Approaches Towards Fighting COVID-19 in Taiwan

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Abstract

The coronavirus disease 2019 (COVID-19) outbreak, which has caused millions of confirmed infections and thousands of deaths, has been the most devastating worldwide crises recently. The main clinical symptoms of confirmed COVID-19 cases include fever, dry cough, general fatigue, respiratory symptoms, diarrhoea and sore throat, similar to those of acute respiratory distress syndrome. SARS-CoV-2, the causative agent of COVID-19, belongs to a novel coronavirus strain against which no drug or vaccine currently exists. Therefore, research units around the world have been actively developing efficient diagnostic tools and new drugs. This review summarises the clinical manifestations of COVID-19, analyses the viral genome sequence and life cycle, identifies methods for preventing viral transmission, discusses possible molecular pharmacologic mechanisms and approaches in the development of anti-SARS-CoV-2 virus therapeutic agents and introduces management measures against COVID-19 in Taiwan, especially policies for a name-based mask distribution system. Finally, we summarise traditional Chinese medicines (TCM) for COVID-19. Based on all the information accumulated in this review, development of novel anti-viral agents, vaccines for SARS-CoV-2 therapy or an effective combination therapy can be expected. Finally, we would like to extend our best regards to the frontline health workers in their global fight against COVID-19.

Key words: COVID-19; SARS-CoV-2; clinical manifestations; preventing viral transmission; molecular pharmacologic mechanisms; Taiwan

Abbreviations

ACE2, Angiotensin-converting enzyme 2; ARDS, Acute respiratory distress syndrome; CQ, Chloroquine; CT, Computed tomography; COVID-19, Coronavirus disease 2019; 3CLpro, 3-chymotrypsin-like cysteine protease; cDNA, Complementary DNA; DPP4, Dipeptidyl peptidase 4; FDA, Food and Drug Administration; ExoN, Helicase and exonuclease; HCQ, Hydroxychloroquine; MERS-CoV, Middle East respiratory syndrome coronavirus; NGS, Next generation sequencing platforms; NSPs, Non-structural proteins; ORFs, Open reading frames; PICALM, Phosphatidylinositol binding clathrin assembly protein; RdRp, RNA-dependent RNA polymerase; rRT-PCR, Real-time reverse transcriptase polymerase chain reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; TCDC, Taiwan Centers for Disease Control; TCM, Traditional Chinese medicines; TFDA, Taiwan Food and Drug Administration; TMPRSS2, Transmembrane protease serine 2.

1. INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak has spread worldwide with an overwhelming speed, infecting at least 4,921,252 individuals and causing 322,039 deaths across almost 200 countries as of 20 May 2020 (Wu, Chen & Chan, 2020). COVID-19, caused by SARS-CoV-2 virus, hit China, the US and European countries considerably hard, with the aforementioned countries becoming the epicentres of the SARS-CoV-2 virus pandemic (Liu, Kuo & Shih, 2020). Based on previous experience with SARS, the Taiwanese government had decided to block viral transmission during its early stages. Presently, early blockage of SARS-CoV-2 transmission has been the key point in protecting against COVID-19 (Liu, Kuo & Shih, 2020; Tsay, Kao, Wang & Lin, 2020). Confirmed cases in Taiwan have been lower than those in other countries. Accordingly, the Taiwan Centers for Disease Control (TCDC) (Wu, Chen & Chan, 2020) had reported 440 confirmed cases and seven deaths on 20 May 2020**(Figure 1A)** . Majority of the confirmed cases were indigenous and imported, with a peak age of 20-29 years **(Figure 1B)** .

Strategies aimed at interrupting interactions between the virus and host have been primarily utilised from the viewpoint of public epidemiology (Chang & McAleer, 2020; Hsu et al., 2020). To contain the spread of the virus, several countries have closed accesses to international flights, locked down the entire country or several cities and instructed the public to follow social distancing measures. Moreover, body temperatures are being measured wherever people congregate and social activities have been diminished in hopes of curbing peak prevalence and death (Hsu et al., 2020; Schwartz, King & Yen, 2020; Wu, Chen & Chan, 2020). No therapeutic agents and vaccines have currently been approved by the US Food and Drug Administration (FDA) (2020a) and Taiwan Food and Drug Administration (TFDA) for SARS-CoV-2 virus infections (2020d). As such, the development of novel agents and vaccines against SARS-CoV-2 has been the most researched subject worldwide.

Taiwan, which is only 81 miles away from the coast of China, with whom Taiwan shares intensive commercial intercourse, has been constantly alert and ready to act on potential epidemics arising from China considering the insufferable experiences gained from the severe acute respiratory syndrome epidemic of 2003. Given that most patients shared nonspecific clinical and laboratory findings, comprehensive surveillance of detailed exposure history for suspected patients and application of rapid detection tools are required. Through the combination of border control, rapid testing and quarantine of individuals with contact history, isolation, real-time linking of informative records with the healthcare system and protection of health care worker safety through Traffic Control Bundling, Taiwan had been able to effectively control the COVID-19 epidemic (Wang, Ng & Brook, 2020; Yen, Schwartz, Chen, King, Yang & Hsueh, 2020).

The current review summarises the clinical manifestations, cases, SARS-CoV-2 viral genome structure and sequence, SARS-CoV-2 viral life cycle, diagnosis, preventive methods and management measures of COVID-19, as well as the name-based mask distribution system in Taiwan. Finally, we provide an overview of the possible molecular pharmacologic mechanisms of anti-SARS-CoV-2 agents and the synthesis of remdesivir (GS-5734), chloroquine (CQ) and hydroxychloroquine (HCQ), as well as summarise traditional Chinese medicines (TCM) for COVID-19.

2. CLINICAL CHARACTERISTICS OF COVID-19

According to current literatures, fever, dry cough and fatigue have been the most common symptoms at the onset of COVID-19, with other symptoms including muscle pain, productive cough, headache, diarrhoea, dyspnoea and haemoptysis **(Figure 2)** (Park, 2020). Symptoms generally appear approximately 5.2 days after COVID-19 (Li et al., 2020a). Although up to 50%-75% of patients with COVID-19 remain asymptomatic, approximately 14% present with serious symptoms requiring hospitalisation and oxygen therapy, while 5% require intensive care. The median duration from symptom onset to intensive care unit admission was around 10 days, while the duration between symptom onset and death ranged from approximately 2 to 8 weeks (Chang, Wu & Chang, 2020; Day, 2020; Li et al., 2020a; Zhou et al., 2020a).

Laboratory findings include elevated lactate dehydrogenase and ferritin levels. Moreover, although white blood cell counts can vary, leucopoenia and lymphopenia have been most commonly observed findings. Chest radiography and computed tomography (CT) findings are diverse and nonspecific, commonly presenting as

multiple ground-glass opacity lesions, bilateral patchy shadowing or local patchy shadowing. Severe cases tend to yield more prominent radiologic findings (Wang et al., 2020a). However, a few cases have presented with no imaging abnormality (17.9% of non-severe cases and 2.9% of severe cases) (Park, 2020). As the disease progresses, multiple ground-glass opacity lesions may progress into consolidation or superimposed interlobular/intralobular septal thickening (i.e., crazy-paving pattern), which may expand consolidation (Tu et al., 2020). Several similarities exist between COVID-19 symptoms and those caused by other atypical pathogens. However, COVID-19 exhibits some distinctive clinical characteristics, including targeting of the lower respiratory tract instead of the upper respiratory tract, which produces symptoms like sneezing, rhinorrhoea and sore throat (Assiri et al., 2013). Moreover, chest radiographs and CT scans upon patient admission revealed an infiltrate in the upper lobe of the lung that was associated with increasing dyspnoea with hypoxemia (Phan et al., 2020). Some patients with COVID-19 also developed gastrointestinal distress, such as diarrhoea, whereas only a low percentage of patients with Middle East respiratory syndrome coronavirus (MERS-CoV) or severe acute respiratory syndrome coronavirus (SARS-CoV) experienced the same (Rothan & Byrareddy, 2020). Lastly, most of the patients with COVID-19 exhibited leucopoenia and lymphopenia on admission. Tan et al. demonstrated that patients with blood lymphocyte percentage (LYM%) $> 20\%$ are in the process of recovery. In contrast, those with $5\% < \text{LYM}\% < 20\%$ are still in danger, while those with $\text{LYM}\% < 5\%$ become critically ill with high mortality rate and require intensive care (Tan et al., 2020). Lymphopenia seems to be an effective and reliable indicator of severity and hospitalisation among patients with COVID-19 (Su & Lai, 2020).

Table 1 presents a classification of the clinical manifestations of COVID-19 in Taiwan (Wang, Ng & Brook, 2020). A few case reports in Taiwan have been published online in **Table 2** . The first 11 patients with COVID-19 in Taiwan (3 males and 8 females) received treatment in a single-occupant negative-pressure room. The median duration of symptom onset following COVID-19 confirmation was 4.2 ± 2.9 days. Common symptoms included cough (60%), fever (50%), flu-like symptoms (40%), rhinorrhoea (30%), and infiltrations on chest radiography (30%). Other less common symptoms included muscle ache (10%), sore throat (10%) and shortness of breath (10%) (Cheng et al., 2020a; Cheng et al., 2020b; Huang et al., 2020b; Lee et al., 2020; Liu, Liao, Chang, Chou & Lin, 2020; Su & Lai, 2020).

3. STRUCTURE, GENOME SIZE AND LIFE CYCLE OF SARS-CoV-2

Coronaviruses mainly cause respiratory and gastrointestinal tract infections and are genetically classified into four major genera: Alpha-coronavirus, Beta-coronavirus, Gamma-coronavirus and Delta-coronavirus (Wu et al., 2020a). Six types of human coronaviruses have been previously identified, which include HCoV-NL63 and HCoV-229E belonging to the Alpha-coronavirus genus and HCoV-OC43, HCoV-HKU1, SARS-CoV and MERS-CoV belonging to the Beta-coronavirus genus (Wu et al., 2020a). Coronaviruses had not attracted worldwide attention until the 2003 SARS pandemic, followed by the 2012 MERS and, most recently, COVID-19 outbreaks (Wu et al., 2020a). Both SARS-CoV-2 and MERS-CoV have been considered highly pathogenic (Singhal, 2020). **Figure 3**shows the schematic structure of SARS-CoV-2 (Lee et al., 2020; Rabaan et al., 2020).

