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A Guideline for Finding Antiviral Agents Targeting Coronavirus Genome Based On the Alcohol Penetration Mechanism

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Abstract

In order to contain the spreading of newly emerged SARS-CoV-2, one or more of the following approaches are required: destabilizing the virion in the environment, disrupting its recognition and entry to host cells, and interfering with its replication inside host cells. Previous research has successfully identified some means to inactivate airborne virions and virion-contaminated surfaces. However, those approaches are not feasible in inactivating virions in environments that are in proxy to human exposure and physiological environment due to their toxicity or inconvenience. While vaccination and therapeutics have been developed for fighting the virus in a physiological environment, the main focus has been using the spike proteins (S) as primary antigenic targets. However, S proteins are subjected to rapid mutation and have a considerable degree of variation across different strains and variants. Thus, antivirals targeting S proteins couldn't be applied universally to cope with rapidly emerging SARS-CoV-2 variants and potential outbreaks of other strains of coronavirus in the future. In this paper, we attempt to review present findings in developing antivirals, and, specifically, analyze the disinfection mechanism of alcohol in an aqueous environment. We introduce a penetration mechanism that could explain the concentration-dependent disinfection potency of alcohol when applied to SARS-CoV-2, and conclude that the interior of the virion is more fragile compared to its exterior. Based on such findings, we aim to propose a guideline for future research to look for antivirals that could target genomic materials of SARS-CoV-2, which could inactivate a spectrum of coronavirus without damaging human cells.

Keywords: SARS-CoV-2; Penetration mechanisms; Lennard–Jones interactions; Viral membrane stability

Introduction

The outbreak of a novel atypical pneumonia disease in 2019 has posed a significant threat to public health across the globe. The pandemic was formally termed by the World Health Organization (WHO) as Coronavirus Disease 2019 (COVID-19), and the virus that caused such a pandemic was then identified as " severe acute respiratory syndrome coronavirus 2", or SARS-CoV-2 in short. To date, there have been more than 300 million confirmed cases and more than 5 million fatalities globally [1- 5].

Coronaviruses are named so due to a shared crown-like protruding structure (spike proteins) presented on the viral surface. They are a group of enveloped, positive-sense RNA viruses that cause a range of diseases in mammals and birds. For instance, SARS-like coronavirus bat-RaTG13 (infects horseshoe bat *Rhinolophus affinis)* shares 96.2% genomic similarities with SARS-CoV-2. Such a finding provides evidence of a possible animal-to-human transmission origin of SARS-CoV-2. 6, 7 SARS-CoV-2 is classified as one of the 7 strains of coronavirus that are capable of infecting humans. Four out of seven strains of human-infecting coronavirus including HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 are termed endemic coronavirus since they usually cause mild symptoms that resemble the common cold.1 SARS-CoV-1 and MERS, on the other hand, have caused regional outbreaks with high fatality rates in 2003 (China) and 2012 (middle east and south Asia), respectively.8, 9 A comparison between different strains of human-infecting coronavirus is summarized in Table 1. [10-15]

The devastating effect of the pandemic caused by SARS-CoV-2 can be attributed to two crucial factors: its improved infectivity that accelerates its spreading. SARS-CoV-2 can be transmitted through direct contact and exposure to droplets or aerosols containing viruses. Such an airborne transmissive mode leads to difficulties in containing its spreading. Moreover, viable viral samples were also collected from fecal samples and sewage, suggesting a potential fecal-oral/ocular route for viral transmission.5, 6 The other key feature that contributed to the challenges presented by the COVID-19 pandemic is SARS-CoV-2's toxicity toward a spectrum of major organ systems, such as respiratory system, immune system, circulatory system, and excretory system. While some patients might be asymptomatic carriers, many patients would develop symptoms including cough, fever, shortness of breath. Occasionally, some patients may also experience headaches, loss of taste and smell, difficulty in breathing, muscle pain, nausea and vomiting, and develop more severe symptoms such as life-threatening pneumonia and kidney failure. The severity of the onset of symptoms is much higher for people with compromised immune systems such as elderly patients and patients with immunodeficiency and usually leads to high fatalities in those populations. 1, 2, 16

