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Review Article

Threats to Arrangements COVID-19

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Abstract

Coronaviruses have a variety of receptors in different areas of the body, including the lungs, vessel endothelial cells, kidneys, bone marrow, central nervous system, and gastrointestinal tract. The nCOVID-19 uses sialic acid receptors, CD13 and ACE2 to enter the host cell. This virus enters to host cell by fusion and rarely through receptor-dependent endocytosis.

There is a risk for the emergence of new strains. The production of therapeutic and prophylactic antibodies against n COVID-19 can utilize the ACE2 S-M-N-E-APN- conserved epitopes. Polychlorinated antibodies can have produced in the horse or cell culture model that these antibodies may be able to elicit an appropriate immune response. It is best to use multiple component immunogens simultaneously to active or passive immunity. Due to the similarity of coronavirus protease with 3 C protease enterovirus drugs Rupintrivir, Quercetin or Luteoloside can be suggested. AIDS protease inhibitors such as Ritonavir also reduce the proliferation of the virus. Because the Neuraminidaseis effective for it released, drugs that inhibit this enzyme, such as Tamiflu, can help. Drugs such as ribavirin can help to control the virus by inhibiting its replication.

Favipiravir that selectively inhibits the RNA-dependent RNA polymerase can decrease its replication. Inflammatory cytokine inhibitors such as chloroquine sulfate, interferon beta, and Tocilizumab may be recommended to reduce inflammation. Hepatitis C virus replication inhibitors such as Sofosbuvir and Ledipasvir may reduce virus replication by inhibiting NS polymerase.

For disinfection against Coronavirus disinfectants (sodium hypochlorite and hydrogen peroxide), ammonium tetravalent detergent (benzalkonium chloride), and herbal phenolic compounds such as carvacrol and Fe3O4 can be used to disinfect the virus. Depending on the characteristics of the virus and its pathogenesis, methods for disinfection, treatment, and prevention can be provided. This article presents the prophylactic and therapeutic therapies' attention to mechanisms of the above.

Keywords: Therapeutic; Prophylactic; COVID-19; Disinfectant; Pathogenesis; Guidelines

Introduction

As a family of Nidoviral order, Coronaviridae comprises two subfamilies: Coronavirinae and Toroviral. The former includes alpha, beta, gamma, and delta Coronavirus genera. Whilst the later comprises Torovirus and Baffin virus genera (Figure 1). SARS-CoV2 or COVID19 is a group in SARS- CoV lineage.

Coronaviruses are made up of spikes (S), membrane (M), envelope (E), and genome, which are a single-stranded, sense positive RNA. The reason why Coronaviruses are classified in the Nidoviral order is the unique characteristics in sub-genomic RNA (sgRNA) with similarity at the 3´ ends.

Torovirus, Severe Acute Respiratory Syndrome Coronavirus (SARS), and the Middle East Respiratory Syndrome Coronavirus (MERS) are similar in genome propagation and organization but different in morphology and genome length. They contain two glycoproteins (E1, E2) and one phosphoprotein. Also, some lineages, including SARS-COV and Coronavirus OC43, have a third hem agglutinin called hemagglutinin esterase.

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Coronaviruses have the largest genome (27 kb-32 kb) among RNA viruses with several ORFs. The composition of the genome is polymerase enzyme (pol) - S - M – N. Recombination observed in the genome, to a large extent, forms three serologic groups: groups one and two are mostly seen in mammals and group three in birds. As the representative of Coronaviruses, Serogroup one includes human Coronavirus (HCOV)-229E, HCOV-NL63, and Porcine Respiratory Coronavirus (PRCV). Serogroup two consists of Mouse Hepatitis Virus (MHV) and HCOV-DC43. Serogroup three includes the avian Infectious Bronchitis Virus (IBV).

Appearance-wise, Coronaviruses contain a large covering with petal-like orbits reminding rings of light around the sun. They are intracellular viruses, replicating within the cytoplasm and Germinating through the Endoplasmic Reticulum (ER) and Golgi bodies. Coronaviruses contain matrix proteins underneath the envelope and barely grow in cell culture. To pass through the host's cells' membrane, Coronaviruses, like many other viruses, bind to receptors by their antigens. Almost all alpha genus members bind to the aminopeptidase N (CD13) receptor. Whilst HCOV- NL63 has a compatible ligand for ACE2 receptor. Beta genus receptors include ACE2 (for SARS and n-COVID19), glycan (for HKU1), CEA (for MHV), DPP4 (for MERS), and NANA (for BCOV).

