Review Article

Use of Complementary Medicine in SARS-CoV-2 and MERS-CoV: a Narrative Review

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Abstract

Severe acute respiration syndrome coronavirus 2 (SARS-CoV-2) is characterized by severe cytokine storm syndrome following inflammation. SARS-CoV-2 is the 7th coronavirus that causes infection in human bodies; SARS-CoV, MERS-CoV, and SARS-CoV-2 can purpose severe diseases. SARS-CoV-2 at once interacts with angiotensin-converting enzyme 2 (ACE-2) receptors inside the body and causes respiratory problems. Interestingly, complementary medicines and herbal drugs affect the expression of IgE and IgG antibodies and improve the immune system; for that reason, complementary medicine could be beneficial for infectious diseases like SARS-COV-2. In this review, we assessed some related articles to evaluate the effect of complementary medicine on SARS-COV2 and MERS-COV.

Keywords: COVID-19, Coronavirus, SARS-COV-2, MERS-COV

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Introduction

SARS-CoV-2

In December 2019, there was an outbreak of unexplainable pneumonia in Wuhan city, Hubei province, China, originating from a single ill health care worker from Guangdong Province[1]. By Jan 7, 2020, it was confirmed that a new type of coronavirus named SARS-CoV-2 (formerly called 2019-nCoV) had emerged[2]. The World Health Organization (WHO) named the Wuhan pneumonia Coronavirus Disease-2019 (COVID-19) on Feb 11, 2020. The fast propagation of this disease is mainly through close contact with infected individuals via respiratory droplets from either sneezing or coughing. Furthermore, there are two other ways of transmitting the virus, including communication and aerosol transmission[3]. The COVID-19 patients showed typical respiratory symptoms (cough, fever, and lung damage) and some other symptoms such as fatigue, myalgia, and diarrhea. Impaired immune regulation is one factor that plays a role in its pathogenesis and results in poor outcomes for COVID-19 patients[4]. Severe acute respiratory syndrome (SARS) was first described during a 2002–2003 global outbreak of severe pneumonia associated with human deaths and person-to-person disease transmission[5]. The etiologic agent was initially identified as a coronavirus by thin-section

electron microscopic examination of a virus isolate. SARS is thought to be caused by an unknown infectious agent[6]. Virions were spherical, 78 nm in mean diameter, and composed of a helical nucleocapsid within an envelope with surface projections[7]. Coronaviruses are single-stranded positive-sense RNA viruses encapsulated within a membrane envelope, and their genome comprises approximately 26-32 kilobases of nucleotides[8]. No specific anti-virus drugs or vaccines are available to treat this sudden and lethal disease. Supportive care and non-specific treatment to alleviate the patient's symptoms are the only options currently. Due to the absence of specific antiviral therapeutics and vaccines, the primary treatment strategy for COVID-19 is supportive care, which is supplemented by the combination of broad-spectrum antibiotics, and antivirals corticosteroids, and convalescent plasma[9].

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) first appeared in China in December 2020 and spread rapidly to other parts of China worldwide. On March 11, 2020, the WHO declared COVID-19 a pandemic[10]. Complications of the disease include lung problems and multiorgan failure. Males, pregnant women, the elderly, and people with underlying conditions (diabetes, pulmonary disease, hypertension, chronic cardiovascular disease, and immunodeficiency) appear at higher risk for COVID-19 and mortality[10, 12]. Children had the lowest incidence of this disease. Most people are asymptomatic or have mild symptoms, so they are essential because they can transmit the disease. The condition has an incubation period, followed by symptoms such as fatigue, cough, and fever[11]. The virus is transmitted mainly by droplets and aerosols; reduced social interactions play an essential role in reducing the prevalence of the disease[12]. On June 1, 2020, There were more than 35,000 complete or nearly complete genomes from the SARS-CoV-2 sequence in general[13]. As of March 22, 2020, the number of deaths was 78,412, and the mortality rate was 0.5% to 5.7%. By May 18, 2020, the death toll had risen to more than 312,000, and the death rate was about 4.08%. By the end of August 2020, more than 25 million cases and 800,000 deaths had been reported worldwide[10-12]. Iran was one of the first countries to encounter the SARS-CoV-2, and the first patient and death were reported on February 19, 2020, in Qom. After a short time, the disease spread throughout the country. In Iran, as of October 23, 2020, 556891 cases and 31985 deaths were reported[14].