Fortunately, various vaccinations, including but not limited to Moderna/NIAID, BioNTech/Pfizer, and BBIBP-CorV, have been developed and reported high efficacy to provide protection against SARS-CoV-2. The majority of the vaccination have focused on spike proteins of the viruses, such as introducing inactivated virus-containing spike proteins or inducing viral spike protein homolog production to trigger immune responses.3 However, SARS-CoV-2 underwent rapid mutations and several variants, such as B 1.1.7 (alpha), B.1.351(beta), B.1.617.2 (delta), C.37 (lambda), B.1.621 (Mu), and B.1.1.529 (omicron) have been identified in different locations.17 With key mutations on spike proteins, these variants are more transmissible and have displayed high penetration rates for many current vaccinations. For instance, the NVX-CoV2373 vaccine has 96.4% effectiveness against non-B.1.1.7 variants, but its protection decreased to 86.3% and 51~60% against B.1.1.7 and B.1.351 variants, respectively.3, [18 – 20] Therefore, it is crucial to investigate therapeutics and vaccinations that would be impacted to a lesser extent by mutations in S proteins.

For instance, extensive research has been conducted in order to expand our understanding of the increased infectivity and toxicity of SARS-CoV-2 and potential means to control its spread. Water is proposed to shoulder several key responsibilities in extending viral longevity, stabilizing viral structure, and facilitating viral entry to host cells. Based on these findings, it has been proposed that water-absorbing materials that dehydrate viral-containing droplets could effectively disinfect coronavirus.[18, 21]

In this paper, we aim to investigate alternatives to tackle the ongoing pandemic and potential solutions to a wide variety of coronaviruses. In section II, we will examine general structural features of coronavirus, and compare different strains of human-infecting coronaviruses, especially differences and similarities of the morphologies and functions of their spike proteins. In section III, we will introduce a mechanism for passage of alcohol through the phospholipid bilayer, penetration mechanism, which leads to inactivation of the virus. The mechanism predicts that the mixture of alcohol-water is antiviral only if alcohol concentration is neither too low nor too high, which is in accordance with experimental observations. The penetration

mechanism may provide us a path for finding potential antiviral agents for different strains of coronavirus by targeting the viral RNAgenome.

Structural Similarities and Differences of Coronaviruses

SARS-CoV-2 is a betacoronavirus that has the largest positive-sense RNA genome of approximately 30 kb in length and it is estimated that ~79.6% of its sequence are identical to that of SARS-CoV-1, another strain of coronavirus that caused the epidemic in 2003.[22- 24]

The genome of SARS-CoV-2 encodes for two polyproteins that would be subsequently processed into 15 or 16 non-structural proteins (NSP), as well as structural proteins: nucleocapsid proteins (N), membrane proteins (M), envelope proteins (E), and spike proteins (S). [14, 18, 22, 25- 28] In recent research21, it has been shown that a functional form of airborne SARS-CoV-2 virion is usually encapsulated in water droplets, which serve as fomite and provide a protective layer and an infection medium. Figure 1 shows a simplified model of a general structure of coronavirus surrounded by a layer of water (dark blue). Once located in a water medium, the polar heads of the phospholipid layer will interact with surrounding molecules to form a hybrid water-lipid interface (light blue) where structural proteins (E, M, S) are soaked within. Such an interface would possess polar properties (shown as $\delta-/\delta+$ partial charges in this layer) to enable interactions with polar materials.

Nucleocapsid proteins are packaged together with RNA molecules in the virion, and play a crucial role in interacting with replication-transcription complexes (RTC) to assist viral RNA synthesis. Except for N protein, other structural proteins are located on the outer phospholipid bilayer membrane and function collectively as a viral-environment interface. The phospholipid membrane of the virus is usually derived from human host cells in which it is infected.[29,30] Therefore, there is a great extent of variations among the composition and morphology of membranes of different virus samples being collected.[22, 27] During an infection process, the viral membrane will fuse with the host cell membrane and deliver internal generic materials.

