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Utilization of physical and chemical microbial load reduction agents for SARS-CoV-2: Toxicity and development of drug resistance implications

Sani Yahaya Najib[1], Yusuf Oloruntoyin Ayipo[1], Abubakar Shaaban[2], Mohd Nizam Mordi[1], Abdullahi Rabiu Abubakar[3], Adekunle Babajide Rowaiye[4], Sayeeda Rahman[5], Rahnuma Ahmad[6], Bushra Ayat Meghla[7], Nihad Adnan[7], Mainul Haque[8*]

[1]Centre for Drug Research, Universiti Sains Malaysia, Pulau Pinang, Malaysia
[2]Department of Pharmaceutical and Medicinal Chemistry, Bayero University Kano, Kano, Nigeria.
[3]Department of Pharmacology and Therapeutics, Faculty of Pharmaceutical Sciences, Bayero University Kano, Kano, Nigeria.
[4]National Biotechnology Development Agency, Abuja, Nigeria.
[5]School of Medicine, American University of Integrative Sciences, Bridgetown, Barbados.
[6]Department of Physiology, Medical College for Women and Hospital, Dhaka, Bangladesh.
[7]Department of Microbiology, Jahangirnagar University, Dhaka, Bangladesh.
[8]Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), Kem Perdana Sungai Besi, Kuala Lumpur, Malaysia.

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ABSTRACT

The novel human coronavirus (CoV) 2019, similar to previous severe acute respiratory syndrome corona virus-1 outbreaks, has posed the unprecedented challenges that have shaped global action on preventive and easy to employ measures and policies, including regular disinfection. There is an indiscriminate use of antimicrobial agents, which may pose toxicity to humans, environmental hazards, and, in some cases, development antiviral drug resistance. This review comprehensively highlights the physical and chemical countermeasures applied to prevent various CoV infections and their potential toxicity on humans and the environment, as well as the danger of developing drug resistance. Literature information was sourced from PubMed, ScienceDirect, Embase, MEDLINE, and China National Knowledge Infrastructure databases using Google Scholars and Free Full PDF as search engines. Articles written in the English language were retrieved and included in the study. Researches covering the literature on physical and chemical severe acute respiratory syndrome corona virus-2 preventive measures, their toxicity, and possible ways of developing drug resistance were also discussed. The literature review reveals that physical inactivation under the influence of temperature, humidity, and light, especially ultraviolet-C radiation, has proven effective in reducing the spread of CoV infections. Similarly, chemical countermeasures such as the use of alcohol- and iodine-based disinfecting agents have demonstrated inhibitory potentials of the viruses on surfaces depending on nature, dose, and exposure time. The inactivation occurs through the interference of these agents with the lipid envelope, thereby disrupting the viral activity. A vast majority of the antimicrobial agents are reported to contain corrosive chemicals that are toxic to humans, especially children, and the environment. The toxicity is due to the unhealthy accumulation and pollution caused by the inappropriate disposal of biomedical waste. This study showed that chemicals might have long-term effects on public health, such as reproductive disorders, chronic obstructive pulmonary disease, cancers, skin damage, and central nervous system impairment. Therefore, further research on long-term preventive alternatives such as the formulation of these agents with natural products as active ingredients is necessary to mitigate the effects of alcohol- and iodine-based chemicals on humans and the environment.

**Corresponding Author*
Mainul Haque, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), Kem Perdana Sungai Besi, Kuala Lumpur, Malaysia E-mail: runurono @ gmail.com

INTRODUCTION

The outbreak of severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) disease, mostly called coronavirus disease-19 (COVID-19), has proven that new infectious diseases can spread in humans rapidly to pose a global public health challenge, especially where the containment of the disease is difficult (García de Abajo *et al*., 2020). This sudden outbreak of COVID-19 has surprised the vast majority of healthcare practitioners and scientists, who are working tirelessly to educate people and combat the pandemic (Rai *et al*., 2020). The SARS-CoV-2 is an enveloped positive-sense, single-stranded ribonucleic acid (RNA) virus belonging to the class of beta-coronaviruses (Anderson *et al*., 2020; Rahman *et al*., 2021). Severe Acute Respiratory Syndrome Corona Virus-1 (SARS-CoV-1) and Middle East Respiratory-Corona Virus (MERS-CoV) are endemic viruses that have previously wreaked havoc on human healthcare systems through animal-to-human, human-to-human, and, recently reported, human-to-animal transmissions making it spread quickly (Ayipo *et al*., 2021; Banik *et al*., 2015; Cleary *et al*., 2020). Currently, no approved antiviral drug is used to treat SARS-CoV and MERS-CoV infections, but the deployment of several effective vaccines against SARS-CoV-2 infection is in progress (Abubakar *et al*., 2020; Amanat and Krammer, 2020; Habas *et al*., 2020; Rahman *et al*., 2021). The SARS-CoV-1 and MERS-CoV are responsible for the epidemics of SARS in 2003 and MERS in 2012. The viruses are easily transmitted through droplets and air (Zhu *et al*., 2020). The effective and quick control of SARS-CoV-2 outbreaks can be achieved through the epidemiological knowledge of the disease, accurate viral detection, preventive strategies, and acceptable hygiene practices to decrease the risk of transmission. Although health practitioners in both developed and developing countries are overwhelmed with the pandemic, the need for a solid motivation to limit the spread and adopt future strategic plans for effective prevention remains necessary (Boyce and Pittet, 2002).

Viruses such as influenza, the common cold rhinovirus, and CoVs can be easily transmitted from an infected person to a healthy individual through coughing, sneezing, talking, and sometimes breathing (Asadi *et al*., 2020). Suggestively, these physiological actions produce aerosol droplets of various sizes and may carry infectious viruses that could initiate new infections, especially when inhaled by individuals (García de Abajo *et al*., 2020). The people at high risk of hospital-acquired infections such as SARS-CoV-2 are the healthcare professionals (HCPs) and emergency rescue workers (Wilson *et al*., 2020). This was evident from early reports of several HCPs infected from the origin of SARS-CoV-2, Wuhan, China (Wang *et al*., 2020a). Not only are these exposed HCPs at higher risk, but they are also potential carriers of the virus, especially those with closer contact with patients such as dentists, emergency physicians, and maxillofacial surgeons. Hence, there is a need for regular disinfection, decontamination, and proper sterilization techniques to prevent viral transmission (Krajewska *et al*., 2020; Peng *et al*., 2020).

One of the recommended practices for inactivating and removing pathogenic organisms from surfaces is disinfecting and sterilizing agents through stipulated procedures and protocols. Disinfection is a process of reducing virtually all recognizable pathogenic microorganisms using chemical agents only (Rai *et al*., 2020). Meanwhile, sterilization eliminates or destroys all microbial life forms by applying both chemicals and heat methods. Both sterilization methods at large are routinely carried out in healthcare facilities (Hassandarvish *et al*., 2020).

There are scientific guidelines and protocols for selecting and using disinfectants in hospitals, laboratories, homes, and public places. This is to minimize health risks and ensure the appropriate use of chemicals (Rutala *et al*., 2000). However, recently, due to the outbreak of COVID-19, there has been an upsurge in the indiscriminate use of alcohol- and iodine-based agents with no adherence to the stipulated guidelines and monitoring protocols for preventing and inactivating SARS-CoV-2 (McDonnell and Russell, 1999). This malpractice exposes humans to public health dangers and environmental hazards. It also has negative consequences on biodiversity due to the toxicological effects of such disinfectants (Agnelo *et al*., 2020; Nabi *et al*., 2020). Therefore, the excessive use of these antimicrobial agents has raised much public health and environmental concerns.

MATERIALS AND METHODS

Literature information was sourced from PubMed, ScienceDirect, Embase, MEDLINE, and China National Knowledge Infrastructure (CNKI) databases using Google Scholars and Free Full PDF as search engines. Articles written in the English language were retrieved and included in the study. This article discussed the physical and chemical countermeasures of microbial reduction agents and the prevention of CoVs, their potential toxicity, and safety to humans and the environment during the COVID-19 pandemic. Lastly, possible ways of developing drug resistance due to indiscriminate production and practices were highlighted.

DISINFECTANTS AND STERILIZING AGENTS

Disinfection is a process that eliminates many or all microorganisms from inanimate objects, whereas sterilization removes all microbes. Agents used to kill pathogenic microbes from inanimate objects or surfaces are called disinfectants, and those capable of destroying all microbes are sterilizing agents (Rutala and Weber, 2013; 2016).

Physical disinfectants and sterilant

Disinfectants that destroy pathogens utilizing physical agents such as heat, pressure, light, and irradiation are referred to as physical disinfection. These agents can directly damage microbes by various mechanisms such as damage to the cell membrane, deoxyribonucleic acid (DNA) or RNA, enzyme, or protein (Rutala and Weber, 2013; 2016).

Heat

Heat treatment is one of the simplest, widely used, most effective, and oldest methods. Heat can be applied in a hydrated (moist heat; 121°C–134°C) or dry state (160°C–180°C). Heat sterilization denatures or coagulates the protein or enzyme of the virus or cell, which causes the cell to die. Dry heat kills microbes through oxidative damage (Popat *et al*., 2010). Incineration, hot air oven, red heat, flaming, and infrared are examples of dry heat sterilization (Rutala and Weber, 2013; 2016). To supply heat, there are various methods as follows.

a. Solar

Solar energy can be used for disinfection. Several reactors are available that can convert energy from solar irradiation (Abraham *et al*., 2015). Ultraviolet (UV) and visible light inactivation is often used along with solar power and can be used alone, such as for black-box solar heaters or solar water heat exchangers. Light is not exposed to the media (Safapour and Metcalf, 1999). It is necessary to use a thermometer or indicator as sunlight may not supply enough heat (Ray and Jain, 2014).

b. Microwave

1–350 GHz is the lethal range of microwave for microbes, with deadly peak effects at 60 GHz (Fleming, 1944; Green *et al*., 1997). Microwaves kill microbes by affecting proteins and depend highly on the molecules' bound water content. Absorbed energy is converted to heat energy (Hong *et al*., 2014; Park *et al*., 2006). It has the advantage of fast heating and lowers energy expenditure, but they need more equipment and technical expertise (Green *et al*., 1997).

Sonication

Sonic or supersonic waves kill microbes by a rapid compression and liquid release, tearing the suspended cells into pieces (Otte *et al*., 2018; Rahn, 1945).

Radiation processes

Electromagnetic radiation (UV light and gamma rays) and particulate radiation such as accelerated electrons are used for sterilization. Radiation targets microbial DNA to kill them. Free radical is produced when exposed to gamma rays, whereas UV light causes excitation. Cobalt-60 is the source of gamma rays. 260 nm is the optimum wavelength of UV sterilization, and a mercury lamp that gives peak emission at 254 nm is a suitable source (Rattanakul and Oguma, 2018).

Pulsed electric field

A system that produces an electric field utilizing two-electrode generates acoustic and shock waves, UV irradiation, and reactive oxygen species. Although it is unaffected by particles, this process is expensive and very effective for disinfection (Anpilov *et al*., 2002; Frey *et al*., 2013; Gusbeth *et al*., 2009; Poyatos *et al*., 2011; Yadollahpour *et al*., 2014).

Hydrodynamic cavitation

Despite having a similar mechanism as sonication, high pressure and local temperatures are achieved by rapid mixing or pumping the process solution. Steam injection, shock wave, high-speed homogenizer, high-pressure systems, and liquid whistle are the types of reactors used (Gogate, 2011; Gogate and Pandit, 2010).

Plasma emission and shock waves

Plasma emission and shock waves, visible light emission, and UV are used for disinfection. The inactivation mechanism is thought to be irreversible destruction of membrane for bacteria and DNA and RNA damage for viruses (Mosqueda-Melgar *et al*., 2008; Sale and Hamilton, 1967; Sabino *et al*., 2020; Stratton *et al*., 2015).

Ultrasound

It is a complex process that inactivates microbes by the growth of bubbles. Dust or bacteria become part of the bubbles in company with vapor and gas. When the bubble collapse, microbes are exposed to high pressure (100 MPa) and temperature (5,000 K) for a few seconds, which cause their inactivation (Crum, 1994; Flint and Suslick, 1991; Suslick *et al*., 1999; Tandiono *et al*., 2011).

Magnetic treatment

Magnetic treatment is a new method of physical disinfection of water. The magnetic field creates a polarizing effect on ions and water molecules when the water and its impurities are in a state of thermodynamic equilibrium. There are several different hypotheses about the mechanism of magnetic treatment, and more research is needed for a better understanding (Biryukov *et al*., 2005; Li *et al*., 2020b; Vaskina *et al*., 2020).

Filtration

It is the process that removes microbes without destroying them. Trapping, sieving, and adsorption within the matrix of filter material is the mechanism involved in the filtration technique (Nnadozie *et al*., 2015).

Chemical disinfectants and sterilant

Disinfectants are chemically diverse agents with small and usually lipophilic molecules that eliminate many pathogenic organisms and penetrate the skin quickly to induce a direct reaction. Therefore, they can destroy pathogenic microorganisms on surfaces (Chernyshov and Kolodzinska, 2020). There are different types of chemical disinfectants, and they kill microbes through other mechanisms.