SARS has a function medical course. Patients usually have flu-like signs of fever, chills, cough, and malaise. Approximately 70% of the sufferers are afflicted by shortness of breath and recurrent or continual fever, while the ultimate 30% display improvement in their situations after the primary week. Approximately 20 % of patients require extensive care remedies consisting of mechanical ventilation. Increased alanine aminotransferase, lactate dehydrogenase, thrombocytopenia, and lymphopenia are detected in SARS patients. In sufferers more youthful than 60 years of age, the expected fatality rate is 6.8%, and in older ones is estimated at 43%. This intense pulmonary harm of SARS patients is induced each through direct viral results and immunopathogenesis factors[15, 16]. Laboratory results of our COVID-19 cohort show creased inflammatory markers, abnormal coagulation values, and elevated cytokines IL-6, IL-8, and TNFα. We report microthrombi in many organ systems, including the brain, besides conspicuous hemophagocytosis and a secondary hemophagocytic lymphohistiocytosis-like syndrome in many of our patients[17]. We report a comprehensive autopsy series of 67 COVID-19 positive patients, revealing that this disease, conceptualized as a primarily respiratory viral illness, also causes endothelial dysfunction, a hypercoagulable state, and an imbalance of innate and adaptive immune systems responses. Novel findings reported here include an endothelial phenotype of ACE2 in selected organs, which correlates with clotting abnormalities and thrombotic microangiopathy, addressing the significant coagulopathy and neuropsychiatric symptoms. Another original observation is macrophage activation syndrome, with hemophagocytosis and a hemophagocytic lymphohistiocytosis-like disorder underlying the microangiopathy and excessive cytokine release. We discuss the involvement of critical regulatory pathways[18].

Available therapies for managing SARS

Pharmacotherapy: There is no confirmed treatment that can facilitate in all cases, but some guidelines have permitted the emergency use of steroids and antivirals

to reduce respiratory symptoms. Since there is no proven effective treatment repurposing existing

Table 1:

Effects/Dosage	Results	References
● A cross-sectional examination was directed among 331 patients. The study instrument remembered a day and a half for the utilization of CAM, segment attributes, wellbeing status, and respondents' discernments and worries about MERS contamination. Chi-square test and strategic relapse were led for information investigation utilizing SPSS ver. 21.0., and a p-worth of under 0.05 was considered genuinely huge for all investigations.	● 76.1% of respondents utilized at least one sorts of CAM modalities during the MERS episode. Utilization of effectively available modalities like multivitamin (51.2%) and food items (32.1%) was generally well known, and most of CAM clients depended on broad communications (52.4%) and the web (27.4%) to acquire data on CAM. The utilization of CAM was related with age somewhere in the range of 40 and 49, age more than 50, earlier CAM use, and disappointment with the public authority reaction to the MERS flare-up.	● Jung Hye Hwang
● A number of medicinal plants, possessing diverse pharmacological properties including antiviral activities, have been used in traditional medicine for thousands of years. Various phytochemicals derived from medicinal plants including alkaloids, steroids, lignans, diterpenoid lactones, aliphatics, glycosides etc. Scientists have been devoted to find new antiviral targets that can be CoVs proteases inhibitors (e.g. lopinavir/ritonavir), polymerases, methyltransferases, replicase inhibitors (e.g. 1,2,4-triazolederivative, remdesivir, disaproxil and lamivudine), kinase signaling pathway inhibitors(e.g. trametinib, selumetinib, everolimus, rapamycin, dasatiniband imatinib mesylate), nucleic acid synthesis inhibitors (e.g. gemcitabine, hydrochlorideribavirin and mycophenolic acid), as well as entry inhibitors clinical trials have been ongoing with some of them. In generally, two potential treatment strategies have been employed for coronaviruses-related diseases: (1) Broad spectrum antiviral drugs and (2) anti-CoV drug discovery involves the de novo development.	● Hundreds of medicinal plants and secondary metabolites have been displayed, identified and analyzed in both preclinical and clinical trials for their medicinal activities; however, some have demonstrated significant antiviral activity in prevention of various viral diseases. Many medicinal plants individually or in combination with different formulations including decoctions, leaf powder, infusions, pastes and pills have been recommended in the eradication and management of various viral infections. Antiviral herbal medicines have been used in many historic viral diseases. Broad spectrum antiviral drugs possesses possible benefits. As for anti-CoV drug discovery involving the de novo development it is aimed to develop specific agents based on the genomic and biologic understanding of the individual CoVs. Ribavirin, lopinavir, ritonavir and combination therapy using interferon α-1 and corticosteroid, used for SARS-CoV patients have not been found so effective therapeutics that have been clearly revealed by previous reports.	● S Gezici, N Sekeroglu
● Melittin and phospholipase A2 compounds present in bee venom are against H1N1 and HIV, and are involved in the management of respiratory, immunological and neurological diseases. Bee venom can be effective for arthritis and Parkinson's disease and also COVID-19.	● Bee venom affects the expression of IgE and IgG antibodies, acting as antagonists against interleukin-6 (IL-6), IL-8, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α), and is effective in the low expression of proinflammatory cytokines, including nuclear factor-kappa B (NF-κB), extracellular signal-regulated kinases (ERK1/2), and protein kinase Akt, BV is also involved in group III secretory phospholipase A2.	● Keneth Iceland Kasozi