Following antigen-receptor binding, Coronaviruses enter cells through endocytosis. Glycoprotein S integrates the envelope with the host's cell membrane. The virus genome, as well as the M protein, has a spiral and flexible symmetry. Coronavirus genera target various species. Alpha coronaviruses infect humans, pigs, dogs, and cats. Beta genus infects humans, camels, cows, and mice. Gamma and Delta often target birds, causing bronchitis. Toro viruses, on the other hand,

infect ungulate animals, birds, and sometimes humans. However, they are widely seen in poisonous animals, causing gastroenteritis.

The SARS virus, classified in serology Group 4, has two types of Spikes on its surface. Some of which are tall petal-like glycoproteins (the universal spike type in all coronaviruses), the others are small Hemagglutinin Esterase (HE) glycoproteins (presented in some coronaviruses). Its seventh new class is found in Wuhan; China isCOVID-19.

Respecting the huge variety of viruses, methods of disinfection, precautionary measures, and treatment methodologies depend on virus characteristics and pathogenesis. In this study, the structure and characterizations of Coronaviruses are discussed. Also, this review aims to address the pathogenicity, preventive precautions, and treatments of nCOVID-19 (Figure 1).

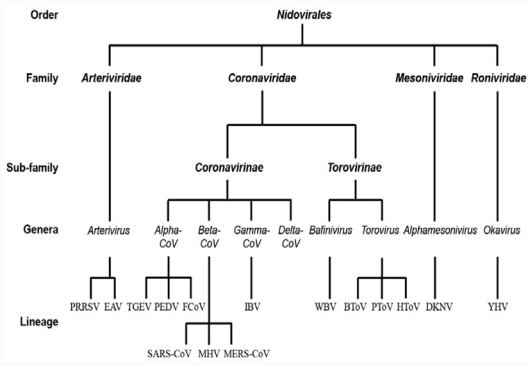

Figure 1: Nirovirales order phylogenic tree (the interaction between niroviridae).

Coronavirus Structure

Glycoprotein S

Coronavirus spike glycoprotein (S glycoprotein/ glycoprotein S) exists on the viral envelope and it is a huge contributor to host cells' receptor recognition and infection. Glycoprotein S is classified in Class I fusion protein helping them to fuse with hosts' cell membranes. Glycoprotein S, which was previously known as E2, is a large, petal-shaped, and highly glycosylated spike at the surface of the virus. Given the sequence similarity to FcγR receptors, glycoprotein S binds to the FC region of IgG resulting in antibodies neutralization and cellular immunity responses stimulation. S-glycoprotein firstly is produced as a long precursor protein with roughly 1300 amino acids. Later, the precursor protein is cleaved to an N-terminal S1 subunit with around 700 amino acids and a C-terminal S2 subunit with almost 600 amino acids. Any alteration or mutation in the S1 sequence affects the antigenicity and pathogenicity of the spike [1-5].

Hemagglutinin Esterase (HE)

Interspersed among S glycoproteins, hemagglutinin esterase projections have two functions: receptor binding function which is specific for O-acetylated sialic acid (O-Ac-Sia), and receptor destroying function specific for sialate-O-acetylesterase (Coronavirus hemagglutinin esterase). Hemagglutinin esterase used to be called ES and only present on the surface of some coronaviruses such as OC43, murine hepatitis virus, SARS, and Turkey Coronavirus (TCOV).

Coronavirus HE has a 30% similarity to the Hemagglutinin-Esterase-Fusion (HEF) protein of influenza C. The emergence of HE on the surface of coronaviruses follow multiple steps: The formation of small spikes on the surface of the virus, the binding of acetylated sialic acid to the projections, inducing hemagglutination and hemadsorption, esterization activity induction, and separation of the acetyl group from acylated sialic acid [1,2,6,7].

