A REVIEW ON NATURAL PRODUCTS AS A POSSIBLE MEDICINE FOR COVID 19 TREATMENT

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

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Brac University
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Declaration

It is hereby declared that

1. The thesis submitted is my original work while completing my degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material that has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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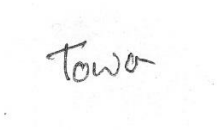

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Approval

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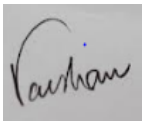

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Ethics Statement

The study does not involve any kind of animal or human trial.

Abstract

The COVID-19 pandemic, which started with the new decade, was influenced by the coronavirus SARS-CoV-2. It has become a global public health challenge and has resulted in enormous losses across the globe. As the need for a treatment therapy has grown critical, all researchers have begun to work to acquire innovative therapeutics to fight COVID-19. Synthetic medications have been repurposed to lower the severity initially, however the consequences are still being studied. Natural compounds could be a crucial source enabling the development for potential COVID-19 treatments in these uncertain situations. SARS-CoV and MERS-CoV were both treated with natural products in the past and also have a long history of being used to treat a wide variety of diseases. Natural compounds have been effectively tested *in vitro* against COVID 19, but their effectiveness and bioavailability *in vivo* have yet to be determined. This review attempts to discuss the discovery of potential natural compounds that may be used for COVID-19 treatment based on mechanisms of action as well as pharmacological applications.

Keywords: Pandemic, COVID-19; SARS-CoV-2; Natural products; Treatment

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List of Acronyms

SARS	Severe Acute Respiratory Syndrome
MERS	Middle East Respiratory Syndrome
WHO	World Health Organization
ORF	Open Reading Frames
NSP	Non-Structural Proteins
SARS-CoV-2	Severe acute respiratory syndrome 2
CoV	Coronavirus

Chapter 1: Introduction

Coronaviruses transmitted from animals to people have infected humans for the third time in three decades (Perlman, 2020). The World Health Organization (WHO) has attributed an outburst of pneumonia around Wuhan City, Hubei Province, on a new coronavirus (CoV) identified as "2019-nCoV," also known as "2019 novel coronavirus" or "COVID-19" (T, 2021). Severe acute respiratory syndrome 2 (SARS-CoV-2) is another term for COVID-19 (H. Li et al., 2020). When examined carefully, a coronavirus can be identified under a microscope because of its distinct appearance, as a "crown" of proteins known as peplomers protrudes from the center of the spherical virus in all directions, and these viruses require proteins like these to determine if they can spread to a new host and cause infection (Alinia-Ahandani & Sheydaei, 2020). The 2002 pandemic of severe acute respiratory syndrome (SARS) sparked widespread concern, and it has been followed by the Middle East respiratory syndrome (MERS) outbreak in 2012 and the COVID-19 pandemic in 2020. Extremely pathogenic SARS-CoVs and MERS-CoVs, such as those found in bats and palm civets or dromedary camels, are known to transmit from these animals to people (T, 2021). SARS initially arose in China early 2002 then rapidly spread around the globe, killing hundreds with the fatality rate around 11 % and a mortality rate of 37%. MERS was originally diagnosed in Saudi Arabia in 2012, and afterwards extended to other nations worldwide. (H. Li et al., 2020). As of September 2021, COVID-19 has infected 221 nations and around 230 million individuals, as well as claiming the lives of approximately 4.7 million people worldwide (Kassaa et al., 2021).

1.1 The History of COVID-19

Tyrrell and Bynoe found a virus they labeled B814 from the nasal wash of a kid suffering from normal cold symptoms in 1965. Medical students who had a common cold at the time of the discovery of a new respiratory virus by Hamre and Procknow in 1966. This strain was referred

to as 229E. Researchers at the National Institutes of Health in Bethesda, followed it up by cultivating two morphologically similar viruses in organ culture, naming them respectively OC38 and OC43. In 1968, the term "coronavirus" was approved (Myint, 1995).

1.2 Classification of Coronaviruses

In the order Nidovirales, and subfamily Orthocoronavirinae there are four genera: Alpha-coronavirus, Beta-coronavirus, Gamma-coronavirus and Delta-coronavirus, which are all members of the Coronaviridae family. According to RNA viruses, the coronavirus genome is the largest ever discovered, is between 26 kilobytes and 32 kilobytes in size. Alpha-coronavirus and Beta-coronavirus infects mammals, whilst the latter two infects birds (H. Li et al., 2020). Alpha- and beta-coronaviruses are two types of coronaviruses that are mostly responsible for

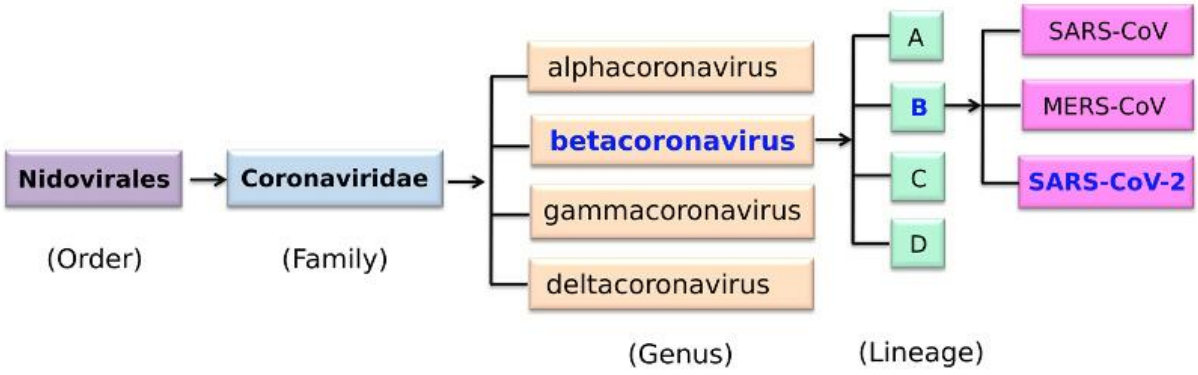


Figure 1: Coronavirus Classification (Santos-Sánchez & Salas-Coronado, 2020)

respiratory tract infections. Bioinformatics research classifies beta-coronaviruses into four subgroups (a, b, c, and d), with SARS-CoV and MERS-CoV belonging to the b and c lineages, respectively. SARS-CoV-2 also corresponds towards the b lineage, according to the sequencing studies and has 89% resemblance to bat SARS-CoV and 82 percent resemblance to human SARS-CoV (Boozari & Hosseinzadeh, 2021).