● This article provides a reportage of 70 patients positive for COVID-19 hospitalized between March 9th and April 4th, 2020. All the patients had similar characteristics including fever, required non-invasive oxygen therapy and presented a CT lung involvement on imaging more than 50%. Among these participants a group of 28 cases received oral bacteriotherapy (OB+), while another group of 42 individuals not supplemented with oral bacteriotherapy was comparison group.	● After a 14day long period of administered bacteriotherapy, a significant lower proportion of respiratory failure (almost eight-fold lower) was present in the OB+ group. Also oral bacterial administration was correlated with the disappearance of diarrhea in all the patients within 7 days. And finally despite the homogeneous ratio of comorbidities in both groups the OB- group showed a higher mortality rate (OB- vs. OB+; 4/42, 9.5% vs. 0/28, 0/0%).	● Gabriella d'Ettorre
● We examined antibodies unique to SARS-COV-2 proteins in 256 saliva samples from convalescent patients 1-9 months after symptomatic COVID-19 (n=74, cohort 1), undiagnosed individuals with self-reported questionnaires (n=147, Cohort 2), and individuals sampled pre-pandemic time (n=35, Cohort 3).	● Salivary IgG antibodies responses in cohort 1 (mostly mild COVID-19) could be detected up to 9 months after recovery, with high correlations between spike and nucleocapsid specificity. The bulk of IgG remained in saliva at 9 months, as shown by blood serology.at this time salivary IgA was rarely observed. Salivary IgG and IgA responses were significantly linked to a recent history of COVID-19like symptoms in Cohort 2.temperature and detergent pre-treatments were also tolerated by salivary IgG. UNLIKE SARS-CoV-2 salivary IgA, which appeared to be transient, salivary specific IgG appears to be stable even after mild COVID-19 infection, as evidenced by blood serology. As a result, saliva-based SARS-CoV-2 antibody testing with self-collection at home may be used as a supplement to traditional blood serology.	● Hassan Alkharaan
● Astragali Radix (Huangqi), Glycyrrhizae Radix Et Rhizoma (Gancao), Saposhnikoviae Radix (Fangfeng), Astractylodis Macrocephalae Rhizoma (Baizhu), Lonicerae Japonicae flos (Jinyinhua), and Forsythiae Frucyus (Lianqiao) which have antiviral,anti-inflammatory, and immunoregulatory impacts.	● National health commission of china hasn`t allowed representation of CMs in prevention program or management of COVID-19 infection.	● Sunil S Nikose
Triterpene glycosides (saikosaponins A, B, C, and) isolated from herbal plants, such as Heteromorpha spp., Bupleurum spp., and scrophulariascorodonia, have antiviral properties against HCoV-22E9.	They were effective for preventing the beginning phase of HCoV-22E9 disease.	
Concentrates from Artemisia annua, Lycoris emanate, Pyrrosia lingua and Lindeatotal have been accounted for the exposition of anti-SARS-CoV impacts. The watery concentrate from Houttuyniacordata, which has been particularly found to show diverse antiviral systems against SARS-CoV that incorporate hindering the viral 3 CL protease and obstructing the movement of viral RNA-dependent RNA polymerase.		

antiviral drugs seems a logical strategy. Several candidates have been proposed as treatments, and much attention has been directed toward redeliver. Another candidate is the orally administered antimalarial drug chloroquine (CQ).