Glycoprotein M

Glycoprotein M is another coronavirus surface protein with a short ectodomain; only a small piece of the N-terminal domain is exposed to the outside of the viral particle. Whilst the rest of the N-terminal as well as the whole C- terminal domain present inside, is attached to the core part of the virus through the C-terminal domain (structure of CoV). The former name of Glycoprotein M is E2. Glycoprotein M functions include: determining the budding spot on the virus surface, arranging viral particles, interfering with the viral nucleocapsid, inducing IFN-α, and determining the virus-hosts Golgi apparatus attachment sites inside the hosts cells [1-7].

E Protein

E protein is the smallest envelope protein. It has been called a small protein before. E protein plays a role in the initiation of virus formation and viral particles assembly. It also has been proposed that E protein possibly induces apoptosis in host cells [1,7-9].

N protein

N protein is an internal 50 kDa-60 kDa multifunctional phosphoprotein, forming nucleocapsid and associating with genomic RNA. The nucleocapsid is a helical ribonucleoprotein consisting of the viral RNA genome and N protein. Coronavirus N also showed regulatory effects on viral genome replication, transcription, and translation. Besides, host cells metabolism could be modulated by N protein. N protein has two RNA-binding domains: an N-terminal RNA binding domain (NTD) and a C-terminal dimerization domain (CTD). These two domains are linked by a Ser/Arg- rich linker. CTD plays a role in N dimers oligomerization. NTD, on the other hand, has an interaction with Transcriptional Regulatory Sequence (TRS) in the viral genome which is a conserved characteristic of coronaviruses replication (coronavirus N-protein).

It has been demonstrated that N protein has an interaction with protein M, resulting in the embodiment of nucleocapsid as a part of the virus and helping to form replicative RNA complex (structure of Cov) (Figure 2).

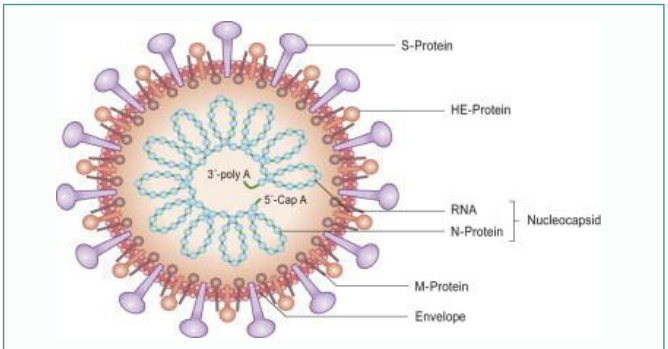

Figure 2: The structure of Coronavirus.

Characteristics of the coronavirus genome

CoVs' genome is polarity positive with a5′-cap and a poly-A tail at the 3′end, resembling most eukaryotic mRNAs. With a length of about 27 kb-32 kb, Coronaviruses have the largest genome among all RNA viruses. Unlike the majority of eukaryotic mRNAs, their genome

contains multiple ORFs, at least 6. At the beginning of the viral genome, 5′ end, there are ORF 1a and ORF b, comprising two/third of the genome, encode non-structural proteins which are directly translated to Replication-Transcription Complex (RTC) named replicase. RTC is a non-structural protein, synthesizing other viral proteins such as spike (S), envelope (E), nucleocapsid (N), membrane (M), etc.

The other one-third of the genome, 3′ region, encodes structural proteins: S, E, N, and M. in addition to these main structural proteins, different coronaviruses, as shown in Figure 2, have specific accessory and structural proteins such as 3a/b protein, 7a/b protein, HE protein, etc. All Coronavirus family members have the same order of the genes: 5′-replicase-S-E-M-N-3′. The translation of replicase, which is the only ORF being translated directly to the protein, depends on the ribosomal signal-frame shift between the intersection of ORF1a and ORF1b. The rest of the genome is used as a template for replication, as well as transcription. There are also one or more accessory genes dispersed among structural protein genes (emerging coronaviruses & the molecular biology of coronaviruses).

To activate the replisome polypeptide, it should be highly proteolytic processed. This is achieved by the Main proteinase (Mpro), also commonly called 3C-like proteinase (3CLpro) because of the similarity to picornavirus 3C protease (coronavirus main proteinase) (Figure 3).