Alcohols

Other than bacterial spores, alcohol can kill microbes efficiently. The antimicrobial effect of alcohol depends on the presence of water, as proteins tend to denature quickly in the presence of water. Ethyl alcohol and isopropyl alcohol are most commonly used in healthcare settings, and their optimum bactericidal concentration is 60%–90% v/v in water. Alcohol-based disinfectant activity against microbes drops when the concentration is below 50% (Block, 2001; Morton, 1950; Jing *et al*., 2020; McDonnell and Russell, 2001). Concentration between 60% and 80% of ethyl alcohol is an effective virucidal agent for all lipophilic viruses and many hydrophilic viruses such as rotavirus and adenovirus, but not hepatitis A virus or poliovirus (Mbithi *et al*., 1990; Tyler *et al*., 1990). On the other hand, isopropyl alcohol is active against lipid viruses (Armstrong and Froelich, 1964; Kampf *et al*., 2020).

Chlorine and chlorine compounds

The most commonly used chlorine disinfectants are the hypochlorites, available in solid (sodium hypochlorite) and liquid (calcium hypochlorite) forms as a household bleach sodium hypochlorite is used as an aqueous solution at 5.25%–6.15% concentration (Rutala and Weber, 1997). Sodium dichloroisocyanurate, chlorine dioxide, and chloramine-T are the chlorine-releasing agents used in healthcare settings as their bactericidal effect is more prolonged (Clasen and Edmondson, 2006; Coates and Wilson, 1989). There are various possible mechanisms of action for these compounds, although the precise mechanism is not known. Sulfhydryl enzymes and amino acids oxidation, losing intracellular contents, protein synthesis inhibition, decreasing uptake of nutrients and oxygen, respiratory component oxidation, DNA breaks, decreased production of adenosine triphosphate, ring chlorination of amino acids, and depressed DNA synthesis are the possible modes of action of these disinfectants (Block, 2001). The combination of these factors or the effect of the disinfectant on a binding site may cause the death of microbes (Hernández-Navarrete *et al*., 2014).

Formaldehyde

Formaldehyde is an effective disinfectant and sterilant in its aqueous and gaseous form (Kinyoun, 2006; Lin *et al*., 2020). The aqueous solution of formaldehyde is known as formalin which contains 37% formaldehyde (McCulloch and Costigan, 1936). Alkylation of the ring nitrogen atoms present in purine bases and sulfhydryl amino groups of the proteins by formaldehyde causes the microbe to be inactivated (Block, 2001). Formaldehyde is a potent carcinogen, and the US Federal Agency on Occupational Safety and Health Administration instructed it to be handled carefully in the workplace. It can be fatal if ingested by employees and can cause skin irritation and respiratory problems (Costa *et al*., 2019; Sweatt, 2020).

Glutaraldehyde

It is a saturated dialdehyde which is not only an effective disinfectant but also a sterilant. An aqueous solution of glutaraldehyde is not sporicidal unless activated by adding an alkylating agent (pH 7.5–8.5) with a shelf-life of a minimum of 14 days. To overcome this limitation, a novel formulation such as glutaraldehyde-phenol-sodium phenate, potentiated acid glutaraldehyde, and stabilized alkaline glutaraldehyde is used, having its microbicidal activity for 28–30 days (Miner *et al*., 1977; Sehmi *et al*., 2016). Glutaraldehyde kills microbes by altering DNA, RNA, and proteins by alkylating the hydroxyl, carboxyl, sulfhydryl, and amino groups (Block, 2001). Because of its excellent biocidal property, ability to work even in the presence of organic load (20% bovine serum), and noncorrosive action to various equipment, it is used widely in healthcare facilities (Lu *et al*., 2020; Rutala *et al*., 1991).

Quaternary ammonium compounds (QACs)

They are an established disinfectant and good cleaning agent. However, cotton and gauze pad-like materials and high-water hardness can make them less microbicidal. The active ingredient can be absorbed by cotton and gauze materials and insoluble precipitates, respectively (Gerba, 2015; Nasr *et al*., 2018). The disintegration of the cell membrane, essential cellular protein denaturation, and energy-producing enzyme inactivation caused by these compounds kill microbes (Kampf *et al*., 2020; Ogilvie *et al*., 2021; Pratelli, 2008; Saknimit *et al*., 1988). Alkyl didecyl dimethyl ammonium chloride, alkyl dimethyl benzyl ammonium chloride, and dialkyl dimethyl ammonium chloride are some of the QACs used in healthcare settings. Fourth-generation QACs, also referred to as twin-chain or dialkyl quaternary (e.g., dioctyl dimethyl ammonium bromide and didecyl dimethyl ammonium bromide), are capable of retaining their activity in hard water and also can tolerate anionic residues (Block, 2001).

Phenolics

Phenols are protoplasmic poisons at high concentrations; they precipitate the cellular proteins by penetrating and distorting the cell wall. Phenol derivatives of **low molecular weight** and phenols of low concentration inactivate (Walsh *et al*., 2019), essential enzyme systems cause critical metabolite leakage, resulting in bacterial death (Block, 2001). *Ortho*-phenylphenol and *ortho*-benzyl-*para*-chlorophenol are commonly used phenol derivatives found in hospital disinfectants, and they work more efficiently than the parent compound. Porous materials absorb the phenolics, and the residual disinfectant is capable of irritating tissue. *Para*-tertiary butyl-phenol and *para*-tertiary amyl phenol in phenolic detergent can cause skin depigmentation (Kahn, 1970).

Peracetic acid

It is an effective agent that works against all microbes and has several advantages. It does not leave any residue, can remove organic material, and does not disintegrate into harmful products such as acetic acid and reactive oxygen species (Ao *et al*., 2021; Block, 2001; Kahn, 1970). Although not clearly understood, it is assumed to work similarly to other oxidizing agents such as protein denaturation, disruption of cell walls permeability oxidation of sulfhydryl and sulfur bonds in enzymes, proteins, and other metabolites (Block, 2001; McDonnell and Russell, 1999). Diluted peracetic acid solution (e.g., 1%) is less stable, but with higher concentration (e.g., 40%), it retains its activity for a more extended period. Its corrosive effect on several metals (e.g., steel, galvanized iron, copper, bronze, and brass) can be minimized by pH modification and additives (Ao *et al*., 2021; Block, 2001; Kahn, 1970).

Hydrogen peroxide

Hydrogen peroxide is a strong and effective biocidal agent and works against a wide range of microbes and spores. It produces destructive hydroxyl free radicals that attack DNA, essential cell components, and membrane lipids. Although aerobic and facultative anaerobes with cytochrome systems can withstand metabolically produced hydrogen peroxide, they cannot tolerate the concentration of hydrogen peroxide in disinfectants (Block, 2001; Ríos-Castillo *et al*., 2017). 3% hydrogen peroxide is an effective disinfectant when used on inanimate surfaces, and 3%–6% concentration is used for soft contact lenses (Silvany *et al*., 1990), ventilator (Judd *et al*., 1968), endoscope (Vesley *et al*., 1992), fabrics (Neely and Maley, 1999), and tonometer biprisms (Lingel and Coffey, 1992).

Ortho-phthalaldehyde

Ortho-phthalaldehyde (OPA) is a clear, pale-blue liquid that contains 0.55% 1,2-benzenedicarboxaldehyde with a pH of 7.5. Despite having a similar mode of action as glutaraldehyde, OPA has less potency in cross-linking. It is reimbursed by its lipophilic aromatic nature that assists its uptake by the outer layer of Gram-negative bacteria and mycobacteria (Simons *et al*., 2000; Walsh *et al*., 1999). OPA kills spores by blocking their germination process (Cabrera-Martinez *et al*., 2002). Although excellent material compatibility, it stains protein in gray and should be handled carefully (Rutala and Weber, 1999).

Iodophors

Iodophors are a mixture of iodin and its solubilizing agent or carrier. They are iodine-releasing agents. The released iodine can penetrate the microbial cell membrane and damage proteins by attacking the sulfuryl and disulfide bonds. It can also damage nucleic acid. Povidone-iodine is the most common and widely used iodophor. They are nonstaining, nontoxic, and nonirritating (Block, 2001; Eggers *et al*., 2018a; 2018b; Gharpure *et al*., 2020; Kariwa *et al*., 2006).

CORONAVIRUSES

The main component of the virus, a nucleic acid, is surrounded by capsids which protect the nucleic acid and facilitate binding of the virus to the host cell. The nucleic acid is the component that codes for the essential element for viral replication (Martin, 2003). Viruses are incapable of replicating when they are outside of the host cell. Still, they can survive for a defined time depending on the environment and infect a suitable host cell to replicate. Viruses use the host cell machinery to replicate (Yeargin *et al*., 2016). They can infect various host cells, including bacteria, and cause disease (Sidwell *et al*., 1966). CoVs are the member of the subfamily Orthocoronavirinae from the family Coronaviridae of the order Nidovirales. They are +ssRNA enveloped viruses (V'kovski *et al.*, 2021). They can infect a wide range of hosts (Saif *et al*., 2019) and cause respiratory disease. Although human coronaviruses (HCoVs) cause mild respiratory diseases and common cold in humans, the adapted forms from the nonhuman host such as SARS-CoV-1, MERS-CoV, and SARS-CoV-2 are capable of causing severe illness (Xu, 2020a).

The novel coronavirus, SARS-CoV-2, contains spike glycoprotein that binds to the sialic acid receptor of the host cell (Tortorici *et al*., 2019). It is an enveloped virus and causes respiratory infection (V'kovski *et al.*, 2021; Xu, 2020b). The binding of the spike glycoprotein to the specific receptor of the human respiratory tract, angiotensin-converting enzyme-2, facilitates viral entry. The low endosomal pH helps with the proteolytic activation of the spike glycoprotein. So, the coating structure that enables the access of the virus to the host cell is a crucial target of antiviral drug discovery (Zhang *et al*., 2020). The disinfectants inactivate viruses by causing damage to either their proteins or their genome (Alvarez and O'Brien, 1982; Dennis Jr *et al.*, 1979; Kim *et al.*, 1980; O'Brien and Newman, 1979; Roy *et al.*, 1981). Disinfecting agents used for different coronaviruses are shown in Table 1.

STABILITY OF SARS-COV-2 IN AIR AND ON DIFFERENT SURFACES

The SARS-CoV-2 is spread on the dry surfaces through respiratory droplets secreted from the infected person's nose, mouth, and eyes and is considered the primary route of transmission of this virus (Chan *et al*., 2020). Low humidity and temperatures increase the viability of SARS-CoV-2 in the droplets (Moriyama *et al*., 2020). HCoVs can remain infectious for 2 hours to 9 days at room temperature on different surfaces (Kampf *et al*., 2020). This time can be up to 28 days for veterinary coronaviruses, and an increase in the temperature to 30°C or more induces shorter endurance of coronavirus (Kampf *et al*., 2020). Studies by Kampf *et al*. (2020) and van Doremalen *et al*. (2020) also showed that SARS-CoV-2 could survive on a variety of surfaces from hours to days (Table 2) (Choi *et al*., 2021; van Doremalen *et al*., 2020). The SARS-CoV-2 was more stable on plastic and stainless steel than on copper and cardboard, and the viable virus was detected up to 72 hours, and its titer was significantly reduced afterward (van Doremalen *et al*., 2020). The virus can remain infectious and feasible in aerosols for 3 hours and on surfaces up to days (van Doremalen *et al*., 2020). The persistence time on inanimate surfaces varied from minutes to days, depending on environmental conditions. SARS-CoV-2 can be sustained in the air in closed unventilated buses for at least 30 minutes without losing infectivity. Additionally, MERS-CoV can survive 28 days or more (Ren *et al*., 2020). Absorbent materials like cotton are safer than unabsorbent materials for protection from virus infection. The risk of transmission via touching contaminated paper is low (Ren *et al*., 2020). However, the significance of indirect communication through contamination of inanimate surfaces is uncertain and requires further investigation (Armstrong and Froelich, 1964; Chan *et al*., 2020; Choi *et al*., 2021; Moriyama *et al*., 2020; Ren *et al*., 2020; van Doremalen *et al*., 2020).

PHYSICAL INACTIVATION OF SARS-COV-2

The inactivation of airborne viruses and those deposited on active surfaces reduces disease transmission, which is a necessary counterpreventive measure in combating the COVID-19 pandemic. Physical factors such as temperature and humidity greatly influence the survival of viruses on surfaces. However, scientists reported the rapid inactivation of gastroenteritis virus (TGEV) and mouse hepatitis virus (MHV) at all humidity levels (Casanova *et al*., 2010). Furthermore, in an indoor space, heat and irradiation such as UV inactivated TGEV and MHV (Casanova *et al*., 2010; Garcia de Abajo *et al*., 2020). Nevertheless, a study has shown that the spread of SARS-CoV-2 is not strongly affected by the change in weather conditions (Casanova *et al*., 2010). Therefore, it is crucial to efficiently decrease viral transmission rates within indoor spaces such as shared offices, classrooms, healthcare facilities, and public transport vehicles. The use of physical disinfecting agents in such areas is easily deployable and economically affordable (Garcia de Abajo *et al*., 2020).

