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Expert Review of Anti-infective Therapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierz20

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To cite this article: Mohammad Heiat, Mohammad-Reza Hashemi-Aghdam, Fatemeh Heiat, Mona Rastegar Shariat Panahi, Hossein Aghamollaei, Mehrdad Moosazadeh Moghaddam, Thozhukat Sathyapalan, Reza Ranjbar & Amirhossein Sahebkar (2021) Integrative role of traditional and modern technologies to combat COVID-19, Expert Review of Anti-infective Therapy, 19:1, 23-33, DOI: 10.1080/14787210.2020.1799784

To link to this article: https://doi.org/10.1080/14787210.2020.1799784

EXPERT REVIEW OF ANTI-INFECTIVE THERAPY
2021, VOL. 19, NO. 1, 23–33
https://doi.org/10.1080/14787210.2020.1799784

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REVIEW

Integrative role of traditional and modern technologies to combat COVID-19

Mohammad Heiat[a], Mohammad-Reza Hashemi-Aghdam[a], Fatemeh Heiat[b], Mona Rastegar Shariat Panahi[c], Hossein Aghamollaei[d], Mehrdad Moosazadeh Moghaddam[c], Thozhukat Sathyapalan[e], Reza Ranjbar [f] and Amirhossein Sahebkar [g,h,i,j]

[a]Baqiyatallah Research Center for Gastroenterology and Liver Disease, Baqiyatallah University of Medical Sciences, Tehran, Iran; [b]Department of Physical Education and Sport Sciences, Islamic Azad University, Fasa Branch, Fasa, Iran; [c]Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran; [d]Chemical Injuries Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran; [e]Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University of Hull, United Kingdom of Great Britain and Northern Ireland; [f]Molecular Biology Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran; [g]Halal Research Center of IRI, FDA, Tehran, Iran; [h]Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran; [i]Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad,Iran; [j]Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland

ABSTRACT

Introduction: With the development of various branches of sciences, we will be able to resolve different clinical aspects of various diseases better. The convergence of these sciences can potentially tackle the new corona crisis.

Areas covered: In this review, we attempted to explore and describe various scientific branches studying COVID-19. We have reviewed the literature focusing on the prevention, diagnosis, and treatment of COVID-19. The primary databases targeted were Science Direct, Scopus and PubMed. The most relevant reports from the recent two decades were collected utilizing keywords including SARS-CoV, MERS-CoV, COVID-19, epidemiology, therapeutics and diagnosis.

Expert opinion: Based on this literature review, both traditional and emerging approaches are vital for the prevention, diagnosis and treatment of COVID-19. The traditional sciences play an essential role in the preventive and supportive care of corona infection, and modern technologies appear to be useful in the development of precise diagnosis and powerful treatment approaches for this disease. Indeed, the integration of these sciences will help us to fight COVID-19 disease more efficiently.

ARTICLE HISTORY
Received 23 May 2020
Accepted 20 July 2020

KEYWORDS
Coronavirus; covid-19; traditional Approaches; modern Technologies; treatment; prevention; supportive Care

1. Introduction

1.1. Background

Novel Coronavirus, which is known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first identified in Wuhan city, China in 2019, followed by infection of millions of people all over the world and has caused several thousands of deaths [1]. On 12 February 2020, WHO named this new coronavirus, SARS-CoV-2 and the disease caused by this virus Coronavirus Disease 2019 (COVID-19). This virus has since been transmitted to more than 200 countries all over the world. SARS-CoV-2 is an enveloped positive-sense RNA virus that is characterized by club-like spikes that project from their surface and belongs to the *coronaviridae* family [2]. Before SARS-CoV-2, six other coronaviruses have been identified, which can cause disease in human beings and are further divided into low-pathogenic and highly-pathogenic viruses. Low pathogenic viruses contribute 10 to 30% of upper respiratory diseases. Highly pathogenic viruses include Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV), which infects lower respiratory tracts and can cause fatal pneumonia [3]. At the beginning of the epidemic of SARS-CoV-2, clusters of CoV infections were reported, all of which were related to the human seafood market. Then cases of human to human transmission by contamination of 15 health care staff after close contact with one patient in Wuhan hospital were reported [4].

1.2. Signs, symptoms and treatment of COVID-19

The mean age of hospitalized patients was 55 years. The incubation period of the disease is 4 to 7 days. The most common symptoms are fever (98.6%), fatigue (69.6%), dry cough (59.4%) and myalgia. In a few patients, rhinorrhea, sore throat and diarrhea may also occur. Some patients develop dyspnea and hypoxemia, which can rapidly progress to acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, coagulopathy, and even multi-organ failure. A chest X-ray or computed tomography scan (CT scan) is recommended to all suspicious patients. Most of the confirmed COVID-19 patients can develop bilateral pneumonia [4]. Some of the laboratory tests can be helpful in early detection of disease including leukocytopenia, lymphopenia, mild increase in C-reactive protein (CRP), increase in prothrombin

CONTACT Reza Ranjbar ranjbarre@gmail.com Molecular Biology Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran; Amirhossein Sahebkar amir_saheb2000@yahoo.com School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Article highlights