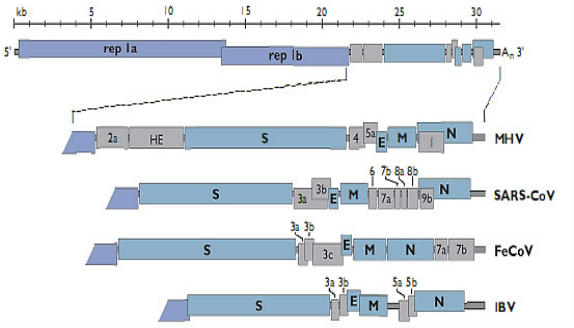

Figure 3: Genomic organization of Coronaviruses.

Coronavirus replication and cycle

As it is shown in Figure 3, the Coronavirus infection cycle starts with the attachment of the virus particle to the host cell's receptors. This triggers some cellular responses ending up with getting the virus genomic RNA (gRNA) translated to RTC inside the host cell's cytoplasm. The newly synthesized RTC facilitates the transcription of gRNA to subgenomic RNA negative strand ((-) sgRNA) which is then transcribed to (+) sgRNA. (+) sgRNA is then translated to structural proteins. The S, E, and M structural proteins are imported to ER and then Endoplasmic Reticulum-Golgi Intermediate Compartment (ERGIC). On the side, another (+) sgRNA is also translated to nucleocapsid which embraces (+) sgRNA and fuses with ERGIC. Once the entire virion is formed in ERGIC, it is going to be wrapped with smooth-walled vesicles and exported from the infected cells (the molecular biology of coronaviruses).

The entire life cycle of the virus has been categorized into three stages: attachment and entry, Gene expression and synthesis of virus components, and assembly.

Attachment and entry: The attachment of coronaviruses to the host cell's receptors is the first step of CoV infection. The virus attaches to the cell by S protein which is formed of two domains: S1 and S2. S1 is the binding site of the protein helping virus-host cellular receptor attachment, while the S2 domain mediates the fusion of the virus and the membrane.

The main host cellular receptors for coronaviruses are: Aminopeptidase N (APN), also called CD13, by HCoV-229E, angiotensin-converting enzyme 2 (ACE2) by SARS-CoV and HCov-NL63, 9-O-acetylated sialic acid by HCoV-OC43 and HCoV-HKU1, and dipeptidyl peptidase 4 (DPP4) by MERS-CoV (virus-host interaction). Aminopeptidase N as metalloprotease is present on the surface of the respiratory and intestinal epithelial cells [1].

Furthermore, there are some other unconventional, non-endosomal ways of entry for coronaviruses. For instance, it has been reported that the low PH of the host cell environment, the role of endosomal cathepsins, transmembrane protease serine 2 (TMPRSS2), airway trypsin-like protease TMPRSS11D, and furin (a serine endopeptidase) also help S protein activation and fusion of the virus (virus-host interaction).

Gene expression and synthesis of virus components: Following the entry of viral nucleocapsid to the host cell, double-membrane vesicles derived from the Endoplasmic Reticulum (ER) are formed to embrace the viral genome. These vesicles help the replication and the expression of the viral genome by concentrating RTC and protecting it from the host's anti-viral mechanisms as well as exonucleases. A proteomics study proposed that above 500 host proteins as well as most viral non-structural proteins contribute to gene expression within the RTC microenvironment. Nsp1, on the other hand, which is another non-structural protein, acts like an inhibitor for the host's ribosomes culminating in a huge mRNA degradation rate in host cells. This ultimately results in exploiting host translation machinery to be used only for viral mRNA translation (proximity labeling & coronavirus infection cycle).

Upon entry of the viral RNA into the cytoplasm due to positive polarity, a portion of the 5' end of the RNA binds to the ribosome and is immediately being translated to RNA polymerase, which mediates both sg mRNA transcription and virus gene replication. The only translatable part of the virus mRNA is the 5′ end part. The transcription process starts with the translation of ORF1a and 1b to pp1a and pp1b polyproteins, respectively. These two polyproteins get cleaved to almost 15 nsp which makes RTC. RTC transcribes the genomic positive-strand RNA to a negative-strand template for both the replication of new genomic RNA and the translation of structural and accessory proteins (virus-host interaction).