SARS-CoV-2 has a genome length of approximately 30 kilobasepairs (kb). Accordingly, SARS-CoV-2 genome sequences from NCBI (Li & De Clercq, 2020; Yen, Schwartz, Chen, King, Yang & Hsueh, 2020), covering between approximately 798 and 29,674 bases, include a variable number of open reading frames (ORFs) (**Figure 4**). The first ORF, representing approximately 67% of the entire genome, encodes two large polyproteins, PP1a and PP1ab, which are proteolytically cleaved into 16 non-structural proteins (NSPs), including papain-like protease, 3-chymotrypsin-like cysteine protease (3CLpro), RNA-dependent RNA polymerase (RdRp), helicase and exonuclease (ExoN). The remaining ORFs encode accessory and structural proteins. The four major structural proteins include the spike surface glycoprotein (S), envelope protein (E), matrix protein (M) and nucleocapsid protein (N) (Adachi, Koma, Doi, Nomaguchi & Adachi, 2020; Boopathi, Poma & Kolandaivel, 2020; Cui, Li & Shi, 2019; Li & De Clercq, 2020). Recent studies have revealed six major non-structural protein subtypes (nsp3, nsp4, nsp6, nsp12, nsp13 and nsp14) for SARS-CoV-2 (Junior, Polveiro, Souza, Bortolin, Sassaki & Lima, 2020). Spike proteins of viruses bind to host

cell receptors for entry. Accordingly, the spike proteins of SARS-CoV-2 and MERS-CoV bind to different host receptors through different receptor-binding domains. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as one of the main receptors with CD209L as an alternative receptor, whereas MERS-CoV uses dipeptidyl peptidase 4 (DPP4, also known as CD26) as its primary receptor (Boopathi, Poma & Kolandaivel, 2020; Chan et al., 2006; Chen, Strych, Hotez & Bottazzi, 2020; Jeffers et al., 2004; Li & De Clercq, 2020; Verdecchia, Cavallini, Spanevello & Angeli, 2020). The cleavage of trimer S protein is initiated by the cell surface-associated transmembrane protease serine 2 (TMPRSS2) and cathepsin (McKee, Sternberg, Stange, Laufer & Naujokat, 2020; Stahlmann & Lode, 2020).

The life cycle of SARS-CoV-2 can be categorised into nine major steps (**Figure 5**). Upon binding to ACE2 and TMPRSS2, SARS-CoV-2 enters host target cells through either fusion or endocytosis (step 1). In the endocytic pathway, the SARS-CoV-2 envelope fuses with the endosome membrane in the lysosomal acid environment, which promotes viral RNA genome release into the host cell cytoplasm (step 2). ORF1a/b encoding 3CLpro is then translated for the replication of genomic RNA (step 3). Thereafter, replicase polypeptide is cleaved (proteolysis), producing NSPs, such as RNA-dependent RNA polymerase (RdRp) and helicase (step 4). SARS-CoV-2 then undergoes viral RNA replication in the host cells (step 5). The viral sub-genome is transcribed (step 6). Viral nucleocapsid (N), membrane (M), envelope (E) and spike (S) are translated through the endoplasmic reticulum and Golgi apparatus (step 7). N protein and other structural proteins interact with viral genomic RNA to pack and form a novel virion (step 8). The assembled virion is then released via exocytosis into the extracellular compartment (step 9). The released viral particle is infectious and may begin a new life cycle (**Figure 5**) (Kupferschmidt & Cohen, 2020; Li et al., 2020a).

4. DIAGNOSTIC METHODS FOR COVID-19 IN TAIWAN

Two approaches have generally been utilised for the diagnostic screening of SARS-CoV-2: (1) real-time reverse transcriptase polymerase chain reaction (rRT-PCR) and (2) rapid screening (Yan et al., 2020; Yip et al., 2020). Detection time and duration until COVID-19 diagnosis are detailed in **Table 3** .

4.1 REAL-TIME REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION TESTING

The rRT-PCR assay utilises viral RNA extracted from patient samples (e.g., material collected through nasopharyngeal and oropharyngeal swabs), synthesises complementary DNA (cDNA) through the action of the reverse transcriptase enzyme, and amplifies target sequences of the viral genome from the cDNA template. RT-PCR can be interpreted semi-quantitatively, with the target amplification speed dependent on the concentration and quality of the viral RNA in the initial sample, thereby allowing the amplification rate to be used as a proxy for the sample viral load (Yan et al., 2020). The three target screening assays include E (envelope) gene assay, RdRp gene assay and N (nucleocapsid) gene assay **(Figure 6)** (Rahman et al., 2020). For a routine workflow, the TCDC recommends the E gene assay as the first-line screening tool, followed by confirmatory testing with the RdRp gene assay. Utilising the RdRp gene assay with dual colour technology can discriminate between SARS-CoV-2 (both probes positive) and SARS-CoV RNA provided that the latter is used as a positive control. Alternatively, laboratories may choose to run the RdRp assay with only the SARS-CoV-2-specific probe. Despite also performing well, the N gene assay had not been subjected to further intensive validation given its slightly inferior sensitivity (Lee et al., 2020; Pujadas et al., 2020).

4.2 RAPID SCREENING

Five antibody-based tests have been used for detecting the presence of IgG and IgM in body fluids, such as whole blood, serum or plasma. The BioMedomics rapid test and Surescreen rapid test cassette utilise lateral flow immunoassays, which are diagnostic devices used to examine antibodies (Li et al., 2020a; Montesinos et al., 2020; Thabet et al., 2020; Vasarhelyi, Kristof, Ostorhazi, Szabo, Prohaszka & Merkely, 2020). Moreover, Goldsite diagnostics had designed a time-resolved fluorescence immunoassay kit, while the Assay Genie rapid POC kit and VivaDiag COVID-19 IgG-IgM test are colloidal gold-based immunoassays for detecting viral infection (Yan et al., 2020). To conduct the assay, a few drops of blood obtained from the general public

using a finger-stick or vein are applied onto the immunoassay. A few drops of buffer solution are then added onto the assay, after which the results will be within 10-15 min at room temperature. RT-PCR testing is used as the reference standard to which immunoassays compared. Among the five rapid screening tests, the BioMedomics IgM-IgG rapid test has been widely used for detecting antibody production in the human body (Huang et al., 2020a).**Table 4** summaries the current diagnostic methods for COVID-19 in Taiwan.

5. POSSIBLE METHODS FOR PREVENTING COVID-19 IN TAIWAN

SARS-CoV-2 possesses several properties, such as transmission from asymptomatic individuals and nonspecific features of COVID-19, and utilises the ACE2 and TMPRSS2 receptors for attachment and transmission (Lange et al., 2020; Pujadas et al., 2020). Both ACE2 and TMPRSS2 proteins are expressed in less than 10% of human respiratory and gastrointestinal tract cells, including nasal goblet secretory cells, lung type II pneumocytes, ileal absorptive enterocytes (Wong, Lui & Sung, 2020; Zhou et al., 2020b; Ziegler et al., 2020). At present, prevention of viral entry into the human body has been the best option for controlling viral spread. The TCDC has established technical guidelines for COVID-19 available at website (Day, 2020). The following are crucial steps for preventing viral spread:

1. **Stay at home:** the general public should avoid travelling to affected countries and regions, as well as contact with animals dead or alive. The general public should make a habit of applying alcohol-based hand sanitisers after entering the rooms.
2. **Maintain decontamination:** Rooms should undergo regular decontamination preferably with 5% to 10% Sodium hypochlorite.
3. **Keep a safe social distance:** the general public must avoid public gatherings. Individuals should preferably maintain a distance of at least 1.5 m (5 ft) between themselves and anyone who is coughing or sneezing indoors. Individuals may maintain a distance of at least 1 m (3 ft) distance between themselves and anyone outdoors.
4. **Maintain clean hands:** Individuals are advised to practice proper hygiene, such as frequent handwashing with soap after sneezing or coughing. Avoid touching any secretions, such as stool or urine. In addition, individuals should refrain from touching their eyes, nose and mouth with unclean hands.
5. **Wear face masks:** Healthcare personnel must use personal protective equipment, such as medical masks (including surgical face masks and N95s), eye protection, gloves, gowns and protective gear. The general public must wear a face mask to help prevent viral transmission. Given the supply shortages, each country has their own recommendations regarding wearing of face masks.

The Taiwanese government has developed guidelines to protect the health and safety of the public from the global novel coronavirus outbreak.**Figure 7** details the processing of the name-based mask distribution system in Taiwan (Lai, Wang, Wang, Hsueh, Ko & Hsueh, 2020). While medical and surgical masks should be prioritised for health care workers, the general public can wear cloth face masks made from household items, such as two layers of cotton fabric, T-shirts or bedsheets.

Medical masks can reduce the transmission of respiratory droplets to others and prevent blood or other potentially infectious materials from reaching the wearer's skin, mouth or mucous membranes. Masks function by filtering 5-μm particles from the air reaching the mouth/nose.**Figure 8 and Table 5** summarise the medical mask materials and associated principles (Bartoszko, Farooqi, Alhazzani & Loeb, 2020; Hirschmann, Hart, Henckel, Sadoghi, Seil & Mouton, 2020; Long et al., 2020; Ma, Shan, Zhang, Li, Yang & Chen, 2020; Saadat, Rawtani & Hussain, 2020). In addition, the structure and composition of the different virus families occur affect their reaction to disinfectants. Components, such as 75% Ethanol (Brewer & Streel, 2020; Henwood, 2020; Zhao, Liu, Liu, Li & Zhang, 2020; Ziegler et al., 2020), Sodium hypochlorite (1000 ppm (0.1%) ˜ 10,000 ppm (1%)) (Henwood, 2020; Kampf, Todt, Pfaender & Steinmann, 2020; Ma, Shan, Zhang, Li, Yang & Chen, 2020), Hypochlorous acid (10 ppm ˜ 30 ppm) (Chen, Zhang, Wang, Zhu & Liu, 2006; Henwood, 2020; Kampf, Todt, Pfaender & Steinmann, 2020; Ma, Shan, Zhang, Li, Yang & Chen, 2020), Chlorine dioxide (Chen, Zhang, Wang, Zhu & Liu, 2006), Soap (Jones, Walsh, Willcox, Morgan & Nichols, 2020; Ma, Shan, Zhang, Li, Yang & Chen, 2020) and Hydrogen peroxide (0.5%) (Caruso, Del Prete, Lazzarino, Capaldi & Grumetto, 2020; Cheng, Wong, Kwan, Hui & Yuen, 2020; Torres et al., 2020) and others (Schrank,

Minbiole & Wuest, 2020; Verbeek et al., 2020) have been used to kill bacteria and viruses. **Table 5** lists the chemical formula and preparation concentration of the disinfectants, as well as associated principles.