HEAT AND ULTRAVIOLET IRRADIATION

Sufficient physical inactivation of SARS-CoV-2 can be achieved through exposure to heat and UV radiation. For instance, more than 50% viral inactivation was effectively achieved within 5 min of exposure of SARS-CoV-2 to heat at 56°C or by applying UV irradiation. The viral cytopathic effect and infectivity were drastically distorted due to physical manipulations on the cells, affecting the titer, stability, and virulence (Kariwa *et al*., 2006). A study revealed that the SARS-CoV-2 virus is highly stable at 4˚C, and when exposed to varying temperatures, exceptionally as high as 56°C, the virus loses its infectivity and virulence. The decrease in viral titer supports heat as a crucial physical inactivator of the virus during the pandemic (Abraham *et al*., 2020; Chin *et al*., 2020). Similarly, prolonged exposure of the virus to heat for about 30 min reportedly affects viral infectivity and stability, and therefore, a high temperate climate might be beneficial in inactivating the virus (Kariwa *et al*., 2006).

Table 1. Disinfectants and their ability to reduce the viral load for different coronaviruses (Bedell *et al*., 2016, Dellanno *et al*., 2009, Eggers *et al*., 2015, Eggers *et al*., 2018a, Emmoth *et al*., 2011, Goyal *et al*., 2014, Hindawi *et al*., 2018, Kariwa *et al*., 2006, Leclercq *et al*., 2014, Noorimotlagh *et al*., 2021, Pratelli, 2007, Pratelli, 2008, Rabenau *et al*., 2005a, Rabenau *et al*., 2005b, Saknimit *et al*., 1988, Sattar *et al*., 1989, Siddharta *et al*., 2017, Tyan *et al*., 2018, Wood and Payne, 1998).

Coronaviruses	Disinfectants (concentration)	Viral load reduction ($\log_{10}$)	Reference
TGEV (transmissible gastroenteritis coronavirus of pigs,a SARS-CoV surrogate)	Three different volumes of Hydrogen peroxide vapor (HPV): 25, 27, and 33mL	>4.94–5.28	Goyal *et al*., 2014
canine coronavirus	2-propanol (70%)	>3.3	Saknimit *et al*., 1988
	2-propanol (50%)	>3.7	
	Formaldehyde (0.7%)	>3.7	
	Sodium hypochlorite (0.01%)	1.1	
	Benzalkonium chloride (0.05%)	0.9	
	Sodium hypochlorite (0.001%)	> 3.7	
	Chlorhexidine digluconate (0.02%)	0.3	
Mouse hepatitis virus, MHV (Strain MHV1 and MHV–N)	Ethanol (70%)	> 3.9	Saknimit *et al*., 1988
	Formaldehyde (0.7%)	> 3.5	
	Benzalkonium chloride (0.05%)	> 3.7	
	Chlorhexidine digluconate (0.02%)	>3.7	
	Sodium hypochlorite (0.01%)	2.3–2.8	
	Sodium hypochlorite (0.001%)	0.3–0.6	
	2-propanol (50%)	0.7–0.8	
MHV (Strain MHV-1)	sodium hypochlorite (0.21%)	≥ 4.40	Dellanno *et al*., 2009
MHV (Strain A59)	Whole-room UV-C disinfection system using an automate, continuous, multiple-emitter	2.71	Bedell *et al*., 2016
CCoV (Strain S37)	Benzalkonium chloride (0.00175%)	3.0	Pratelli, 2007
	Didecyl-dimethyl-ammonium chloride, DDA (0.0025%)	> 4.0	
CCoV (Strain S378)	Formaldehyde (0.009%)	> 4.0	Pratelli, 2008
Feline coronavirus,FCoV [Strain DF2, American Type Culture Collection (ATCC) VR-2004]	Ammonia disinfection (25%)	> 5.0	Emmoth *et al*., 2011
Human coronavirus, HCoV (Strain 229E)	Ethanol (70%)	> 3.0	Sattar *et al*., 1989
	Glutardialdehyde (2%)	> 3.0	
	Benzalkoniumchloride (0.04%)	< 3.0	
	Sodium hypochlorite (0.5%)	> 3.0	
	Sodium hypochlorite (0.1%)	> 3.0	
	Sodium hypochlorite (0.01%)	< 3.0	
HCoV (Strain 229E, ATCC VR-7)	Sodium hypochlorite (0.5%)	≥ 4.50	Tyan *et al*., 2018

Coronaviruses	Disinfectants (concentration)	Viral load reduction ($\log_{10}$)	Reference
HCoV (ATCC VR-759, strain OC43)	Benzalkonium chloride (0.2%)	0.0	Wood and Payne, 1998
SARS-CoV-1 (Isolate Frankfurt-1)	Ethanol (80%)	≥ 4.25	Rabenau *et al*., 2005a, Rabenau *et al*., 2005b, Siddharta *et al*., 2017
	Ethanol (85%)	≥ 5.5	
	Ethanol (95%)	≥ 5.5	
	Isopropanol (45%), n-propanol (30%)	≥ 4.25	
	2-propanol (100% and 70%)	≥ 3.31	
	2-propanol (75%)	≥ 4.0	
	Desderman N (0.2% 2-biphenylol, Ethanol 78%)	≥ 5.01	
	2-propanol (45%), 1-propanol (30%)	≥ 2.78	
	Glutaraldehyde (0.5%)	≥ 4.01	
	Formaldehyde (0.7% and 1.0%)	≥ 3.01	
	Incidin plus (2%) glucoprotamin (26%)	≥ 1.68	
	Temperature (4°C)	0	
	Temperature (56°C)	≥ 5.01	
	Temperature (60°C)	≥ 5.01	
SARS-CoV-1 (Strain Tor 2)	Gamma irradiation at 1 Mrad from a cobalt-60 source	> 4.0	Siddharta *et al*., 2017
	Glutaraldehyde, 2.5%	> 4.0	
SARS-CoV-1 (Hanoi strain)	Povidone iodine (PVP-I), 1%(1 min)	> 4.0	Kariwa *et al*., 2006
	PVP-I, 0.47%	3.8	
	PVP-I, 0.25%	> 4.0	
	PVP-I, 0.23%	>4.0	
MERS-CoV [Strain Erasmus Medical Center (EMC)]	Ethanol (80%)	>4.0	Siddharta *et al*., 2017
	2-propanol (75%)	≥4.0	
MERS-CoV(MERS-CoV/Hu/Taif/SA/2015)	amotosalen and Ultraviolet A disinfection	>4.67	Hindawi *et al*., 2018
MERS-CoV (Hu/France–FRA2_ 130569/2013 (FRA2))	Heat inactivation by three different temperatures;		Leclercq *et al*., 2014
	Temperature 65 °C (1 min)	4.0	
	Temperature 56 °C (25 min)	4.0	
	Temperature 25 °C (2 h)	0	
MERS-CoV (Isolate HCoV-EMC/2012)	PVP-I, 1.0%	4.3	Eggers *et al*., 2015
	PVP-I, 4.0%	5.0	
	PVP-I, 7.5%	4.6	
MERS-CoV (Isolate HCoV- EMC/2012)	0.23% PVP-I	≥ 4.4	Eggers *et al*., 2018a

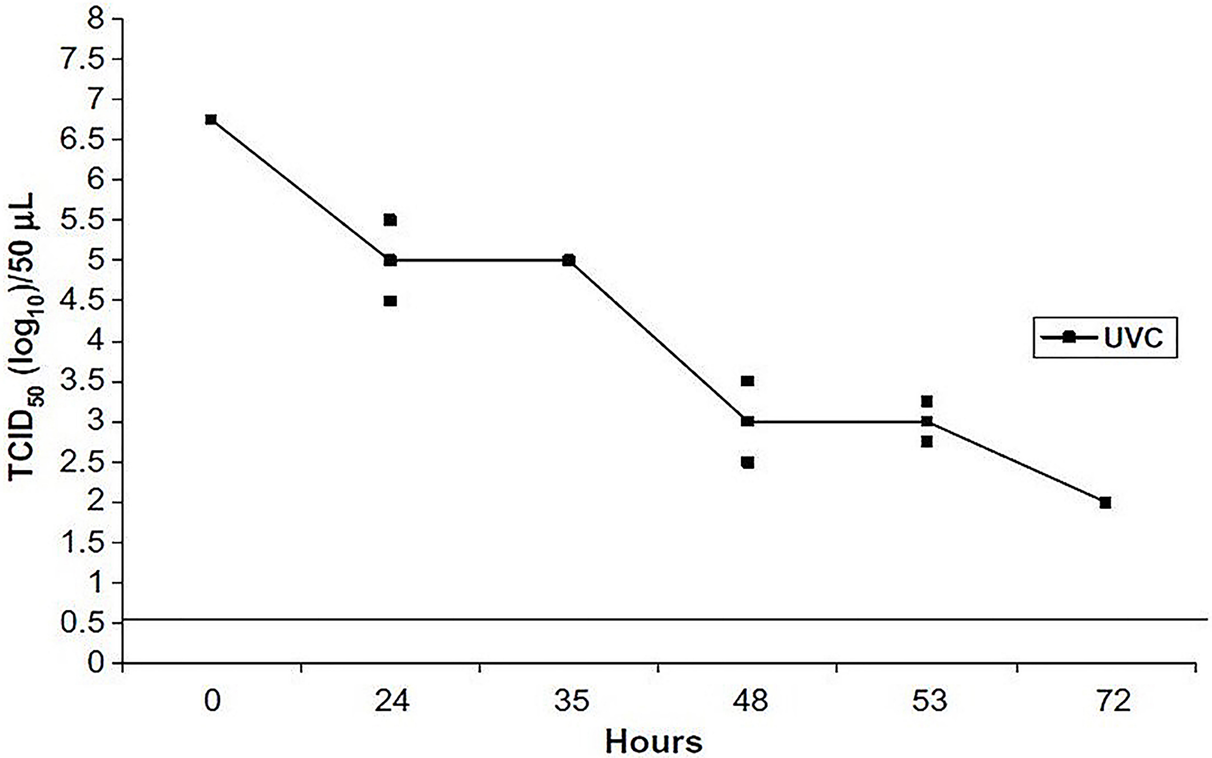

Figure 1. Effect of UV-C radiation on the infectivity of CCoV *in vitro*. Virus aliquots were placed at about 4 cm from the UV-C source, then removed, and then titrated by the TCID50 assay at fixed time points. The straight line delineates the detection limit of the test (reprinted with permission from Pratelli *et al.* (2008), licensed under CC-BY-4.0, Copyright, (2008), @ Elsevier Ltd.).

Furthermore, UV, especially UV-C radiation, is one of the primary methods for the physical inactivating of viruses. It is harmful to pathogenic microorganisms due to its molecular damage to RNA and DNA bases. At the range of 200–280 nm wavelength, specifically using fluorescence light of 254 nm, UV-C reportedly inactivates influenza and SARS-CoV-2 viruses. Thus, using these specific lights in the sterilization process in hospitals, laboratories, and homes is essential (Abraham *et al*., 2020; Derraik *et al*., 2020; Garcia de Abajo *et al*., 2020). A previous study revealed the advantages of UV-C in preventing infection by viruses, especially SARS-CoV-2 (Mackenzie, 2020; Szeto *et al*., 2020). In animals, UV-C has proven to decrease Canine CoV (CCoV), seen in puppies (Fig. 1). Therefore, this can ideally experiment on human CoVs (Pratelli, 2008).

Moreover, UV-C is recently used in reducing air transmission of viruses. It is also an essential method of inactivating viruses and, therefore, can experiment in the disinfection process against the SAR-CoV-2 (Beck *et al*., 2017; Mphaphlele *et al*., 2015; Xia *et al*., 2019). However, precautionary measures should be adopted in applying UV-C light as a sterilization method because it can significantly damage eyes and produce carcinogenic effects considerably if the recommended limit exceeds (Garcia de Abajo *et al*., 2020).

Several other scientific studies also highlighted the importance of UV-induced viral inactivation. Inagaki *et al*. (2020) reported the concentration-dependent rapid inactivation of SARS-CoV-2 upon exposure to UV light-emitting diode (LED) of wavelength 280 ± 5 nm and subsequent decrease in cytopathic effect. In addition to heat and UV, sunlight is one of the physical inactivation processes of the SARS-CoV-2 virus. It was reported that bright day sunlight above sea level causes variations in the life cycle of CoVs and rapidly inactivates the virus on the surface. This implies that viruses in indoor and outdoor spaces are affected by the different amounts of radiation. However, this needs to be further investigated to ascertain the effects of sunlight (Fig. 2) (Ratnesar-Shumate *et al.*, 2020). The variations in the reported cases of CoV infection across various temperate regions have not realistically proven the hypothesis. For instance, the total reported cases in France as of November 2020 stand at 2,086,288 (3.19%). In comparison, a less temperate Ukraine recorded 583,510 (1.34%) with a death rate of 2.26% and 1.78%, respectively (Quinn *et al*., 2021), indicating the need for further investigation to assert the hypothesis.