***Remdesivir*:** Remdesivir is the only FDA-approved

drug for treating COVID-19 patients. The active form of remdesivir acts as a nucleotide analog with a wide range of activity against many RNA viruses. It is administered intravenously as a loading dose followed by 7 to 10 days of daily infusions. Animal studies have exhibited an intense efficacy against SARS-CoV-2[19]. In patients treated with Remdesivir, the mean recovery time was 15.84 days, and the mortality rate was 11.3%. But the most notable point in the recent study of SARS-CoV2 is that No drug reduced mortality, initiation of ventilation, or hospitalization duration and appeared to have little or no effect on hospitalized patients[20].

***Hydroxychloroquine/chloroquine*:**

Hydroxychloroquine (HCQ) is an orally administered drug with immunomodulatory features that has a better safety profile than chloroquine (CQ)[21]. Chloroquine can enhance the endosomal pH needed by the virus to fuse with the host's cell membrane. This mechanism results in the inhibition of viral infection in vitro[22]. According to the SARS-CoV2 pandemic situation, a clinical trial of limited size in France provided the first published evidence. Their report states that HCQ may be a viable treatment option against COVID-19[23]. CQ and HCQ are weakly basic 4-aminoquinolines that enter the acidic compartments of host cells, and the concentration of these drugs can accumulate in cells through a process known as lysosomal trapping[24, 25].

Therapeutic complements

***herbal medicines*:** There is no established or recommended therapeutic agent for SARS-CoV2. Accordingly, herbal medicines are used by many people in the community. According to the result of evidence-based research, at least four herbal medications could prevent or supplement the treatment of SARS-CoV2. These four candidates are as follows: Echinacea purpurea (purple coneflower), Curcumin (Curcuma longa), Cinchona sp (Chincona L., Raiatea), and Xanthorrhizol (Java turmeric)[26].

***Meditation and Yoga*:** It has been found that meditation, as well as yoga practices, is capable of significantly increasing vagal tone and therefore could not only be effective against psychologic stress-based issues, including trauma[27, 28]; but inflammatory-based diseases as well[29]. Moreover, Meditation and Yoga may increase the activity of Melatonin. The functions of Melatonin are immense. These include a wide range of anti-inflammatory, antioxidant, and anti-infectious immune-enhancing actions on most of the cells and organs of the body that have been examined, including the brain, heart, visceral organs, bone, muscle, and skin[30].

***Oral Bacteriotherapy*:** As claimed by an Italian group, a particular bacterial formulation used as oral bacteriotherapy is responsible for a significantly lower proportion of respiratory failure (almost eight-fold lower) in patients positive for SARS-CoV2 infection. These outcomes also enforce the role of a gut-lung axis (GLA). Alterations in intestinal microbiota can affect the intestine and the pulmonary immune response through the lymphatic and circulatory system[31].

***Ozone therapy*:** Ozone therapy (OT) employs a gas mixture of O2/O3. The primary mechanism of O2/O3 in human physiology fits the concept of oxidative preconditioning[32]. There is preclinical and clinical evidence to support the potential role of OT in the prevention and management of cytotoxicity induced by different drugs and diseases, including viral diseases[33-35]. Ozone can inactivate viruses via direct oxidation of its components[36]. However, the viricidal activity in vivo becomes uncertain when viruses are in biological fluids or, worse, when they are intracellular because the cell's potent antioxidant system protects viral integrity[37].

***Bee venom*:** An immunity against COVID-19 among beekeepers in Wuhan province, PR China, had signalized the idea of using Bee venom (BV) therapy as a complementary medicine despite its toxicity[38]. Bee venom is cytotoxic at high doses. However, low doses and controlled concentrations of BV (range from 1 to 3 μg/ml) operate a range of anti-inflammatory responses[39-41]. BV suppresses inflammatory cytokines, including interleukin-6 (IL-6), IL-8, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α)[42].