- The new Coronavirus pandemic has become a major crisis all over the world.
- Several branches of science can resolve numbers of different clinical aspects of this disease.
- To tackle COVID-19, the convergence of various scientific modalities is necessary.
- There is growing evidence that lifestyle modification and traditional medicine can offer preventive and supportive care against corona.
- On the other hand, modern approaches such as biotechnology and bioinformatics can play key roles in the diagnosis and treatment of coronavirus infection.

time (PT) and partial thromboplastin time (PTT) and an increase in lactate dehydrogenase (LDH). Severe cases can increase leukocytes, granulocytes, D-dimer, creatine kinase (CK), and creatinine [5,6]. In the chest CT scan, patchy bilateral shadows or bilateral ground-glass opacities are seen in all patients with pneumonia [6]. Due to a large number of infected people that were exposed in the seafood market in Wuhan city, China, COVID-19 probably has a zoonotic origin [7]. After transmission to humans, COVID-19 is spread by human to human transmission through droplets and direct contact [8]. It is proved that COVID-19 can be spread from asymptomatic carriers to other people [9]. Despite several treatment methods tested in people infected with SARS-CoV -2, there is no specific treatment for this disease.

1.3. Study attitude and vision

The Corona epidemic has now become an important public issue in the community. As this trend continues, in addition to imposing heavy financial and life costs a widespread psychological burden will be created, which leads the community to a crisis. SARS-CoV-2, with all its virulence, has emerged as a full-fledged deadly pathogen, and it is unclear how long it will continue behaving such way. To conquer and repel its hegemony, a collaboration between various scientific disciplines is necessary. This approach will pave the way for successfully overcoming this crisis and planning for similar events in the future.

2. Method: search strategy

After a preliminary literature review about COVID-19, a research committee consisting of experts was created, and the topics of the primary research were presented. Eventually, based on the literature findings and the experiences of the committee members, the keywords were selected, and contiguous words were constructed. The predominant focus was the prevention, diagnosis and treatment of COVID-19. Science Direct, Scopus and PubMed were targeted as key data resources. The most relevant reports from recent two decades were collected utilizing keywords such as SARS-CoV OR MERS-CoV OR COVID-19 OR 2019-nCoV OR SARS-CoV-2 AND epidemiology, therapeutics, treatment, transmission, prevention, detection and diagnosis. A combination of traditional and modern sciences was organized, and the gist of scientific reports was elicited, categorized and summarized. The results were divided into two main sections Figure 1. The first section was on prevention and supportive care with a focus on traditional sciences and the second section was on the diagnosis and treatment with a focus on modern sciences. Figure 1

3. Findings

3.1. Prevention and supportive care

COVID-19 disease is now a worldwide health problem due to the severity of the outbreak and the epidemic spreading. Lack of approved medication and vaccination for the disease and the likelihood of the disease entering areas devoid of the disease is alarming. Therefore, for the proper control of this contagious disease, collecting useful and practical information on prevention, continuous monitoring, updating of

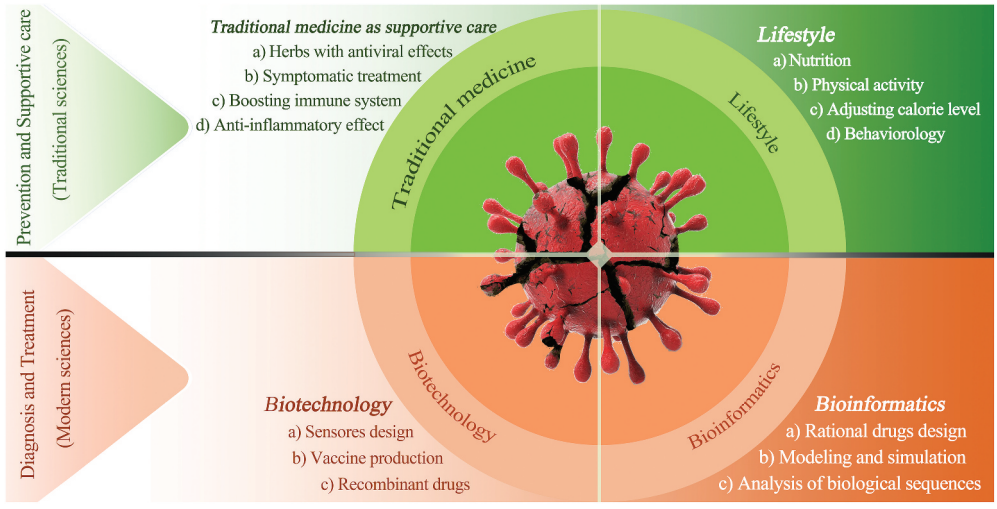

Figure 1. Convergence of traditional and modern science to manage the coronavirus; prevention and supportive care with focus on traditional sciences, diagnosis and treatment with focus on modern sciences.

information, and analysis of published data from affected areas are considered as top priorities. According to data obtained through a comprehensive search of scientific resources, it was concluded that lifestyle and traditional medicine guidelines could play a significant role to achieve COVID-19 disease prevention.

3.1.1. Lifestyle

Lifestyle includes daily behaviors and performance of people in work, activities, entertainment and diet [10]. Lifestyle focuses on health education and health promotion. According to WHO statistics, 60% of a person's health is related to lifestyle [11]. Many diseases such as cardiovascular diseases, hypertension, overweight and metabolic problems are caused by an unhealthy lifestyle [10].