It is imperative to note that fomites, inanimate objects contaminated with infectious agents, serve as a medium for spreading endemic diseases, including coronaviruses. Therefore, there is a need to decontaminate and inactivate surfaces and other indoor places to avoid spreading the disease (Castaño *et al*., 2021; Choi *et al*., 2021). Physical inactivation is relevant to disease control due to the destruction of the glycoprotein and the lipid membrane bilayer of the virus leading to molecular structural damage. The UV-C light is proven to effectively reduce the cytopathic effects of the virus, reducing the air transmission of viruses. Hence, UV-C light is essential for further advances in curbing the spread of viral diseases, including SARS-CoV-2.

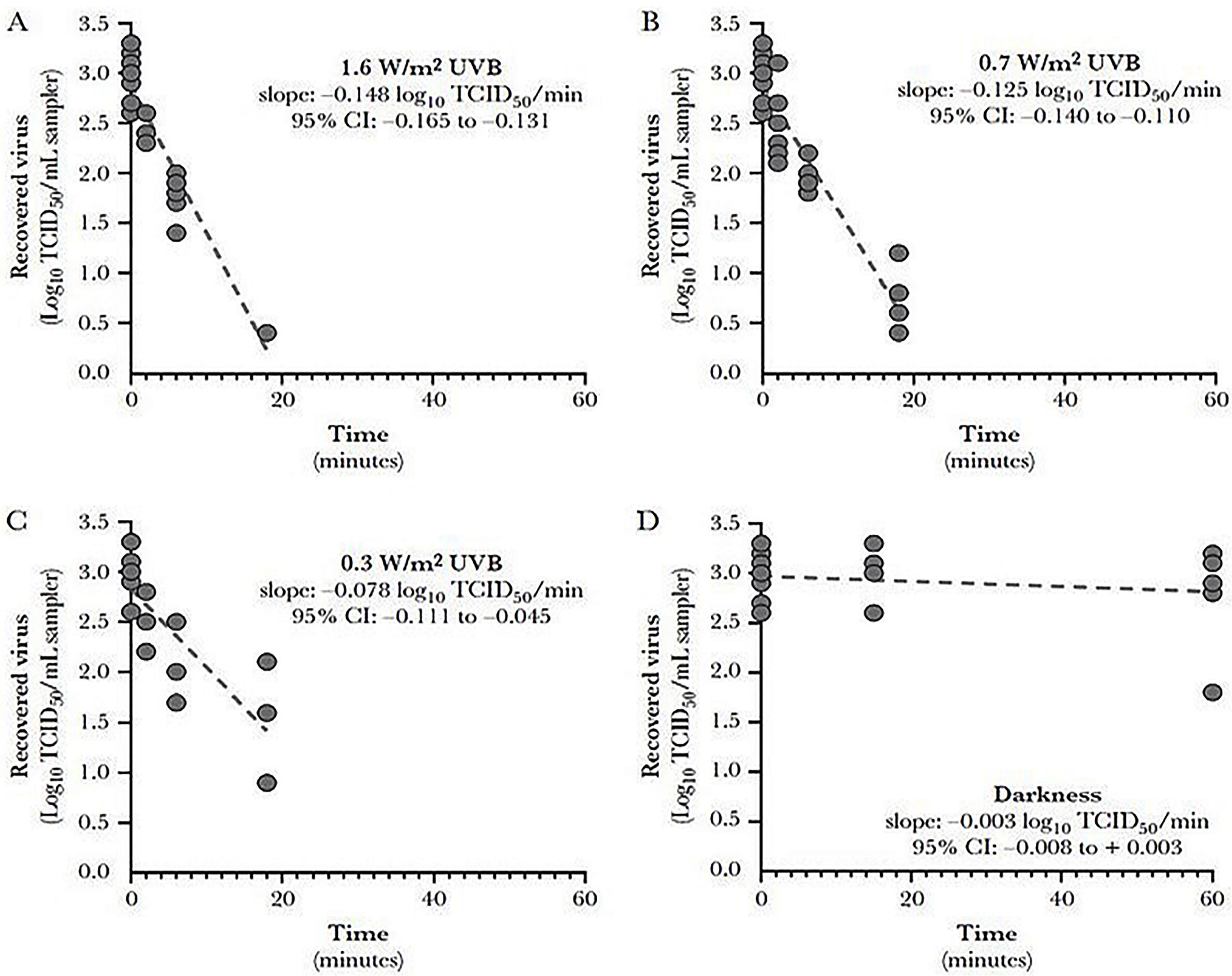

Figure 2. Inactivation rates for SARS-CoV-2 suspended in simulated saliva as a function of UVB irradiance. Linear regression fits SARS-CoV-2 suspended in simulated saliva and recovered from stainless steel coupons following exposure to different light conditions. Inactivation rates for exposure to any level of UVB irradiance were significant than those observed in darkness ($p < 0.001$). Additionally, the inactivation rates observed for UVB irradiances of 1.6 and 0.7 W/m^2 were significantly greater than those observed for 0.3 W/m^2 ($p \leq 0.065$). The slope of the regression line for darkness was not significantly different from zero. Goodness of fit parameters, specifically r^2 and standard deviation of the residuals (RMSE), for each fit were (A) $r^2 = 0.922$ and RMSE = 0.24; (B) $r^2 = 0.906$ and RMSE = 0.28; (C) $r^2 = 0.670$ and RMSE = 0.40; and (D) $r^2 = 0.041$ and RMSE = 0.32. CI, confidence interval; $TCID_{50}$, median tissue culture infectious dose (reprinted with permission from Ratnesar-Shumate *et al.* (2020), licensed under CC-BY-4.0, Copyright (2020), @ Elsevier).

CHEMICAL INACTIVATION OF SARS-COV-2

Some of the most influential and domestic-friendly disinfectants are recommended by the World Health Organization (WHO) for hand rubbing include ethanol (80% v/v) and isopropanol (75% v/v) (Pittet *et al*., 2009). Classes and examples of common disinfectants are depicted (Table 3) (Al-Sayah, 2020; Benzoni and Hatcher, 2019; Kim *et al*., 2018), commonly applied during the COVID-19 pandemic (Chernyshov and Kolodzinska, 2020). Unfortunately, disinfection alone may not prevent the spread of any pandemic. General hygienic conditions such as hand washing using soap and water, antiseptic, and hand sanitization, especially using alcohol-based sanitizers or hand rubs, are essential in curbing pandemic spread (Gold *et al*., 2021). Gold and Avva (2018) reported the WHO definition of alcohol-based hand rub (ABHR) as "an alcohol-containing preparation (liquid, gel or foam) designed for application to the hands to inactivate microorganisms and temporarily suppress their growth. Such preparations may contain one or more types of alcohol, other active ingredients with excipients, and humectants" (WHO, 2009). Other classes that are nonalcohol-based are also available. Still, they are less preferred by health agencies like the Centre for Disease Control and Prevention (CDC) (Berardi *et al*., 2020) and the WHO (Kampf and Kramer, 2004; Todd *et al*., 2010) in fighting COVID-19. They have low efficacy and a narrow spectrum of activity compared to alcohol-

Table 2. Sustainability of SARS-CoV-2 on different surfaces as reported by Choi *et al.* (2021) and van Doremalen *et al.* (2020).

Type of surface	Viability of SARS-CoV-2
Copper	>4 hours
Stainless steel	3 days
Glass	2 days
Plastic	4 days
Wood	4–5 days
Cardboard	1 day
Clothing	2 days
Paper	4–5 days

Table 3. Commonly used disinfectants and other additional compounds.

S/No.	Classification	Examples
1	Alcohols	Ethanol, isopropanol
2	Aldehydes	Glutaraldehyde
		Calcium dihydroxide, calcium hydroxide, calcium magnesium oxide, calcium magnesium tetrahydroxide, calcium oxide
3	Bases	Carbonates
		Sodium carbonate, sodium carbonate peroxyhydrate, ammonium bicarbonate, ammonium carbonate
5	Chlorine and chlorine compounds	Chlorine dioxide, hydrochloric acid, hypochlorous acid, sodium chlorite, sodium hypochlorite, sodium dichloro-S-triazinetrione (sodium dichloroisocyanurate)
6	Glycols	Triethylene glycol, 1,2-hexanediol
7	Iodophors	Polyvinylpyrrolidone iodine
		α-Hydroxy acids
9	Organic acids	Citric acid, glycolic acid, lactic acid
		Caprylic acid (octanoic acid), pelargonic acid (nonanoic acid)
10	Peroxygen compounds	Hydrogen peroxide, peroxyacetic acid (peracetic acid), potassium peroxymonosulfate
11	Phenolic compounds	Ortho-phenylphenol, ortho-benzyl-para-chlorophenol, thymol, chlorocresol

based products and hence the recommendation and acceptability of alcohol-based products (Yip *et al.*, 2020).

Most disinfectant products contain additional ingredients which aid in fighting several pathogenic organisms. Such active ingredients include QACs, hydrogen peroxide, peroxyacetic acid, isopropanol, ethanol, sodium hypochlorite, octanoic acid, phenolic, trimethylene glycol, L-lactic acid, and glycolic acid (Table 2) (Nawrocki *et al*., 2010). On many occasions, the products are designed to achieve particular needs and avoid the harmful effects of the chemicals involved. For instance, isopropanol is irritating to the skin; as such, emollients (glycerol or propylene glycol) are added to decrease possible skin irritations when applied (Berardi *et al*., 2020). It is essential to carefully read the labels of all products before use to avoid toxic and harmful effects on human health.

IODINE-BASED AGENTS

Povidone-iodine, chemically known as polyvinylpyrrolidone (PVP-I), is an iodine-based synthetic polymer obtained by polymerizing a monomeric compound *N*-vinylpyrrolidone. The PVP-I can incorporate hydrophilic and hydrophobic compounds due to its chemical characteristics such as nontoxic, stability of pH, high temperature-resistant, compatibility, inert, and biodegradable properties. These properties enable the PVP-I to be formulated in various domestic personal hygiene solutions to effectively prevent pathogenic microorganisms, including the CoVs disease (Kurakula and Rao, 2020). The virucidal activities of five personal hygiene products including antiseptic solution (10%), skin cleanser (7.5%), gargle/mouth wash (1%), gargle/mouth wash (1.0%, 1:2 dilution), and throat spray (0.45%) were reported to contain PVP-I at different percentages. They have been assessed against SARS-CoV-2 using suspension, cytotoxicity (on Vero E6 cells), and virus kill-time assays. The products demonstrated satisfactory virucidal activity of ≥ 99.99%, equivalent to 4 $\log_{10}$ reductions of viral titer against SARS-CoV-2 just within a 30 s period of contact. Anderson *et al*. (2020) reported the virucidal activity of different PVP-I products (Table 4) (Hassandarvish *et al*., 2020). Similar action has been previously

Table 4. Virucidal activity of PVP-I products against SARS-CoV-2 virus with 30s contact time as rreported by Hassandarvish *et al.* (2020).

PVP-I product	Reduction in viral titers ($\log_{10}$ $TCID_{50}$/ml)
Antiseptic solution (PVP-I 10.0%)	≥4.00
Throat spray (PVP-I 0.45%)	≥4.00
Skin cleanser (PVP-I 7.5%)	≥4.00
Gargle/mouth wash (PVP-I 1.0%)	≥4.00
Gargle/mouth wash (PVP-I 1.0%, 1:2 dilution)	≥4.00

Table 5. Virucidal activity of various concentrations of PVP-I in mouthwash against SARS-CoV-1, SARS-CoV-2, MERS-CoV, influenza virus A, and rotavirus as reported by Bidra *et al.* (2020b) and Eggers *et al.* (2018a).

Virus	Povidone-iodine concentration (%)	$\log_{10}$ reduction factor with a 95 % confidence interval					
		Clean conditions				Dry conditions	
		15 seconds	**30 seconds**	**60 seconds**	**120 seconds**	**15 seconds**	**30 seconds**
Influenza virus A subtype HIN1	0.23	**5.67 ± 0.43**	**5.67 ± 0.42**	nd.	nd.	**6.00 ± 0.47**	**6.00 ± 0.47**
	0.023	**4.50 ± 0.54**	**4.83 ± 0.68**	nd.	nd.	0.33 ± 0.63	0.50 ± 0.65
	0.0023	0.83 ± 0.54	1.00 ± 0.70	nd.	nd.	0.17 ± 0.58	0.17 ± 0.58
SARS-CoV	0.23	**4.60 ± 0.80**	nd	nd.	nd.	**4.40 ± 0.79**	nd.
MERS-CoV	0.23	**4.40 ± 0.79**	nd.	nd.	nd.	**4.40 ± 0.87**	nd.
SARS-CoV-2	1.5	3.0	3.33	nd.	nd.	nd.	nd.
	0.75	3.0	3.33	nd.	nd.	nd.	nd.
	0.5	3.0	3.33	nd.	nd.	nd.	nd.
Non-enveloped human rotavirus	0.23	**≥ 4.67 ± 0.42**	**≥ 4.67 ± 0.42**	**≥ 4.67 ± 0.42**	**≥ 4.67 ± 0.42**	nd.	nd.
Strain Wa	0.023	1.83 ± 0.54	2.00 ± 0.60	2.00 ± 0.60	2.17 ± 0.61	nd.	nd.
	0.0023	-0.33 ± 0.42	0.00 ± 0.60	0.17 ± 0.61	0.67 ± 0.42	nd.	nd.