Assembly: Once all viral proteins are formed, the newly synthesized genomic RNA along with N protein, which is also called capsid protein, are assembled and form a helical nucleocapsid in the cytoplasm. S, E, and M proteins that have been synthesized in the cytoplasm fuse with the ER membrane. Then a piece of ER containing viral proteins becomes mature and forms the Endoplasmic Reticulum and Golgi Compartment (ERGIC). ERGIC moves towards the host cell membrane and gets out of the cell into large vesicles called smooth-wall vesicles through exocytosis. CoVs, apposite to many enveloped viruses, do not promote the egress process through the interaction of the viral proteins and the host proteins the Endosomal Sorting Complexes Required for Transport (ESCRT). Instead of using ESCRT, some coronaviruses use HE and S proteins for cell-to-cell fusion. The

case often occurs at alkaline and neutral pH (1 & membrane binding proteins) (Figure 4).

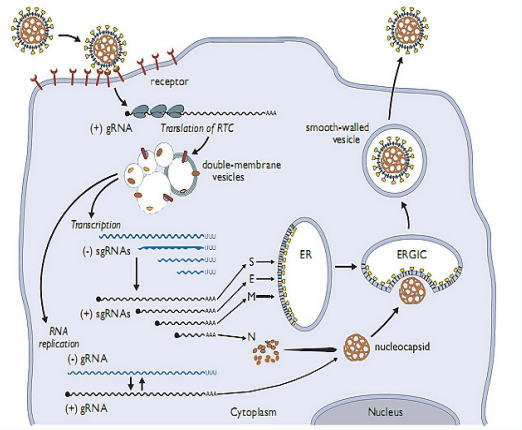

Figure 4: Coronavirus replication cycle.

Pathogenicity

Coronaviruses are largely species-specific. Most animal coronaviruses tend to resemble gastrointestinal and gastrointestinal epithelial cells. The optimal growth temperature of the virus is 33°C-35°C. Transmission occurs through the respiratory tract and causes the following diseases [10-18].

Respiratory disease: Human Coronaviruses usually cause a fever-free cold in adults. The second most common cause of colds is the rhinovirus. The incubation period is 2-5 days. The duration of the illness is one week. SARS caused a pandemic in 2003, is a cause of severe respiratory illness, with a 6-day incubation period and death due to progressive respiratory failure in approximately 10% (highest deaths in the elderly). Common symptoms include fever, cough, shortness of breath, gastrointestinal symptoms, diarrhea, and symptoms in severe cases are pneumonia, Acute Respiratory Syndrome, kidney failure [1].

Gastrointestinal disease: There are several intestinal Coronaviruses in animals, one of which is the Transmissible Gastroenteritis Virus (TGEV). Porcine Respiratory Coronavirus (PRCV) has also been identified. PRCV virus is derived from the TGEV virus with a mutation in glycoprotein S1 [1].

Neurological disease: Ways to Transmission.

- Close contact with an infected person
- Handling contaminated equipment
- Through the digestive tract

Safety

Safety is not perfect.

Laboratory detection

Antigen and nucleic acid identification are performed. Serology: ELISA, Hemagglutination, Immunofluorescence

Culture is difficult, cell culture from the human fetus can be used [1].

Coronavirus control

1. Isolation of patients
2. Quarantine people who have been in contact with patients
3. Restrictions on trips
4. Use of gloves, guns, protective goggles, and respirator masks by health workers.

Treatment and prevention

It lacks specific treatment & vaccine.

Discussion

Vaccine strategies

Understanding the virulence factors and the pathogenesis of the virus is important for selecting a vaccine candidate. Due to recombination and antigenic and host variation of the coronavirus, multicomponent vaccines should be used.

Glycoprotein S is a large and petal-shaped glycoprotein at the virus surface that plays a role in binding the virus to the host cell and FCγR receptors to the FC portion of IgG and inducing neutralizing antibodies and stimulating cellular immunity. But the problem is the variation or mutation in the S1 sequence that causes antigenicity and pathogenicity. Therefore, according to the bioinformatics analysis of the conserved regions of the nucleic acid sequence of this gene candidate.

Glycoprotein Hemagglutinin Esterase (HE) is only present at the level of some coronaviruses such as OC43, murine hepatitis virus (serology group 2), and Turkey Coronavirus (TCOV) that involves in binding to acetylated sialic acid. Glycoprotein M is a membrane glycoprotein and its former name is E2. The N-terminal portion is short and outside the virion surface. Its C-terminal region crosses the membrane and attaches to the core portion of the virus. Its roles include: Determine the location of the budding virus, Assembly of viral particles, Interference with virus nucleocapsid, Induction of IFN-α, The role of an integral protein in the Golgi apparatus Protein E is a small, envelope membrane protein. It is inside the virus membrane and is the smallest virus covering protein. Its role is the assembly of viral particles and possibly host cell apoptosis.