The function of the immune system changes at different stages of life so that the immune system is not fully developed at birth but is fully functioning by adulthood. However, any immunocompromising condition is considered as a significant contributor to increased susceptibility to SARS-CoV-2 infection [12]. Healthy lifestyles such as exercise and healthy nutritional habits can play the most crucial role in boosting the immune system throughout life [13]. Here's a look at lifestyle main variables that play major roles in people's health.

3.1.1.1. Nutrition. A healthy, balanced diet is necessary for maintaining a healthy immune system. People with malnutrition are more likely to be infected, and there is evidence that deficiency of some nutrients can alter immune responses [14]. Many nutrients called micronutrients (vitamins, minerals, antioxidants) are involved in the proper functioning and strengthening of the immune system.

3.1.1.1.1. Vitamins. Vitamins play a vital role in the proper functioning of the body immune system. Severe vitamin D deficiency causes a wide range of pulmonary diseases, including acute viral respiratory infections [15], asthma, chronic obstructive pulmonary disease and cancer. The action of vitamin D on the innate immune responses, such as the production of antimicrobial peptides and autophagy, as well as its effect on adaptive immune responses, such as increased regulatory lymphocytes, is well established [16]. The renin-angiotensin system, containing the Angiotensin-I-converting enzymes (ACE1 and ACE2), is a complex bio-system that plays an important role in a variety of biological functions including blood pressure regulation and water balance in the body [17]. ACE2 has been described as a vector of SARS and SARS-COV2 and COVID-19 viruses [18]. Since ACE2 is a specific receptor for coronavirus, an increase in vitamin D levels by affecting specific ACE2 receptors prevents the virus from binding to its specific receptor [18].

There have been several reports suggesting that vitamin C may positively affect the immune system, such as phagocyte function, modulation of T-cell function, and interferon production [19]. It has been shown that vitamin C may reduce the risk of lower respiratory tract infections [19]. The dose of vitamin C needed to achieve the minimum level of plasma concentration to prevent infection is 100 to 200 mg daily. However, a higher dose of vitamins is necessary to cure the increased inflammatory response and metabolic demand for the treatment of infections [20]. Other vitamins such as Vitamin E [21], Vitamin A [21], B6 (Pyridoxine) and B12 (Cobalamin) have also been reported to be involved in boosting of the immune system and prevent viral infections through the production of white blood cells including T-cells.

3.1.1.1.2. Minerals. Some minerals, such as zinc, improve different aspects of the immune system [22]. Zinc is crucial for the normal growth and function of neutrophils, T-cells, and B-cells and natural killer cells (NK-cells) [23]. The antioxidant properties of Zn also prevent the inflammatory damage caused by ROS activity. It also reduces the expression of inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) [23]. Zinc deficiency, commonly found in the elderly, disrupts immune function, decreases resistance to pathogens, leading to an increased incidence and increased duration of pneumonia [24]. Other minerals such as selenium also reduce inflammation due to its antioxidant properties and enhance the immune system through the synthesis of glutathione peroxidase, which protects neutrophils [25].

3.1.1.1.3. Antioxidants. Although it seems that excessive intake of micronutrients may be harmful in some cases, beneficial effects have been observed for high intake of some antioxidants [21,26]. Consumption of high doses of antioxidants, especially water-soluble antioxidants such as vitamin C, reduces cortisol and IL6 and can thus boost the immune system, especially in people with environmental and mild physical stresses [27]. Another type of antioxidant is resveratrol. It the most well-known stilbenoid polyphenolic compounds found in red grapes, blueberries [28], peanuts [29], rhubarb [30], and some other plants. Resveratrol interferes in immune cell regulation, pro-inflammatory cytokine synthesis and immune gene expression [31]. Resveratrol can induce toll-like receptor (TLR) expression and pro-inflammatory genes. The antioxidant activity of resveratrol and its ability to inhibit the enzymes involved in the production of eicosanoids contribute to its anti-inflammatory properties [31].

3.1.1.2. Probiotics. The therapeutic effect of probiotics has been shown in several diseases. One function of probiotics is to regulate the host immune response. Studies on the biological effects of probiotics on host immunity indicate that they regulate the function of systemic immune cells, mucosal immune system and intestinal epithelial cells. Thus, probiotics can be a therapeutic potential for diseases associated with the immune response, such as allergies, eczema, viral infections, and vaccination responses [32].

3.1.1.3. Maintaining body weight balance (calorie restriction) and physical activity. One of the known effects of calorie restriction (CR) is the improving T-cell mediated immune function [33]. It has been demonstrated that CR elevates the level of resistance to influenza viral infection by increasing the number of T-cells [33]. Regular exercises with moderate-intensity (e.g. fast walking, gentle swimming, cycling, and gentle aerobics) have a positive effect on maintaining body immune efficiency. In contrast, some studies

have shown that vigorous-intensity activities result in a decrease in IgA, an increase in cortisol concentration and ultimately a weakening of the immune system [34,35].