The bolded numbers indicate no significant change in cleaning and drying conditions in reducing viral titer value from 4.00 to 6.00 $\log_{10}$ TCID50/ml, equivalent to ≥ 99.99% just after 15 seconds of contact time using Povidone-iodine concentration.

reported for the products against SARS-CoV-1 and MERS-CoV, suggesting their applicability as effective disinfectants in preventing CoV infections (Hassandarvish *et al*., 2020).

In another separate study, the virucidal effects of an oral antiseptic PVP-I solution at concentrations of 0.5%, 1.0%, and 1.5% were evaluated *in vitro* against SARS-CoV-2 using 70% ethanol as a positive control. The infectivity of the virus was demonstrated and quantified using dilution assay and the reduction of log value (LRV) in comparison with the positive control (ethanol) and negative control (water). The results indicate that SARS-CoV-2 viruses become inactivated by all tested concentrations after 15 s of administration better than 70% ethanol, whose inactivation effect was later 30 s. At each concentration, 0.5%, 1.0%, and 1.5% solutions show a virus titer and LRV of < 0.67 and 3.0, respectively, compared to 70% ethanol with virus titer of 1.5 and LRV 2.17 after 15 s. The oral antiseptics display a potent virucidal activity even at a low concentration of 0.5%, suggesting its applicability and effectiveness in preprocedural oral rinsing as adjunctive treatment in patients infected with SARS-CoV-2 (Bidra *et al*., 2020b). Similarly, PVP-I oral antiseptic rinses show more potent virucidal activity *in vitro* at concentrations of 0.5%, 1.25%, and 1.5% compared to hydrogen peroxide (H_2O_2) at 1.5% and 3.0%. At the same time, ethanol and water serve as positive and negative controls, respectively. Subsequently, the SARS-CoV-2 strains were entirely inactivated by the tested concentrations of PVP-I after 15 and 30 s of contact time. Simultaneously, minimal virucidal effects were observed with H_2O_2 at lower and higher concentrations, suggesting PVP-I preprocedural oral rinsing preference over H_2O_2 (Bidra *et al*., 2020a). The PVP-I at a concentration of 0.23% was reported to rapidly inactivate SARS-CoV, MERS-CoV, influenza virus A (H1N1), and rotavirus after 15 s of exposure. In another study, when used as mouthwash at 7% concentration, PVP-I possesses virucidal activity against SARS-CoV-1, MERS-CoV, and influenza virus A quantitatively using suspension assay. Furthermore, PVP-I at a dilution ratio of 1:30 with water (concentration of 0.23%) inactivated SARS-CoV-1, MERS-CoV, influenza virus A, and rotavirus and significantly decreased viral titer value from 4.00 to 6.00 $\log_{10}$ $TCID_{50}$/ml, equivalent to ≥ 99.99% just after 15 seconds of contact time. However, Eggers *et al.* (2018a) and Bidra *et al.* (2020b) reported little or no significant change when extending contact time (Table 5). Therefore, PVP-

I's comprehensive coverage and effective inactivation make it an oropharyngeal agent of choice for protecting individuals from viral infections (Eggers *et al*., 2018a).

Some PVP-I products were reported to effectively reduce SARS-CoV-2 infectivity below detectable limits, similar to 70% ethanol (Kariwa *et al*., 2006). They have overwhelming acceptability as disinfectants due to their broad virucidal activity against many pathogens. Therefore, this suggests a strong indication that PVP-I products are adequate for the inactivation of SARS-CoV-2 and other pathogenic microorganisms. However, the inefficiency of iodine-based compounds has been documented earlier for environmental/surface disinfection of hepatitis A virus (HAV). Similarly, few other studies found Iodophors with less virucidal efficacy (Bond *et al*., 1983; Lloyd-Evans *et al*., 1986; Sattar *et al*., 1989). In addition, many iodine-based products and their by-products such as diatrizoate, iomeprol, and iopamidol are unavailable for surface disinfection due to their staining and toxicity pollution properties to the environment and in some instances highly persistent and difficult to remove from surfaces. Accumulation of such compounds in large amounts might pose potential threats and destabilization of the ecosystem. Therefore, iodine-based products are mostly not recommended for surface disinfection (Steger-Hartmann *et al*., 2002).

ALCOHOL-BASED AGENTS

Alcohol-based hand preparations containing isopropanol, ethanol, n-propanol, or their combinations are undoubtedly some of the most frequently used hand rubs during the SARS-CoV-2 pandemic and other viral pandemics such as MERS. The effectiveness of the preparations depends on the type of alcohol and the quantity applied, concentration, and time of exposure (Boyce and Pittet, 2002; Todd *et al*., 2010). The enveloped viruses, including SARS-CoV-2, SARS-CoV-1, and MERS-CoV, possess a lipid layer protecting the viral core, of which most antiseptic agents can effectively inactivate within 1 min of exposure (Wang *et al*., 2020b). One of the strategic approaches to inactivate CoVs is to target the lipid envelope, representing the organism's virucidal potency. In the 2003 SARS outbreak, the strategy was applied using 60%–70% ethanol concentration to decontaminate viral material detected on surfaces within a hospital effectively. Therefore, ethanol at higher concentrations will effectively interfere with the lipid envelope of CoV (Hulkower *et al*., 2011; Sattar *et al*., 1989).

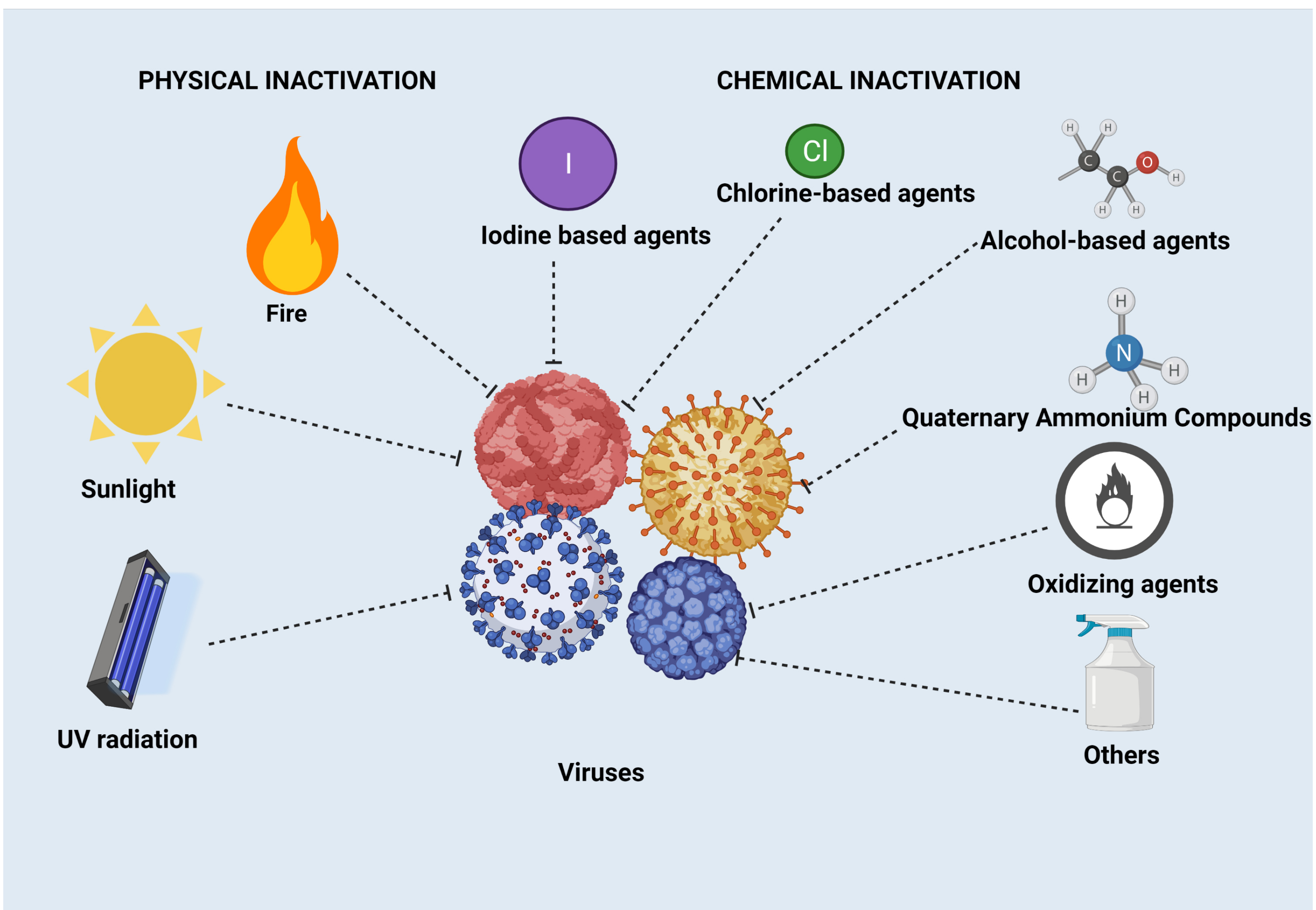

Figure 3. Physical and chemical inactivation of SARS-CoV-2.

Studies have also indicated that, to effectively inactivate the lipid envelope of some viruses, alcohol-based antiseptic preparations such as isopropanol at 70%–91.3% and ethanol at 60%–71% concentrations are highly recommended (Berardi *et al*., 2020; Kampf *et al*., 2020). The United States Federal Drug Agency reaffirmed the concentration-dependent effectiveness of some alcohol-based disinfectants and recommended them during the COVID-19 health emergency (Baye *et al*., 2021). Furthermore, the CDC recommends a baseline concentration of 60% for ethanol preparations meant for healthcare and the public for adequate disinfection, especially when foam and water are not easily accessible (Ramphul and Mejias, 2020). Moreover, a recent study conducted on Zika virus, Ebola virus, SARS-CoV-1, and MERS-CoV indicated that alcohol-based formulations such as ethanol 80% (v/v), isopropyl alcohol 75% (v/v), or the combination of both preparations effectively killed the envelope viruses and therefore, the WHO recommended the concentrations during the SARS-CoV-2 pandemic (Siddharta *et al*., 2017). To further buttress this point, commercially available alcohol-based hand sanitizers in the US market with a concentration of 70% ethanol effectively decreased the amount of SARS-CoV-2 virus below the threshold limit of >3 log10 reductions (Leslie *et al*., 2021). Similarly, ethanol at >30% concentration efficiently inactivated the virus when exposed within 30 seconds (Kratzel *et al*., 2020). The alcohol-based sanitizers have a significant setback in skin dryness, primarily when used for a long time. Therefore, emollients such as glycerol and glycerine are added to overcome such effects (Ahmed-Lecheheb *et al*., 2012).

Generally, alcohol-based hand sanitizers are the most commonly employed hand rubbing disinfecting agents against SARS-CoV-2 and other endemic viruses. One of the most common added ingredients in alcohol-based disinfectants with potential antiviral activity is the QACs, with a broad spectrum of activity against enveloped viruses and CoVs. Illustrations regarding different types of disinfectants that are physical and chemical inactivation of SARS-CoV-2 are shown in Figure 3.

OTHER DISINFECTANTS

Other essential disinfectants effective in decontaminating and inactivating viruses include chlorine-based, halogen compounds, potent oxidizing agents, and sodium hypochlorite (Chernyshov and Kolodzinska, 2020; Pradhan *et al*., 2020). Recently, large amounts of chlorine-based disinfectants have been widely used to control the spread of the SARS-CoV-2 outbreak in environments due to low cost and effectiveness on viral infection. Chlorine-based disinfectants are the most common agents that threaten aquatic life and the environment. Halogen compounds such as hypochlorous acid and hypochlorite ions are effective in decontamination and inactivating viruses and pathogenic microorganisms. Scheme 1 represents how sodium hypochlorite solutions can be prepared by reacting chlorine and sodium hydroxide solutions to give hypochlorous acid (HOCl) and sodium hypochlorite (NaOCl) solution (Pradhan *et al*., 2020).

$$Cl_2 + H_20 \xrightarrow{\text{favored in alkaline pH}} HOCl + H^+ + Cl^-$$
$$HOCl + NaOH \xrightarrow{\text{favored in alkaline pH}} NaOCl + H^+$$

Scheme 1. Formation of sodium hypochlorite solution.