MERS-CoV: Center East Respiratory Condition Covid (MERS-CoV) is a novel Covid found in 2012 liable for people's intense respiratory disorders. Even though not affirmed at this point, numerous observations and phylogenetic investigations propose a bat beginning. The illness is vigorously endemic in dromedary camel populaces of East Africa and the Center East. It is muddled concerning when the infection was acquainted with dromedary camels, yet information from examines that researched put away dromedary camel sera and

topographical circulation of included dromedary camel populaces proposed the disease was available in dromedary camels for a very long while back. Even though bats and alpacas can fill in as expected repositories for MERS-CoV, dromedary camels appear to be the lone creature have liable for the overflow of human contamination. One investigation specifically revealed the discovery of MERS-CoV RNA in the milk of five out of seven contaminated dromedary camels[43]. An immunization communicating the MERS-CoV spike protein appeared to give mucosal insusceptibility in dromedary camels with proof of serum killing antibodies and a critical decrease in discharged irresistible infection and viral RNA records in inoculated creatures[44]. Considering observation and epidemiological examinations, MERS-CoV taints dromedary camels, which fill in as a repository with a spell over human diseases through close dromedary camel contacts[45]. The specific transmission courses are not very well understood. Still, direct contact with Dromedary camels or the treatment of surfaces or articles defiled with dromedary camels' respiratory or fecal material should represent a danger for disease. As well as assessing MERS-CoV circulation and the disease trouble in dromedary camel populaces, screening diverse geographic regions may help foresee when MERS-CoV was acquainted with dromedary camels. Truly and up to the mid-20th century, both dromedary and Bactrian camels assumed a fundamental part in conveying travelers and products in North Africa, the Center East, and East Asia. They were imported to Australia in the nineteenth century for a similar explanation. After creating cars and using trains, the use and travel of dromedary and Bactrian camels between nations was restricted[46].

The origin of coronavirus is unclear, but virological and genetic studies have shown that bats are natural hosts for SARS-CoV and MERS-CoV and palm civet and camel are intermediate hosts before transmission to humans. How SARS-CoV, MERS-CoV, and SARS-Cov-2 infect humans through animals is unknown yet. Maybe it is related to direct contact with intermediate hosts or to eat raw meat or infected milk. MERS-CoV possibly spreads by droplet transmission and close contact transmission between humans. It has been an epidemic in hospitals. MERS-CoV was first diagnosed in Saudi Arabia in April 2012(in a hospital in Al-Zarqa, Jordan). It spread to 27 countries in the Middle East, Asia, North America, and Europe[47]. 85% of reported cases came from Saudi Arabia. MERS-CoV appears to prefer males, as approximately 64% of patients are male. (With a nearly 35% case-fatality rate), Also, a seasonal pattern of topics has been observed, with a peak each year between April and June. Enhanced case detection and active surveillance programs can be the reason for the current upsurge in the number of infected patients[48].

Coronavirus, spreading worldwide, is one of the most potent viruses that infect humans. Of the six types of coronavirus that infect people, which cause them to cause colds and coughs, Corona is the strongest, as it belongs to a family of viruses similar to the Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome "SARS". [DU1]Corona has been called "the coronavirus", because it bears crown-like nails that protrude from the virus's surface. The virus envelops in greasy partial bubbles, which collapse upon contact with soap or alcoholic and sterile substances[49].

How does it enter the body?

According to a report by the American "New York Times" entitled "How does the coronavirus infect cells?", The virus enters the body through the nose, mouth, or eyes. It then attaches to the cells in the airways that produce a protein called angiotensin-converting enzyme 2 (ACE 2). It is possible that the virus has attached itself to the proteins in the bats' bodies, or it may have attached to a similar protein. After the virus enters the human body, the virus attacks the cell by combining its lipid membrane with its inner membrane - the cell consists of a fatty membrane that protects it from a possible attack before entering it - and as soon as it enters, the coronavirus releases an extract from a genetic material called "RNA", which is an acid. The nuclear component of chromosomes transmits genetic traits from parents to children.

Cell hijacking: After entering the cell, hijacking it begins, as the virus releases the genetic material, which reaches about 30,000 genetic letters, which are the materials that carry the disease, so the infected cell reads the genetic letter to make particular proteins, which will keep the immune system in a position critical. After hijacking the cell, the latter creates new

mutations and proteins that make up more copies of the coronavirus. Then new copies of the virus are collected and carried to the cell's outer edges, where the disease is spread.