1.3 SARS, MERS, and COVID-19

The novel coronavirus SARS-CoV-2 is linked to viruses that cause SARS as well as MERS. This coronavirus, however, appears to be associated with milder symptoms than other coronaviruses. SARS-CoV-2 has been proven to be far more broadly diffused in the environment than SARS and MERS, with the majority of transmission happening via nosocomial pathways (Petrosillo et al., 2020). SARS was initially detected in February 2003, although cases were later traced back to November 2002 and it rapidly spread to 26 countries before being controlled after four months also it infected more than 8,000 individuals and 774 of the died. There have been no reported SARS infections after 2004, according to the National Institute of Allergy and Infectious Diseases (NIAID), which is most likely owing to prevention efforts (Richa, 2021). MERS was initially diagnosed throughout Saudi Arabia around 2012, according to the World Health Organization, and has since disperse to 27 nations as well 2,519 infections and 866 fatalities from its start until January 2020 and approximately 80% of all documented occurrences in individuals have originated in Saudi Arabia (Richa, 2021). In comparison with SARS and MERS, SARS-CoV-2 has inflicted more infections, with millions affected as it has spread over the globe and is yet uncontained. Bats, according to researchers, are the most likely hosts for these coronaviruses. It is worth mentioning that both SARS-CoV and SARS-CoV-2 show connections to China's local market. Early SARS cases had been associated with wild animals present in Guangdong markets, notably palm civets, since a CoV strain derived from palm civets is homologously identical to the SARS-CoV strain that caused the disease. In Chinese horseshoe bats a SARS like viral strain was isolated which shared 88% to 92 % genetic similarities with CoV strains obtained from humans and civet cats, indicating that bats seems to be the primary reservoir of SARS-CoV, with palm civets acting as intermediary hosts in the virus's transmission (W et al., 2006). MERS-CoV is also considered to have been originated in bats, as evidenced by the fact that the PCR amplification of nucleic

acid from bat feces yielded an RNA fragment that had 100% match of the nucleotide with MERS-CoV from an individual affected in the same region. Furthermore, MERS-CoV samples from dromedary camels and humans were shown to have 99.2 % to 99.5 % genetic homology (Zhu et al., 2020). SARS-CoV-2 transmission seems to be more complicated and equivalent to SARS-CoV since it was associated to business activities in a Wuhan local market. Additionally, researchers discovered that Bat-CoV RaTG13 (a bat-CoV) and SARS-CoV-2 are genetically

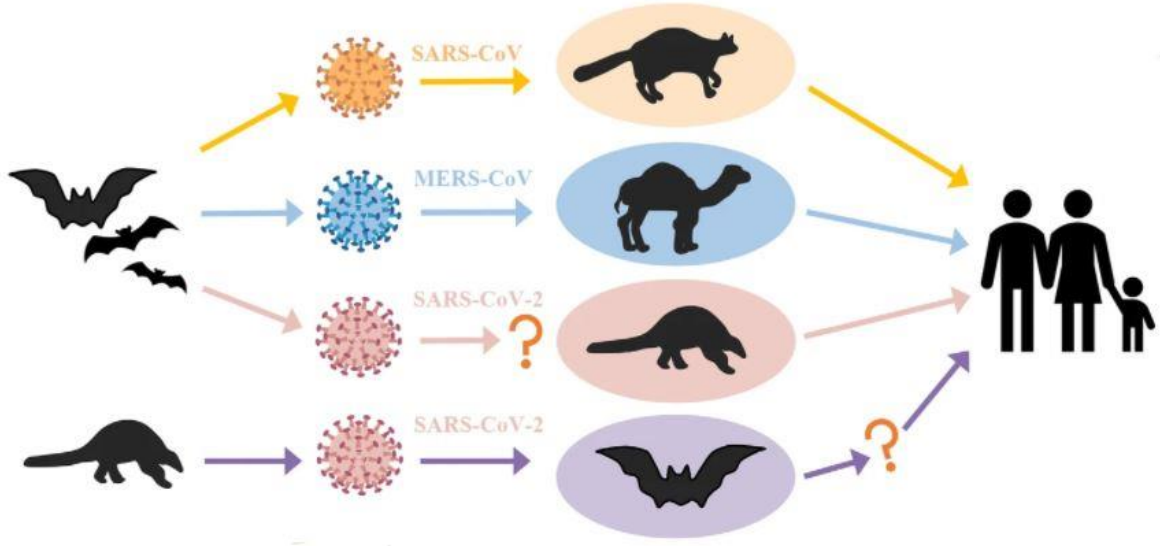


Figure 2: Reservoirs of Coronaviruses(Zhu et al., 2020)

identical, leading them to believe that bats could be the natural reservoir of SARS-CoV-2. Several research investigated the phylogenetic relationship among SARS-CoV-2, RaTG13, and pangolin-CoV and discovered pangolins were the natural reservoir of SARS-CoV-2. Another research revealed pangolins as a natural SARS-CoV-2 reservoir, however not as same proportion as RaTG13. (Zhang et al., 2020).

1.4 Genome, Structure, & Replication of SARS-CoV-2

The genome of the coronavirus seems to be 26–32 kb length, with 6–11 open reading frames (ORFs) generating 9680 amino acid polyproteins. Only two-thirds of the virus's RNA is found in the first ORF (ORF1a/b), which is in charge of translating two polyproteins, pp1a and pp1ab, as well as encoding non-structural proteins (nsp). The remaining ORFs are in charge of encoding extra and structural protein (Guo et al., 2020). SARS-CoV-2 has two flanking untranslated regions (UTRs), one on 5' end of 265 nucleotides and one at the 3' end of 358

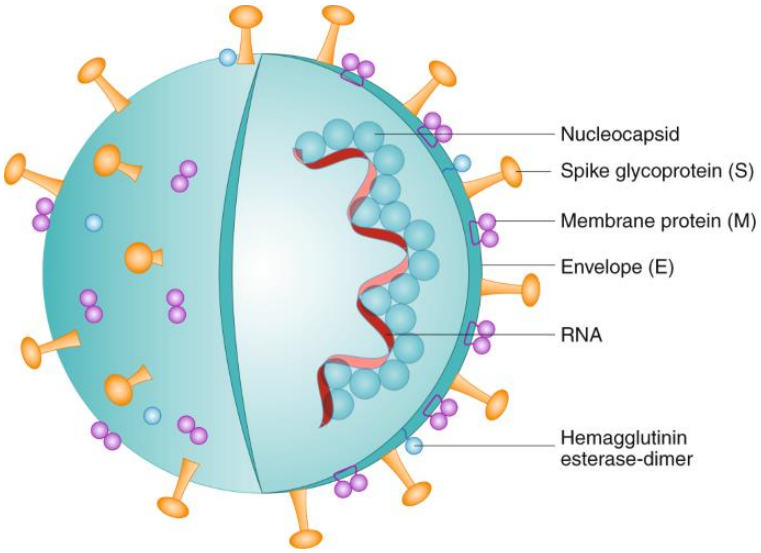


Figure 3: SARS-CoV-2 Structure (Florindo et al., 2020)

nucleotides. SARS-CoV-2 and SARS-CoV sequencing variants were shown to have no significant differences. The nsp is made up of two viral cysteine proteases, chymotrypsin-like, 3C-like, or main protease and papain-like protease, along with helicase, RNA-dependent RNA polymerase, and additional replication and transcription-related proteins (Fuk-Woo Chan et al., 2020). Spike (S), membrane (M), envelop (E), and nucleocapsid (N) are four structural proteins produced by the remaining segment of the viral genome. The S1 subunit of the S protein's receptor-binding domain (RBD) was shown to have a key function in direct host entrance. M protein aids in the formation of virions and the binding of nucleocapsid. E protein has a role in viral pathogenicity by assisting in virus assembly and release. N protein is responsible during

packing the encapsulated DNA into virions. An IFN- activity antagonist has been discovered in Orf3b, one of the N proteins, which is beneficial for viral replication because it inhibits IFN-β activity in synthesis and signaling (Tsang et al., 2020). SARS-CoV-2 primes the S protein with the TMPRSS2 serine proteases, using the same ACE2 receptor as SARS-CoV. When spike proteins attach to their respective subcellular ACE2 receptors, they undergo structural changes that trigger endosomal entrance of the viral envelope proteins. Replicase polypeptides pp1a and pp1b are then degraded by viral proteases in the host cytoplasm. Coronavirus