The envelope(E) protein, also called glycoprotein, is the smallest in size among all structural proteins. It is found in great amounts on host cell intracellular trafficking sites and is closely related to the virus assembly and budding. Membrane(M) proteins are the most abundant structural proteins and define the shape of the virion. These two structural proteins (M and E) are similar to those possessed by other human-infecting betacoronavirus and are thus considered to be highly conserved within this genus.[22] In contrast, S protein represents the greatest degree of variation among different strains of coronavirus. Due to its role in facilitating virus-host cell recognition, binding, and fusion, it is regarded as one of the most prominent targets for vaccination and therapeutics.[15, 22, 23, 25, 31]

A spike protein consists of two subunits: a trimeric subunit S1 that is responsible for binding to host receptors and a trimeric S2 subunit that facilitates the fusion of host and virus membranes.19 As the virus enters the host body, the S1 subunit would associate with the corresponding receptors on the host cell. Such association would lead to either proteolytic activation or pH acidification, which induces conformational changes of the spike proteins. For instance, the heptad repeat 1 (HR1) and heptad repeat 2 (HR2) domains of the S2 subunit would interact to form a six-helical bundle (6-HB).32- 35 The formation of such a complex would bring the viral membrane into proximity with the membrane of the host cell and leads to subsequent fusion. [36]

Compared to other components, the S protein has the greatest structural variation among different strains of coronavirus, especially the S1 subdomain of the S protein.25 Coronavirus that infects human beings can be categorized into two genera. One is beta-coronavirus, including SARS-CoV-1, MERS, SARS-CoV-2, OC43, and KHU-1. The other one is alpha-coronavirus that includes the other two less lethal and less infectious strains, namely, 229E and NL[63.14, 37] A study based on infectious bronchitis coronavirus, a gamma coronavirus (avian, non-human) revealed key evolutionary evidence of coronavirus structures. All strains of coronavirus have galectin, which could act as a viral lectin that helps viral cell entry.[14, 31] However, at the N-terminus domain (NTD) of S1, betacoronavirus has a unique ceiling-like structure composed of various loops, a structure that is missing in alpha-, and delta- strains or partially presented in gamma strains and other genera. At the C-terminus domain (CTD) of S1, all genera have two beta-sheets except for betacoronavirus, at which the absent 5-stranded beta-sheet is replaced by alpha-helix and coil complexes.

In addition, it was discovered that the S1 domains of different genera of coronavirus also adopt different packing modes: β-coronavirus and γ-coronavirus S1 are packed via cross-subunit quaternary packing mode, where one CTD binds to one NTD and two CTD from other subunits. As a result, the folded S1

adopts a concealed/lied-down conformation that might help them to evade the immune system. In contrast, α- coronavirus and δ-coronavirus S1 are packed using the intra-subunit quaternary packing mode, where S1-NTD binds to S1-CTD on the same subunit. This conformation might have the binding site more exposed and more vulnerable to immune attack[31].

Moreover, there are also significant structural differences among different beta coronaviruses, which determine the types of host-cell receptors they would interact with. Different betacoronavirus can be further subdivided into different lineages: A, B, C, and D. Of the human-infecting coronavirus, SARS-CoV-1 and -2 are lineage B betacoronavirs, MERS is a lineage C betacoronavirus, OC43, and KHU-1 are Lineage A betacoronavirus. Different lineages of coronaviruses' cell entry processes are mediated by different host cell receptors: Angiotensin receptor 2 (ACE2) for lineage B, Dipeptidyl-peptidase 4 (DPP4) for lineage C, 9-O-acetylated sialic acids for lineage A.[14, 15, 31, 38] Cross-receptor binding is essentially not viable, so receptor-virus interaction for each lineage is unique. Interestingly, lineage B betacoronavirus is also subdivided into different clades based on their receptor binding domain (RBD) structure and non-structural protein 12 (NSP 12).[31, 39] It is notable that SARS-CoV-1 belongs to clade 1, but the SARS-CoV-2 cladogram is more ambiguous: it is more similar to clade 2 in terms of its NSP 12 but resembles much of clade 1 RBD characteristics. For example, 14 consensus ACE2 interacting residues formed contact points that are observed in clade 1 but not clade 2 or clade 3.14 (See Figure 2)

Although RBD of SARS-CoV-2 and SARS-CoV-1 are very similar, there are two key differences: First, SARS-CoV-2 is more potent in terms of the ACE2- spike protein affinities due to additional residue interactions: Additional hydrophobic interactions at F486, additional hydrogen bonding at Q493(viral) and ACE2 E35, additional salt-bridge at K417 (viral) and ACE2 D30. These interactions are absent in SARS-CoV-1. Paradoxically, the S protein of SARS-CoV-2 is mostly in the lying-down position, suggesting that it has less chance to interact with ACE2. Thus, an alternative strategy is required to explain the discrepancy between the decreased exposure of SARS-CoV-2 S protein and its increased infectivity.[15, 25]

