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A COMPREHENSIVE REVIEW ON MANAGEMENT AND PREVENT OF SARS-COV2

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Abstract

Coronavirus disease 2019 (COVID-19) has affected almost every country in the world by causing a global pandemic with a high mortality rate. Lack of an effective vaccine and/or antiviral drugs against SARS-CoV-2, the causative agent, has severely hampered the response to this novel coronavirus. Natural products have long been used in traditional medicines to treat various diseases, and purified phytochemicals from medicinal plants provide a valuable scaffold for the discovery of new drug leads. In the present study, we performed a computational screening of an in-house database composed of ~1000 phytochemicals derived from traditional Saudi medicinal plants with recognised antiviral activity.Coronaviruses are enveloped positive-strand RNA viruses belonging to family Coronaviridae and order Nidovirales which cause infections in birds and mammals. Among the human coronaviruses, highly pathogenic ones are Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) which have been implicated in severe respiratory syndrome in humans. There are no approved antiviral drugs or vaccines for the treatment of human CoV infection to date. The recent outbreak of new coronavirus pandemic, coronavirus disease 2019 (COVID-19) has caused a high mortality rate and infections around the world which necessitates the need for the discovery of novel anti-coronaviral drugs.

Key words - SARS-CoV-2, MERS-CoV, RT-PCR, radiology, respiratory tract infection.

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1. Introduction

The World Health Organization declared a pandemic when SARS-CoV-2, a new coronavirus from the same family as SARS-CoV and Middle East respiratory illness coronavirus (MERS), spread over the world (Pascarella et al., 2020). CoVs are a diverse genus of RNA viruses found in a wide range of animals. They have been linked to respiratory, hepatic, neurological, and gastrointestinal issues in people, as well as serious and even fatal infections [1,2]. The novel coronavirus mostly infects the lungs and uses the same receptor as SARS-CoV angiotensinconverting enzyme 2 (ACE2). It is primarily transmitted through the respiratory tract. The predominant cause of contagion is clearly human-to-human aerosol transfer, which occurs mostly through contaminated droplets, hands, or surfaces [3].

Alpha-, beta-, gamma-, and deltacoronaviruses are the four subfamilies of coronaviruses. While alpha- and betacoronaviruses are thought to have originated in mammals, particularly bats, gamma- and deltacoronaviruses are thought to have originated in pigs and birds. The genome is between 26 and 32 kb in size. Beta-coronaviruses, one of seven coronavirus subtypes that may infect humans, can cause serious sickness and death, whereas alpha-coronaviruses induce asymptomatic or minimally symptomatic infection [4]. A series of acute atypical respiratory disease cases were reported in Wuhan, China, in December 2019. This quickly spread from Wuhan to other parts of China. It wasn't long before it was determined that a new coronavirus was to blame. Due to its strong homology (80%) to SARS-CoV, which caused acute respiratory distress syndrome (ARDS) and high mortality during 2002–2003,[5] the novel coronavirus was dubbed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, 2019-nCoV). The SARS-CoV-2 outbreak was thought to have started as a result of a zoonotic transmission linked to a seafood market in Wuhan, China. Human to human transmission was later discovered to have had a significant role in the ensuing outbreak [6]. Coronavirus disease 19 (COVID-19) was the disease caused by this virus, and the World Health Organization proclaimed a pandemic (WHO). COVID-19 has affected a vast number of persons around the world, with cases documented in over 200 nations and territories [7,8]. According to the Center for Systems Science and Engineering (CSSE) at John Hopkins University, over 4.91 lakh instances had been documented worldwide as of August 27th, 2020 [9]. The SARS-CoV-2 virus primarily affects the respiratory system, although it also affects other organ systems. In the first case series from Wuhan, China [10] lower respiratory tract infection symptoms such as fever, dry cough, and dyspnea were noted. There were also headaches, dizziness, widespread weakness, vomiting, and diarrhoea [11]. COVID-19 respiratory symptoms are now well acknowledged to be quite diverse, ranging from minor symptoms to severe hypoxia with ARDS. The interval between the commencement of symptoms and the development of ARDS was as brief as

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9 days in the Wuhan study mentioned above, indicating that respiratory symptoms could worsen quickly [10]. This disease has the potential to be fatal. An increasing number of individuals with life-threatening illnesses have died throughout the world. According to epidemiological research, mortality rates are greater in the elderly population [12] and significantly lower in children [13,14]. There is currently no specific treatment available, and medical management is primarily supportive. Several medications have been tried in clinical trials, including lopinavir, ritonavir, remdesivir, hydroxychloroquine, and azithromycin [12,15,16], but none have yet been proved to be a definitive treatment. Clinical trials are being used to evaluate more treatments. To prevent the virus from spreading further, a huge number of countries have imposed social isolation and lockdown measures. We will review our present understanding of COVID-19 and examine the underlying mechanism to explain the symptomatology's heterogeneity, with a special focus on the differences between children and adults.[17]