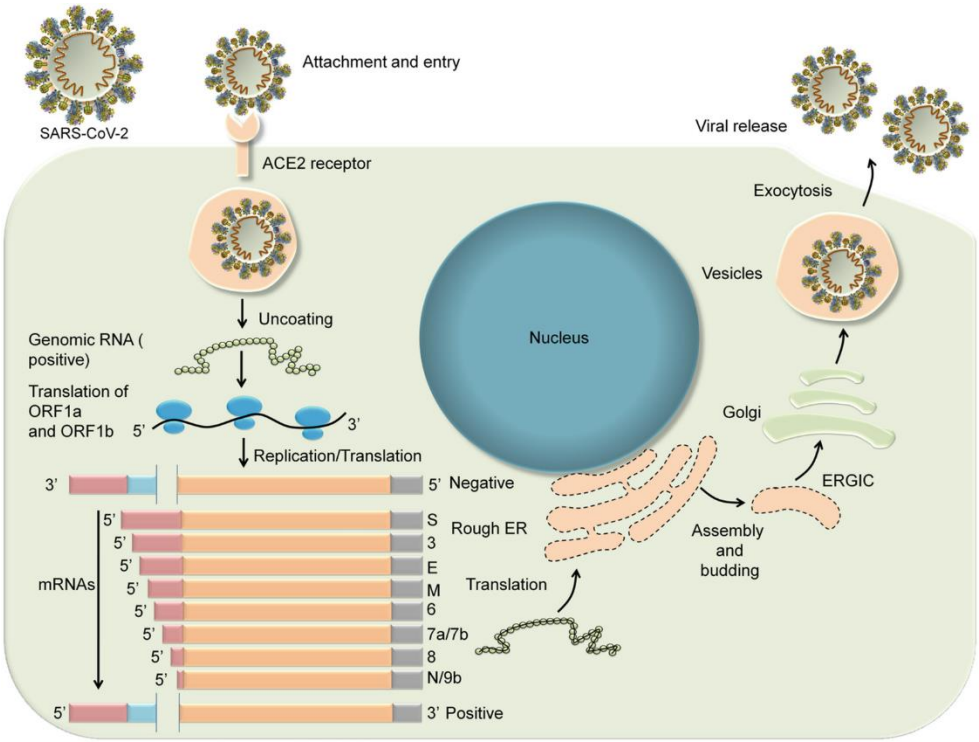


Figure 4: SARS-CoV-2 Replication (Kumar et al., 2020)

replication is a ribosomal frame shifting process that produces genomic and many sub-genomic RNA copies, along with sporadic transcription that codes for the critical protein. The Endoplasmic Reticulum (ER) and Golgi complex interact with RNA and protein during virion formation. The release of virions is controlled by vesicles within the cell (Kumar et al., 2020).

1.5 Current state of COVID-19

It's no surprise that viruses, especially the CoV, are prone to mutation. SARS-CoV-2, lineage B.1.1.7 (Alpha), was discovered in September 2020 throughout UK that quickly spread to other

countries, including the United States of America and Bangladesh, due to its increased infectiousness (Galloway et al., 2021). In South Africa, a variant termed B.1.351 (Beta) was discovered and contained a mutation N501Y that was comparable to the mutation reported in the UK. Since the middle of 2020, another very contagious strain, P.1 (Gamma), has been spreading in Brazil, which is a part of the Japanese B.1.1.28 lineage which had been broken out from the original strain (*Science Brief: Emerging SARS-CoV-2 Variants | CDC*, 2021). In December 2020, the CoV variant B.1.617.2 (Delta) was detected in India. This variety proved to be more infectious than any other version, and it was attributed to the outbreak of a second global pandemic, as it was expected to be 60% more contagious than Alpha (Rio et al., 2021).

Table 1: Coronavirus Variants (Biswas, 2021)

Country/Region	Scientific Name of the variant	WHO Name
Kent, UK	B.1.1.7	Alpha
South Africa	B.1.351	Beta
Brazil	P.1	Gamma
India	B.1.617.2	Delta

1.5 Epidemiology

Infectious diseases spread due to a variety of reasons, including transmission pathways, infectious origins, and susceptible recipients. Respiratory secretions, direct touch, and surface contamination are all ways for SARS-CoV-2 to transmit, with the Chinese National Health Commission mentioning the possibility of airborne transmission as an additional means of transmission (Boozari & Hosseinzadeh, 2021). Every individual is deemed susceptible based on current epidemiologic characteristics, and the average age is about 50 years. One study discovered that those over 60 had greater concentration of blood urea nitrogen and

inflammation indicators, as well as more bilateral lobe lesions, than people under 60. Patients over the age of 60 are more likely to get pulmonary edema and have a longer duration of disease than those under the age of 60 (Wang et al., 2020). Incubation period for SARS-CoV-2 is expected to be 3–7 days on average (with a range of 2–14 days), showing that the virus has a protracted period of transmission. The duration of non-SARS human CoVs, SARS-CoV, and MERS-CoV is comparable. There is evidence that COVID-19 individuals who are incubating the asymptomatic SARS-CoV-2 virus are also capable of spreading it. Since most SARS-CoV cases are caused by so-called "superspreaders," the virus is unable to infect others throughout the incubation stage of the illness. It is encouraging to see that these findings support the World Health Organization's current recommendation for 14-day active monitoring. (H. Li et al., 2020). Reproduction number R nought (R_0), which is a key limit for the virus's ability to spread, can be indirectly defined as a person who has been infected produces secondary infections. Liu et al. evaluated the R_0 of SARS-CoV-2, reporting estimations spanning from 1.4–6.49, with a mean of 3.28. If R_0 is greater than one, then number of infected patients is projected to increase exponentially (Y et al., 2020). Cough, fever, muscle pain and fatigue all are common COVID-19 symptoms also sputum secretion, headache, hemoptysis, and diarrhea were less frequent symptoms. Furthermore, dyspnea affects more than half of patients, and it takes an average of 8.0 days from the start of the disease to the beginning of dyspnea. The blood counts of COVID-19 patients indicated lymphopenia, according to a systematic analysis of 19 studies including 2,874 patients, the majority of whom were from China. Prothrombin times were also prolonged, moderate thrombocytopenia was seen, and D-dimer levels were increased (Tsang et al., 2020).