3.1.1.4. Behaviorology. The importance of lifestyle in causing diseases has led to the formation of a new branch of medicine called behaviorology that emphasizes the modification of lifestyle for the prevention and treatment of diseases [36]. One of the goals of health education is to change the behavior to create a healthy lifestyle [37]. Behavioral changes can be effective in reducing stress and mental pressure. Scientific studies indicate a relationship between stress and life-threatening infections [38]. Individuals with a chronic stress index appear to be susceptible to the viral infection, whose molecular basis involves modulation of T lymphocytes and hypothalamic-pituitary-adrenal axis as well as altered the production of cytokines and hormones by the immune system and brain [39]. Another aspect of behaviorology can be focused on preventing the transmission of viral diseases especially for new corona diseases including staying at home except to get medical care, calling ahead before visiting doctor, cleaning hands, avoiding to share personal household things, cleaning all high contact surfaces [40].

3.1.2. Traditional medicine as supportive care

For thousands of years, medicinal plants have been used to improve immunity and even cure various diseases. Today, traditional medicine as a supportive and preventive medicine is popular among individuals, and many people use the properties of herbs on the advice of specialists. For confronting the coronavirus, the potential of traditional medicine can be exploited to fight against the virus and to control the specific symptoms of SARS-CoV-2 [41].

3.1.2.1. Herbs with antiviral effects. Traditionally, medicinal herbs have been used in many cases, including for the treatment of infectious diseases. Various researches on these plants have shown that some of these plants have antiviral activity [42]. Approximately 25% of clinically used drugs are of natural origin [43]. Therefore, there is a constant need for research to discover new and effective antiviral agents with a herbal origin. There is ample evidence to confirm the antiviral effects of some herbs. Statti et al. findings demonstrated that a herb such as *Rhus coriaria L* could be considered as one of the prominent herbs in traditional medicine with antiviral effects on influenza A, cytomegalovirus (CMV), and herpes simplex virus (HSV) viruses [44]. *Chelidonium majus* is another type of medicinal plant that has a long history in traditional Chinese, Indian and European medicine and has been shown to have several antiviral effects [45]. It can also inhibit the spread of influenza A virus [46]. Yellow and black *Terminalia chebula* species are another type of medicinal plants that inhibits the replication of the Herpes Simplex virus (HSV) [47]. *Licorice* extract has also been used as a new therapeutic approach for the treatment of viral myocarditis and influenza [48,49].

3.1.2.2. Inhibition of specific symptoms of COVID-19 (symptomatic treatment). As mentioned earlier, the new coronavirus mainly affects the lower respiratory tract and causes fatal pneumonia. Fever, fatigue, dry cough and myalgia are the most common symptoms. A percentage of patients rapidly suffer from ARDS and even multiple organ failure such as heart and renal failure [3]. The approach of reducing the specific symptoms of SARS-CoV-2 virus that inhibit pulmonary inflammatory reactions and dyspnea, immunomodulation, hemodynamic homeostasis and protecting the function of heart, kidneys and gastrointestinal during the inflammatory responses in the body can aid in the improvement of the patient's general condition. One of the most important herbs that can be used to inhibit inflammatory responses is *Alcea biennis winterl*. It has anti-cough and anti-inflammatory properties and heals pulmonary immunologic responses through its polysaccharide mucilage [50]. Another herb is *Viola odorata* that can effectively participate in the anti-inflammatory, antipyretic and pain relief that are beneficial effects in COVID-19 [51]. *Malva sylvestris* is expectorant and is effective in treating respiratory tract inflammation [52]. *Chamomile* has long been used in the treatment of intermittent fever [15]. The hemodynamic modulating effects of chamomile tea have been proven. Other pharmacological properties include anti-inflammatory, sedative, and spasmolytic activities [53]. Some of the most important herbs commonly used for pulmonary and inflammatory diseases in Iranian traditional medicine have been summarized in Table 1.

3.2. Diagnosis and treatment

Early detection of COVID-19 infection is one of the most effective ways of preventing widespread epidemics. Therefore, early detection can provide, first of all, observing the conscious quarantine principles to control the outbreak, and second, early detection can increase the chance of more effective and faster treatment. Unfortunately, there is no definitive treatment for COVID-19, but looking at the potential of modern sciences such as biotechnology and bioinformatics, can give hope to establish effective diagnostic and therapeutic approaches in the near future. In this review, we have attempted to point out the potential of these two scientific axes that can be used to diagnose and treat COVID-19 disease.

3.2.1. Biotechnology in diagnosis & treatment

Biotechnology techniques and new approaches come into play to address the viral disease to provide methods for both detection and treatment. In this section, some of the important methods are reviewed [74].

3.2.1.1. Biotechnology and diagnosis

3.2.1.1.1. Aptamer based sensors. Aptamers are defined as single-stranded nucleotide sequences [single-stranded deoxyribonucleic acid (ssDNA) or ribonucleic acid (RNA)] [75] which are synthesized through a technology called the Systematic Evolution of Ligands by Exponential Enrichment (SELEX) [76]. Specific aptamers against coronaviruses can be served as powerful detector elements in a variety of sensors [77]. Generally, based on the transducer, they are categorized into electronic, electrochemical and optical aptasensors. Optical sensors include SPR-based, colorimetric-based, chemiluminescence (CL) aptasensor, fluorescence and SERS-based

Table 1. List of the most important and commonly used herbs for respiratory and inflammatory diseases in traditional medicine.