A finding suggests that SARS-CoV-2 has a unique furin-like cleavage site (FCS) RRAR (Arginine-Arginine-Alanine-Arginine) that is not found in S proteins of other betacoronavirus. RRAR at S1/S2 cleavage site is suspected to play a role in improving the fusion capacity. However, its effectiveness is not significant in the presence of human airways trypsin/trypsin-like proteases (HAT).[15, 33]

As discussed above, spike protein is considered a key component of coronavirus that is believed to account for the increased infectivity of SARS-CoV-2 and is a prominent candidate for therapeutics target.[14, 15, 25] However, the spike protein of coronavirus is thus also subjective to evolutionary pressure and undergoes rapid mutations. It has been observed that the spike proteins of SARS-CoV-2 have had mutations and produced diverse variants that have increased transmissivity, fatality, or ability to neutralize current antibodies. Notably, variant B.1.617 (also known as Delta variant), which was first identified in India in October 2020, harbored mutations in the N-terminus region and RBD (the most prominent point of mutations are E484Q and L452R) that lowers sensitivity to antibodies and increased ACE2-RBD affinity. These changes lead to more probable immune evasion and a higher transmissivity rate.[40- 42]

N protein, also called nucleocapsid protein, is the only type of coronavirus structural protein that is not displayed on the viral surface. Instead, it is located within the proteinous membrane of the virion and facilitates the package of the viral RNA genome. While not directly interacting with the host cell membrane, it has been identified as a key player in the viral life cycle. For instance, it could help viral budding when localized to ER and Golgi apparatus and could induce host cell translational shutoff that lead to diminished cell defense mechanisms and rapid proliferation of viral genome.[28, 29, 43, 44]

Non-structural proteins (NSP) refer to a group of viral proteins that does not account for structural features of coronaviruses. They are produced by splicing two elongated segments of the viral genome and are responsible for a variety of key viral functions. For instance, NSP 12 is an RNA-dependent RNA polymerase that shoulders key responsibilities in the replication of the viral genome in host cells. Notably, however, it has been proposed that loss of some NSP, such as NSP 14 and NSP 3, which is not universally presented across different strains of coronavirus and thus is proposed to be less significant in impacting viral function. [29, 45, 46]

Envelope protein (E), also called glycoprotein due to sugar molecules found to be attached to it, is the smallest structural protein possessed by coronaviruses. Generally, it is [76–109] amino acids in length, ranging from 8.4 to 12 kDa in size. Its structure and composition are relatively conserved across β-coronaviruses. Envelope protein is responsible for a variety of

both pre-infection and post-infection activities of coronavirus. For instance, it contains a protein (zo-1) (PDZ)-binding motif (PBM) that closely interacts with host cells and facilitates virion-host cell recognition. In addition, it is also presented in great amounts in host cell organelles after infection to facilitate viral protein trafficking.[43, 47]

Membrane protein (M) is a crucial component of coronavirus that provides structural support and protection against external agents. It is thus the richest protein in any coronavirus and conserved across beta-coronaviruses. In addition, M protein also plays a crucial role in stabilizing and integrating other proteins presented on the viral surface, such as E and S proteins. It has been proposed that M protein might aid viral entry into host cells by modifying spike proteins and could potentially be a primary immunogen. However, more findings are required to substantiate these hypotheses.[30, 47, 48]

Compared to spike proteins that undergo rapid evolution, the remaining components of the virion are relatively stable in structures and properties. Therefore, we may propose that a potential therapeutics or antiviral agent could target more conserved components, for example, the viral genome.

Inactivation of Coronavirus by Alcohols: Penetration Mechanism

Alcohol, namely ethanol, isopropanol, and n-propanol are common components of hand rub rinses, gels, and foams that are used for disinfection.[49] However, such disinfection is possible only if alcohols are mixed with water, with a certain range of alcohol concentration. For instance, concentrations of ethanol and isopropanol within 62-80 vol% are very effective, while for 95 vol% the solution failed to effectively disinfect the SARS-CoV-2 virus, suggesting that water-alcohol interaction plays a central role in disinfection processes.[50] In this section, we will provide explanations associated with such a phenomenon and a proposed mechanism of how the disinfection could occur.