1.7 Pathogenesis

Virus replication is predicted to spread from the mucous membranes of the upper respiratory system towards the lower respiratory tract as well as the intestines, eventually leading to a moderate viral load in the blood. Only a few diseases have been brought under control and are no longer causing symptoms. Non-respiratory complications including significant liver and heart damage, renal failure, and diarrhea have also been reported by some individuals. Several human organs produce ACE2, hence SARS-CoV-2 may infect the nasal mucosa including the

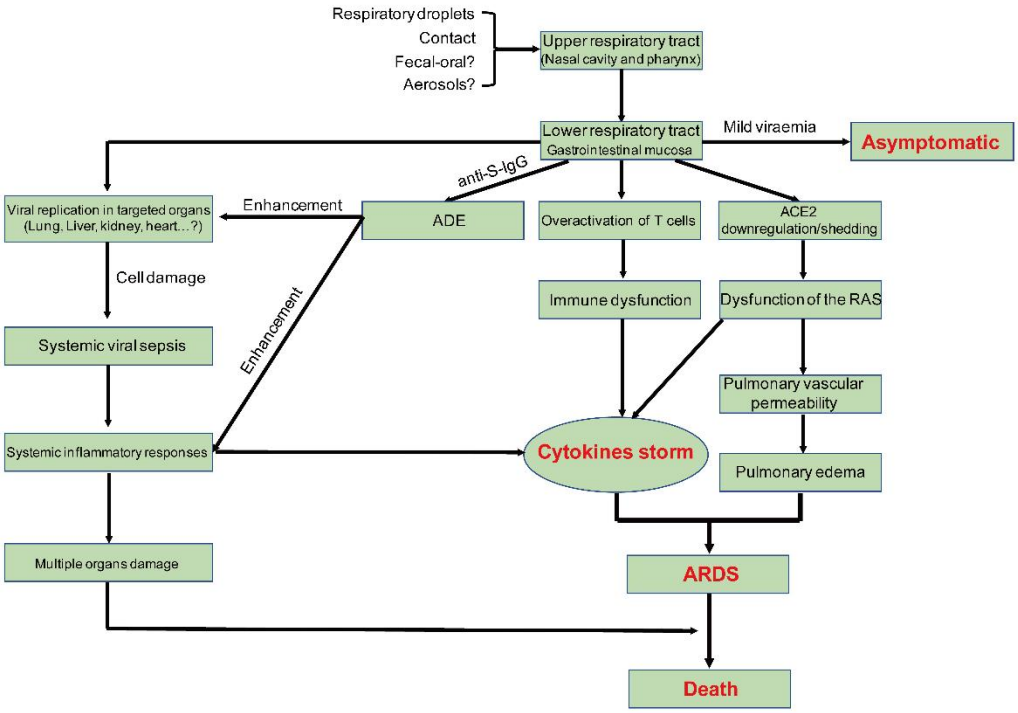


Figure 5: Postulated pathogenesis of SARS-CoV-2 infection (Jin et al., 2020)

bronchial tubes , lungs as well as the esophagus and kidneys (Jin et al., 2020). Following the collection of biopsy samples from the lung tissue of the first victims of COVID-19, certain pathogenic characteristics of the virus have been linked to acute respiratory distress syndrome (ARDS), according to researchers. In patients who need mechanical ventilation, SARS-CoV-2 infections are linked to ARDS, as determined by histological examinations of the respiratory tract. The tissue samples from the lungs investigated also showed interstitial mononuclear inflammatory infiltration. There was evidence of viral cytopathic alterations in the intra-

alveolar spaces, as shown by amphiphilic, granular cytoplasm. There were several multinucleated giant cells in the intra-alveolar spaces, each having a big nucleus, conspicuous nucleoli, and amphiphilic-granulated cytoplasm, indicating the presence of viral cytopathic-like mutations (H. Li et al., 2020). COVID-19 patients exhibit considerably higher concentration of chemokines and cytokines in their bloodstreams such as IL1RA, IL1-β, IL7, IL8, IL9, IL10, GMCSF, FGF2, IFN, GCSF, MCP1, IP10, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. High concentration of pro-inflammatory cytokines such as IL2, IL7, IL10, IP10, MCP1, GCSF, MIP1α, and TNFα have been discovered in a few instances of seriously ill patients admitted to the ICU, and it is believed that they contribute to the patients clinical severity (Rothan & Byrareddy, 2020).

1.8 Rationale of the study

Natural products are a great source of metabolites, which are used to cure a variety of ailments, as is well known in the medical world. Natural products may also aid to boost the immune system of the person who consumes them. Natural compounds have a long and effective history as medications, particularly in traditional Chinese medicine. There are yet no immediate and relevant treatments available to treat COVID-19 infection. Various medications are being repurposed to fight against the crisis, but research has yet to confirm their effectiveness. Researchers are aiming to create a COVID-19 medication that can be produced swiftly and distributed to as many people as possible. The resemblance between SARS-CoV-1 and COVID-19 may also provide information for the development of innovative treatments to combat the disease.

1.9 Aim & Objectives of the study

Aim: The aim of this review is to assess as well as suggest natural products as a potential treatment for COVID-19

Objectives: The specific objectives of the study are:

- to give a concise assessment of the clinical characteristics of SARS-COV-2, along with strategies to treating this infection using a variety of natural products.
- to raise awareness of natural products as potential COVID-19 therapeutic strategies.
- to inspire research into natural products, not just as a COVID-19 treatment, but for a wide range of other pharmacological purposes as natural products are more cost efficient and environmentally friendly than synthetic ones.

Chapter 2: Methodology

2.1 Study Design:

This review study has been organized in such way that it focuses on answering the following questions:

- What is coronavirus?
- History of coronavirus
- What are the treatment strategies for COVID-19?
- How might natural products be used to treat COVID-19?
- Natural products that could be used to treat COVID-19.
- Current application of natural products
- Natural derivatives to inhibit coronaviruses
- Future implication of natural products and COVID-19

2.2 Literature Search:

A comprehensive study of the literature was undertaken in order to gather all of the information that was used to write this review article. Various trustworthy sources, such as peer-reviewed media and online academic databases, as well as books, journals and magazines were used to compile the information. The following is a list of various articles that were thoroughly studied for the sake of this present study.

- PubMed
- Elsevier
- Wiley
- Nature
- Springer Link

- Science Direct

The keywords that have been used to avail the data are: coronavirus, COVID-19, natural products, SARS, MERS, natural derivatives, SARS-CoV-2, anti-viral agents, terpenoids, alkaloids, traditional medicine etc. This study aims to include all of the data regarding natural products which have been identified and are now being researched by different scientists all over the globe in the previous several years, including those that have been recognized recently.

Chapter 3: Treatment

3.1 Current management of COVID-19

Controlling the spread of infection is the first step in the management of a disease. As a pandemic such as COVID-19 spreads, it is critical to investigate the cause and take various preventative measures. Because of this SARS-CoV-2 outbreak, there have been a lot of new investigations on specialty treatments, vaccine development, and dissemination. There are currently available therapies for treating COVID-19 infection, including small molecule medications that limit virus penetration into host cells or inhibit virus replication or repair, as well as biologics/antibodies that regulate COVID-19-associated inflammation in order to reduce the disease-associated pathologies (Wiersinga et al., 2020). The following overview of accomplishments includes information on therapeutics, as well as various protective effects.

3.1.1 Prevention of disease transmission

COVID-19 spreads mostly by respiratory droplets, it also has the capacity to spread even before symptoms appear. Two steps must be made to stop the virus from spreading: first, an infected person must be segregated from others and must only have limited contact with those who are not affected; second, the likelihood of transmission per interaction must be decreased in attempt to eliminate the infection from spreading (Howard et al., 2021).

3.1.2 Therapeutics for COVID-19

Although a variety of vaccines have been licensed for usage across the globe, there is no particular treatment or preventative measure in place for COVID-19 at this point. As a result of inequities in vaccination production and availability, there is an increasing need for a treatment therapy that is both safe and highly effective. Note that the process of identifying novel compounds for COVID-19 is time-consuming, expensive, and difficult to complete.