2. Mechanism of SARS-CoV-2 incursion into host cells

Coronaviruses are 30 kb enclosed positive-sense single-stranded RNA viruses with a single stranded RNA genome. They may infect a wide range of hosts [18]. Based on their genetic structure, they are primarily classified into four genera:,,, and. Only animals are infected by and coronaviruses [19]. Human coronaviruses, such as 229E and NL63, are coronaviruses that cause the common cold and croup. Coronaviruses, on the other hand, include SARSCoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2. Attachment, penetration, biosynthesis, maturity, and release are the five phases in the virus's life cycle with the host. Viruses enter host cells by endocytosis or membrane fusion after binding to host receptors (attachment) (penetration). Viral RNA reaches the nucleus for replication once the viral contents are released into the host cells. Viral proteins are made from viral mRNA (biosynthesis). Then, after maturity, more virus particles are created and discharged. Spike (S), membrane (M), envelop (E), and nucleocapsid (N) are the four structural proteins found in coronaviruses [20]. Spike is a transmembrane trimetric glycoprotein that protrudes from the viral surface and controls coronavirus diversification and host tropism. Spike is made up of two functional subunits: S1 is in charge of attaching to the host cell receptor, while S2 is in charge of fusing the viral and cellular membranes. SARS-CoV has been found to have a functional receptor in the form of angiotensin converting enzyme 2 (ACE2) [21]. The spike for SARS-CoV-2 linked to ACE2 according to structural and functional studies [22,24]. The lung, heart, ileum, kidney, and bladder all had significant levels of ACE2 expression [25]. On lung epithelial cells, ACE2 was significantly expressed. Further research is needed to see if SARS-CoV-2 attaches to another target. Following SARS-attachment CoV-2's to the host protein, the spike protein is cleaved by proteases. A two-step sequential protease cleavage model for activating SARSCoV and MERS-CoV spike protein was presented as a model, consisting of priming cleavage at the S1/S2 cleavage

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site and activation cleavage at the S′2 site, a location close to a fusion peptide within the S2 subunit [26,27,28]. S1 and S2 subunits remain non-covalently linked after cleavage at the S1/S2 cleavage site, and the distal S1 subunit aids in the prefusion stabilisation of the membrane-anchored S2 subunit [23]. Following cleavage at the S′2 location, the spike is probably activated for membrane fusion by irreversible conformational changes. The coronavirus spike is unique among viruses in that it may be cleaved and activated by a variety of proteases [29]. The presence of a furin cleavage site ("RPPA" sequence) at the S1/S2 site distinguishes SARS-CoV-2 from other coronaviruses. In contrast to SARS-CoV spike, which was integrated into assembly without cleavage, the S1/S2 site of SARS-CoV-2 was completely cleaved during biosynthesis [23]. Although other proteases such as transmembrane protease serine 2 (TMPRSS2) and cathepsin L have cleaved the S1/S2 site [28,30], the widespread expression of furin renders this virus extremely deadly.[31]

3. RT-PCR assay and CT scans in the diagnosis of COVID-19

The COVID test is performed using the RT-PCR technique, and the test sample can be obtained using a nasopharyngeal or oropharyngeal swab. [32,33,34] The RT-PCR is a genetic test that combines reverse transcription of RNA into complementary Deoxyribonucleic acid (DNA) and RT-PCR amplification of particular DNA targets. [35] Although the RT-PCR test is still the gold standard for determining the presence of COVID-19 infection, [36,37] it has stringent laboratory requirements and takes a long time to provide findings. [38,39] The first RT-PCR findings for patients with COVID-19 infection were shown to be falsenegatives in several investigations. [39,40] These false-negative results must be taken seriously, especially in persons who have symptoms and are suspected of being infected with COVID-19. CT scans of the chest are commonly used to detect pneumonia, thus they might be helpful in diagnosing COVID- 19.[41,42]. During a single breath-hold, an unenhanced high resolution CT (HRCT) of the chest is obtained. After that, CT images are rebuilt and sent for interpretation and diagnosis. [43] Ai et al. (2020) conducted a research to assess the use and consistency of chest CT scans in the diagnosis of COVID-19, and discovered that the majority of patients (98 percent, n 14 56/57) had first positive chest CT scans before or within six days of the onset of the disease.[41] This is consistent with previous research, which revealed that positive COVID-19 diagnoses were available three days earlier with chest CT scans than with the RT-PCR test. [38,42,44,45,46,47,48,49] This suggests that chest CT scans may be useful for identifying infection at an early stage.