Herb name	Effect	Specifications	Reference
Alcea spp.	Anti-inflammatory activity, Antitussive, Febrifuge	*Alcea* with the antioxidant and anti-inflammatory compounds interferes with the process of epithelial cell damage and perform its anti-inflammatory effect	[53 54]
Viola odorata	Mucoactive agent, Febrifuge, Expectorant	High amounts of mucilage	[55]
Malva sylvestris L	Mucoactive agent, Febrifuge, Antitussive, Anti- inflammation immunomodulatory properties	The bioactivity is mediated by antioxidants, such as polyphenols, vitamin C, vitamin E, β-carotene and flavonoid constituents as macrophage and T helper-1 (Th-1) activators.	[56 57 58]
Rosaceae (Rosa damascene, Rosa canina)	Antiviral activity, Febrifuge, Radical scavenging activities.	Inhibition of - CD4/gp120 interaction - Viral enzymes reverse transcriptase (RT) and protease - Significant reduction in CRP - Down-regulatory effect on COX-1, COX-2, and LTB4	[59 60 61]
Glycyrrhiza glabra	Mucoactive agent, Anti-inflammatory activity, Antitussive, Expectorant activities, Anti-viral effects	Anti-inflammation and transforming growth factor (TGF) signal pathway	[62 63]
Chamomile	Boosting immune system Febrifuge, Antitussive	Apigenin which is one of the major flavonoids has been reported to inhibit the proteolytic activity of SARS-CoV 3 C-like protease (3 CLpro).	[64 65 66]
Boswellia serrata	Anti- inflammation	Inhibition of TNF-α, complement, and IFN-γ	[67]
Lamiaceae family (Salvia officinalis, Hyssopus officinalis)	Anti- inflammation, Expectorant	Inhibition of - microsomal PGE2 synthase-1 - lipoxygenase (LOX)	[68 69]
Zingiber officinale	Anti-inflammatory, Respiratory protective	- Inhibiting the production of TNF-α - Activating Akt and NF-κB	[70]
Borago officinalis	Significant improvement in cough, Dyspnea, Sputum production, Airway hyper-responsiveness	Inhibition of - TNF-α production - PGE2	[71 72]
Uncaria tomentosa	Anti-inflammation	- Inhibition of TNF- α production - Reducing NF-κB activation	[73]

aptasensors. CL aptasensor is briefly described here due to its application in the detection of severe acute respiratory syndrome coronavirus (SARS-CoV). In this aptasensor, the aptamer as a capturing element binds to the SARS-CoV N protein. To transduce the signal, an enzyme-labeled secondary antibody to the N protein is applied. The sensor detected the N protein at approximately 2 pg/ml [78].

3.2.1.1.2. Nanobody based sensors. Nanobodies are the variable domains of heavy chain antibodies (HCAbs). HCAb is found in camelids [79]. Due to the unique characteristics of nanobodies such as small size, high stability and solubility, and high affinity and specificity against targets, nanobodies can be an ideal candidate for the development of antibody-based biosensor [80]. The small size and available sequence of nanobodies, facile engineering to improve the directional immobilization, are the main factor to the development of an ideal biosensor. Several nanobody based biosensors were developed for the diagnosis of bacteria, toxin and cancer cells. Spike protein of COVID −19 can be a target to produce a high-affinity nanobody. For this purpose, a recombinant or native form of protein should be available to immunization of camels and creating an immunized cDNA library. Appropriated binder to spike proteins (S-protein) can be achieved by phage display and panning procedure. This nanobody can be used to the establishment of different corona biosensor.

3.2.1.1.3. Nanoporous membrane and microfluidic biosensor. By the use of nanoporous membrane-based biosensors, the detection of small molecules such as viruses is now possible [81]. Several types of these biosensors are widely studied. For example, nanoporous alumina membrane-based ultrasensitive DNA biosensor was designed by employing 5′-aminated DNA probes immobilized onto the alumina channel walls, to detect the particular sequence of the Dengue virus (DENV) genome, a single positive-stranded RNA virus [82].

Microfluidic biosensors are another approach to detect coronaviruses. One outstanding development is a microfluidic fluorescence detector, designed for quick and high sensitivity detection of SARS-coronavirus [83].

3.2.1.1.4. Reverse transcriptional loop-mediated isothermal amplification (RT-LAMP). Loop-mediated isothermal amplification (LAMP) is defined as a method, which can amplify particular sequences of nucleic acids at a stable temperature. This method, in combination with reverse transcriptase (RT-LAMP), is aimed to concurrently creating cDNA from an RNA template and amplifying DNA. So this technique is specialized for detecting RNA viruses. Ahn et al. recently have conducted a study to develop a multiplex RT-LAMP diagnostic method, effective in simultaneous detection of multiple influenza viruses [84].

3.2.1.1.5. Silicon nanowire (SiNW)-based sensor. Silicon nanowire is another biosensor that is rapid and sensitive for the detection of reverse transcription-polymerase chain reaction (RT-PCR) product of Dengue virus serotype 2 (DEN-2). Onto the SiNW surface, a particular peptide nucleic acid (PNA) is bound covalently. Following the one-step RT-PCR amplification, the obtained DEN-2 complementary fragment

is applied to PNA. To check the hybridization, the SiNW impedance is measured before and after the binding of PNA to DEN-2 fragment. The detection is at fM concentrations [85].