Based on the low-frequency Raman spectroscopy and Monte Carlo simulation of water-alcohol interactions, water molecules, and alcohol molecules do not mix in random orders as an ideal solution does.[51 – 53] Their mixtures are composed of microheterogeneity and a structural transition of solvent clusters. For instance, the Raman spectra for water-ethanol mixture shown in low-frequency regions display the existence of two association states of molecules: aggregated water and aggregated ethanol. At a smaller ethanol mole fraction ($\chi e < 0.22$), only a water aggregation state was observed53 and each ethanol molecule is completely hydrated. When the ethanol mole fraction is larger ($\chi e \sim 0.57$), the total energy of Coulombic interactions (which represent hydrogen bonding interactions) is the same as that of the Lennard- Jones interactions (hydrophobic interactions) among the alkyl groups of alcohol molecules [See Figure 1(b) in ref. 53]. Therefore, at high alcohol concentration ($\chi e > 0.57$), the aggregation of the alkyl groups becomes a significant factor. In contrast to a situation where ethanol concentration is low($\chi e < 0.22$), ethanol molecules aggregate and each water molecule is completely solvated in the ethanol medium at the high alcohol abundance.

Amphiphilic molecules are suitable for rupturing, penetrating, and possibly passing through a phospholipid bilayer surrounding eukaryotic cells and enveloped virions. Based on this property, there have been thorough investigations on the biocidal utilities of common amphiphilic compounds, including alcohols, povidone-iodine, sodium hydroxide, quaternary ammonium compounds, peroxyacetic acid, and glutaraldehyde.[54] In this section, we shall present a molecular-based mechanism for the passage of alcohol (including ethanol, propanol, and isopropanol) through a phospholipid bilayer. It was experimentally found that ethanol and isopropanol are very effective in inactivating coronavirus when mixed with water and alcohol concentration is within [62-80] vol%50. In contrary to an expectation of a linear correlation between alcohol concentration and disinfection effectiveness, however, at a concentration of 95 vol % or higher, the antimicrobial effect of alcohol diminishes and enables the survival of infectious viruses.[50]

Alkyl groups of alcohol molecules, including methyl, ethyl, and isopropyl, are better electron donors than hydrogen atoms. Thus, oxygen atoms of alcohol molecules are also richer in electron density compared to those of water molecules. Hence, a hydrogen atom of any given water molecule has a higher probability of making a stronger hydrogen bonding (HB) with an oxygen atom of an alcohol molecule rather than the oxygen atom of another water molecule. In follow-up studies, mixing enthalpy of ethanol/water was found to be negative. Its value varies from -0.145 to -0.594 kJ/mol, depending on the alcohol concentration. [55] Mixing enthalpy for isopropanol-water and propanol-water mixtures are negative at low alcohol concentrations, for which Lennard-Jones (hydrophobic) interactions are insignificant.56 In addition, from a thermodynamic perspective, entropy incrementation due to the mixing is also in favor of the mixing of two species. In conclusion, based on the evidence presented above, any alcohol (A) molecule in a bulk phase of a low alcohol

concentration mixture has a higher probability to be hydrogen-bonded to water (W) molecules.

The extent of HB between water and alcohol, shown for the fully-hydrogen-bonded state in Figure 3, depends on the thermal molecular energy or temperature. The dependency trend of such an interaction is similar to the case for pure water, and thus we expect the temperature increase of the mixture will reduce the extent of HB for both species similarly. Hence, the ratio of the HB remains almost the same as that of the fully- hydrogen-bonded state.

As shown in Figure 3, the mixture is made of WA4 units. In such a unit, each W is associated with 4 As, where each A is shared by 3 WA4 units. Hence, for each W in the mixture, the net contribution of A molecules is $4 \times ⅓$ on average. Therefore, the mole fraction for A in such a mixture is given by $\frac{4}{3} / (1 + \frac{4}{3}) = 0.57$. That is, a 57 mol percentage of alcohol is needed to make a full hydrogen bonding with all water molecules in a given mixture. Using the values of density for water and ethanol at an ordinary condition (25 oC and 1 atm), such a concentration corresponds to roughly 81 vol % for ethanol. This value is comparable to 80 vol% reported by Meyers et al.50 as the highest alcohol concentration that the alcohol-water mixture has the most effective antiviral property. We may expect that when the χe value is approximately 0.57, the mixture is in a state with no aggregated phases. However, distancing from this point will lead to either an aggregated-water phase or aggregated-alcohol phase, at the low and high alcohol concentrations, respectively. Having such a perspective, the mechanism of the passage of alcohol molecules through the phospholipid bilayer can readily be understood as described in the following paragraphs.