The hypochlorous acid is a potent oxidizing agent with higher biocidal potency compared to NaOCl. The recommended disinfectant concentration of sodium hypochlorite is 5% in 1:100 dilutions for effective mopping of nonporous surfaces at ≥ 10 min contact time. In contrast, 30 min contact time is required (Carr *et al*., 1996; Chen *et al*., 2016). Sodium chlorite is another essential disinfectant with proven efficacy against HAV compared to other disinfectants such as chlorhexidine digluconate, sodium hypochlorite, phenol, sodium phenate, and diethylenetriamine disinfectants (Abad *et al*., 1997). However, sodium chlorite was ineffective at 0.275% concentration against HAV (Mbithi *et al*., 1990). Recently, a more environmentally friendly chemical, N-decyl dimethyl ammonium chloride or bromide, effectively inactivates SARS-CoV-2 on surfaces within 0.5 min in a laboratory experiment. Therefore, this could be suggested to disinfect surfaces contaminated with the virus (Xiling *et al*., 2021).

Oxidizing agents are one of the most effective disinfectants that inactivate viruses and other pathogenic microorganisms. Oxidizing solid compounds such as 1% hydrogen peroxide are disinfectants in intraoral procedures due to their effectiveness (Ather *et al*., 2020; Diegritz *et al*., 2020; Izzetti *et al*., 2020; Jamal *et al*., 2021; Zimmermann and Nkenke, 2020). Hydrogen peroxide is recommended because it can inactivate SARS-CoV-2 through an oxidation mechanism (Peng *et al*., 2020). Furthermore, it is worth noting that 62%–71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite, and povidone-iodine can rapidly inactivate CoVs such as SARS and MERS on inanimate surfaces within 1 min of exposure (Kampf *et al*., 2020). A study by Mileto and coworkers reported the inactivation of SARS-CoV-2 using a diluted solution of 3% H_2O_2 with citric acid and an aqueous solution of sodium percarbonate on surfaces within 5 and 15 minutes, respectively, while H_2O_2 with no additives displayed little or no virucidal activity (Ayipo *et al*., 2021; Brown *et al*., 2021).

Similarly, a combination of 0.1% chlorhexidine, 0.05% cetylpyridinium chloride, H_20_2 0.1% chlorhexidine, and 0.05% cetylpridiniumchloride inactivated SARS-CoV-2 particles within 30 s application as a mouth rinse, while H_2O_2 and chlorhexidine alone have no virucidal effects. Therefore, the combination might be used in preprocedural mouth rinse during dental treatments (Koch-Heier *et al*., 2021). Moreover, in SARS-CoV-2 positive subjects, 1% hydrogen peroxide used as mouth rinse could not reduce oral viral load. Therefore, hydrogen peroxide preparation alone is not recommended as an oral rinse to destroy the SARS-CoV-2 virus (Gottsauner *et al*., 2020). Other commonly used disinfectants include peroxides and peracids, which act by generating free radicals. These free radicals oxidize the important biochemical content of the virus, including nucleic acid, proteins, and lipids bilayer, and subsequently inactivate the virus. However, the free radicals-based preparations are usually considered the last option as disinfectants, replacing formaldehyde due to their severe systematic and neurological toxicity associated with their exposure. Hence, this limited their use against the SARS-CoV-2 virus (Songur *et al*., 2010).

Most disinfectants meant for household use have additional ingredients, such as the same amount of 0.50% triclosan, 0.12% parachlorometaxylenol, 0.23% pine oil, and 0.10% QACs, which are invariably reported to inactivate hepatitis virus. Among these compounds, QACs are the most common ingredients in more than 200 disinfectant preparations against the SARS-CoV-2 pandemic (Cegolon *et al*., 2020; Dellanno *et al*., 2009). There are three classes of QACs identified to have antiviral activity against CoVs and other pathogenic microorganisms, namely, (i) cetylpyridinium chloride, which is used to reduce pathogenic organisms in the mouth. It is also used in cosmetics as cleaning and personal care agents, (ii) ammonium chloride, an antiviral agent in many disinfectant preparations, and (iii) miramistin, which has a broad spectrum of activity against nonenveloped and enveloped viruses (Cegolon *et al*., 2020; Sanderson *et al*., 2003). Therefore, these agents can be formulated with other disinfectants for effective decontamination and inactivating viruses and other pathogenic microorganisms through additive and synergistic activity (Dellanno *et al*., 2009). This is evident when two formulated detergents containing QACs demonstrated an efficient inactivation of the SARS-CoV-2 by disrupting the lipid envelope and the spike glycoprotein of the virus, which eventually would have invaded lung cells of the host when interacting with the angiotensin-converting enzyme-receptor of the infected person (Schrank *et al*., 2020). In another research, it was indicated that a combination of commercially available disinfectants containing about 70% alcohol with N-alkyldimethylbenzylammonium chloride produced a reduction in viral titer by 2.03-fold.

Table 6. Effective antiseptics for different HCoVs (Chin *et al*., 2020, Eggers *et al*., 2018a, Kratzel *et al*., 2020, Rabenau *et al*., 2005a, Rabenau *et al*., 2005b, Ren *et al*., 2020, Saadatpour and Mohammadipanah, 2020, Saknimit *et al*., 1988, Sattar *et al*., 1989, Siddharta *et al*., 2017).

HCoV strain	Antiseptic (concentration)	Viral load reduction ($\log_{10}$)	Reference
HCoV 229E	Povidone iodine (PVP-I) (2.3% to 7.5%)	> 3.0 to >5.0 (dependent on concentration)	Sattar *et al*., 1989
	Ethanol (70%)	3.9	Saknimit *et al*., 1988
	Tetra-para-sulfonato-calix [33]arene (C[33]S) 0.1%	3	Geller *et al*., 2010
	Chlorhexidine gluconate + cetrimide + ethanol (0.05% + 0.5% + 70%)	≥ 3	Sattar *et al*., 1989
	Chlorhexidine gluconate + ethanol (0.1% + 70%)	≥ 3	Sattar *et al*., 1989
SARS-CoV-1	2-propanol (100%)	≥ 3.3	Rabenau *et al*., 2005a
	2-propanol (75%)	≥ 4.0	Siddharta *et al*., 2017
	2-propanol (70%)	≥ 3.30	Rabenau *et al*., 2005a
	Ethanol (95%)	≥5.50	Rabenau *et al*., 2005b
	Ethanol (80%)	≥4.30	Siddharta *et al*., 2017
	Ethanol (78%)	≥5.0	Rabenau *et al*., 2005a
	2-propanol + 1-propanol (45% + 30%)	≥ 2. 8 / ≥4.3	Rabenau *et al*., 2005a, Rabenau *et al*., 2005b
	Isopropanol + glycerol + hydrogen peroxide (75% + 1.45% + 0.125%)	Not determined (ND)	Siddharta *et al*., 2017
	Povidone iodine (PVP-I) (0.23%)	≥4.4	Eggers *et al*., 2018a)
MERS-CoV	Glycerol +Isopropanol + hydrogen peroxide (1.45% + 75% + 0.125%)	ND	Siddharta *et al*., 2017
	Povidone iodine (PVP-I) (0.23%)	≥4.4	Eggers *et al*., 2018a
	2-propanol (75%)	≥4.0	Siddharta *et al*., 2017
SARS-CoV-2	Isopropanol + hydrogen peroxide + glycerol (75% + 0.125% + 0.725%)	≥5.9	Kratzel *et al*., 2020
	Ethanol (70%)	3.9	Saknimit *et al*., 1988
	Povidone iodine (PVP-I) (7.5%)	ND	Ren *et al*., 2020
	Chlorhexidine (0.05%)	ND	Chin *et al*., 2020

In contrast, phenolic disinfectant (o-phenyl phenol and p-tertiary amyl phenol) with ortho-phthalaldehyde reduced the titer value by 2.27 folds, indicating superior efficacy of the first combination against TGEV (Hulkower *et al*., 2011). Only two disinfectants, containing Nalkyldimethylbenzylammonium chloride and Lysol, demonstrated excellent activity below the viral reduction factor against poliovirus, indicating not all products are effective against viruses (Rutala *et al*., 2000). In another study, QAC's, hydrochloric acid, and sodium hypochlorite-based formulations inactivated SARS-CoV-2 and other coronaviruses with virucidal efficacies between ≥ 3 and ≥ 6 $\log_{10}$ reduction factors (Ijaz *et al*., 2021). Consequently, a viral reduction factor of >3 has been suggested as the most effective benchmark for inactivation of virucidal activity of CoVs and other life-threatening infections during surface decontamination (Abad *et al*., 1997; Hulkower *et al*., 2011; Rutala *et al*., 2000). However, natural products with disinfectant properties such as vinegar were less toxic and effective than commercial household disinfectants against some pathogenic organisms (Schrank *et al*., 2020).

Antiseptics

Substances that arrest microbial growth or activity, especially in or on living tissue, by either inhibiting their action or destroying them are antiseptics (Patterson, 1932). Skin can be contaminated directly when contact with patient secretions or indirectly by touching contaminated surfaces (L'Huillier *et al.*, 2015). Some chemical disinfectants that are safe to use in or on tissue are used as antiseptics. Table 6 shows the efficacy of the antiseptics used for HCoVs.

Antimicrobial Resistance

Antimicrobial agents are natural, synthetic, or semisynthetic substances capable of killing or inhibiting microbial growth *in vivo* by interacting specifically with a target component (Donaghy *et al*., 2019). The ability of a microorganism to grow despite an antimicrobial agent is referred to as antimicrobial resistance (AMR), which can be acquired or intrinsic (Wales and Davies, 2015). Unlike antimicrobial agents, disinfectants and sanitizers nonspecifically target multiple components of microbes, frequently causing lethal damage to their membranes or damaging their proteins by reacting with a functional group. Because of their nonspecific nature and multiple modes of action, the microbes are less likely to become resistant to these chemicals (Donaghy *et al*., 2019; Wales and Davies, 2015). It is unclear that the COVID-19 pandemic has increased AMR. Many patients infected with COVID-19 were treated with antibiotics due to secondary bacterial coinfection (Rodrigo *et al*., 2020). About 70% of the COVID-19 patient who was hospitalized received antibiotics and often broad-spectrum antibiotics, whereas only 16% developed secondary coinfections (Abelenda-Alonso *et al*., 2020; Beović *et al*., 2020; Langford *et al*., 2020). The increased use of antibiotics is seen in nursing homes and long-term care facilities. A possible increase in self-medication with antibiotics is seen in some countries or regions of the world, increasing the risk of rising AMR (Nasir *et al*., 2020).

Despite having huge factors that increase the risk of raising AMR during this pandemic, some factors might favor decreasing AMR. A study result shows that only 1.3% of COVID-19 patients from the Intensive care unit and no other units got infected with nosocomial superinfection with AMR bacteria (Fattorini *et al*., 2020). Another study shows that only 3.5% of COVID-19 patients got bacterial coinfection (Langford *et al*., 2020). A significant decrease in international air travel also decreased AMR bacteria and genes (Kommenda, 2020; Murray, 2020).

RESISTANCE OF PATHOGENIC ORGANISMS TO INACTIVATING AGENTS

A considerable number of disinfectants containing antibiotics have been used in public. The high concentration of these disinfectants wastewater and the soil leads to environmental and aquatic toxicity and, in some cases, resistance to viruses (Chen *et al*., 2021; Wang *et al*., 2020b). Resistance poses a serious global concern, thereby exposing the vast, vulnerable population to devastating situations. Many disinfectants contain chlorine-releasing agents. Excessive use of these can give rise to chlorine-tolerant microbes, which are also competent cells and can more efficiently transfer plasmids (Jin *et al*., 2020). Therefore, it is pertinent to monitor disinfectants for potential risks of developing resistance due to the discriminate application of the agents during the pandemic period (Berardi *et al*., 2020; Dellanno *et al*., 2009; Okeke *et al*., 2005).

Moreover, the CDC and the European Committee for Standardization recommend methods and testing protocols for disinfectant preparations to effectively determine efficiency and inactivation potential against viruses, especially on enveloped viruses. This represents the vast majority of emerging infectious diseases. Therefore, it is recommended to use tested and well-recommended formulations such as PVP-I and ethanol preparations less susceptible to resistance development when used appropriately (Boyce and Pittet, 2002; Eggers, 2019). As discussed under iodine-based disinfecting products, PVP-I is one of the most widely used alternative antiseptics to alcohol prepared in clinical settings for disinfecting skin during and after surgical operations. It inactivates resistant strains of pathogenic microorganisms effectively (Gottrup *et al*., 2014). It was demonstrated by Eggers *et al*. (2018), that iodine has superior activity against enveloped and nonenveloped viruses (Table 7), hence its lack of cross-resistance among many pathogens. Besides its inability to develop resistance, PVP-I has been more effective and superior to chlorhexidine against pathogenic microorganisms, especially handwashing disinfectants (Eggers, 2019).

So far, no significant resistance has been acquired by iodine, mainly when used for specific purposes and stipulated

Table 7. Comparison of anti-viral activities of standard antiseptic classes as indicated by Eggers *et al.* (2019).

