Review Article

ROLE OF PHYTOCHEMICALS IN THE TREATMENT OF COVID 19: AN UPDATE

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ABSTRACT:
WHO declared the Outbreak of novel coronavirus disease as a global health emergency on 30th January, 2020. COVID-19, previously known as 2019-nCoV originated from Wuhan, China, at the end of 2019 with symptoms ranging from the common cold to fatal diseases in population worldwide. Due to the lack of specific treatment and vaccine, main strategy for COVID-19 management is supportive therapy complemented by antibiotics, antimalarials, anti-virals, corticosteroids, and convalescent plasma. There is a dire need for the development of an anti-COVID-19 treatment that is effective against antigenically diverse viruses. At present, there is nor specific neither effective treatment that targets coronavirus; in fact, the development of such treatment may take months or even years, so we must focus on treatments related to natural origin. Therefore, the use of traditional medicinal plants with the potential of targeting SARS-CoV-2 and its pathways can be suggested as a possible therapeutic approach.

Key Words: Phytochemicals, Herbal, COVID-19

COVID-19: INTRODUCTION

The family of Coronaviridae consists of single-stranded RNA viruses, which were considered as the source of respiratory tract infections and common cold in the elderly and people having weak immunity. In 2003, Severe Acute Respiratory Syndrome (SARS) caused by agents belonging to the beta coronavirus subfamily emerged in China and presented a need for research on SARS related coronavirus. After 9 years, Middle East Respiratory Syndrome (MERS) appeared in Saudi Arabia, having 2492 confirmed cases.[1] At the end of 2019, a disease resembling pneumonia emerged in Wuhan, China, which was later named SARS-CoV-2. It was thought to spread from animals to humans.

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COVID-19 became the pandemic hazard to the health of the community. Most of the patients suffered from respiratory difficulty, body aches, fatigue, dry cough, fever, shortness of breath, and in some cases, pneumonia. There was an enormously accelerated transmission of this disease in humans.[2] The exact source or origin of that virus was not known; however, some investigations showed its origin from the Wholesale market of Wuhan Seafood. This association indicated the transmission of the virus from animals to humans and then from humans to humans which in turn lend a hand in spreading the disease world wide.[3]

Coronavirus was considered as a pandemic by the officials of the World Health Organization (WHO) on 11th March 2020. Almost 14, 36198 cases of COVID-19 were recorded on 9thApril 2020, including 85,522 deaths resulting in a 5.95% fatality rate.[4] Outbreak of coronavirus affected almost 209 countries out of which Pakistan was ranked as one of the most affected countries. The highest number of coronavirus cases were recorded in the

USA to date. After USA, the maximum number of cases was recorded in Italy, followed by Spain. China, the neighboring country of Pakistan, was highly affected by COVID-19. From the west, Italy, and from the north, Iran had the highest number of COVID-19 related mortalities.[5] WHO warned about its rapid spread because this pandemic took only 67 days to reach 100,000 cases from the first reported case, 11 days for 2nd 100,000, 4 days to reach 3rd 100,000, and in just another 2 days' positive cases reached up to 4th 100,000. Asymptomatic patients also became one of the sources of spreading the infection. The first case of coronavirus was reported in Pakistan on 26th February 2020 in Karachi. Later on, coronavirus positive cases were reported in Pakistan due to travel history from Iran, Saudi Arabia, and Italy.[6] On 10th April 2020, 54706 suspected cases were reported in Pakistan. The attack rate of coronavirus was estimated almost to 2.3 per 100,000 population of Pakistan. According to the update on 10th April 2020, almost 49% of cases were reported from Punjab. Sindh reported the second-highest number of cases of coronavirus (26%) followed by KPK (13.2%).[4]

The management and prevention of COVID-19 is an essential issue. Collective efforts should be made by the government and the public to control this disease, such as cleaning of our surroundings and to avoid coughing and sneezing in public places.[7]

Given the current situation, the availability of thorough information for everyone is of utmost importance as this disease presents with a different pattern in each individual.