Spread the infection: Each infected cell can release millions of copies of the virus before it finally collapses and dies. Viruses may infect neighboring cells or end up in droplets escaping from the lungs. The cause of the Middle East Respiratory Syndrome is the newly diagnosed Middle East Respiratory Syndrome, which is an RNA-containing type that belongs to the beta-corona virus, which differs from SARS and coronavirus. Phylogenetics's genetic factors have been classified into two biotic subspecies. The early cases of MERS were listed under the biological strand (EMC / 2012 and Jordan-N3 / 2012), while the new cases were generally genetically different (which were listed under the biome b). The virus proliferates in LLC-MK2 cells and Vero cells. A study was conducted between 2010 and 2013. The incidence of MERS was evaluated in 310 single-humped Arab camels, as high standards of MERS-CoV antibodies were detected in the blood serum of these animals. Another serial study of the Middle East Respiratory Syndrome-Coronavirus was conducted from the nose swabs of single-humped Arabian camels in the Kingdom of Saudi Arabia, where they were discovered to be infected with a sequence identical to the previous sequence of human isolation. It has also been discovered that some individual camels have more than one genetic variant in their nasopharynx. A report was also submitted of a Saudi man who became ill seven days after taking the topical nasal medication for several sick camels. Later, it was discovered that he and one of the camels had identical strains MERS-Coronavirus. How the virus is transmitted from camels to humans has not been discovered. Still, the World Health Organization recommends avoiding direct contact with camels, eating well-cooked camel meat, and pasteurizing camel milk. The Saudi Ministry of Agriculture advised people avoid direct contact with camels or wear respirator masks around camels[50]. It has been reported that the white blood cell count is low in MERS patients, especially with low lymphocytes. The World Health Organization recommended taking samples from the lower part of the respiratory system by washing the bronchi and alveoli to conduct a polymerase chain reaction test, taking a sputum sample, or tracheal aspirate because it carries high amounts of the virus. There are also studies using samples of the upper part of the respiratory system using a swab Pharynx. According to Nature Communications, a team of researchers has designed a peptide that can block the entry of the Middle East Respiratory Syndrome (MERS-CoV) coronavirus into host cells. The virus - which may have originated in camels - is associated with a mortality rate of 42%, and scientists are doing their best to find a way to stop its transmission. A team of researchers recently in China and the United States crystallized a single unit (subunit) of the protein that the virus uses to adhere to and enter host cells and were able to analyze its three-dimensional structure. They used this architecture as a model to design binding peptides that inhibit protein and membrane fusion and thus interfere with the virus's entry into its host cells. "There is no generic anti-MERS-CoV drug currently on the market," said Shibu Jiang, a molecular virologist at the Institute of Medical Microbiology, Fudan University, China, and one of the study's authors. "Some non-specific antivirals, such as ribavirin and interferon alpha-2b, have been used in clinics to treat patients with infection, but their effectiveness has not been confirmed." The team believes that the peptides they have designed could be developed into less toxic drugs and more effective in fighting the coronavirus that causes respiratory syndrome in the Middle East[51]. The first case of Middle East Respiratory Syndrome due to Coronavirus (MERS-CoV) was reported in Saudi Arabia in 2012, with the first evidence of the virus in camels. And like many viruses, the viral parts of the MERS-CoV are formed from the RNA genome coated with a protein coat housed in a lipid envelope. The protruding protein spikes in the lipid envelope - known as spines - bind to the host cell's surface receptors. This binding mediates the fusion of the lipid viral envelope with the host's lipid cell membrane and the subsequent entry of the virus into the host cell. The team hypothesized that, in the next phase of this association with S1, S2 changes its morphology by inserting a portion of its sequence - a so-called fusion peptide-into the host cell membrane, forming a hexagonal bundle - the fusion nucleus - into the host cell membrane between two regions of subunits. S2 is known as

heptavalent repeaters 1 and 2 (*HR1* and *HR2*). To test this hypothesis, they created a protein consisting only of *HR1* and *HR2* to stimulate the formation of an isolated fusion nucleus and then crystallized it, examining its structure to see if it formed a hexagonal bundle. As they expected, they found a hexagonal bundle fusion nucleus and used their solution to design peptides to bind and inhibit *HR1* and *HR2* domains. The tests revealed one particularly potent peptide. The next step, Jiang said, is to conduct preclinical trials on animal models such as monkeys as soon as possible, to be followed by clinical trials. "Unfortunately, Jiang continues, however, none of the pharmaceutical companies that we approached have shown interest in developing any anti-MERS-CoV drug because the market is unpredictable in the future." Jiang successfully developed anti-SARS-CoV peptides in his lab in 2003, but pharmaceutical companies lost interest in developing treatments when the epidemic was brought under control. “The continued identification of new treatments for MERS-CoV is a worthwhile endeavor given the unknown future nature of the disease’s spread,” said Matthew Freeman of the Maryland School of Medicine, a global expert in microbiology and immunomodulators SARS[51]. "The development of new treatment strategies - whether based on a peptide, antibody, vaccine, or drug - is an investment worth trying"[52].