Antiseptic type	Inactivates	
	Enveloped viruses	**Non-enveloped viruses**
Quaternary ammonium	+	+
Chlorine	+	+
Ethanol	+	Variable
Iodine	+	+
Phenolic	+	Variable

procedures (Eggers, 2019). Iodine maintains equilibrium due to constant replacement by the PVP-bound iodine, leading to disruptions and leakage of the organism (Mayer *et al.*, 2001). Therefore, the long-lasting efficacy and continuous supply of iodine during its action suggest decreased possibility of resistance developed by many pathogenic organisms (Eggers, 2019). In summary, PVP-I and ethanol preparations are less susceptible to resistance development when used appropriately and adequately. PVP-I's constant equilibrium supply and efficacy during its action against viruses make it one of the disinfectants of choice for many decades. The development of resistance to various disinfectants and antimicrobial agents is demonstrated (Fig. 4).

TOXICITY OF INACTIVATING AGENTS

The WHO's declaration of COVID-19 as a global pandemic and misinformation on the public health emergency leads to misconceptions, rumors, and subsequently cynicism on the disease by some individuals (Xu and Li, 2020). In addition, misinformation on the use of disinfectants triggers panic, anxiety, and hysteria in people. Thus, individuals adopt inappropriate, excessive, and unethical actions such as the application of equipment sterilizers on the skin, washing food products with disinfectants, and in some instances, ingesting chemicals, all in the name of preventive measures. The SARS-CoV-2 pandemic has skyrocketed the demand for disinfectants globally, exposing human, environmental, and aquatic life to the toxic effects of these chemicals (Sefah *et al.*, 2020). This could culminate in increasing secondary disasters detrimental to the fragile healthcare system (Rai *et al.*, 2020). Residual chemicals left on the surfaces can be inhaled and cause serious health problems such as allergic reactions and asthma (Medina-Ramón *et al.*, 2005). The long-term effect of such substances could be harmful to health, causing chronic diseases like cancer and central nervous system (CNS) impairment. Other effects include oxidative damage and reproductive disorders (Choi *et al.*, 2020). Most of these cleaning agents contain harmful materials and are corrosive to both humans and the environment; therefore, caution and strict adherence to safety and protocol measures must be exercised when applying disinfecting agents on both humans and the environment (Arevalo-Silva *et al.*, 2006; Nabi *et al.*, 2020; Sawalha, 2007; Sharafi *et al.*, 2020).

In humans, toxicity due to disinfectants is usually experienced upon long-term exposure to the agents through mouth, skin, and inhalation routes. The toxicological effects

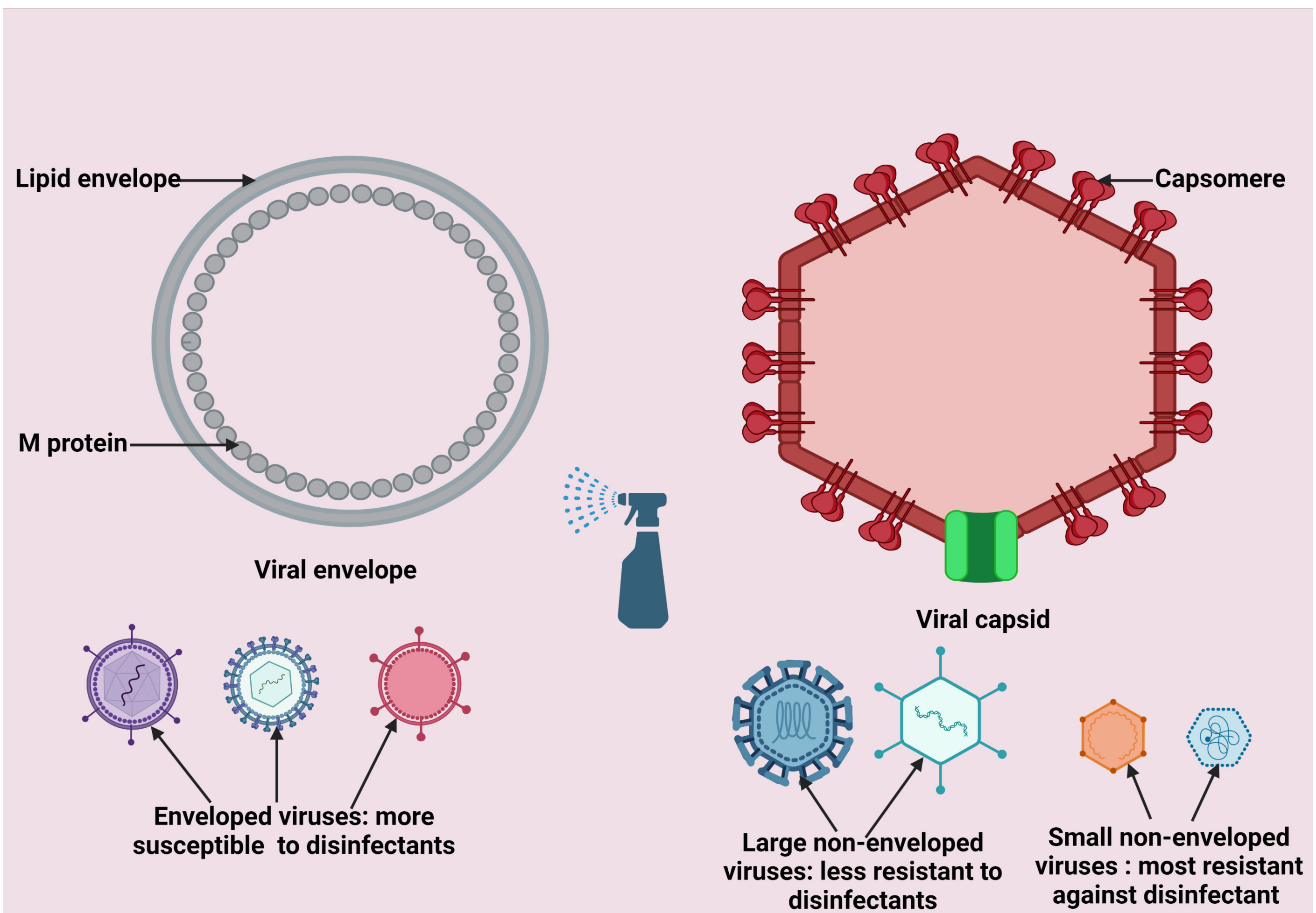

Figure 4. Processes of developing resistance by commonly used disinfectants and other antimicrobial agents.

vary according to the course and the type of the disinfecting agent. For instance, alcohol-based disinfectants and sanitizers display short contact time on humans due to their volatility. They are considered less harmful than other less volatile agents with extended contact time. Therefore, alcohol-based disinfectants are mostly recommended for homes and hospitals (Li *et al*., 2020a). Other agents such as hypochlorous and peroxides are primarily used in dental clinics due to their ability to produce aerosols at a low cost to prevent contact with most patients (Scarano *et al*., 2020). It was reported that most chemical disinfectant by-products increased the risk of chronic obstructive pulmonary disease (COPD) like asthma and irritation of the eyes and skin, primarily when misused. Other hazards include cancers and reproductive and respiratory disorders (Chen *et al*., 2021; Rume and Islam, 2020; Sharafi *et al*., 2020). Children are the most affected when exposed to hazardous chemicals, with reported cases of dysbiosis in the infant gut leading to overweight and obesity (Chen *et al*., 2021). Excessive use of alcohol-based hand sanitizer as a protective measure for the current pandemic has caused alcohol toxicity (Ghafoor *et al*., 2021). It can also increase the risk of other viral infections such as norovirus outbreaks (Blaney *et al*., 2011). Some ABHR or sanitizers contain nonvolatile biocides such as benzalkonium chloride, chlorhexidine digluconate, didecyldimethylammonium chloride, polihexanide, triclosan, or octenidine dihydrochloride (Kampf, 2016). Although they do not have any proven health benefit or superior bactericidal efficacy, they can raise AMR (Kampf, 2016; Kampf *et al*., 2017; Palumbo *et al*., 2017). Chlorhexidine, povidone-iodine, benzalkonium chloride, or octenidine are used in some alcohol-based skin antiseptics (Kampf, 2016). Of these, only chlorhexidine and octenidine have proven health benefits in preventing infection despite some risks (Chaiyakunapruk *et al*., 2002; Darouiche *et al*., 2010; Dettenkofer *et al*., 2010; Harnoss *et al*., 2018; Mimoz *et al*., 2015; Tuuli *et al*., 2016). Other agents such as glutaraldehyde and ethylene oxide were also reported to cause severe lung disease (Dumas *et al*., 2019). Therefore, caution should be exercised, especially when mixtures of disinfectants are preferred. For instance, the combination of bleach with an acid-based cleaner could release gaseous chlorine or hypochlorous acid. When inhaled, even in small amounts, it may cause acute severe lung injury (Bracco *et al*., 2005). People are exposed to toxic effects of these chemicals with an increased risk of COPD, asthma, and eye irritation due to the knowledge gap in safe preparations of cleaning and disinfecting agents, even among adults. Therefore, discourage self-preparation without the requisite skills and knowledge (Casey *et al*., 2017; Dumas *et al*., 2019; Gharpure *et al*., 2020; Weinmann *et al*., 2019). Moreover, a study indicated that about 5% of cancer in children and 30% of childhood asthma are linked to long-term chemical exposures due to the inability to handle or use the chemicals properly and subsequently damaging essential organs in the body (Landrigan *et al*., 2002). Another necessary caution is excessive, frequent, and vigorous hand rubbing when using alcohol-based antiseptics, which could be inhaled and may generate potential threats to eyes and skin and subsequently lead to contact and allergic dermatitis to mild or moderate inflammatory effects (Shetty *et al*., 2020).

During the COVID-19 pandemic, there was an increase in biomedical and untreated wastes (Wang *et al*., 2020b), which endangers both humans and the environment. Chlorine-based disinfectants are the most widely used agents on environments during the SARS-CoV-2 pandemic, thereby causing high residual concentrations in water bodies, soil, and the environment. Ultimately, these affect agricultural production due to excessive chlorine (Cl^-), soil degradation, and ecosystem destruction. A high chlorine residue concentration on the soil affects the ecosystem by reacting with bromide in raw materials or soil and organic matter. This subsequently leads to disinfectants-by-products formations, especially trihalomethanes and bromides, toxic to the environment (soil), human, and aquatic animals (Srivastav *et al*., 2020). Chlorine-based disinfectants are prone to the formation of carcinogenic chloramines and nitrosamines, observed in drinking water around Washington D.C (Montazeri *et al*., 2017; National Research Council, 1980). However, chlorine-based disinfectants' toxic effects on plants are short-lived and quickly neutralized by some organic matters in the soil (Montazeri *et al*., 2017). The aquatic animals are also endangered due to exposure to toxic by-products of the disinfecting chemicals (Nabi *et al*., 2020; Sharafi *et al*., 2020). Also, disinfecting water for consumption using chlorine produces products and, when used for the long-term, may be harmful to aquatic and human life, causing chronic diseases such as cancer (Agnelo *et al*., 2020; Srivastav *et al*., 2020). The excessive applications of disinfectants undoubtedly increase their presence within the ecosystem, causing air, water, and soil pollution.

In summary, even though some disinfectants are toxic to individuals and the environment, they are essential in curbing the spread of COVID-19. The vast majority of the disinfectants, such as alcohol and chlorine-based products, are mainly used on humans and the environment, respectively. Frequent exposure to disinfectants during the COVID-19 pandemic poses risks of chronic diseases such as cancers, respiratory, and reproductive disorders. Therefore, guidelines, procedures, and recommendations made by WHO, CDC, and other recognized health agencies should be followed to minimize the health risks associated with exposure to chemical disinfectants. Possible toxicity and other health hazards resulting from disinfectant use are demonstrated (Fig. 5).

MITIGATING STRATEGIES TO REDUCE THE TOXIC EFFECTS OF INACTIVATING AGENTS

The COVID-19 pandemic posed several challenges and seemed unmanageable through current preventive measures and strategies (Habas *et al*., 2020; Rahman *et al*., 2021). Disinfectants are essential prophylactic agents; however, there is indiscriminate disinfectant use during the pandemic. Despite having a beneficial role in controlling and preventing SARS-CoV-2, there are concerns regarding the large-scale use of disinfectants, including the toxic effect on human health and the chance of developing drug resistance. Various national and international healthcare authorities, that is, WHO (2020) and CDC (Government, 2021), have developed recommendations for the appropriate utilization of suitable disinfectants to prevent the pandemic.