Pathophysiology:

The coronaviruses are enveloped RNA viruses and utilize host cell's machinery for replication of their genome. SARS-CoV-2 contains four major structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N); 16 non-structural proteins and eight accessory proteins.[8] The infection process begins when a virus enters the human lung cells by endocytosis then binds to the alveolar angiotensin-converting enzyme (ACE) 2 using S proteins, which are activated by Transmembrane Protease Serine 2 (TMPRSS2). The viral E proteins then fuse with the endosomal membrane and release the viral genome into the host cell cytoplasm.[9]

Later, viral RNA-dependent RNA polymerase (RdRp) mediates the genome replication and transcription of subgenomic RNA. This leads to the synthesis of viral proteins. These proteins get inserted in the endoplasmic reticulum (ER) and later moved into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC), where the viral genomic RNA is packed and encapsulated by N proteins to form mature virions.[10] The viral proteases: 3-chymotrypsin-like protease (3CLpro) and Papain-like protease (PLpro) cleave peptides of virus and convert them into basic units that are involved in the replication.[11] Then virions are expelled out by exocytosis.[9] Consequently, the host's immune system gets activated, and inflammatory cytokines like interleukins and TNF-α are produced. Eventually, the uncontrolled inflammatory response may lead to lethal conditions like respiratory depression or shock, resulting in patient's death.[12]

The detailed insight into the pathogenesis reveals that S protein, TMPRSS2, RdRp, 3CLpro, and PLpro can be targeted for the development of COVID-19 therapy.

Prophylaxis and Allopathic Treatment:

Scientists are working all around the world to develop a vaccine for coronavirus including whole virus (inactivated and live attenuated) vaccines, genetic (DNA or RNA) vaccines, viral vector vaccines (vaccines using adenoviruses or other viruses) and protein-based (virus-like particle recombinant) vaccines. For prophylaxis, supplements are being advised, including zinc, vitamin C, D, and E, to boost immunity in an individual for natural combat against the virus until a

vaccine is developed. Based on observations and researches, different drug groups are being used for the treatment, such as anti-viral drugs that inhibit viral replication, ion channels as well as serine proteases. Anti-viral drugs that are available for herpes, hepatitis, acquired immunodeficiency syndrome, and influenza had been used effectively in earlier outbreaks of viral infections such as SARS-CoV, Ebola hemorrhagic fever and MERS-CoV, so these are also being given for treating COVID- 19.[13] Antimalarial drugs with compounds like antifolate, aryl amino-alcohol, and artemisinin are also being given as these inhibit viral growth, but their disadvantage is the development of antimalarial drug resistance.[14] Researchers suggest that hydroxychloroquine (HCQ) or it's combination with azithromycin (AZ), which is an antibiotic drug decreases viral load in COVID-19.[15] Teicoplanin, another antibiotic previously showed efficacy in inhibiting the first stage of the viral cycle of MERS coronavirus in cells of human. Therefore, it has potential in the treatment of patients with Coronavirus.[14] Whereas, doxycycline inhibits the virus's serine protease as well as post-infection replication, thus reducing viral load.[16] ln addition, tetracyclines can also exert its anti-inflammatory capabilities along with other anti-inflammatory drugs such as inhibitors of JAK-STAT, which are used against rheumatoid arthritis. Some of the recent studies showed that Baricitinib, along with Remidesivir, decreases viral load.[17] Drugs such as aspirin, acetaminophen, and colchicine have also been studied and observed to have a role in COVID-19.[15]

Various studies identified positive outcomes of treatment with corticosteroids, especially in the SARS-CoV outbreak, as these were used because of their ability to modulate the inflammatory response but for a short period of time. Laboratory studies suggest that corticosteroid such as dexamethasone's one or two doses administered in infection's acute phase may be helpful in alleviating the early pro-inflammatory response, but their prolonged use may enhance viral replication.[18] The high fatality rate is linked to coagulopathy occurring in coronavirus infection, and increased levels of D-dimers (important coagulopathy marker) are also seen. Pro-inflammatory cytokines lead to severe lung inflammation and impairment of pulmonary functions in COVID-19 patients. Marked elevation in D-dimers is because of severe inflammation, which stimulates fibrinolysis. Therefore, blocking thrombin by anti-coagulants such as heparin can alleviate the inflammatory reaction, as well as the anti-inflammatory function of heparin, can also play a role in this case.[19]