Chest CT scans in all COVID-19 patients exhibit characteristic radiographic findings, according to several studies.[39,40,50] According to the Chinese National Health Commission, chest CT is very useful in detecting COVID-19, monitoring disease development, and assessing therapy options. [51] According to Lee et al. (2020), most clinics in China now choose to employ CT over other investigative methods. This

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preference might be due to the availability of CT equipment in China, CT's capacity to detect patients early, worries about the specificity of other tests, and the absence of virus-testing kits. [52] The American College of Radiology (ACR), on the other hand, opposes the use of chest CT as a first-line investigative technique for patients with suspected COVID-19 illness. [53] This might be owing to CT's limited specificity in distinguishing COVID-19 from other diseases with similar symptoms. Similarly, the Royal College of Radiologists (RCR) said that CT has a well-established function in the evaluation of patients with acute respiratory distress, particularly those who are clinically deteriorating. They did reaffirm, however, that CT should not be utilised to diagnose individuals with suspected coronavirus infection. [54] Another rationale for not using CT as a solitary diagnostic technique for individuals with COVID-19 might be additional hygiene concerns. This involves sanitising and cleaning the scanning rooms in radiology departments, as well as regulating ventilation and airflow. [51,55]

In comparison to the CT chest, recent investigations have indicated that RT-PCR has low sensitivity (60e71%) in identifying patients with COVID-19 infection. (39,56,57) Fang et al. (2020) alluded to CT chest's great sensitivity (98%) when compared to RT-PCR testing (71 percent). [57] This is consistent with the findings of Xie et al. (2020), who looked at 167 individuals and discovered that 3% (n ¼ 5) of them had initially negative RT-PCR nasopharyngeal and/or throat swabs but had positive chest CT scans. [40] Huang et al.(2020), confirmed this discovery, reporting that a laboratory test revealed a normal white blood cell count and a negative RT-PCR assay, but a chest CT scan revealed numerous peripheral ground-glass opacities (GGO) in the lingual regions. 1 Low viral load in test samples and/or laboratory mistakes may be to blame for false-negative findings, and the patient may need to be retested.[39,57] Test kits, on the other hand, are in low supply or unavailable in some locations. [56] As a result, some hospitals have begun to utilise chest CT scans as a main tool for diagnosing COVID-19, while the American College of Radiology (ACR) urges radiographers and radiologists to proceed with care. [53]

In a research by Xie et al.(2020), it was discovered that all patients had early COVID-19 CT imaging characteristics, such as GGO and/or mixed GGO and mixed consolidation, which were validated by a positive RT-PCR assay during the isolation phase. [40] Symptomatic individuals may exhibit alterations in chest CT scans prior to the start of apparent symptoms, according to Shi et al. (2020). (58) Following up with chest CT scans, according to Shi and colleagues, might help with continuous monitoring of disease changes throughout therapy. [58] Wu et al. (2020) discovered that the majority of the patients had minor symptoms and high temperatures, but their chest CT scans revealed severe lung abnormalities. They emphasised the need of using chest CT scans to assess the degree of COVID-19 infection. [59]

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Guan et al. (2020) and Chuang et al. (2020) reported that 20% (n=230/1099) and 14% (n=3/21) of patients with clinical symptoms and positive RT-PCR results had normal chest CT findings, respectively.[60,61] Yang et al. discovered similar findings (2020). [37] Despite the fact that chest CT scans have a greater sensitivity for COVID-19 diagnosis than the RT-PCR test, Pan et al. (2020) and Fang et al. (2020) point out that chest CT scans have a low specificity. [57,62]] In a recent research of 1,014 patients with COVID- 19.[21] Ai et al. (2020) discovered that chest CT scans showed limited specificity (25 percent). This might be because to radiologists' difficulty in differentiating COVID-19 from other illnesses on chest CT images. Furthermore, Li and Xia (2020) discovered that two COVID-19-infected individuals did not show CT characteristics typical of COVID-19.[38,42,44,45,46,47,48,49] When patients come with a fever and cough of unknown aetiology, the differential diagnosis of COVID-19 should be explored. All radiologists should also be aware with the normal COVID-19 results on chest CT scans, according to the guidelines. [36,56] Furthermore, radiologists should pay close attention while interpreting CT images and be able to distinguish the characteristics of COVID-19 patients from motion artefacts, as some of these patients may struggle to follow breathing instructions during CT scans. [38] According to the findings, chest CT imaging alone may not be enough to rule out the diagnosis of COVID-19. As a result, early chest CT scans in combination with other research techniques, such as the RT-PCR assay, may be necessary.[63,64]

4. Conclusion

As noted before, COVID-19 has become a global concern, due to widespread outbreaks and lack of treatment. Therefore, it is necessary to find and evaluate treatment methods more quickly in this case computer methods are very effective and helpful. The predicted binding and ranking of drugs will also be useful to interpret the results of ongoing clinical trials that are testing existing drugs for effectiveness against COVID-19. Notwithstanding the limitations, it has been described several diseases and traits which may be causally related to ACE2 expression the lung, which in turn may mediate susceptibility to Sars-CoV-2 infection. In addition, the proteome-wide MR analysis revealed proteins that could lead to changes in ACE2 expression. Subsequent drug repositioning analysis highlighted several candidates that may warrant further investigations.

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