Current therapeutic possibilities for COVID-19 may be divided into antiviral medicines, repurposed antiviral medications, immunomodulators, and adjunctive therapies.

Antivirals: A moderate infection of COVID-19 may not need any antiviral therapy at all for those who have it. According researchers when it comes to influenza and SARS infections, using antiviral medicine as soon as possible will help to shorten the illness's duration. However, even though randomized clinical trials are required, many of these antiviral medicines are currently being developed according to *in vitro* and extrapolation data (Şimşek Yavuz & Ünal, 2020).

- Remdesivir: GS-441524, a monophosphate analog of adenosine that acts as a cyano-substituted adenosine analog, is the active ingredient in Remdesivir. A RdRp inhibitor that binds to RdRp active site, prevents viral replication from taking place. Remdesivir was used to treat Ebola patients for a short period of time, however it was eventually taken off the market due to the efficacy of other therapies. SARS-CoV, MERS-CoV, and other RNA viruses have been treated with Remdesivir, an antiviral medication. On October 22, 2020, the Food and Drug Administration (FDA) authorized Remdesivir in purpose of treating COVID-19 patients, becoming it first pharmaceutical to be authorized by the FDA for this usage. Remdesivir was granted conditional approval by the European Commission in July 2020, which came before the FDA's acceptance (FDA, 2020; Ita, 2021).
- Favipiravir: Favipiravir, an antiviral medication that is taken orally, prevents RNA virus transcription by inhibiting RdRp. Many nations, including Japan, China, and Russia, have licensed the antiviral medication favipiravir for use in treating all influenza subtypes. Ebola virus infection may now be treated with favipiravir. In studies, favipiravir was demonstrated to efficiently suppress SARS-CoV-2 in Vero E6 cells. Following clinical testing, favipiravir has been discovered as a feasible therapeutic

option for mild to severe COVID-19 infection. (Cai et al., 2020; Devaux et al., 2020; Udwadia et al., 2021).

Repurposed Antiviral:

- Chloroquine /Hydroxychloroquine: *In vitro* studies have demonstrated that chloroquine as well as its derivative hydroxychloroquine are effective against influenza A, B, and A H5N1 viruses, along with hepatitis A and C viruses, HIV, poliovirus, hepatitis A and C viruses, rabies and poliovirus, and also the Crimean–Congo hemorrhagic fever and Ebola viruses and various DNA. SARS-CoV-1 was the first coronavirus to benefit from chloroquine's possible therapeutic advantages. Additionally, studies in epithelial lung cell cultures showed that chloroquine prevented the reproduction of HCoV-229E *in vitro*. A wide variety of mechanisms of action can be observed in CQ and HCQ. In order to prevent viral particles from attaching to cellular receptors, impair viral replication in its early stages, and interfere with viral protein post-translational modification, it is feasible to raise the pH of endosomes. The inflammatory response against SARS-CoV-2 is decreased due to a reduction in ILs such as interleukin-1β and IL-6, as well as immunomodulatory effects (Devaux et al., 2020; Vincent et al., 2005).
- Nitazoxanide: Nitazoxanide is an antiparasitic that may be used as a treatment option. Parasites, Gram positive as well as Gram negative bacteria, viruses, even fungi are all inhibited by it. This medicine may be used to treat influenza and various notable respiratory viruses, as well as Hepatitis B and C, HIV, and MERS-CoV. Nitazoxanide is presently being studied to see whether it can be used independently or in conjunction with Ivermectin, Hydroxychloroquine, or Azithromycin to treat COVID-19. Nitazoxanide is a feasible alternative for reuse in COVID-19 because it protects the lungs while decreasing multi-organ damage (Lokhande & Devarajan, 2021; Rossignol, 2016).

Immunomodulators: Aside from viral impacts, the innate immunity of the host plays a significant role in disease progression. According to Li and his research team, if the immune system is out of balance, the subsequent immunopathogenesis contributes to disease development. A unique adaptive immune response may prevent the disease from progressing throughout the incubation phase and early stages of the infection. In very rare cases can cytokine release syndrome in the latter stages of infection lead to a more serious medical condition (G. Li et al., 2020). As a result, in COVID-19 patients, regulating innate immunity might be a viable treatment option.

- Bevacizumab: An eye condition and a variety of cancers can both improve from the use of the bevacizumab. Subsequent studies have showed that in COVID-19 vascular endothelial growth factor (VEGF) levels have risen, whereas Bevacizumab suppresses VEGF. VEGF is one of the most effective permeability-inducing factors, contributing to edema and progression of lung disease. The most recent clinical trials using bevacizumab have shown that it is clinically effective in terms of increasing oxygenation and decreasing the time spent on oxygen support. As a result, it potentially be effective in the treatment of COVID-19 patients (Garcia et al., 2020; Pang et al., 2021).
- Corticosteroid: In addition to rheumatoid arthritis, dermatoses, allergic reactions, and respiratory issues, dexamethasone is an artificial adrenal corticosteroid that has anti-inflammatory properties. It may be used to treat all of these conditions as well as others. Patients receiving chemotherapy often get Dexamethasone to help manage the negative effects of their chemotherapy drugs, which is why it is so widely prescribed. Oxygen-dependent patients with COVID-19 are often given dexamethasone while in the hospital. Dexamethasone was shown to lower the 28-day death rate among COVID-19 patients who were randomly allocated to get invasive ventilators or oxygen alone in a

study, but not in patients who received no respiratory support (Águas et al., 2021; Italian Group for Antiemetic Research, 2000; Peretto et al., 2020).

Adjunctive Therapies:

- Convalescent Plasma: Five critically sick COVID-19 patients received 12 days of convalescent plasma transfused with SARS-CoV-2-specific antibody binding titers more than 1:1,000 and neutralization titers greater than 40, the viral load decreased to less than 40 in all five patients after 12 days. In accordance with the results of the study, four out of five patients saw a resolution of their ARDS symptoms by the 12th day after their transfusion. According to the results of this study, convalescent plasma may aid in the clinical recovery of critically sick patients (C. Shen et al., 2020).

3.2: Treatment Strategies

The rapid spread of SARS-CoV-2 demands a therapeutic medication or vaccine to prevent or cure COVID-19 infection. There has been minimal research into potential treatment options or vaccine alternatives as a result of the virus's rapid spread around the globe. Despite the scarcity of studies on SARS-CoV and MERS-CoV pathogenesis, it is evident that the viruses' transmission routes are similar. CoVs' structure and viral particles particle are crucial to understand in order to avoid COVID-19 outbreaks and cure existing cases. To aid in the development of a treatment plan, the following strategies may be used:

3.2.1 Viral attachment inhibition

The viral adhering to the suitable host cells is the first stage in the process of an infection. One of the most fundamental means of viral attachment is the interaction of the viral glycoprotein with the host cell's carbohydrate. Coronavirus glycoproteins are required for virus fusion and receptor degradation. For viral release, the receptor-destroying enzyme (RDE) must function (Mesecar & Ratia, 2008). The hemagglutinin–esterase (HE) glycoprotein in coronaviruses are

essential for both binding to and degrading receptors. The spike (S) glycoprotein identifies host cells, and the virus-host membrane is fused (Boozari & Hosseinzadeh, 2021). The S glycoprotein is broken into two subunits by the host cell protease: the S1 subunit, which adheres to host cell surface receptors, and the S2 subunit, it is responsible for virus fusion with the host genome. Because SARS-CoV-2 glycoprotein targets and binds angiotensin-converting enzyme 2 (ACE2) in coronavirus subgroup B, it is thought to represent a significant receptor (Hoffmann et al., 2020). According to the research, of published findings, medicinal plants *Polygonum multiflorum* and *Rheum officinale* can inhibit S protein and ACE2. S protein and ACE2 interaction was dose-dependently inhibited by emodin, an active component in this genus having an anthraquinone structure which has side chains that affect S protein and ACE2 binding in SARS-Cov2 and it's reasonable to assume that emodin might be used as a treatment (Ho et al., 2007).