The entry of the virus will be blocked if neutralizing monoclonal antibodies are developed against ACE2 receptors; this will lead to a marked reduction in the severity of disease.[20] Similar to other viral infections, convalescent plasma therapy can also be effective in COVID 19. A study showed a good survival rate after using convalescent plasma in combination with a systemic corticosteroid. After infusion of convalescent plasma, the patients have shown improvement in oxygenation as well as a decrease in inflammatory markers in their Chest X-ray findings.[21]

Herbal Therapy:

Drug development against COVlD- 19 appears to be a "need" in the current situation as it is a rapidly evolving epidemic, but developing new drugs still needs some time as the safety profile cannot be known over a short period of time.[8] For this lethal viral disease, where no definite pharmacological drugs are currently available for prevention or treatment, many researchers are focusing on phytochemicals and herbal therapy.[22]

Since ancient times, many cultures have been using herbs and plants for the treatment of

various diseases, including infections due to their medicinal properties. Greeks used to treat infections with herbs like ood (Paeonia emodi Royle.), za'fran (Crocus sativus L.), mushk (Moschus moschiferus L.), olive gum,zanjabeel (Zingiber officinale Roscoe), amber (Liquidambar acalycina) and sibr (Aloe vera L.) due to their antioxidant and anti-inflammatory actions.[23] Anti-viral activity of many natural substances from different habitats and geographical locations has been established.[24]

A glance in the past reveals that plants and herbs possess medicinal properties for preventing viral spread like SARS (Severe Acute Respiratory Syndrome). Compounds, including quercetin, which is a flavonoid and found in fruits and vegetables, show increased binding affinity to the key targets of SARS-CoV-2.[8,9,24] This inhibits viral replication, as well as its transmission.[25] In Chinese medicine, berberine, an isoquinoline derivative alkaloid isolated from many medicinal plants, also has importance in the treatment of influenza virus infections.[26] Many medicinal plants from India also exhibit anti-viral, anti-inflammatory and antioxidant properties which make them highly recommendable for the clinical therapy of COVID-19.[27]

In this regard, Nigella sativa (N.sativa), also called black seed or kalonji, could be considered as a natural substitute to chloroquine. N.sativa contains numerous phytochemicals out of which, nigellimine resembles chloroquine, which inhibits replication of SARS-CoV-2 in the same fashion. This anti-viral effect can be augmented by Zinc supplements, as the major components of N. Sativa helps Zn^{+2} entry into lung cells, which are the target of SARS CoV-2. In previous studies, the anti-viral activity of thymoquinone and black seed oil against influenza virus (H9N2) has also been reported.[28,29]

Several other food components could also help in the development of specific bioactive component which can cause damage to the DNA gyrase of coronavirus.[30] Honey has a virucidal effect on several enveloped viruses such as HIV, influenza virus, HSV, and VZV.[26] Flavonoids derived from Sena or Salvia officinalis and other natural compounds lead to immune induction. Such compounds are present abundantly in pomegranate, garlic, ginger, turmeric, black pepper, and tea.[26]

Other plants have been reported to boost immunity.[31] Ursolic acid and oleanolic acid act by inhibiting the main protease of coronavirus.[32] Asparagus racemosus has shown anti-viral activity[13]. Eucalyptol from eucalyptus oil is also showing anti-viral potency.[33]

CONCLUSION:

Researchers and clinicians are trying their best to find propose effective drugs to deal with this pandemic. This review warrants more in vitro and in vivo studies on naturally occurring plants as these appear to be potential phytochemicals for treating viral infections and can help in the development of new drugs for Covid-19.

AUTHOR'S CONTRIBUTION:

MR: Conception of idea and study design
MNZ: Drafting article
NY: Drafting article and study design
MIP: Data analysis
FAK: Data collection

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