COVID19 recently has been a massive threat to man's kind. There are no specific therapies for such a disease. However, some agents were used for MERS (Middle East respiratory syndrome). LPV is a proper inhibitor for protease activity of coronavirus; LPV also blocks the MERS-COV replication cycle in the post-entry step[53]. By using RTV (Ritonavir), we can inhibit the *CYP3A*-mediated metabolism of LPV by increasing the serum concentration of LPV[54]. Only a few promising treatments are coming in the future. The combination of lopinavir, ritonavir, and interferon-beta -1b has displayed excellent results in common marmosets and currently is in a randomized control trial[55-60].

Animal studies of MERS: Prophylactic LPV/r, combined with IFN-beta, can slightly reduce the viral loads. The LPV/r and IFN-beta mix can improve pulmonary function but cannot reduce viral replication and lung hemorrhaging[61].

Clinical studies of MERS: After two days of treatment with LPV/r, interferon, and ribavirin on patients, it exposed resolution of viremia, but eventually, the patient died from septic shock[62]. But, on another patient from Korea, the same treatment caused a complete recovery. These simple examples can open up the efficiency of LPV against MERS[63].

MERS-COV induces immune responses which cause severe lung damage and eventually lead to death. Corticosteroids are common treatments for patients with such a disease, but the crucial question is if this strategy is safe and effective enough or not. It determined that corticosteroid consumption did not reduce deaths, but was associated with increased hospitalization duration. Corticosteroid is used in MERS-COV infection. It delays virus clearing and does not convincingly improve survival or reduce hospitalization duration or ICU admission rate[64-67].

Results[WU2]

Research article: Complementary and alternative medicine use among outpatients during the 2015 MERS outbreak in South Korea: a cross-sectional study.

Methods: A cross-sectional examination was directed among 331 patients. The study instrument remembered a day and a half for the utilization of CAM, segment attributes, wellbeing status, and respondents' discernments and worries about MERS contamination. Chi-square test and strategic relapse were led for information investigation using SPSS ver. 21.0. A p-worth of under 0.05 was considered genuinely enormous for all inquiries.

Results: 76.1% of respondents used at least one CAM modality during the MERS episode. Utilization of effectively available modalities like multivitamins (51.2%) and food items (32.1%) was generally well known, and most CAM clients depended on broad communications (52.4%) and the web (27.4%) to acquire data on CAM. The utilization of CAM was related to age somewhere between 40 and 49, age more than 50, earlier CAM use, and disappointment with the public authority’s reaction to the MERS flare-up.

Conclusions: CAM was generally utilized by outpatients during the 2015 MERS flare-up in Korea, and broad communications were the fundamental wellspring of data. Setting up a media stage is of fundamental significance to give reliable data and

guarantee the security of its utilization[68].

Research article: Novel SARS-CoV-2 and COVID-2019: Current Perspectives on Plant-Based Antiviral Agents and Complementary Therapy.

Methods: Current Perspectives on Plant-Based Antiviral Agents and Complementary Therapy Coronaviruses (CoVs) are one of the most prominent families of viruses that interact with components of host cells at many levels, suggesting this causes the pathogenesis. After SARS and MERS epidemic, many genetic and molecular mechanisms of the human CoVs have been explored, but there are some challenges with the new highly pathogenic SARS-CoV-2 coronavirus and COVID-19 outbreak. One of the main reasons is that RNA viruses can quickly change their genomes. Therefore, the identified agents, drugs, or vaccines are not adequately evaluated for in vitro and in vivo studies. Coronaviruses are single-stranded positive-sense RNA viruses.