3.2.2 TMPRSS2 inhibition

Epithelial cells from different organs were found to be important in identifying the mechanism of SARS-CoV-2 infection, including those of the aerodigestive tract, express the cell-surface protein TMPRSS2. Research into cancer has led to several discoveries concerning TMPRSS2, which is one of science's serendipities (Stopsack et al., 2020). According to Rahman et al. the critical function performed by this protease, which is involved in the stimulation of viral spike proteins, has the potential to be utilized as a prospective approach to block virus entrance into host cells, as it provides a SARS-CoV-2 potential treatment. They proposed 12 distinct natural metabolites as prospective possibilities. Marine soft corals (*Formosan gorgonian*), algae from the *Sargassum* group, mushrooms from the *Paxillus* group and angiosperms, like magnolia vine (*Shisandra sphenanthera*), branched asphodel (*Asphodelus ramosus*), green tea (*Camellia sinensis*) are natural sources of the metabolites. (Rahman et al., 2020).

3.2.3 3CLpro/Mpro inhibitors

All CoVs share the 3C-like protein, which is required for the conversion of polyproteins into mature NSPs such as RdRp and helicase, along with other things. The 3CLpro enzyme, additionally referred as major protease (Mpro), aids in proteolysis, viral replication, and transmission (Pillaiyar et al., 2016). It is a promising target for antiviral treatment therapy because of its vast spectrum of activities (Boozari & Hosseinzadeh, 2021). *Scutellaria baicalensis* compounds were screened in an enzymatic assay to see whether the components may block 3CLpro of SARS-CoV-2. Both baicalin and baicalein, two bioactive components of the plant S. baicalensis, were reported to exhibit antiviral activity in SARS-CoV-2 infected cells and to be unique blockers of 3CLpro. First non-peptidomimetic noncovalent blocker of 3CLpro of SARS-CoV-2, Baicalein was used to identify the crystal structure of this natural substance in association with this protease, which demonstrated an essentially unique binding mechanism (Su et al., 2020).

3.2.4 RNA-dependent RNA polymerase inhibitors (RdRp)

During viral replication and transcription, RdRp is required in the vast majority of RNA viruses. It is possible that blocking viral replication by targeting the RdRp's active site, which has been shown to be the most stable and exposed component of the virus, might be an effective therapeutic strategy (Aftab et al., 2020). Potential RdRp inhibitory activity of the biflavonoid skeleton have been identified, with amentoflavone and robustaflavone being the most promising candidates. It was discovered that *Dacrydium araucarioides* has a sotetsuflavone with bioflavonoid structure, and the sotetsuflavone compound was shown to be the most effective inhibitor of the RdRp of the Dengue virus in an *in vitro* research (Coulerie et al., 2013). Similarly, baicalin and baicalein have been discovered to be possible RdRp inhibitors in another research (Zandi et al., 2021).

3.2.5 Papain-like protease (PLpro) inhibitors

Replicase polyproteins 3CLpro/Mpro and Papain-like protease (PLpro) cleave the two polyproteins, resulting in the generation of sixteen mature non-structural proteins (nsp1-16), which results in maturation of the non-structural proteins. SARS-CoV-2 PLpro has also successfully demonstrated to inhibit interferon-induced antiviral responses in the host, which is an additional role of the virus. Researchers believe that anti-SARS-CoV-2 PLpro drug may improve antiviral immunity as well as lower viral infection (Jiang et al., 2022). As a consequence of the extensive study done on SARS-CoV-1 and MERS PLpro, SARS-CoV-2-fighting compounds have been discovered. Multiple inhibitor classes have been discovered so far, each of which has the potential to permanently attach to the active cysteine residue and so reduce the PLpro activity. Thioamides, thiopurines, tanshinones, diarylheptanoids, and geranylated flavonoids are some of the types of compounds that belong to this category (Capasso et al., 2021).

3.3 Different Classes of Natural Products

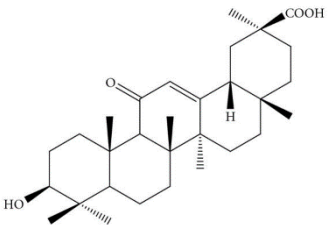
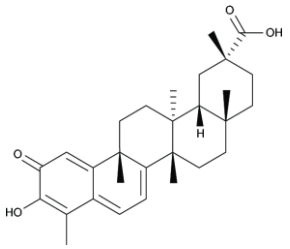
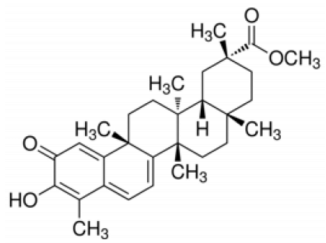
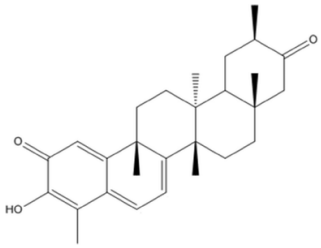
Preliminary *in vitro* studies on COVID-19 treatment for SARS have demonstrated that natural compounds have the potential to be successful. Natural products which are proven to help in COVID-19 therapy have been reported in the literature and will be addressed further below.

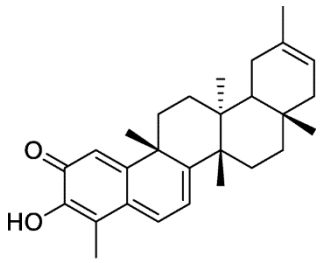
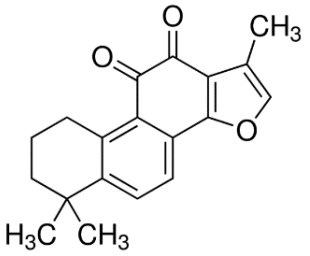
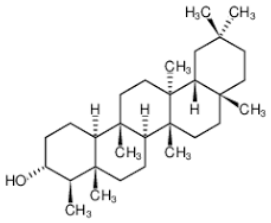
3.3.1 Terpenoid derivatives