6. CURRENT THERAPEUTIC MODALITIES FOR COVID-19 IN TAIWAN

Given the lack of clinical evidence supporting the efficacy of any existing anti-viral agent or vaccine against COVID-19, supportive treatments for clinical conditions in the early stages is imperative. Taiwanese guidelines propose the immediately provision of supplemental oxygen therapy to patients with respiratory distress, hypoxemia or shock. In addition, conservative fluid management should be employed among patients with COVID-19 when no evidence of shock is present. Details and targets of supportive treatments for clinical conditions in Taiwan are presented in **Table 6** (Wang, Ng & Brook, 2020).

Several ongoing clinical trials have evaluated the following direct treatments for SARS-CoV-2: chloroquine (Aralan®), hydroxychloroquine (Plaquenil®), arbidol (Umifenovir®), camostat mesylate (Foipan®), remdesivir (GS-5734), favipiravir (Avigan®), ribavirin (Rebetol®), lopinavir/ritonavir (Kaletra®) and interferon-α, interferon-β (Kupferschmidt & Cohen, 2020). The chemical structures of hydroxychloroquine (Plaquenil®), chloroquine (Aralan®), remdesivir (GS-5734), favipiravir (Avigan®), ribavirin (Rebetol®), lopinavir/ritonavir (Kaletra®), and camostat mesylate (Foipan®) are presented in **Figure 9** . Accordingly, the Taiwanese guidelines indicate that early 7-day treatment with hydroxychloroquine (Plaquenil®) may be considered after doctors' evaluation and informed consent.**Table 7** details the dosages of hydroxychloroquine (Plaquenil®) and special considerations, including adverse effects (retinopathy and QT prolongation) (Wang, Ng & Brook, 2020). Currently, three clinical trials on COVID-19 are ongoing in Taiwan (NCT 04292899, NCT 04292730 and NCT 03808922), with remdesivir as the primary anti-COVID-19 agent being focused in **Table 8** (Tu et al., 2020). **Table 9** and**Figure 10** subsequently summarise ongoing therapeutic agents against COVID-19 and their molecular pharmacologic mechanisms.

Suitable therapeutic agents against SARS-CoV2 carry the following actions:

(1) Block coronavirus-host interactions and attachments: Camostat mesylate (Foipan®) (Huang, Song, Huang & Sun, 2020; Rahman, Basharat, Yousuf, Castaldo, Rastrelli & Khan, 2020) and arbidol (Umifenovir®) (Vankadari, 2020; Zhu et al., 2020).

(2) Trigger lysosomal activation and disrupting intracellular trafficking: Hydroxychloroquine (Plaquenil®) and chloroquine (Aralan®) (Li et al., 2020a; Pastick et al., 2020; Piszczatoski & Powell, 2020; Shukla, Archibald, Shukla, Mehta & Cherabuddi, 2020) .

(3) Inhibit RNA-dependent RNA polymerase: Remdesivir (GS-5734), favipiravir (Avigan®) (Ahsan, Javed, Bratty, Alhazmi & Najmi, 2020; Amawi, Abu Deiab, AA, Dua & Tambuwala, 2020; Du & Chen, 2020; McKee, Sternberg, Stange, Laufer & Naujokat, 2020; Wu et al., 2020b).

(4) Interfere with RNA metabolism required for viral replication: Ribavirin (Rebetol®) (Chan, Wong & Tang, 2020; Jean, Lee & Hsueh, 2020; Martinez, 2020).

(5) Inhibit 3CLpro: Lopinavir/Ritonavir (Kaletra®); (Ahsan, Javed, Bratty, Alhazmi & Najmi, 2020; Martinez, 2020; Simsek Yavuz & Unal, 2020).

(6) Functioning as immunotherapeutic agents: Type 1 interferon, IFN-α, pegylated interferon α-2a and α-2b and interferon-β (Ahsan, Javed, Bratty, Alhazmi & Najmi, 2020; Chan, Wong & Tang, 2020; Martinez, 2020; Sallard, Lescure, Yazdanpanah, Mentre & Peiffer-Smadja, 2020).

6.1 BLOCKING CORONAVIRUS–HOST INTERACTIONS AND ATTACHMENTS: CAMOSTAT MESYLATE (FOIPAN®) AND ARBIDOL (UMIFENOVIR®)

Camostat mesylate (Foipan®) is a serine protease inhibitor that inhibits TMPRSS2 and blocks virus entry into lung cells (Rahman, Basharat, Yousuf, Castaldo, Rastrelli & Khan, 2020). *In vitro* studies have shown that camostat mesylate (Foipan®) inhibits TMPRSS2 and blocks SARS-CoV and human coronavirus NL63 infection of HeLa cells (Huang, Song, Huang & Sun, 2020; Rahman, Basharat, Yousuf, Castaldo, Rastrelli

& Khan, 2020). Hoffmann et al. demonstrated that SARS-CoV-2 exploits ACE-2 for entry and serine protease TMPRSS2 for S protein priming (Hoffmann, Kleine-Weber & Pohlmann, 2020; Hoffmann et al., 2020; Hoffmann, Schroeder, Kleine-Weber, Muller, Drosten & Pohlmann, 2020). Moreover, reports have shown that camostat mesylate (Foipan®) blocks SARS-CoV-2 infection of Calu-3 lung cells *in vitro* (Huang, Song, Huang & Sun, 2020). Accordingly, four clinical trials on camostat mesylate for COVID-19 are currently ongoing worldwide (NCT 04353284, NCT 04321096, NCT 04338906 and NCT 04355052) (Tu et al., 2020).

Arbidol (Umifenovir®) is a small indole-derivative agent used for the treatment of respiratory viral infections (Amawi, Abu Deiab, AA, Dua & Tambuwala, 2020; Deng et al., 2020; Vankadari, 2020; Zhu et al., 2020).*In vitro* and *in vivo* studies have demonstrated that arbidol inhibits a number of enveloped or non-enveloped RNA or DNA viruses, including influenza viruses A, B, C, SARS-CoV, adenovirus, poliovirus, rhinovirus, coxsackievirus, Hantaan virus, Chikungunya virus and Hepatitis B and C viruses (Deng et al., 2020; Dong, Hu & Gao, 2020; Wang et al., 2020b). Arbidol (Umifenovir®) interacts with aromatic residues within the viral hemagglutinin glycoprotein and inhibits viral entry (Hulseberg et al., 2019; Kadam & Wilson, 2017; Zeng, Yang & Liu, 2017). A total of eight clinical trials on arbidol for COVID-19 have been ongoing worldwide (NCT 04350684, NCT 04286503, NCT 04260594, NCT 04323345, NCT 04273763, NCT 04306497, NCT 04261907 and NCT 04333589) (Tu et al., 2020).

6.2 TRIGGERING LYSOSOMAL ACTIVATION AND DISRUPTING INTRACELLULAR TRAFFICKING: CHLOROQUINE (ARALAN®) AND HYDROXYCHLOROQUINE (PLAQUENIL®)

Chloroquine (Aralan®), a well-known anti-malarial and anti-autoimmune agent, has long been used to treat malaria and autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis. Hydroxychloroquine (Plaquenil®) is synthesised by introducing a hydroxyl group into chloroquine. Animal studies had demonstrated that hydroxychloroquine (Plaquenil®) was much less toxic than chloroquine (Li et al., 2020a; Pastick et al., 2020; Piszczatoski & Powell, 2020; Shukla, Archibald, Shukla, Mehta & Cherabuddi, 2020).

Reports have shown that chloroquine and hydroxychloroquine increase endosomal and lysosomal pH (alkalinises vacuolar pH) and then disrupt intracellular trafficking (Annangi, 2020; Badyal & Mahajan, 2020; Colson, Rolain, Lagier, Brouqui & Raoult, 2020; Ferner & Aronson, 2020; Sturrock & Chevassut, 2020). Recent studies have demonstrated that chloroquine reduces the expression of phosphatidylinositol binding clathrin assembly protein (PICALM), a cargo-selecting clathrin adaptor that senses and drives membrane curvature, which regulates endocytosis (Dong, Hu & Gao, 2020). *In vitro* studies have demonstrated that chloroquine significantly inhibits SARS-CoV-2 from infecting Vero E6 cells. One of the mechanisms for the chloroquine-mediated effects against SARS-CoV-2 is the decrease in the ability of cells to perform clathrin-mediated endocytosis of nanosized structures due to PICALM suppression (Dong, Hu & Gao, 2020).

Clinical investigations have shown that patients with COVID-19 had high concentrations of cytokines, such as IL-1β, IL-1β, IL-2, IL-6, IFNs and MCP-1 (Lagunas-Rangel & Chavez-Valencia, 2020; McGonagle, Sharif, O'Regan & Bridgewood, 2020; Ren et al., 2020), in their plasma, subsequently causing a cytokine storm. In addition, hydroxychloroquine has been demonstrated to exhibit anti-inflammatory activity and can significantly decrease the IL-1, IL-6, TNFα and TNF production through Toll-like receptor (TLR)/NF-ϰB signalling (Aizawa, Imaizumi, Hirono, Watanabe, Tsugawa & Tanaka, 2019; Clancy, Markham, Reed, Blumenberg, Halushka & Buyon, 2016).