3.2.1.1.6. Graphene-based biosensor. By using Field Effect Biosensing (FEB) and a monoclonal antibody, which is covalently bound to graphene, a biosensor can be designed, for detection of the Zika viral antigens. The quantitative data can be obtained from the graphene platform, which provides a proper tool for both the diagnostic application and clinical researches [86].

3.2.1.2. Biotechnology and therapeutics

3.2.1.2.1. Vaccine production. Although vaccination is categorized among preventive strategies, we discuss here biotechnology to develop a new generation of viral vaccines Table 2. Viral vector expression systems are introduced as promising tools for vaccine production. Vaccines obtained through this system, can increase immunogenicity in the absence of adjuvant and create a strong cytotoxic T lymphocyte response, which eventually leads to the elimination of infected cells [87]. Several viral vectors have been developed such as Measles virus (MV), Retrovirus, Lentivirus, Vaccinia virus, Adenovirus, Adeno-associated virus, Cytomegalovirus and Sendai virus. Each of these vectors has its advantages, which includes long-term gene expression, high titer production, and high immunogenicity. By emerging the techniques of biotechnology, many approaches have been offered as proper means to fight against viral infections. Applying newly developed methods to recognize microbial epitopes to identify their immune responses, has caused production of subunit vaccines with promising properties [88,89]. A unique form of a protein subunit vaccine candidate was investigated, using recombinant proteins correlated with several domains of the spike protein of SARS-CoV. The folded domain obtained from T4 bacteriophage was fused to the carboxy-termini domain of SARS-CoV spike protein. Antibody titration of the vaccinated mouse by this recombinant subunit vaccine has created a notably, high titers of neutralizing antibody [90].

Virus-like particles (VLPs) are defined as extremely organized repetitive structures of viral proteins which recently researchers have shown interest in [91]. Adaptive and innate immune responses are both stimulated by VLPs and are associated with antigen-presenting cells. Two categories of VLPs exist, which include enveloped and non-enveloped one. Wang et al. reported a MERS-CoV VLPs construction which induced specific humoral and cellular immunity in rhesus macaques [92].

3.2.1.2.2. Recombinant drugs. The production of recombinant drugs through advances in biotechnology has revolutionized the world of drug manufacturing. Manufacturing of recombinant medications is one of the most powerful tools to conquer COVID-19 Table 2. Drug-delivery systems are intelligent methods sometimes developed through biotechnological recombination. Bahrini et al. introduced a novel viral-specific drug delivery approach in which a high-affinity recombinant fusion protein composed of human IFN and mouse lactadherin binds with, phosphatidylserine (PS: an anionic phospholipid) of hepatitis C virus (HCV) envelope and blocked its replication in the cells [93].

3.2.1.2.3. Molecular drugs. Modified or unmodified single-stranded nucleic acids are subjected to act as antisense strand and hybridize with the viral RNA and hinder the function of RNA virus (21). The findings of the studies of Ahn et al. proved that antisense peptide nucleic acids suppress SARS-CoV viral replication [94]. Aptamers participate in treatment as new molecular drugs via controlling the cell-surface receptors or the virus surface proteins resulting in hindering the entrance of the virus. For instance, nucleolin as an aptameric cell-surface receptors target is a cellular protein which is assumed to be linked with entry or attachment of the virus [95,96]. HA12-16, an RNA aptamer, blocked the influenza virus surface glycoprotein hemagglutinin (HA) by impairing the receptor-binding domain of the HA protein [97]. Another method of action is impeding the replication of the virus as RNA aptamer can potentially inhibit the HCV non-structural 5B polymerase, which is essential for the HCV RNA replication [98].

3.2.2. Bioinformatics

The development of new and powerful bioinformatics tools dedicated to biological information, data mining and analysis has been able to enhance scientific and applied research in the biological sciences. The breadth of bioinformatics includes tools for the prediction of the structure and functions of biomolecules, sequence analysis, gene discovery and biomodeling. The development of bioinformatics tools has changed the pattern of research in basic and applied biological sciences and enabled scientists to gain knowledge of complex biological systems.

Bioinformatics tools can efficiently respond to questions around COVID-19. So that it can determine the viral origin, detect the similarity between isolates, identify the single point mutations and calculate the speed of viral genome changes. But in the absence of a definitive drug for COVID-19, perhaps the most valuable bioinformatics application is drug design. We have reviewed the bioinformatics approach to reach a potential drug against COVID-19.

3.2.2.1. Rational screening for potential drugs. In the last two decades, new techniques and strategies have been widely used in drug discovery. In this regard, some approaches are highlighted to demonstrate recent advances in this area [99,100]. During COVID-19 pandemic challenge, an increasing number of academic groups are attempting to apply novel computational methods of drug discovery and design tools to identify more precisely targeted treatments. Computer modeling approaches such as molecular dynamics (MD) simulation technique could help in understanding the dynamics and conformational changes induced by the novel discovered drugs [101]. Crystal structures of SARS-CoV2 main proteins such as protease have provided the potential opportunity for structure-based drug designing [102]. Computational drug design could target the proteins of SARS-CoV2 by high throughput virtual screening of millions of molecules and natural compounds databases followed by docking procedure. The ligands which exhibit better

Table 2. Pharmaceutical companies involved in developing drugs/vaccines (Clinical trials) for the treatment of coronavirus especially COVID-19. (www.clinicaltrialsarena.com).