Glycyrrhiza glabra, a plant in the Leguminosae family, as well as its active metabolite glycyrrhizin, which has a saponin structure, have been found to inhibit the growth and replication of a multitude of viruses, namely HIV, hepatitis A, B, and C, herpes simplex type 1 virus, cytomegalovirus and varicella-zoster virus. According to the results of a 2003 clinical trial, glycyrrhizin demonstrated potential antiviral activity against two strains isolated of coronavirus acquired from patients. SARS-associated virus replication has already been demonstrated to be suppressed by glycyrrhizin, suggesting the prospect that it might be used to

treat SARS-Cov-2 (Cinatl et al., 2003) (Nassiri Asl & Hosseinzadeh, 2007). A group of terpenoids known as quione-methide triterpenes, which are found solely in plants belonging to the Celastraceae family, such as *Tripterygium regelii*. Celastrol, pristimerin, tingenone, and iguesterin were the four quinone-methide triterpenoid derivatives extracted from CHCl3 extracts after further bioactivity-guided fractionation and against 3CLpro, these drugs exhibited significant inhibitory action (Ryu et al., 2010). It has been discovered that the plant *Salvia miltiorrhiza* has a unique class of tanshinones with an abietane diterpene structure, which was previously undiscovered. Tanshinones have been shown to have anti-tumor properties as well as potential effect on the cardiovascular system, in addition to their anti-inflammatory qualities. Because these substances selectively suppress the SARS-CoV 3CLpro and PLpro enzymes, it is necessary to determine which enzymes are inhibited by the substance in issue to understand about the substance's mechanism of action. The results of several studies have shown that different types of tannenones have different inhibitory activities on PLpro, with some being more potent than others (Park, Kim, et al., 2012). I*n vitro* anti-HCoV activity of triterpenoids produced from *Euphorbia neriifolia* leaves was investigated in 2012, and the results were promising. 23 chemicals were extracted from *E. neriifolia* in this research, including 22 triterpenoids and one flavonoid glycoside, and they were all shown to be beneficial. After testing the isolates' anti-HCoV-229E activity using friedelane derivatives, it was discovered that the isolates had the highest level of viral inhibition. 3β-Friedelanol, which has a triterpenoid structure, had shown to have more powerful antiviral action and enhanced cellular viability after being incubated with HCoV than the other isolates (Chang et al., 2012).

Table 2: Terpenoid derivatives

Name	**Structure**	**Mechanism of Action**	**Reference**
Glycyrrhizin		Inhibits growth and replication of virus	(Cinatl et al., 2003)
Celastrol		Inhibits 3CLpro	(Ryu et al., 2010)
Pristimerin		Inhibits 3CLpro	(Ryu et al., 2010)
Tingenone		Inhibits 3CLpro	(Ryu et al., 2010)

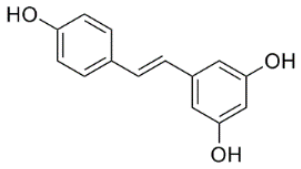
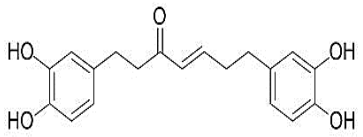
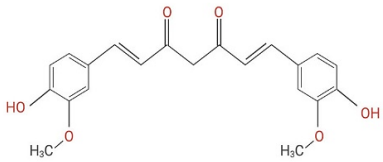
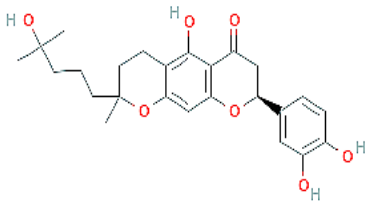
Iguesterin		Inhibits 3CLpro	(Ryu et al., 2010)
Tanshinones		Inhibits PLpro	(Park, Kim, et al., 2012)
3β-Friedelanol		Viral inhibition	(Chang et al., 2012)

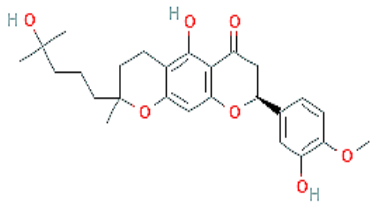
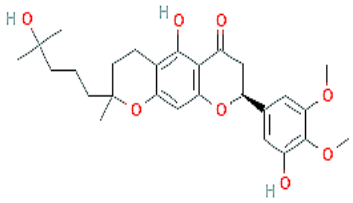
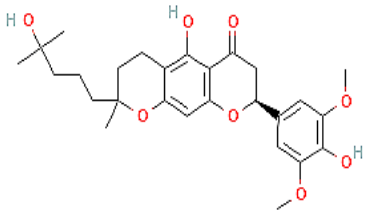
3.3.2 Polyphenols and flavonoid derivatives

A significant family of natural compounds with antiviral properties, polyphenols are particularly effective in preventing virus entrance and infection during the early stages of a virus' life cycle. Plants that contain resveratrol, a stilbenoid, include *Vaccinium macrocarpon*, *Vitis vinifera*, and *Polygonum cuspidatum*. The *Vitis vinifera* fruit, also known as the grape, and even the seeds and leaves of the grapevine are often used in herbal medicine, and the fruits of the grapevine are used as a nutritional supplement. Resveratrol may be found in a variety of various foods. Resveratrol has been demonstrated to provide a number of pharmacological and therapeutic advantages, including cardioprotective, hepatoprotective, anti-inflammatory, neuroprotective, and antibacterial effects (Nassiri-Asl & Hosseinzadeh, 2009). Researchers

have previously shown that the antioxidant resveratrol may limit the production of nitric oxide in tissue, hence decreasing the risk of inflammation. Resveratrol also has antioxidant properties, eliminating free radicals from the body and so reducing the growth of tumors as well as the onset of age-related diseases. *In vitro* research has revealed, resveratrol dramatically reduces MERS-CoV infection as well as replication while also increasing MERS-CoV survival chance. Because of this, resveratrol is an effective anti-MERS agent and has the potential for becoming a viable solution for SARS-CoV-2 infection (Lin et al., 2017). Polyphenols of the diarylheptanoid family have been found in a wide range of plants, including *Alpinia, Zingiber, Curcuma,* and *Alnus*, to name just a few. PLpro was more effectively inhibited by hirsutenone, a diarylheptanoid substance derived from the *Anguilla japonica* plant. Curcumin, a diarylheptanoid produced from the *Curcuma longa* plant, possesses anti-inflammatory, anti-hyperlipidemic, and antibacterial activities, among others. Curcumin has been demonstrated to have an inhibitory effect on PLpro. According to the SAR analysis, α,β-unsaturated carbonyl moiety is crucial because of the antagonistic action of the compound (Park, Jeong, et al., 2012). One of the most well-known polyphenol-rich plants, *Paulownia tomentosa*, has been used in Chinese medicine for a long time to address a variety of ailments. The fruits of this plant have been linked to a reduction in the frequency of asthmatic episodes. Geranylated flavonoids, the plant's principal bioactive ingredient, are also known to have a hypotensive impact. Cytotoxic, anti-inflammatory, and antibacterial properties have been shown in several research on this plant. Twelve PLpro-inhibiting flavonoids were discovered, five of which were novel containing a unique substance 3,4-dihydro-2H-pyran moiety. Tomentin A, B, C, D, and E were the flavonoids' official designations. All of the extracted compounds were confirmed to be capable of inhibiting the enzyme, however these newly discovered substances proved to be the most potent inhibitors (Cho et al., 2013) (Cho et al., 2012).