Protein N is the virus's nucleocapsid and is a phosphoprotein related to genomic RNA. Three domains have relatively protected. It is carried by the virus ligand to the 229E-COV cell receptor (CD13) APN. Aminopeptidase N as metalloprotease is present on the surface of the respiratory and intestinal epithelial cells. The murine coronavirus hepatitis receptor, CEA (Super familial Ig Carcinoembryonic Antigen) is a humanized OC43 receptor, acetylated sialic acid (NANA) that binds to HE and S glycoproteins.

The coronavirus ligand is S, but those with HE binds to sialylated sialic acid receptor SARS, angiotensin-2, or angiotensin-2-modifying enzyme [2].The enzyme that converts angiotensin in the lungs produces angiotensin 2, a vasoconstrictor enzyme that raises blood pressure. The CD13 receptor is present on the surface of the respiratory epithelial, intestinal, myeloid cells, vascular endothelial cells. Sialic acid receptors are found in all organs in all vertebrates. The mammalian central nervous system has the highest concentration of this substance. Most body fluids include saliva, gastric juice, serum, urine, milk, and tears. Because the coronavirus has a variety of receptors throughout the body, including the lungs, bone marrow, kidneys, central nervous system, and endothelial cells, it can cause a variety of complications.

Therefore, for the preparation of the conserved protein APN

(CD13) - S-M-N-E probably plays an important role in virus protection and inhibition. The production of therapeutic antibodies against n COVID-19 can utilize the ACE2 S-M-N-E-APN- fusion protein. Polychlorinated antibodies produced in the horse or cell culture model may be able to elicit an appropriate immune response. Because viruses the recombination is high, it is advisable to design a multi-component vaccine against important viral pathogenesis epitopes that inhibit co-binding, permeability, uncoating, replication, and assembly of the virus.

Drugs

Because the virus first converts its polyprotein by a protease to several proteins for pathogenesis, it can be controlled by selecting the appropriate drug. Due to the similarity of coronavirus protease with 3C protease enterovirus drugs Rupintrivir, Quercetin or Luteoloside can be suggested. AIDS protease inhibitors such as Ritonavir can reduce the severity of the disease and the proliferation of the virus due to its similarity to the coronavirus. Because the virus binds to the sialic acid receptor and requires the Neuraminidase enzyme to be released, drugs that inhibit this enzyme, such as Tamiflu, can help. Base analogous drugs such as ribavirin can help control the virus by inhibiting its replication.

Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazine carboxamide) is an anti-viral agent that selectively and potently inhibits the RNA-dependent RNA polymerase can decrease its replication. Inflammatory cytokine inhibitors such as chloroquine sulfate, interferon beta, and Tocilizumab may be recommended to reduce inflammation. Hepatitis C virus replication inhibitors such as Sofosbuvir and Ledipasvir may reduce virus replication by inhibiting NS polymerase.

Disinfectant suggestion

The best way to prevent Coronavirus is to stay home and cut off the transmission chain of infection. One of the most useful methods of prevention is the use of proper disinfectants against the Coronavirus. Because Coronavirus is an enveloped virus, it is easily eliminated by detergents and alcohol. Therefore, the best disinfectant recommendation is to use a combination disinfectant to ensure that the virus is eliminated. The following formulation is recommended for use in a combination disinfectant (Cationic detergent, oxidizer, phenolic compound).

Hypochlorite Sodium (0.1%) +Benzalkonium Chloride (0.1%)+Hydrogen Peroxide (0.25%)+Carvacrol Essence (0.1%)+1% Fe3O4.

This compound can be used as a disinfectant for hands, face, and inhalers. Coronavirus is more vulnerable because it is enveloped. Uncoating of this virus occurs in an acidic medium faster, so it is recommended to use a combination of detergent, oxidizer, and phenolic disinfectants to inhibit both the uncoating of the virus and its proliferation. Lemon essence and carvacrol not only have phenolic compounds and antibacterial but also cause a pleasant smell and stimulate the opening of the alveoli of the lung and are likely to be useful in removing and inhibiting the virus.

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