The molecular pharmacologic mechanisms of chloroquine and hydroxychloroquine are summarised in **Figure 11** . A total of 52 clinical trials on chloroquine and 150 clinical trials on hydroxychloroquine for the treatment of COVID-*19* have been ongoing (Tu et al., 2020). *Given that* chloroquine and hydroxychloroquine are longstanding therapeutic agents widely used for disease treatment in hospitals, several ongoing clinical trials on COVID-19 have focused on both.

6.3 INHIBITING RNA-DEPENDENT RNA POLYMERASE: REMDESIVIR (GS-5734) AND FAVIPIRAVIR (AVIGAN®)

Remdesivir (GS-5734), a phosphoramidate prodrug of an adenine-derivative agent, was originally developed by Gilead Sciences (Gilead Sciences Inc., Foster City, CA, USA) (patent holder) for the Ebola virus (Augustin, Hallek & Nitschmann, 2020; Cao, Deng & Dai, 2020; Li, Wang, Cao, Sun, Li & Li, 2020; Reina, 2020). Meanwhile, favipiravir (Avigan®), a guanine-derivative agent, has been approved for influenza A infection among patients resistant to Tamiflu and Relenza treatment in Taiwan (Jean, Lee & Hsueh, 2020; Li et al., 2020a; Lu, Chen & Chang, 2020). Remdesivir and favipiravir are incorporated into nascent viral RNA and inhibit the RNA-dependent RNA polymerase (RdRp) (Jean, Lee & Hsueh, 2020; Lu, Chen & Chang, 2020). This results in the premature termination of the viral RNA chain and consequently halts the replication of the viral genome. Recent *in vitro* studies have reported that remdesivir and favipiravir possess bioactivities against SARS-CoV-2 (Choy et al., 2020; Jean, Lee & Hsueh, 2020; Simsek Yavuz & Unal, 2020). Our preliminary studies using Discovery Studio 2020 (DS 2020) software revealed that remdesivir and favipiravir had a strong binding ability to RNA-dependent RNA polymerase (RdRp) **(Figure 12 and Supplementary Table 1).** A total of 19 clinical trials on remdesivir and 12 clinical trials on favipiravir for the treatment of COVID-*19* are ongoing (Tu et al., 2020). On April, 29, 2020, *a* National Institutes of Health clinical trial reported remdesivir accelerates recovery from COVID-19. On May, 1, 2020, the US FDA issued an emergency authorisation for the use of investigational remdesivir in the treatment of suspected or laboratory-confirmed COVID-19 among adults and children hospitalised with severe disease (Zhou et al., 2020a). This is positive and exciting news for the treatment of COVID-19.

6.4 INTERFERING WITH RNA METABOLISM REQUIRED FOR VIRAL REPLICATION: RIBAVIRIN (REBETOL®)

Ribavirin, a guanosine-derivative agent, had been approved for the treatment of Hepatitis C virus infection. Recent studies have demonstrated that ribavirin can be used to treat respiratory syncytial virus and SARS-CoV by inhibiting viral RNA synthesis, viral mRNA capping and RNA-dependent RNA polymerase (Elfiky, 2020a; Elfiky, 2020b; Guzik et al., 2020; Jean, Lee & Hsueh, 2020). Five clinical trials on ribavirin for the treatment of COVID-19 have been ongoing worldwide (Tu et al., 2020).

6.5 INHIBITING 3-CHYMOTRYPSIN-LIKE CYSTEINE PROTEASE (3CLPRO): LOPINAVIR/RITONAVIR (KALETRA®)

Lopinavir and ritonavir have been widely used for treating HIV infection. However, early studies have demonstrated that lopinavir and ritonavir are active against SARS-CoV and MERS by inhibiting 3CLpro via proteolysis in SARS-CoV (Costanzo, De Giglio & Roviello, 2020; Deng et al., 2020; Ye et al., 2020). However, Cheng et al. demonstrated that Kaletra® did not shorten the duration of SARS-CoV-2 infection among patients with mild pneumonia in Taiwan (Cheng et al., 2020a). Our preliminary studies using Discovery Studio 2020 (DS 2020) software showed that lopinavir and ritonavir had strong binding ability to 3CLpro**(Figure 13 and Supplementary Table 1).** A total of 45 clinical trials on Kaletra® for the treatment of COVID-19 have been ongoing worldwide (Tu et al., 2020).

6.6 ΦΥΝΌΤΙΟΝΙΝΓ ΑΣ ΙΜΜΥΝΟΤΗΕΡΑΠΕΥΤΙΌ ΑΓΕΝΤΣ: ΤΨΠΕ 1 ΙΝΤΕΡΦΕΡΟΝ, ΙΦΝ-α, ΠΕΓΨΛΑΤΕΔ ΙΝΤΕΡΦΕΡΟΝ α-2Α ανδ α-2Β ΑΝΔ ΙΝΤΕΡΦΕΡΟΝ-β

During viral infection, type I interferon synthesis is initially induced, which subsequently activates both innate and adaptive immune response against the virus. The type I interferon family consists IFN-α, IFN-β and other subtypes (Andreakos & Tsiodras, 2020; Du et al., 2020; Sallard, Lescure, Yazdanpanah, Mentre & Peiffer-Smadja, 2020). When the virus infects target cells, RNA sensors induces interferon regulatory transcription factor translocation into the nucleus, which promotes type I interferon secretion. The secreted interferon interacts with interferon receptors on the cell membrane, which promotes phosphorylation of STAT1/2 transcriptional factors (Nelemans & Kikkert, 2019; Vidal, 2020). The phosphorylation of STAT1/2 re-localises to the nucleus, binds to interferon-stimulated response element responsible for activating interferon-stimulated genes, which then produces more type I interferon. Upon type I interferon secretion, type I interferon-mediated innate immunity is triggered. Natural killer cells then become active and destroy infected cells. Type I interferon binds to the interferon receptors on cytotoxic T cells ($CD8^+$ T

cells), subsequently killing infected cells through cellular immunity (Langevin, Aleksejeva, Passoni, Palha, Levraud & Boudinot, 2013). In addition, type I interferon stimulates B cells and induces neutralising antibody production, which plays a protective role by limiting later-phase infections and preventing future re-infections (Nelemans & Kikkert, 2019). Treatment with IFN-α2b significantly reduced the duration of SARS-CoV-2 in the upper respiratory tract and reduced inflammatory cytokine IL-6 and CRP in COVID-19 patients (Zhou et al., 2020c).

Cells infected with SARS-CoV and MERS-CoV exhibited reduced type I interferon. As such, it can be speculated that SARS-CoV-2 utilises a similar manner for type I interferon reduction. Previous studies have reported that type I interferon treatments improved anti-SARS-CoV and anti-MERS-CoV activity among infected mice and had synergistic effects with ribavirin against SARS-CoV in vitro (Morgenstern, Michaelis, Baer, Doerr & Cinatl, 2005). Immunocompromised patients are at higher risk for severe COVID-19 than the general public. Type I interferon treatments can thus be a safe and efficient approached against SARS-CoV-2 infection (Mantlo, Bukreyeva, Maruyama, Paessler & Huang, 2020; Sallard, Lescure, Yazdanpanah, Mentre & Peiffer-Smadja, 2020). A total of 37 clinical trials on interferon for COVID-19 have been ongoing worldwide (Tu et al., 2020). **Figure 14** presents a schematic overview of the type I interferon-mediated immune response mechanism following SARS-CoV, MERS-CoV and SARS-CoV-2 infection.

7. SYNTHESIS OF REMDESIVIR, CHLOROQUINE AND HYDROXYCHLOROQUINE

Remdesivir (Compound **12)** was synthesised by Siegel et al. as illustrated in **Scheme 1 (Figure 15)** (Siegel et al., 2017)**.** The iodo-based compound **1** was reacted with Turbo Grignard reagents via metal–halogen exchange, followed by the addition of ribolactone **2** to afford the glycosylation product**3** . Treatment of **3** with TMSCN, TMSOTf and TfOH at -78 afforded **4** , which yielded benzyl deprotection product**5** after reacting with BCl_3. Acetonide protection of the 2',3'-hydroxyl moieties with 2,2-dimethoxypropane in the presence of H_2SO_4 afforded**6** . 2-Ethyl-1-butanol **7** and L-alanine **8** were treated with $HCl_{(g)}$ to generate ester product**9** , which was reacted with $OP(OPh)Cl_2$ under base conditions, followed by 4-nitrophenol to obtain the*p* -nitrophenolate 2-ethylbutyl-L-alaninate prodrug precursor**10** . The coupling reaction between **6** and **10**under $MgCl_2$ generated **11** , after which in situ acetonide deprotection was performed through concentrated HCl to afford target molecule remdesivir (Compound **12)** .

As shown in **Figure 16** , chloroquine (Compound **25)** was synthesised by Drake N. L. et al. and Price Ch. C. et al. as described in **Scheme 2** (Drake, Creech & et al., 1946; Price & Roberts, 1946)**.** Accordingly, 4,7-Dichloroquinoline **19** was prepared from 3-chloroaniline **13** via 1,4-addition with ethoxymethylenmalonic acid **14** , thermal heterocyclisation, hydrolysis, decarboxylation and $POCl_3$ chlorination. Novaldiamine **24** was synthesised following three steps. Acetoacetic ester **20** alkylation with 2-diethylaminoethylchloride **21** generated 2-diethylaminoethylacetoacetic acid ester **22** , which yielded 1-diethylamino-4-pentanone **23** upon acidic hydrolysis using hydrochloric acid and simultaneous decarboxylation. Reductive amination of this compound with hydrogen and ammonia using Raney nickel as a catalyst yielded **24** . Nucleophilic aromatic substitution of chlorine at C-4 in **19** with novaldiamine **24** generated the desired molecule chloroquine **25** .