Drugs/ Vaccines	Company	Description
Drugs	I-Mab Biopharma	A neutralizing antibody, as a treatment for cytokine storm in patients with a severe case of coronavirus infection. The drug targets the human granulocyte-macrophage colony-stimulating factor (GM-CSF), which is responsible for acute and chronic inflammation.
	Medicago	This company is developing drug candidates against COVID-19 after having produced Virus-Like Particles (VLP) of the coronavirus.
	Tiziana Life Sciences	A monoclonal antibody for the treatment of COVID-19. It is a human anti-interleukin-6 receptor (IL-6 R), which helps in preventing lung damage and elevated levels of IL-6.
	OyaGen	Broad-spectrum antiviral drug which has demonstrated interesting effects in laboratory-based assays against the coronaviruses SARS-CoV-2 and MERS-CoV. It was strongly more effective than a positive-control compound, chlorpromazine HCl, at inhibiting SARS-CoV-2 from replicating in cell culture.
	BeyondSpring	A small molecule agent for treatment of various infections including COVID-19. It has the ability to activate CD4+ helper T cells and CD8+ cytotoxic T cells and generating an immune response in the body. If combined with another COVID-19 vaccine, the drug has the ability to generate long-term protection against viral infections
	Regeneron and Sanofi	As fully-human monoclonal antibody is approved to treat rheumatoid arthritis and is known to block the interleukin-6 (IL-6) pathway, which causes an overactive inflammatory response in the lungs of COVID-19 patients.
	Emergent BioSolutions	Two plasma-derived product candidates based on hyperimmune platforms for the treatment of coronavirus. The hyperimmunes are polyclonal antibodies derived from plasma, which are capable of generating an immune response and protecting against infection. COVID-HIG derived from human plasma while COVID-EIG is derived from equine plasma.
	Gilead Sciences	An Ebola drug which according to a report by The New England Journal of Medicine (NEJM) when administered to a coronavirus patient appeared to have improved the clinical condition.
	Roche	A drug for the treatment of severe complications related to coronavirus. It has the ability to prevent cytokine storms or overreaction of the immune system, which is considered as the main reason behind organ failure leading to death in some coronavirus patients.
	Biocryst Pharma	As an antiviral drug has shown broad-spectrum activity against a wide range of pathogens including coronavirus. It is a nucleoside RNA polymerase inhibitor that disrupts the process of viral replication.
	Synairgen Research	A drug, produced from a formulation of naturally occurring Interferon-β, which is administered through a nebulizer and is delivered directly to the lungs to reduce the severity of the infection caused by coronavirus.
Vaccines	Airway Therapeutics	A novel human recombinant protein (rhSP-D) as a vaccine for coronavirus. It has shown efficacy in preclinical studies in reducing inflammation and infection in the lungs. Also, this vaccine generating an immune response against various respiratory diseases.
	Altimmune	An intranasal Covid-19 single-dose vaccine based on a vaccine technology platform that is similar to an influenza vaccine
	Inovio Pharmaceuticals and Beijing Advaccine Biotechnology Company	A novel coronavirus vaccine. The company has started pre-clinical testing for clinical product manufacturing. This company aims to produce one million doses of the vaccine by the end of 2020 to perform additional clinical trials or emergency use.
	Algernon Pharmaceuticals	A potential vaccine for the treatment of COVID-19 which is an N-methyl-d-aspartate (NDMA) receptor glutamate receptor antagonist. It has demonstrated efficacy in improving survivability in mice infected with H5N1.
	University of British Columbia and APEIRON Biologics	A vaccine which is being tested in China in a phase one pilot trial as a treatment for COVID-19.
	Moderna and the National Institute of Allergy and Infectious Diseases (NIAID)	A vaccine for coronavirus which targets the Spike (S) protein of the coronavirus. The first vials of the vaccine have been manufactured at Moderna's Massachusetts manufacturing plant and shipped to NIAID for phase one human clinical trial.
	The MIGAL Research Institute	An Infectious Bronchitis Virus (IBV) vaccine developed to treat avian coronavirus has been modified to treat COVID-19. The IBV vaccine was developed after four years of research and has high genetic similarity to the human coronavirus. The vaccine has genetically modified to treat COVID-19 and will be available in the oral form.
	Tonix Pharmaceuticals	The vaccine is a modified horsepox virus developed using Tonix's proprietary horsepox vaccine platform. It is designed to express a protein derived from the virus that causes the coronavirus infection.
	Clover Biopharmaceuticals and Trimer-Tag technology	A vaccine based on the trimeric S-protein (S-Trimer) of the COVID-19 coronavirus, which is responsible for binding with the host cell and causing a viral infection.

binding affinities are optimized by MD simulation. These drugs could show both the strong inhibitory effect of the target protein and antiviral activity.