Results: The coronavirus SARS-Cov was identified in 2000 as a cause of severe pneumonia, SARS, and MERS; SARS-CoV-2 results from cross-species transmission from bats to humans. The high transmissibility of SARS-CoV-2 in the human population has been attributed to an enhanced affinity of the SARS-CoV-2 spike protein for the human cellular receptor. SARS-CoV-2 has a high spread from human to human. It's an RNA virus that is considered to be able-antagonize. *cGAS-STING* activity can also be inhibited by *cGAS-STING* activation. Accumulating evidence indicates that RNA viral infection can also lead to the activation of *STING* because of viral–cellular membrane fusion and viral infection-induced mitochondrial damage. We evaluated the innate immune modulation by various viral structural and accessory proteins.

Conclusions A unique pathogenic feature of COVID-19 is a heightened suppression of innate immunity and elevated inflammatory responses. Innate immune suppression by SARS-CoV-2 is poor. They have now identified several SARS-CoV-2 viral proteins that differentially target distinct human innate immune responses. A unique pathogenic feature of COVID-19 is heightened. Suppression of innate immunity and elevated inflammatory responses. Innate immune suppression by SARS-CoV-2 is poorly understood. We have identified several SARS-CoV-2 viral proteins that differentially target distinct human innate immune responses[69].

Research article: Bee Venom—A Potential Complementary Medicine Candidate for SARS-CoV-2 Infections

Methods: In this article, we investigate the cause of the infectious condition caused by the SARS-CoV-2 virus. And then, the use of bee venom, despite its toxicity, is mentioned to treat various diseases. The compounds in bee venom cause inflammatory reactions, and these compounds and enzymes have anti-inflammatory, anti-viral, anti-bacterial, anti-cancer, and anticoagulant effects. It is also effective for immunological diseases such as arthritis, Parkinson's disease, inflammatory diseases, and asthma. Finally, it investigates the influence of compounds in bee venom (melittin) on the envelope of the SARS-CoV-2 virus.

Results: Coronavirus causes acute respiratory syndrome following inflammation by cytokine storm syndrome. The virus binds to angiotensin-converting enzyme receptors in the human body. Bee venom affects the expression of IgE and IgG antibodies, which can be effective as complementary medicine in treating some diseases such as arthritis and Parkinson's disease. Melittin and phospholipase A2 compounds present in bee venom act as antagonists of enveloped and non-enveloped viruses, including H1N1 and HIV, by acting as antagonists against interleukin-6 (IL-6), IL-8, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α). Melittin is effective in the low expression of proinflammatory cytokines, including nuclear factor-kappa B (NF-κB), extracellular signal-regulated kinases (ERK1/2), and protein kinase Akt; Bee venom is also involved in group III secretory phospholipase A2 (in the management of respiratory and neurological diseases). Vaccination of bee venom is performed to create immunity against cytomegalovirus and suppress and suppress metastases through the PLA2 and phosphatidylinositol-(3, 4)-bisphosphate pathways.

Conclusions: Melittin and phospholipase A2 in bee venom have anti-inflammatory properties that effectively manage neurological and immunological diseases and can positively affect the treatment of Covid-19. Bee venom is now an essential candidate for complementary therapy and immunity against SARS-CoV-2[70].

Research article: Challenges in the Management of SARS-CoV2 Infection: The Role of Oral Bacteriotherapy as Complementary Therapeutic strategy to avoid the Progression of COVID-19.

Methods: This article reports 70 patients positive for COVID-19 hospitalized between March 9th and April 4th, 2020. All the patients had similar characteristics, including fever, required non-invasive oxygen therapy, and presented a CT lung involvement on imaging more than 50%. Among these participants, 28 cases received oral bacteriotherapy (OB+), while another group of 42 individuals not supplemented with oral bacteriotherapy was the comparison group.

Results: After a 14day long period of administered bacteriotherapy, a significantly lower proportion of respiratory failure (almost eight-fold lower) was present in the OB+ group. Also, oral bacterial administration was correlated with the disappearance of diarrhea in all the patients within seven days. finally, despite the homogeneous ratio of comorbidities in both groups, the OB- group showed a higher mortality rate (OB- vs. OB+; 4/42, 9.5% vs. 0/28, 0/0%).

Conclusion

The minimal number of complementary medication therapies described in this review shows some promising results. It seems to help the human against the SARS-CoV-2 and MERS infection until reaching a safe and permanent immunization. However, Bee venom and bacteriotherapy can help the patients with SARS and MERS infections. They can reduce the patient's symptoms, but during these infections, the WHO and national guidelines should be followed, too.

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None.

Conflict of interest

The authors further declare that they have no conflict of interest.

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