Finally, we provide two methods (pathways) for the synthesis of hydroxychloroquine by Synthia Organic Retrosynthesis Software (Merck, Taiwan) in the **Supplementary document.**

8. TRADITIONAL CHINESE MEDICINES (TCM) TCM AND COVID-19

The clinical practice of TCM in Taiwan has been extraordinarily limited given the few confirmed cases and well-established protocols of modern Western medication for patients with COVID-19 in Taiwan (Wang, Ng & Brook, 2020). Thus, we surveyed the literature regarding the design, efficacy and safety of TCM alone or in conjunction with medical therapies mostly published in China and highlight several of them (in the following sections or in **Table 10**) (Luo et al., 2020a; Luo et al., 2020b; Ma et al., 2020; Ni, Zhou, Zhou, Zhao & Wang, 2020; Qing, Zhang, Bai & Luo, 2020; Ren, Zhang & Wang, 2020; Rosa & Santos, 2020; Ul Qamar, Alqahtani, Alamri & Chen, 2020; Wan et al., 2020; Wang et al., 2020c; Zhang, Zhang, Lv, Sa, Zhang & Lin, 2020). Based on more than 3500 years of Chinese medical practice, TCM has spread to many countries worldwide, has profoundly influenced people's lives and has gradually assimilated with

modern Western medicine and therapy. In recent decades, mounting evidence has suggested that TCM can be helpful in the prevention and treatment of human virus-related disorders, including influenza, liver diseases and acquired immune deficiency syndrome (Chan, Wong & Tang, 2020; McKimm-Breschkin, Jiang, Hui, Beigel, Govorkova & Lee, 2018; Teschke, Larrey, Melchart & Danan, 2016; Zhang, Cong, Zhang, Guo & Li, 2020). For instance, Jinxin oral liquid, modified from Ma Xing Shi Gan Decoction, has been proven to be therapeutically effective and safe in the treatment of viral pneumonia both in clinical and experimental studies (Lin et al., 2016). However, the detailed intracellular mechanisms remain largely unknown. The central dogma for pneumonia TCM therapy includes excreting phlegm, reducing fever, relieving cough and dyspnoea and resolving all disorders (Gray & Belessis, 2020; Ho, Chan, Chung & Leung, 2020; Lin et al., 2016; Zhang, Zhang, Lv, Sa, Zhang & Lin, 2020).

After the COVID-19 outbreak, TCM scheme had been included into the guidelines for the diagnosis and therapy of COVID-19 in China (Chan, Wong & Tang, 2020; Ho, Chan, Chung & Leung, 2020; Hu, Logue & Robinson, 2020). Among all the TCMs examined in clinical practice, the Qing Fei Pai Du Decoction has been reported to be most effective and safety for COVID-19 (Ren, Zhang & Wang, 2020). Specifically, Shuang Huang Lian oral liquid treatment helped patients recover from the infection with few apparent side effects (Ni, Zhou, Zhou, Zhao & Wang, 2020). Ma Xing Shi Gan Decoction, for instance, has been shown to reduce inflammation responses and suppress the cytokine storm, thereby protecting the pulmonary alveolar-capillary barrier, alleviating pulmonary enema and reducing body temperature (Wang et al., 2020c). Lastly, using the prediction system based on molecular interaction simulation and docking score calculation, Ul Qamar and colleagues have proposed that 9 out of 32,297 anti-viral TCMs in the database have the highest affinity with the viral 3-chymotrypsin-like cysteine protease enzyme, which is critical for the proliferation and life cycle of COVID-19 (Ul Qamar, Alqahtani, Alamri & Chen, 2020). Generally, TCMs capable of reducing fever, relieving cough through improved immunity have been candidates for patients suffering from COVID-19. These may include glycyrrhiza, ephedra, bitter almond, gypsum, reed root, amomum and trichosanthes (Luo et al., 2020b). The researches in China has patterned several TCMs, including Reduning injection, Suhuang Zhike capsule and Xue Bi Jing, for the treatment of COVID-19 (Wang, Chen, Lu, Chen & Zhang, 2020).

As shown in **Table 10** , healthy individuals can also take TCMs to prevent COVID-19 by strengthening whole-body immunity (Chan, Wong & Tang, 2020; McKimm-Breschkin, Jiang, Hui, Beigel, Govorkova & Lee, 2018; Teschke, Larrey, Melchart & Danan, 2016; Zhang, Cong, Zhang, Guo & Li, 2020). Chinese doctors have also recommended Buzhong Yiqi Decoction, Yu Ping Feng San, Yin Qiao San and Sang Chu Yin for adjusting endogenous Qi and preventing infection. Moreover, Yin Qiao San may be effective in reducing self- or clinically confirmed fever, with or without a sore throat, and reversing the damage to the respiratory tracts, while Sang Chu Yin is capable of relieving cough and reducing sputum production. The two aforementioned groups belong to the mild stage. According to the TCM theory, the target organ of COVID-19 is the lungs, while the aetiology can be attributed to a 'damp and toxin plague'. The network pharmacology analysis showed that Qing Fei Pai Du Decoction has an overall multi-component and multi-target regulatory effect. In addition, it exerted protective effects for the heart, kidney and other organs. Other TCMs, such as Jin Hua Qing Gan Granule, Lian Hua Qing Wen Capsule, Xue Bi Jing Injection, Hua Shi Bai Du Formula and Xuan Fei Bai Du Granule, have also been used for the treatment of clinically severe/critical disease, during which personalised medication and care is of extreme importance (Luo et al., 2020a; Luo et al., 2020b; Ma et al., 2020; Ni, Zhou, Zhou, Zhao & Wang, 2020; Qing, Zhang, Bai & Luo, 2020; Ren, Zhang & Wang, 2020; Rosa & Santos, 2020; Ul Qamar, Alqahtani, Alamri & Chen, 2020; Wan et al., 2020; Wang et al., 2020c; Zhang, Zhang, Lv, Sa, Zhang & Lin, 2020).

We believe that more convenient methods for the early detection of COVID-19 via genotyping will emerge in the near future. Within a short span of time, suspected individuals could also be detected and identified through several biomarkers, such as those related to their anti-inflammation, anti-oxidant, anti-viral and anti-mutational capacities. After genotyping procedures, each subject could be prescribed appropriate and personalised TCM treatments among those listed in **Figure 17** for the effective prevention of COVID-19 or its progression into severe or critical disease. Overall, TCMs can help reduce the typical COVID-19 progression to mid/moderate and severe/critical disease. Even among severe/critical cases, TCMs can still

serve as a complementary and integrative therapy to modern Western medicine to shorten the recovery period and relieve symptoms among patients with COVID-19.

9. CONCLUDING REMARKS

This review describes several clinical manifestations of COVID-19, analyses the SARS-CoV-2 genome and outlines the life cycle of SARS-CoV-2. Several methods have been used to examine SARS-CoV-2 infections. For example, RT-PCR has been applied for RNA detection, while rapid screening has been used for antibody or virus detection. The Taiwanese government has established several policies for controlling viral spread. Despite the lack of medications for COVID-19, many clinical trials have been proposed for its treatment. In addition, several TCMs have been discussed for the readers' reference.

To avoid direct contact with suspected COVID-19 cases, viral secretions and infected droplets, the following relevant preventive measures should be followed:

(1) Pay attention to and cooperate with the latest epidemic prevention policies issued by the government.

(2) Maintain hand hygiene habits, particularly avoiding touching the eyes, nose and mouth with unclean hands.

(3) Maintain social distancing or wear masks, avoid crowded public places and taking public transportation.

(4) Reduce hospital visits except for urgent medical needs.

(5) Comply with relevant regulations if home quarantined or in isolation.

(6) Stop working or going to school when sick.

(7) Inform your medical providers about your travel history, contact history, occupation and cluster history.

We expect Taiwan to globally interact and cooperate with other countries to develop rapid and accurate screening assays, produce vaccines, design novel agents against SARS-CoV-2 and reduce the side effects of therapeutic TCMs. Ultimately, our long-term goal is to be free from COVID-19.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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Figure legends

Figure 1. Confirmed cases in Taiwan. (A)*Number* of *confirmed cases* of coronavirus (COVID-19) in Taiwan from January to May *2020* . (B) The numbers are divided into several 10-year age groups.

Figure 2. Symptoms of SARS-CoV-2. Symptoms of SARS-CoV-2 include fever, dyspnoea, cough and loss of taste or smell.

Figure 3. The schematic structure of SARS-CoV-2. SARS-CoV-2 encodes four major structural proteins, including the envelope (E) protein, membrane (M) protein, nucleocapsid (N) protein and spike (S) protein.

Figure 4. The genome size of SARS-CoV-2. The *length* of the SARS-CoV-2 *genome* is approximately 30 kb.

Figure 5. The life cycle of SARS-CoV-2. The SARS-CoV-2 life cycle consists of nine major stages: virus entry either via fusion (1A) or via endocytosis (1B), (2) viral RNA release, (3) translation of viral replication machinery protein, (4) proteolysis, (5) RNA replication, (6) sub-genomic transcription, (7) translation of viral structure protein, (8) virion assembly and (9) virion release.

Figure 6. Three candidate diagnostic reverse transcriptase polymerase chain reaction assays for SARS-CoV-2. The relative genome positions of virions are used to assay for SARS-CoV-2. The three target screening assays include the E (envelope) gene assay, RNA-dependent RNA polymerase (RdRp) gene assay and N (nucleocapsid) gene assay.

Figure 7. Policies for controlling mask distribution and mask wearing to prevent viral transmission in Taiwan.

Figure 8. Design of the three-layer non-medical face masks for the protection of the general public against viral infection. The three-layer material is made from pure polypropylene melt-blown polymer (middle layer), placed between two non-woven fabric layers. The outer layer is fluid repellent, while and inner layer absorbs moisture.

Figure 9. Chemical structures of hydroxychloroquine, chloroquine, remdesivir, favipiravir, ribavirin, lopinavir/ritonavir, arbidol and camostat mesylate.

Figure 10. Molecular pharmacologic mechanisms of ongoing therapeutic COVID-19 agents.

Figure 11. Molecular mechanisms of chloroquine and hydroxychloroquine.