Table 3: Polyphenols and flavonoid derivatives

Name	**Structure**	**Mechanism of Action**	**Reference**
Resveratrol		Inhibits Replication	(Nassiri-Asl & Hosseinzadeh, 2009) (Lin et al., 2017)
Hirsutenone		Inhibits PLpro	(Park, Jeong, et al., 2012)
Curcumin		Inhibits PLpro	(Park, Jeong, et al., 2012)
Tomentin A		Inhibits PLpro	(Cho et al., 2013)

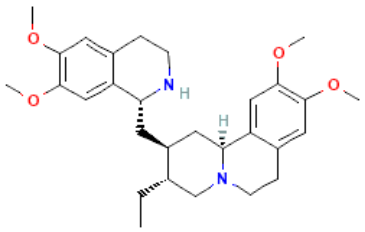
Tomentin B		Inhibits PLpro	(Cho et al., 2013)
Tomentin C		Inhibits PLpro	(Cho et al., 2013)
Tomentin D		Inhibits PLpro	(Cho et al., 2013)

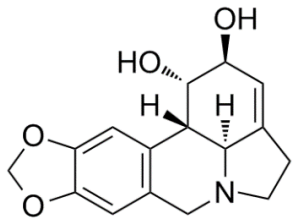
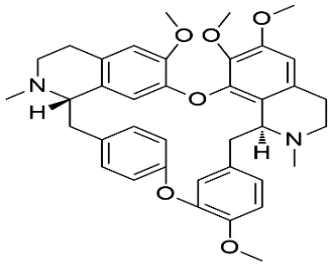
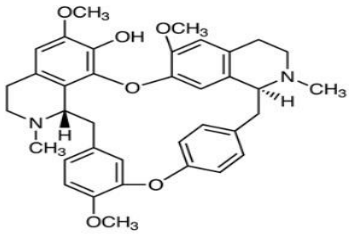
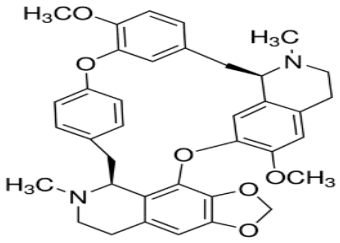
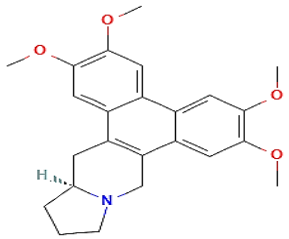
3.3.3 Alkaloid derivatives

Carapichea ipecacuanha roots contain the active agent emetine, it comprises an alkaloid structure having anti-protozoal as well as anti-vomiting activities. Coronaviruses including MERS-CoV, HCoV-OC43, and HCoV-NL63 were all shown to be significantly inhibited by emetine when tested *in vitro*. Emetine potentially has the additional benefit of preventing MERS-CoV from invading host cells. According to the same study, lycorine from the *Lycoris radiata* extract of the Amaryllidaceae family has the potential to limit the reproduction of coronaviruses, including MERS-CoV, HCoV-OC43, and HCoV-NL63. Furthermore, lycorine has been found to reduce viral replication in the neurological system of BALB/c mice and to prevent HCoVOC43-induced death (L. Shen et al., 2019). The bisbenzylisoquinoline alkaloids

discovered in *Stephania tetrandra* root have a diverse set of biological characteristics, particularly antioxidant, anticancer, and anti-inflammatory activity. The major bioactive alkaloids in *S. tetrandra* are tetrandrine, fangchinoline, and cepharanthine, which have shown significant suppressed viral reproduction as well as antiviral efficacy against HCoV-OC43 infections (Kim et al., 2019). In a number of researches, it was discovered that tylophorine was effective. *Tylophora indica* is the source of tylophorine and its analogs, which are alkaloid compounds with a phenanthroindolizidine alkaloid structure. In addition to anti-leukemic and anti-asthmatic properties, phenanthroindolizidines contain anti-inflammatory, anti-anaphylactic, and anti-bacterial properties. The anti-CPE function of tylophorine compounds in Vero 76 cells was studied, and it was observed that the tylophorine compounds had a growth inhibitory effect on the cells' capacity to reproduce (Yang et al., 2010). Additional research revealed tylophorine, may suppress both virus-induced RNA replication and cell-induced JAK2-driven dominant NF-B activation, which seems to be a typical immunological response of host cells in CoV infections. (Yang et al., 2017).

Table 4: Alkaloid derivatives

Name	**Structure**	**Mechanism of Action**	**Reference**
Emetine		Inhibits Replication	(L. Shen et al., 2019)

Lycorine		Inhibits Replication	(L. Shen et al., 2019)
Tetrandrine		Inhibits Replication	(Kim et al., 2019)
Fangchinoline		Inhibits Replication	(Kim et al., 2019)
Cepharanthine		Inhibits Replication	(Kim et al., 2019)
Tylophorine		Inhibits Replication and Inflammation	(Yang et al., 2017)

Chapter 4: Discussion

Plants have been considered as a source of a broad variety of therapeutic substances in traditional medicine for centuries, and this practice persists till today. This ongoing COVID-19 outbreak, that has become a global public health problem from its beginning, is an example of an epidemic or pandemic that has happened because of viruses' propensity to spread swiftly and their role in the majority of acute and chronic respiratory diseases (Abo-Elghiet et al., 2021). In the US and various countries throughout the world, natural products have traditionally been treated respiratory infections. Several of these treatments are currently available as pharmaceuticals, over-the-counter supplements, and dietary supplements in the US as well as other places of the world. When the product's safety qualities are examined as a whole, they are often deemed adequate in terms of overall protection against possible injury. Natural products have the potential to be extremely effective disease prevention strategies in the long run. In the great majority of circumstances, there is no need to be worried about natural product stability in the human digestive system. Natural substances provide less of a risk than conventional preventative measures since they contain a low pH, digestive enzymes, and beneficial microbes in the stomach. Natural products have the particular feature of being exceptionally safe, effective, and long-lasting forms of treatment owing to their natural longevity. Natural products have the potential to be a highly capable strategy in our battle against COVID-19 because of the characteristics stated above.

Chapter 5: Conclusion and Future Prospect

Global public health has been threatened by the COVID-19 pandemic, causing significant worry. The novel coronavirus is prompting researchers throughout the globe to search for a vaccine or treatment. Natural treatments for COVID-19 are being investigated in this study, which builds on prior natural substances shown as being beneficial in SARS treatment and MERS. In a dose-dependent way, Emodin, a natural substance, inhibited both S protein and ACE2 while preventing the virus from attachment. Natural substances have been shown to reduce the activity of particular enzymes that limit viral replication. Natural antiviral drugs against SARS and MERS-CoV and other coronaviruses has been a top focus since the current crisis of coronaviruses. Viruses can be prevented and treated using natural compounds. This approach could be valuable in increasing and financing research initiatives on natural compounds that may prevent and cure COVID-19. Since much current research is theoretical and requires analytical confirmation, there is still much to learn about biochemical applications, extraction, and manufacturing. Natural product research could benefit from more in-depth study.

Natural products have the potential to be a successful preventative and therapeutic for a wide range of ailments, along with viral infection. COVID-19 treatment utilizing natural products could be a means to moving toward research on natural compounds in order to uncover new metabolites to boost immunity. To encourage and promote the use of natural products, additional research could be beneficial, such as SAR analysis of the natural compound; clinical trials of herbal extract; identifying the compound for the appropriate indication; pharmacodynamic and pharmacokinetic properties of the compounds; the efficacy and toxicity of the compound in the establishment of a new possible treatment approach against COVID-19 infection.

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