In pure water, the molecules are orderly arranged along with the phospholipid layer, with a thickness of about 3 nm.57 In bulk water surrounding the orderly arranged layer, the distribution of water molecules is less organized. In an alcohol-water mixture with low alcohol concentration, each A molecule is surrounded and hydrogen-bonded by three W molecules and almost has no chance to get inside the lipid channels since the majority of channel entrances are effectively blocked by water molecules, as shown in Figure 4(a). As a result, alcohol molecules are unable to access the genetic materials located inside the virion to perform disinfection functionalities. As alcohol concentration increases, some of the A molecules will enter the interface and substitute for water molecules within. Once in the interface, an alcohol molecule may arrange in a manner that its alkyl group, R, is situated inside the channel to interact hydrophobically with the lipid channel of the phospholipid bilayer. Due to greater hydrophobic interactions, a larger alkyl group has a greater chance to adopt such a penetrating arrangement. For instance, the possibility for ethanol penetration on phospholipid layers is higher than that of methanol.58 Once an A molecule enters the channel, thermal motion and diffusion will drive it further in, and enable it to drag another A molecule hydrogen bonded to it in the interface into the channel. By successive displacing and dragging, more A molecules would get inside the channel. This mechanism will generate a flow of alcohol that penetrates the lipid layer and enters into the core of the virus, as illustrated in Figure 4(b). On the basis of such a penetration mechanism, the virus is expected to be disinfected by the mixture, in which alcohol goes through the nucleocapsid proteins and damages the genomic DNA or RNA, due to the reactivity of nitrogen and oxygen atoms of the nucleic acids.[59]

When alcohol concentration is too high, however, the interface is mainly occupied by A molecules, which are hydrogen-bonded to the polar groups of the phospholipid. These A molecules are arranged in a conformation that their alkyl groups accumulate at the exterior of the interface and interact with each other hydrophobically. In this situation, the aggregate formed by those alkyl groups will block the entrances of channels and prevent the entering of any molecule into the channels, see Figure 4(c). Because alcohol molecules are unable to reach the interior of virion through the penetration mechanism discussed above, no disinfection is expected at high alcohol concentration.

Mechanisms of Antiviral Chemical Agents for Coronavirus

Three key steps in effective viral infections are: maintaining the stability of virions in the environment, recognizing and entering the host cell, and replicating additional viral components. Therefore, most disinfectants target viral membranes (in the case of enveloped viruses), proteins, and genomic materials to compromise one or more viral functionalities described above. [60, 61]

Research on quaternary ammonium compounds (QACs), a group of amphiphilic surfactants that interact favorably with the viral lipid membranes, has shed light on how alcohol molecules might disinfect the virions. Some common QACs include benzalkonium chloride, didecyldimethyl ammonium chloride, alkyl dimethyl benzyl ammonium saccharinate, and cetyl pyridinium chloride.[62] During QAC-viral interactions, the membrane structure will be disrupted, and potentially followed

by penetration and insertion of QACs that further destabilize the viral membrane and lead to the exposure of the genomic materials[63].

Some research found that alcohol, including ethanol, propanol, isopropanol, and dichlorobenzyl alcohol, like amphiphilic QACS, could alter the conformation of the viral phospholipids bilayer by lateral expansion and vertical shrinkage.[64, 65]Such conformational change causes the membrane of coronavirus to become less rigid and more susceptible to foreign species. In addition, alcohol is also suggested to be able to directly denature viral proteins, such as spike protein key to the infection process of SARS-CoV-2. With the compromised membrane, there is a higher chance that alcohol will reach the genomic materials of the virus (RNA in the case of SARS-CoV-2) and damage the genome.