Figure 12. Molecular docking of remdesivir and favipiravir binding to the RNA-dependent RNA polymerase (RdRp). (A) The right portion is the structure of remdesivir, while the left portion shows its molecular docking using Discovery Studio 2020. Remdesivir is presented using a stick model. The carbon atoms of remdesivir are coloured green. (B) The right portion shows the structure of favipiravir, while the left portion is its molecular docking using Discovery Studio 2020. Favipiravir is presented using a stick model. The carbon atoms of favipiravir are coloured green.

Figure 13. Molecular docking of ritonavir and lopinavir binding to the 3-chymotrypsin-like cysteine protease (3CLpro). (A) The right portion is the structure of ritonavir, while the left portion shows its molecular docking using Discovery Studio 2020. Ritonavir is presented using a stick model. The carbon atoms of ritonavir are coloured green. (B) The right portion is the structure of lopinavir, while the left portion shows its molecular docking using Discovery Studio 2020. Lopinavir is presented using a stick model. The carbon atoms of lopinavir are coloured green.

Figure 14. Schematic overview of type I interferon-mediated immune response mechanism for SARS-CoV, MERS-CoV and SARS-CoV-2.

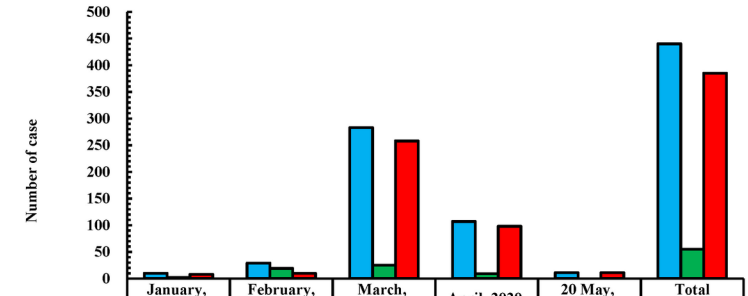
Figure 15. Synthesis of remdesivir.

Figure 16. Synthesis of chloroquine (CQ).

Figure 17. Traditional Chinese medicine (TCM)-based treatment for patients with distinct clinical manifestations.

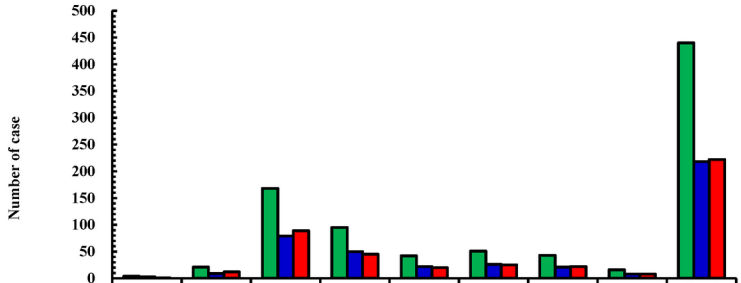
Figure 1

A.



	January, 2020	February, 2020	March, 2020	April, 2020	20 May, 2020	Total number
Confirmed case	10	29	283	107	11	440
Indigenous	2	19	25	9	0	55
Imported	8	10	258	98	11	385

B.



	<9	10-19	20-29	30-39	40-49	50-59	60-69	>70	Total number
Total	4	21	168	95	42	51	43	16	440
Male	3	9	79	50	22	26	21	8	218
Female	1	12	89	45	20	25	22	8	222

