat SARS-CoV-2-linked disease, it is necessary to block its evasion from the immune system.

It is claimed that the coronavirus pandemic can be significantly downed or ceased by urgent popular consumption of high amounts of vitamin C and for treatment of people who become infected with COVID-19, higher vitamin D_3 doses might be useful. It seems necessary to activate the body's maximum antioxidant capacity and natural immunity to minimize the symptoms of any virus attack. Vitamin C can be administered concurrently with potential medications to treat the disease in acute conditions. The oral administration of vitamin C up to the daily threshold of bowel tolerance will be effective for most people. For serious cases, intravenous infusion of vitamin C is recommended. Besides, it is claimed that the overactivity of immune cells results in lung injury following COVID-19 pneumonia. Some published open-label studies also recommend that intravenous injection of high-dose vitamin C can be a safe and useful option for treatment COVID-19 in its early stages.

Although antiviral activity of vitamin C has been recognized and approved in some previous literature, but its impact has not been widely broadcasted and, in particular, insufficient information has been provided on its effect on coronavirus. In addition, although vitamin C is important for the human body and helps reduce inflammatory response, there is no firm evidence to support that consumption of high amounts of vitamin C can be effective in prevention or treatment of COVID-19. Further, as stated in Therapeutic Goods Administration (TGA) [48], there is no clinical investigation and evidence to support intravenous high-dose vitamin C in the management of COVID-19 and more research is needed before any recommendation for the use of intravenous vitamin C in the treatment of COVID-19 can be made. In addition, as recommended by [49], randomized controlled trials and large population studies should be conducted to find the effectiveness of higher vitamin D_3 doses in the treatment of COVID-19.

From the above discussion, it is evident that understanding the disease and its effect on the immune system will improve disease management. According to the previous research, the immune system has a fundamental protective function against most infectious diseases such as SARS-CoV-2. The effectiveness of CAMs in boosting immune response against infection diseases has been extensively investigated. This study has also investigated the role of CAMs in infectious diseases and COVID-19. Specifically, an attempt has been made to clarify whether or not the use of vitamins has the potential to help to prevent and/or treat COVID-19. This study according to the previous research found that the use of CAMs can be an effective way in boosting immune response against the infections. In addition, it was found that the use of vitamins, in general, is beneficial in improving immune health and function. However, as a few clinical investigations show the effectiveness of CAMs in the prevention and treatment of infectious diseases, further studies through clinical and consumers' experience analysis on CAMs are required to come to robust conclusions in the effectiveness of CAMs for prevention and treatment of infectious diseases.

Overall, it is worth to further assess the benefits of CAMs, specially vitamins, for prevention and treatment of infectious diseases in general and COVID-19 in particular in the early stage of infection. The public should be assured that a lot of organized scientific studies on therapy for COVID-19, both locally and internationally, are being quickly produced. Therefore, credible evidence accompanied and supported by appropriate research is essential to ensuring public health in dealing with the current COVID-19 pandemic and improving public awareness on the undue promotion of fake medicine, especially in the current context.

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