The other most considerable pathway is repurposing approved drugs to select the best for treatment of the life-threatening condition of COVID-19 by analysis of MD simulation, multi-target assessment, the use of crystal structure for the generation of the target sequence, sequences analysis and the use of molecular docking tools. In this process, two main approaches could be applied. The first one is a target-based approach, in which the drug and the target interact with each other leading to the generation of repurposed drugs mainly against non-structural proteins. The second one contains disease-based approaches in which the drug databases are employed to determine new indications for already approved drugs from comparisons of characteristics of diseases [103].

Very recently a COVID-19 Docking Web Server was introduced. By using this server, ligands with potential interaction to a different structure of COVID-19 can be predicted [104]. Interaction between spike protein of this virus and 78 kDa glucose-regulated protein (GRP78) was predicted. The authors concluded that if the interaction between GRP78 and COVID-19 spike protein was inhibited, the rate of viral infection might

be reduced [105]. Prediction of GRP78 structure and its role in human disease was reported previously [106,107].

Drug-target interaction deep learning model is a powerful method for searching drugs which can interact with targets. By using this model, Beck et al. reported several commercially available antiviral medicines with the potential to interact with different structural and non-structural proteins of COV ID-19 [108]. For example, they showed that some antiviral drugs could interact with 3C-like proteinase of new coronavirus. Several other commercial drugs have the potential to be used as an RNA-dependent RNA polymerase inhibitor. Potential inhibitor of the 3CL protein of COVID-19 between clinically approved drugs was investigated, and ten predicted candidates were introduced [109]. In another study, Macchiagodena et al. used Structure-Based Ligand Design and Molecular Modeling to find ligand with binding affinity to the main protease of SARS-CoV-2. In their research, they proposed a chlorophenyl-pyridyl-carboxamide derivative as the most potent binding agent [110]. The main protease of this virus was a target in the other in silico study. For example, a deep learning-based method, DFCNN, was used to screen ligands to 3CL protein [111]. The results showed that there are several potential drug candidates for using a protease inhibitor of COVID-19. They also proposed several predicted tripeptides that have high possibility to bind with the protease by DFCNN score.

Herbal derived component is an interesting candidate for finding anti-viral agents. For example, in the study conducted by Qamar et al., a medicinal plant library was screened to find potential anti-viral component against COVID-19 [112]. After molecular docking and molecular dynamics simulations, they reported nine phytochemical constituents with potential to be used as a drug to control COVID-19. It seems that other researchers will continue this type of virtual screening and after optimization and experimental studies, proposed leads can be used for the treatment of new coronavirus infection.

4. Expert opinion

Coronavirus disease (COVID-19) began in December of 2019 in Wuhan, China, and quickly spread to a large number of people and created an epidemic in Wuhan and throughout China. It also spread rapidly to other countries around the world within two months, causing a crisis in many of these countries. Given the rapid epidemic of the virus as well as how it can be transmitted from person to person, prevention, early detection, and treatment are crucial to breaking the virus transmission cycle.

Biology this time showed its power in a short positive-sense RNA genome in the form of a crowned virus. This relatively short genetic fragment, using all its virulence, disrupted the world discipline and showed that the split between the sciences could create an empty backyard that provides an excellent opportunity for invasion. Corona sent a valuable message that there should be no boundary between sciences and that the solution will not be within a single science, and the convergence of sciences is necessary.

Although the present study has been designed with the mentioned approach, it should be noted that it was not possible to present the greatness of the various sciences that have created much foliage over the years and each of which is divided into many sub-branches. Coronavirus fulfilled a series of significant events only by its 70–90 nm body.

In the area of prevention and supportive cure, the traditional sciences can be significantly helpful. Lifestyle modification, like change people's behavior will be quite effective and have a preventive action. Taking micronutrients such as vitamin D, C and Zn have a proven role in boosting the immune system. Avoiding anxiety and stress and maintaining peace of mind is essential in correct management and supporting immune system function. In case of infection, in addition to general recommendations, the use of traditional medicine sources, including medicinal herbs that have anti-inflammatory, cough-reducing as well as sedative properties, are effective in controlling symptoms of COVID-19.

As reviewed here in this article, several modern sciences are crucial to detect and diagnosis of viral infections, including Coronaviridae family, *which* COVID-19 is a member. Generally, biotechnology and bioinformatics can be seen as helpful tools in both disease detection and treatment. In biotechnology field, biosensors including aptamer-based sensors, nanobody-based sensors, electrochemical nanoporous membrane-based biosensor and other reviewed biosensors are applicable in the detection of the genetic material of the virus at fM concentrations with high accuracy. The use of biotechnology in vaccine production has captured the researchers' attention. Vaccines such as VLPs and protein subunit vaccines are worth mentioning due to their possible ability to generate immunity against viral infection. The emergence of recombinant and molecular drugs own their presence to biotechnological tools. Bioinformatics is the basic knowledge, and its application has been proven in fields such as nanomedicine and drug design. Using bioinformatics databases and tools enables the researchers to design and predict the results before any experiment in the lab. Taken together, the literature review suggests that by utilizing and integrating traditional and modern sciences, COVID-19 disease will be conquered.

Acknowledgement

Thanks to guidance and advice from "Clinical Research Development Unit of Baqiyatallah Hospital", Tehran, Iran.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Reza Ranjbar http://orcid.org/0000-0001-8593-1514
Amirhossein Sahebkar http://orcid.org/0000-0002-8656-1444

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