Figure 2

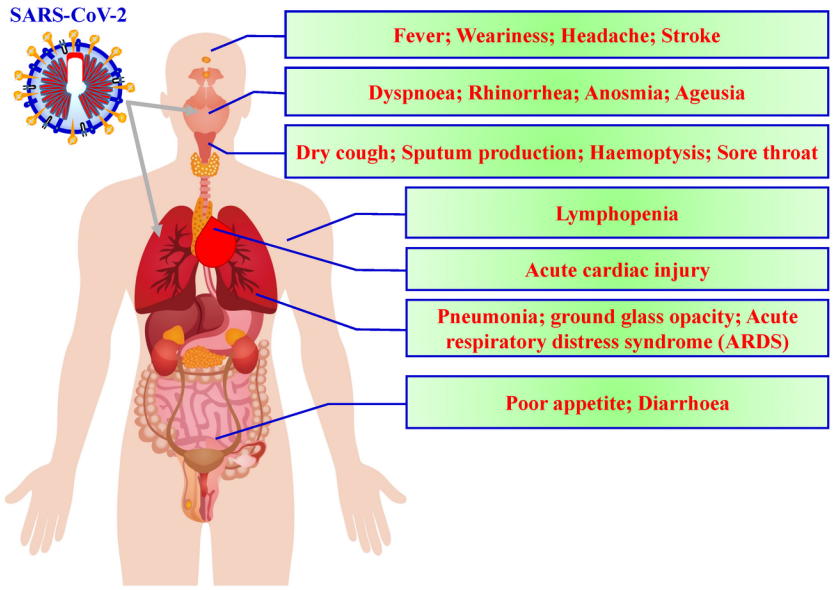


Figure 3

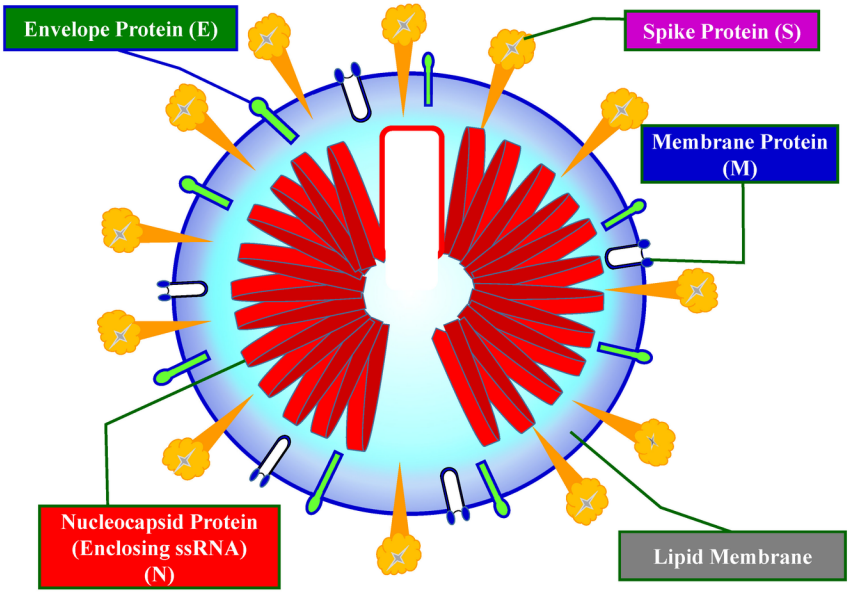


Figure 4

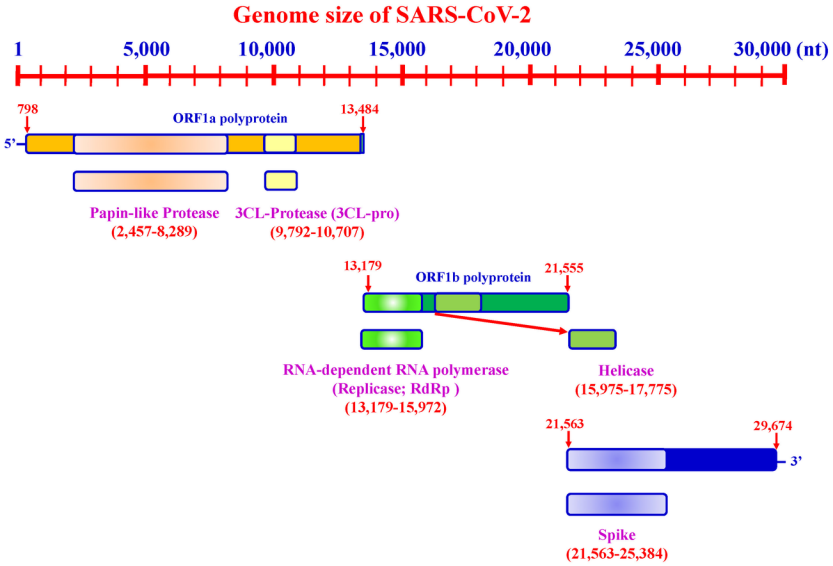


Figure 5

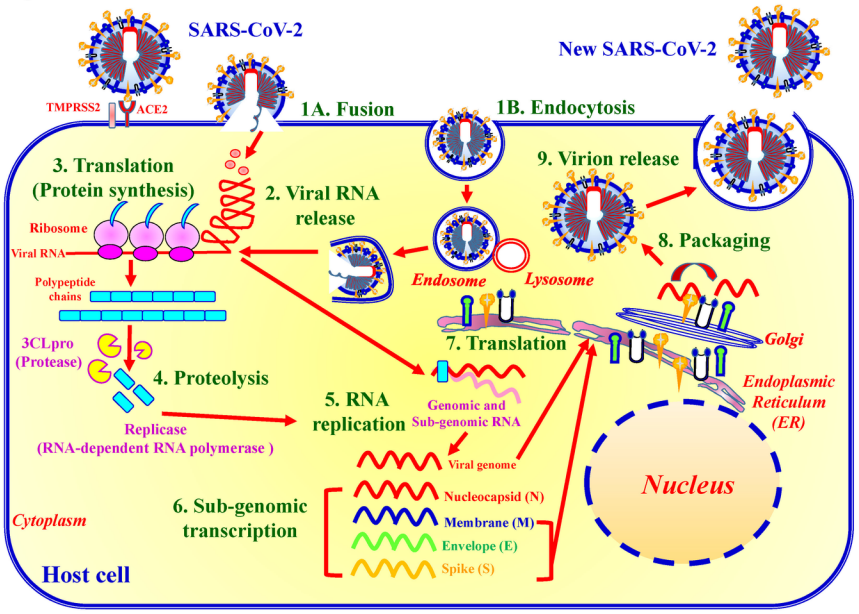


Figure 6

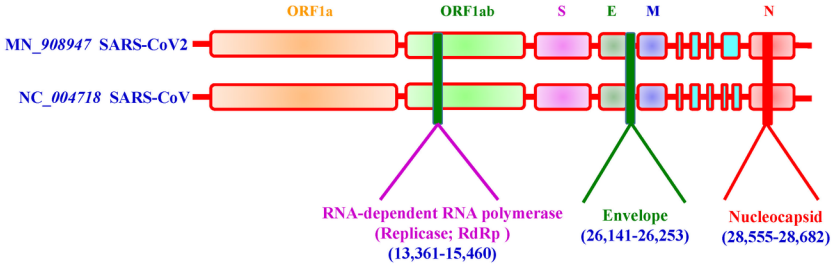


Figure 7

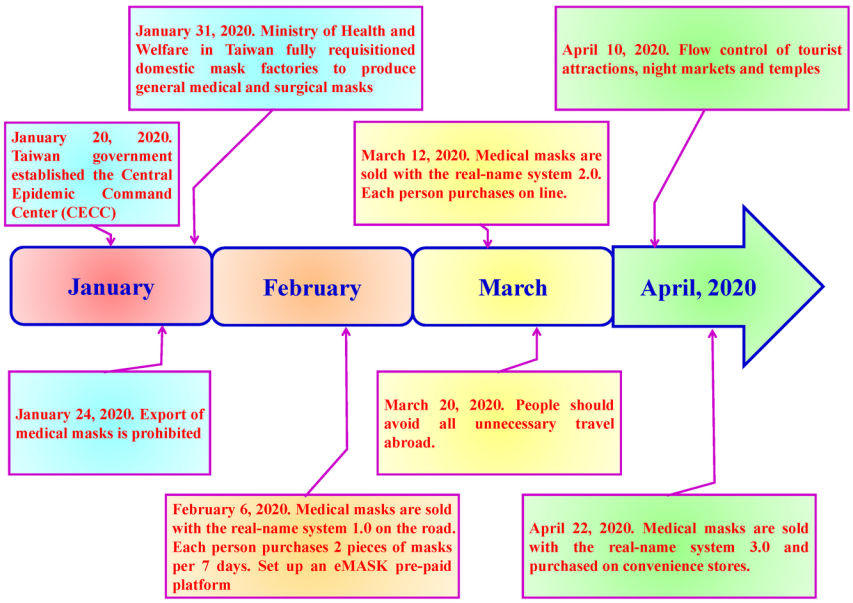


Figure 8

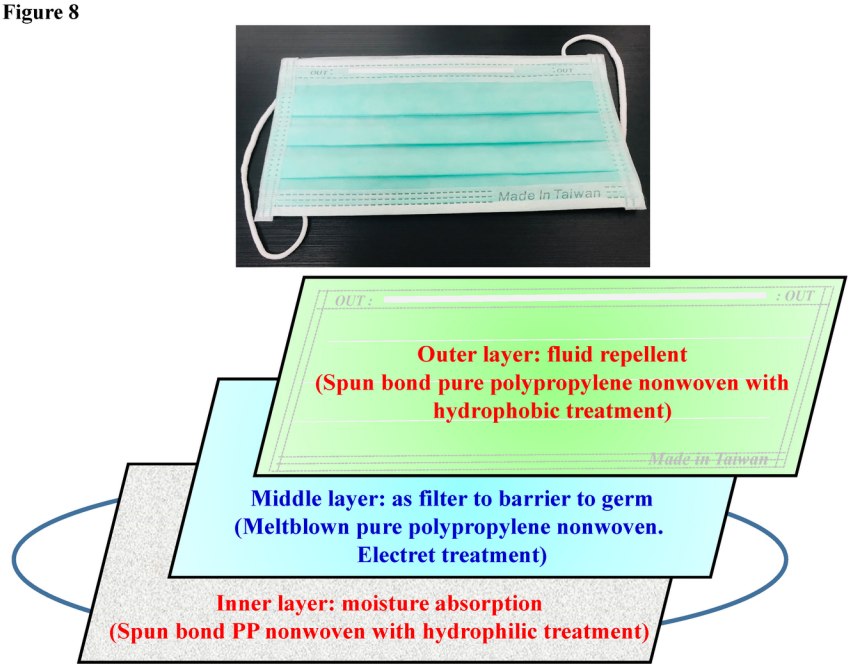


Figure 9

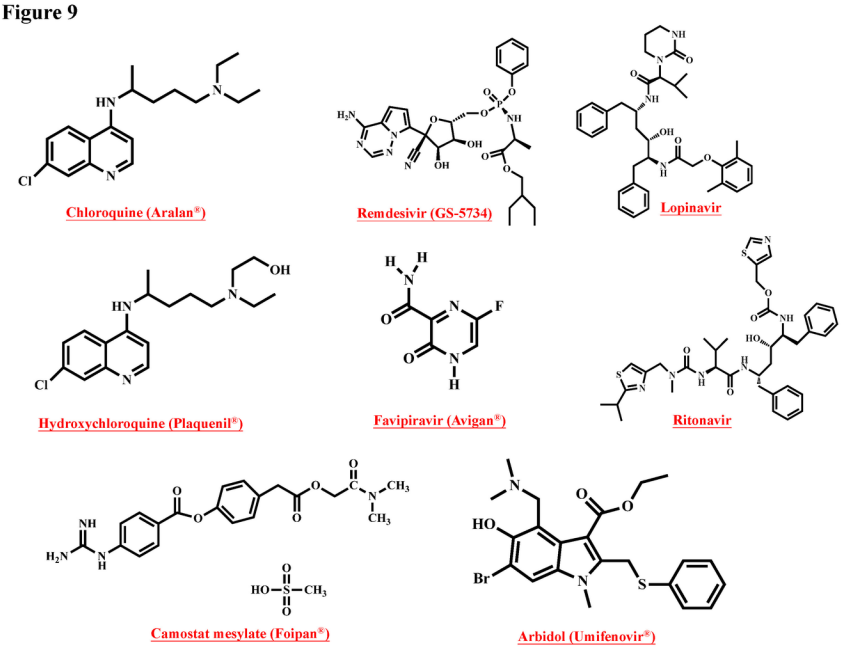


Figure 10