Despite these findings, alcohol loses its antiviral properties at a very high concentration50, where all virus components except genomic materials and nucleoproteins are still exposed to the alcohol. Thus, we suspect that the antiviral properties of alcohol are not limited to the ones suggested in previous research, but due to its damage to nucleocapsids and, most likely, to the genomic materials, hence that alcohol could penetrate the phospholipid bilayer of coronaviruses. We hypothesize that alcohol molecules inactivate the virus primarily by reacting with the viral genome. Chemically, the damage may be attributed to the hydrogen bonding of alcohol to nucleophilic centers of the nucleobases or phosphate of the backbone, or alkylation of genomic materials. [59, 66, 67] However, the specific mechanisms associated with the genomic inactivation are still elusive.

Discussion and Conclusion

In order to cope with the pandemic caused by SARS-CoV-2, it is crucial to contain its spreading by inactivating the virions. Many approaches, such as dehydration, application of heat, disinfecting chemicals, have been investigated and applied for inactivating airborne viruses and viruses on contaminated surfaces based on the viral structure and their interactions with the environment.21 Nevertheless, these approaches are either not feasible in the physiological environment or pose considerable health hazards, and thus could not be utilized to disinfect virions in human bodies. Thus, it is crucial to investigate antivirals that could be applied to inactivate SARS-CoV-2 in a physiological environment. A lot of the research projects have focused on targeting spike proteins (S) of SARS-CoV-2 to achieve disinfection due to high specificity and the crucial roles spike proteins play in viral infection, including virus-host cell recognition, bonding, and viral proliferation. However, as discussed in section II, spike protein is one of the primary sites of viral mutation; in this situation, the effectiveness of antivirals targeting S proteins could be evaded by altered S protein conformation and functionalities, which are partially illustrated in Figure 2. In contrast to S protein, the genome of coronavirus is more conservative across different variants and strains; thus, it could be an ideal candidate for the antiviral target. In a simulation study, the mixture of alcohol (ethanol or n-propanol) and water with only 5 and 10 mol% alcohol could significantly influence model phospholipid bilayer diamitoylphosphotidycholine (DPPC).[65] However, at such low alcohol concentrations, experimental observation reveals that the mixture would not inactivate the virus.50 Therefore, even though the mixture of low alcohol concentration can alter the configuration of the phospholipid bilayer, that alternator does not lead to the inactivation of coronavirus. In section III, we introduced the penetration mechanism that could account for the concentration-dependent disinfecting ability of the alcohol-water mixture and suggests that the disinfection would occur only if alcohol molecules pass through the bilayer and damage the core of the virus, possibly through alkylation. Such observations further show that the interior of viruses is more fragile than its exterior to light and chemicals when exposed to them.[68, 69] However, further research is required to substantiate specific mechanisms of such damage as they are incompletely understood.

This finding, along with previous findings indicating that the viral genome is a potential target for antivirals, shed light on the development of possible amphiphilic chemicals that can target the viral genomic materials as antivirals through mechanisms that are similar to the alcohol penetration mechanism presented in add here III. Like alcohol, the affinity of such chemicals has to be so low that it would not chemically react with the exterior of the virus. In addition, since the genomic materials are more chemically conservative, one may expect that such possible antivirals would disinfect all strains as well as variants of coronavirus with minimal potency compromisation. In the alcohol penetration mechanism, a concentration of alcohol that is not feasible in a physiological environment is required to achieve effective disinfection. Therefore, in order for the application of antiviral agents to the physiological environment to be practical, the antiviral molecules will also need to be hydrogen-bonded to the interface more strongly than water, so that even at a low concentration, a significant number of the molecules can be replaced by water molecules at the interface.

It is noteworthy that while viruses derive their membranes from eukaryotic host cell membranes, the virus lacks many components that are unique to host cells such as host cell membrane proteins. These components could potentially prevent the entry of antivirals into the human cells and thereby decrease the antiviral agents' toxicity to human beings. Such discrepancies could further aid the progress in developing and selecting antivirals that target only coronavirus without passing through the plasma membrane or causing damage to the host cell genome.[70]

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Contributions

Conceptualization, investigation, data analysis, writing of the manuscript, editing, and reviewing were conducted by both authors cooperatively. All authors have read and agreed to the published version of the manuscript.

Ethics Declaration

The authors declare that they have no conflicts of interest.

This article does not contain any studies involving animals performed by any of the authors.

This article does not contain any studies involving human participants performed by any of the authors.

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