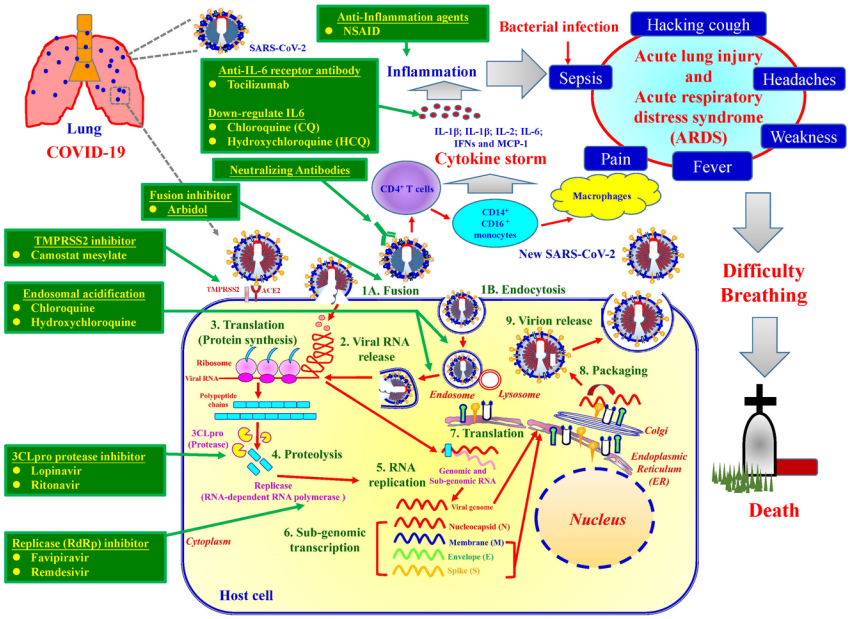


Figure 11

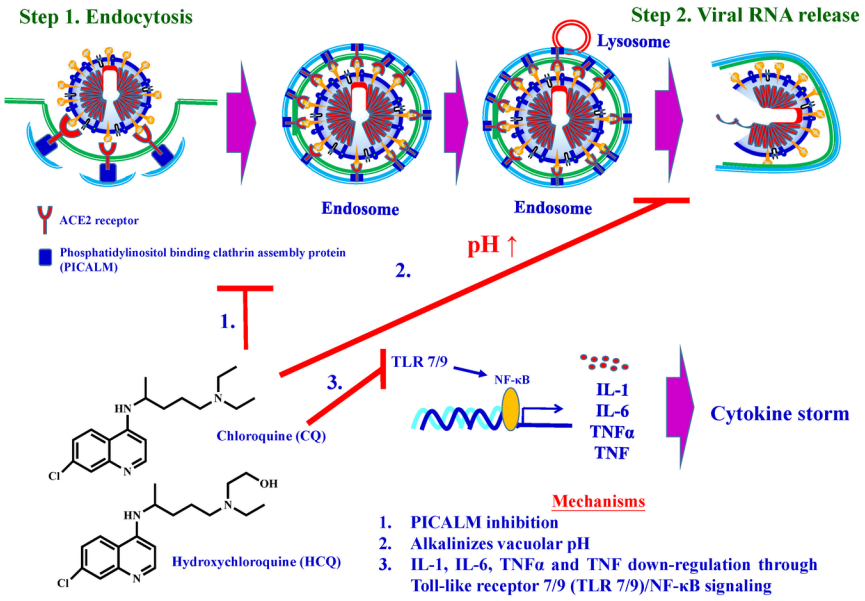


Figure 12

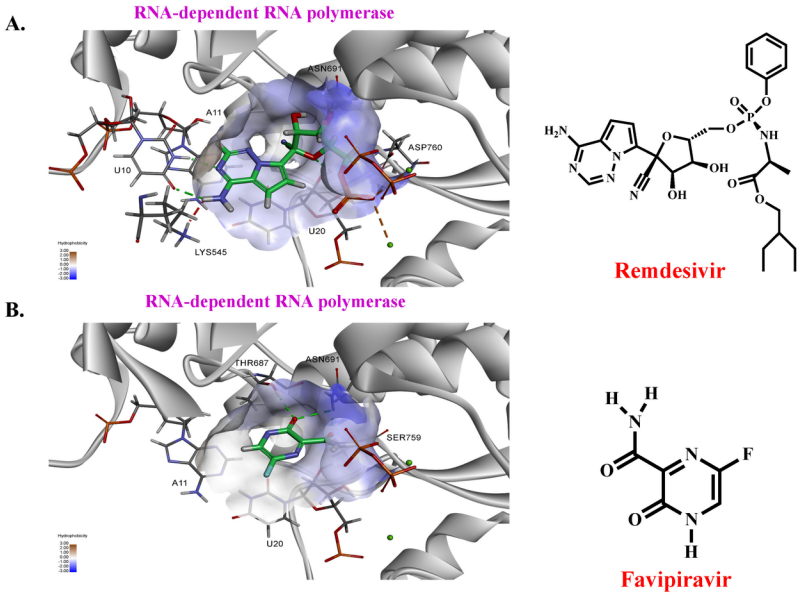


Figure 13

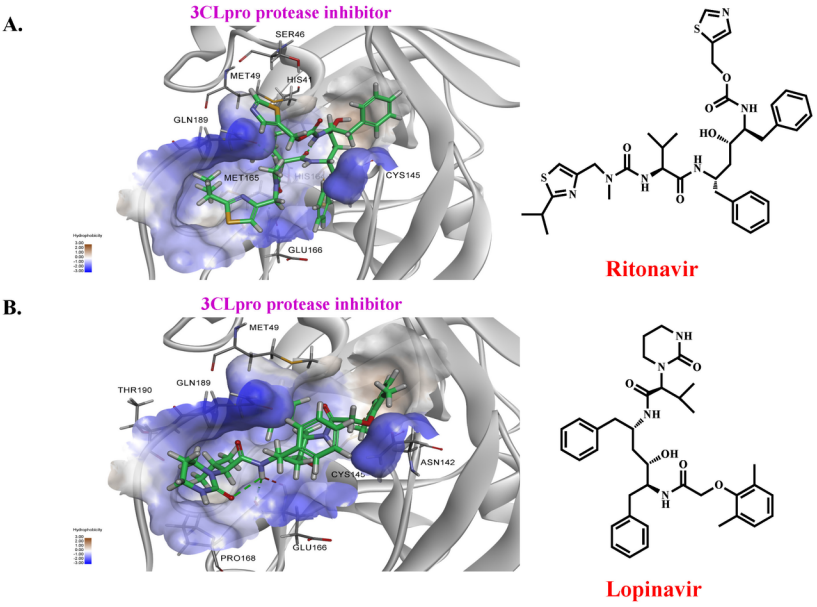


Figure 14

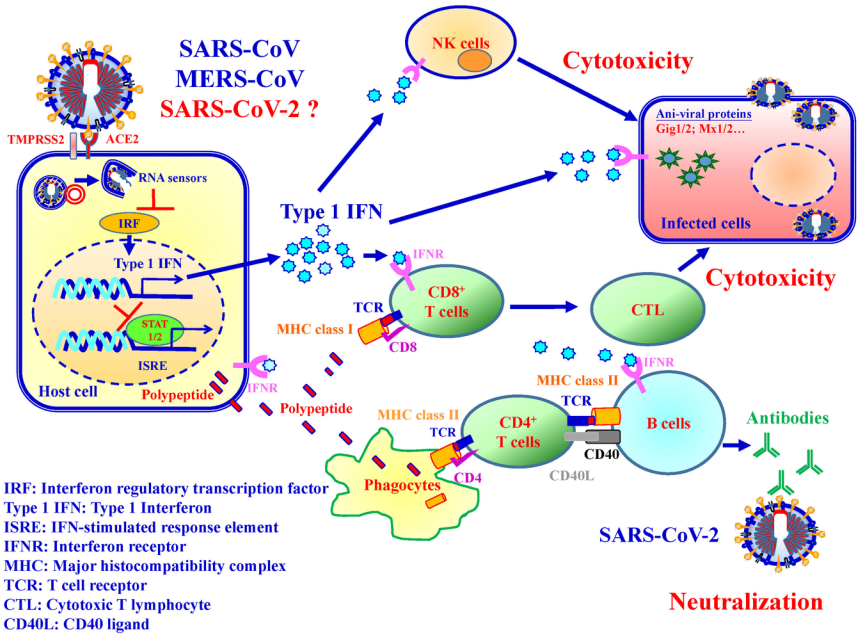


Figure 15

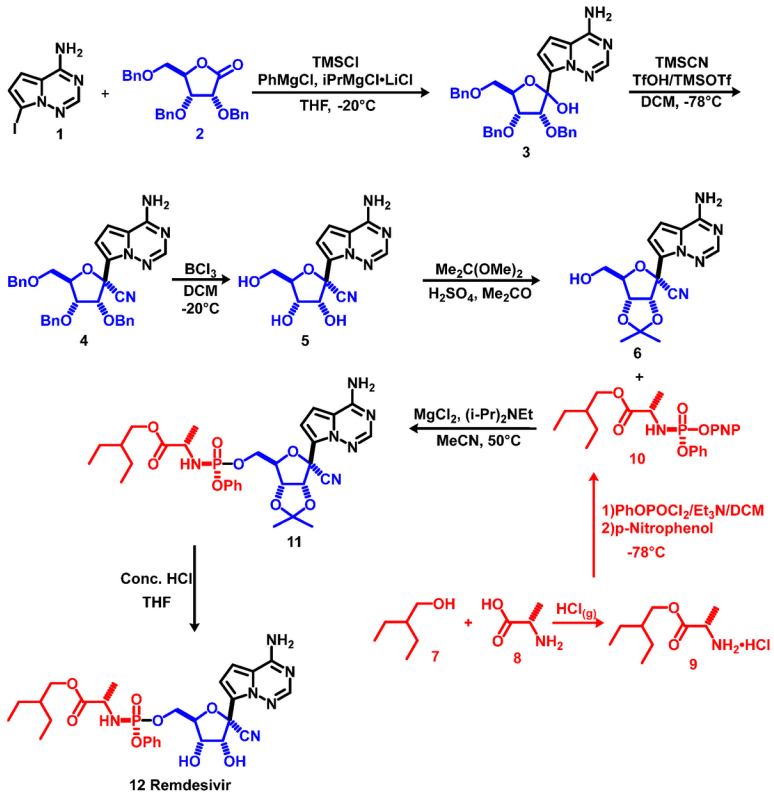


Figure 16

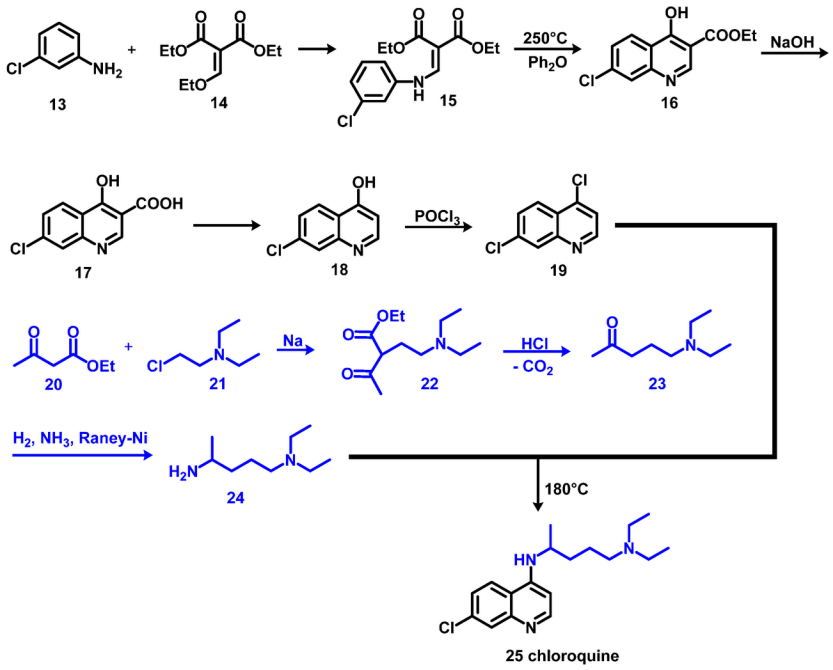
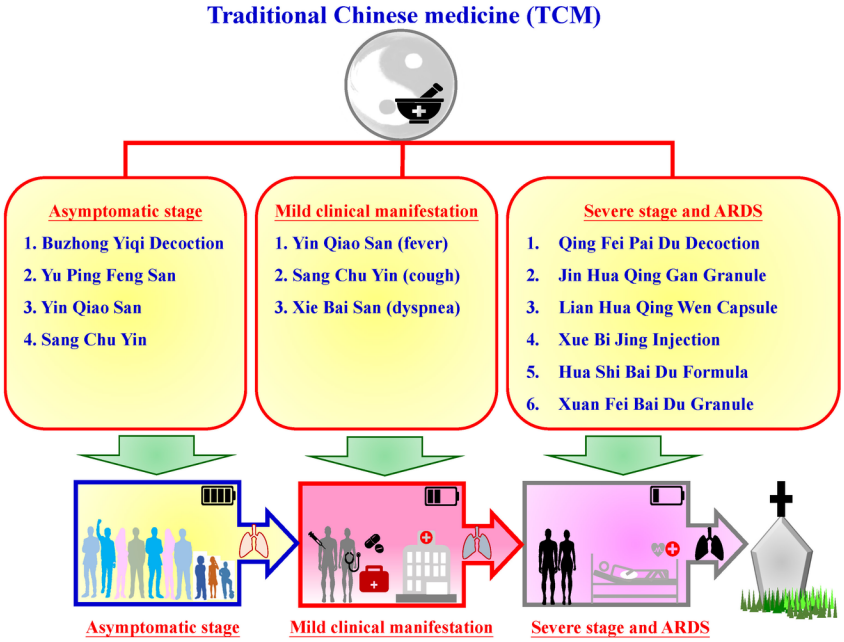


Figure 17



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