The following essential mitigation strategies are recommended to reduce the toxic effects of disinfectants in humans and the environment (Chen, 2020; Dhama *et al*., 2021):

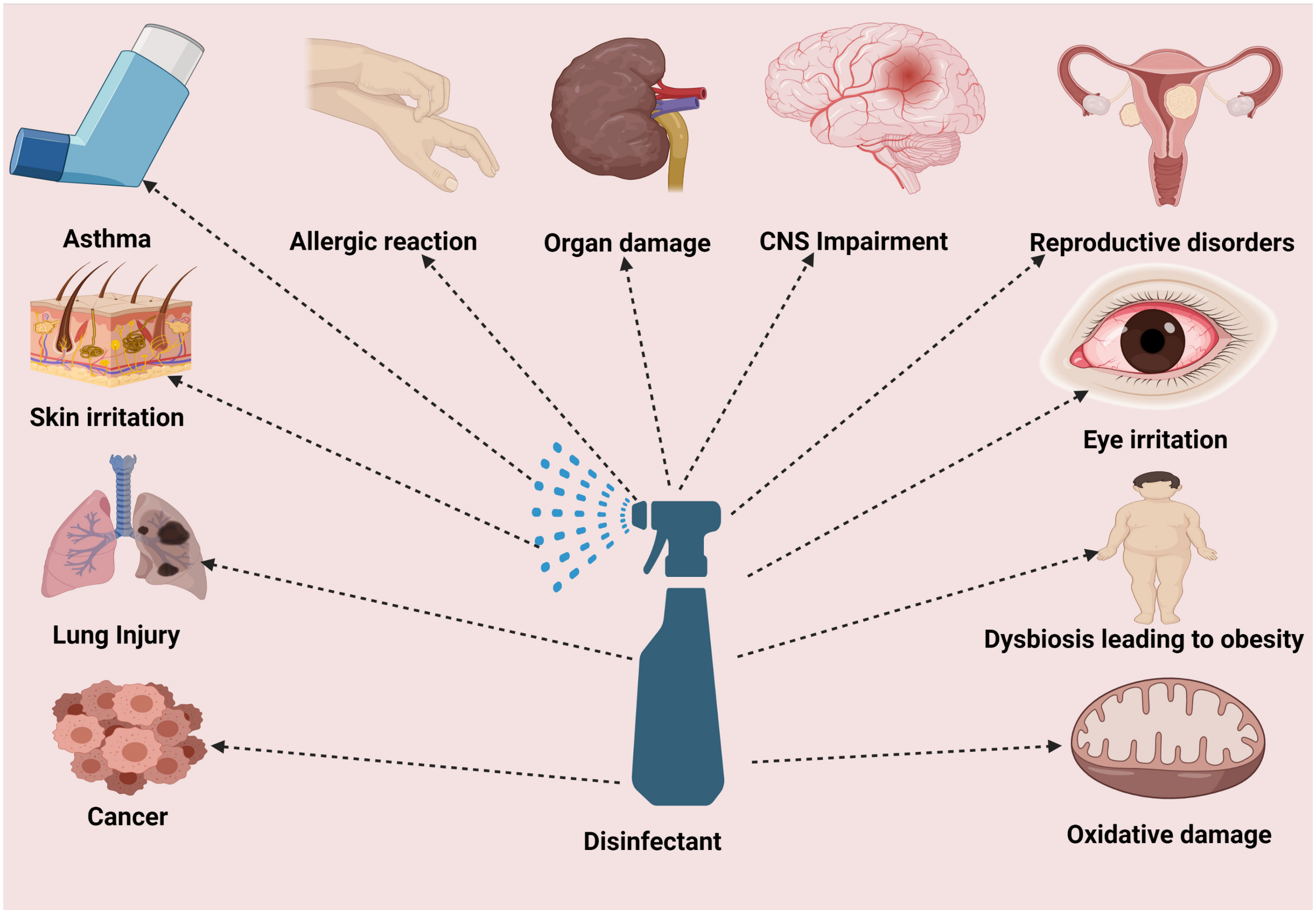

Figure 5. Demonstration of toxicity and health-related hazards by disinfecting agents.

1. Use of natural disinfectants, for example, sunlight and plant-based disinfectants.
2. Use only recommended dose of disinfection.
3. Substitute cleaning and disinfectant sprays with liquid products that are manually applied with a cloth.
4. Increase ventilation during and following treatment.
5. Follow label usage instructions and avoid mixing cleaning and disinfectant products.
6. Avoid using cleaning and disinfectant products around children.
7. Allow the area being treated to air out the following application.
8. Clearly label disinfectants and store them away from children and pets.
9. Avoid any accidental leakage of disinfectants into water.
10. Development of nanomaterials or nanoparticles for surface decontamination.
11. Improve personal protective equipment (PPE) worn by users.
12. Incorporation of nanobiotechnology to develop PPEs and sanitization.
13. Efficient disposal of PPEs and medical waste using techniques like incineration and vitrification.
14. Provide proper worker training in safe cleaning and disinfection practices.
15. Strictly follow national health and safety guidelines for using disinfectants.

CONCLUSION AND RECOMMENDATIONS

COVID-19 is a highly infectious and transmissible disease. The inability to detect symptoms within a few days of getting infected by individuals further complicates its proper prevention and disinfection process, especially in a frequented indoor space. Initially, when the disease was declared a public healthcare emergency by the WHO, different nations adopted temporary confinement of people indoor to curb the disease spread. Nonetheless, this policy has negatively impacted the global economies, individuals' psychological and mental health, and the overwhelming healthcare system. Briefly, this article highlighted the relevance of physical inactivation, such as temperature and humidity, controlling the viral survival on the surfaces, and ultimately reducing the virus's transmission through droplets. Although the SARS-CoV-2 is highly stable at 4°C, it becomes inactive when exposed to high temperatures. The UV radiation, incredibly the UV-C light, has also proven to effectively reduce air transmission of several pathogenic diseases, including airborne viruses, hence essential in curbing the spread of SARS-CoV-2. However, due to the harmful effects of UV radiation on normal cells, especially at high wavelengths, its use is limited.

Consequently, the application of UV radiation for the control of SARS-CoV-2 infection requires specifications with lesser health-damaging effects on humans and animals. Furthermore, the literature review emphasized the commonly used disinfectants during the SARS-CoV-2 pandemic, such as alcohol- and iodine-based products. The alcohol-based disinfectant represents the widest hand-rub antiseptics recommended by various health agencies and organizations, including the WHO and CDC, during the SARS-CoV-2 outbreak. The alcohol-based disinfectants are easily accessible and effective in preventing the spread of SARS-CoV-2. The iodine-based counterpart has also proven efficacious against many pathogenic microorganisms over many years. Most of its preparations demonstrated efficient virucidal activity against SARS-CoV-1, MERS-CoV, and SARS-CoV-2, suggesting its broad applicability on many viral diseases. However, a high concentration of these disinfectants in wastewater and the soil leads to environmental and aquatic toxicity and, in some cases, resistance to viruses. Notably, the residual chemical remaining on the surfaces or inhaled by individuals may have long-term effects on public health, such as reproductive disorders, COPD, cancers, skin damage, and CNS impairment. Therefore, further research on long-term preventive alternatives such as formulating disinfectants with natural products as active ingredients is necessary to mitigate the effects of alcohol- and iodine-based chemicals on humans and the environment.

Additionally, effective technologies and strategies need to be developed for minimizing these toxic effects and drug resistance. Safe, eco-friendly technologies should be used to produce safe, effective, and affordable disinfectants using nanotechnology and nanomedicine. Comprehensive guidelines for rational disinfectants are also necessary at regional, national, and international levels to reduce the toxic effects on humans and the environment.

PROFESSIONAL ANNOTATION

Disinfection pronounces a procedure that eradicates several or all infective microbes, excluding bacteriological spores, on nonliving objects (Baron *et al*., 1996; Basta and Annamaraju, 2020; Council, 1977; Protano *et al*., 2019; Rutala and Weber, 2008; Rutala and Weber, 2016). Nevertheless, sterilization labels a method that abolishes or exterminates all microbiological life forms and is regularly conducted in all sorts of healthcare facilities by physical or chemical approaches (Anderson *et al*., 2018; Ling *et al*., 2018; Protano *et al*., 2019; Rutala and Weber, 2008; Rutala and Weber, 2016). The disinfection of health professional hands is a significant avenue to transfer through healthcare providers. It was first noticed by the Hungarian Obstetrician Professor (Dr.) Ignaz Phillip Semmelweis in 1847 (Haque, 2020; Haque *et al*., 2018). Dr. Ignaz Phillip Semmelweis is primarily known as the father of infection control (Flynn, 2020; Habboush *et al*., 2021 a). The essential standing of hand sanitization and other issues in managing infection control has been similarly advocated by Florence Nightingale, Oliver Wendell Holmes, Louis Pasteur, Joseph Lister, and Robert Koch (Ataman *et al*., 2013; Gebel *et al*., 2013; Görig *et al*., 2019; Glass, 2014; Haque *et al*., 2020; Hillier, 2020; Kampf *et al*., 2009; La Rochelle and Julien, 2013; Lane *et al*., 2010; Pitt and Aubin, 2012; Smith *et al*., 2012; Tulchinsky and Varavikova, 2014; Tyagi and Barwal, 2020; Worboys, 2013). After that, the importance of hand hygiene practice was validated through multiple scientific works and remains essential and pertinent (Allegranzi and Pittet, 2009; Magiorakos *et al*., 2010; Mathur, 2011; Reichardt *et al*., 2013).

Healthcare-associated infections (HCAIs) and community infections remain safety concerns for health professionals and patients (Monegro *et al*., 2021). Thereby, it increases considerable morbidity and mortality and prolongs the hospital stay and healthcare overhead length (Badia *et al*., 2017; Grant *et al*., 2017; Jia *et al*., 2019; Zhou *et al*., 2019). Therefore, multiple studies revealed that efforts need to promote infection preventive strategies in all healthcare facilities and communities to avert infection and maximize healthcare benefits (Cheung *et al*., 2019; Schmid *et al*., 2018; Wagh and Sinha, 2018; Worth *et al*., 2018). Infection management denotes the strategy and measures to be implemented to curb and curtail the spreading and propagation of HCAIs infections in different types of healthcare facilities that include ambulatory surgical centers, birth centers, blood banks, clinics, and medical offices, diabetes education centers, dialysis centers, hospice homes, hospitals, primary healthcare centers, imaging and radiology centers, mental health and addiction treatment centers, nursing homes, orthopedic and other rehabilitation centers, urgent care, telehealth, and communities (Boev and Kiss, 2017; Collins, 2008; Gandra and Ellison, 2014; Guzman, 2021; Haque *et al*., 2018; Hsu, 2014). The infection control strategy was reported as a well-established practice in US hospitals in the early 1950s (Dixon, 2011; Habboush *et al*., 2021a; Monegro *et al*., 2021). Additionally, multiple pieces of research revealed that efficient practice infection prevention program reduces morbidity, mortality, healthcare financial overhead, and disability-adjusted life years (DALYs) and maximizes proper utilization of healthcare (De la Rosa-Zamboni *et al*., 2018; Friedrich, 2019; La Rochelle and Julien, 2013; Zacher *et al*., 2019). The health management system progressively recognizes the importance of surface disinfection (Gebel *et al*., 2013). Notwithstanding, several unanswered questions remain to be determined (Gebel *et al*., 2013).

Surface disinfection is an essential procedure in healthcare facilities and infectious diseases such as COVID-19. It is vital to curbing contagious diseases and reducing the risk of direct and indirect contact transmission from healthcare personnel to patients. This could decrease surfaces to act as reservoirs for various infectious diseases (Donskey, 2013). For many years, alcohol-based preparations have been used as low-level disinfectants in hospitals against bacteria. Recently, a combination of alcohol-based and QACs was used to disinfect surfaces against Ebola viruses and several coronaviruses. The antiseptic preparations are used due to their ability to evaporate rapidly and short contact time on the skin, therefore, less damaging the skin due to lesser exposure to the agents (Boyce, 2018). Most of these disinfectants, such as chlorine-based, are inexpensive and readily available in rural and urban areas (Gallandat *et al*., 2021). However, disinfections are necessary to inactive and reduce the viral load on surfaces. However, many disadvantages follow. The high amount of surface disinfectants is corrosive to the environment, especially iodine-based disinfectants. Also, most of these disinfectants cause irritation when applied in high concentrations and on stain surfaces and can be quickly inactivated by organic matter (Gallandat *et al*., 2021).

Moreover, some disinfecting agents have antibacterial agents in their formulation; inappropriate exposure to bacteria could cause bacterial resistance development (Chen *et al*., 2021). In some cases, prolonged exposure to these disinfectants could cause serious health problems such as cancers, respiratory problems, and genetic defects in an unborn baby (Ahmed-Lecheheb *et al*., 2012; Choi *et al*., 2020). In most cases, not all disinfectants products eradicate the coronaviruses. Therefore, further investigation on individual disinfecting agents is required to validate their merit and demerit potentials further.

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Ethics approval and consent to participate: This is a review paper. Thereby does not require Institutional Review Board's approval and consent.

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AUTHORS' CONTRIBUTION

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

CONSENT FOR PUBLICATIONS

All authors reviewed and approved the final version and have agreed to be accountable for all aspects of the work, including any issues related to accuracy or integrity.

COMPETING INTEREST

The authors declare that they have no competing interests.

ABBREVIATIONS

AMR:	Antimicrobial resistance
CNS:	Central nervous system
CDC:	Centre for Disease Control and Prevention
CNKI:	China National Knowledge Infrastructure
DNA:	Deoxyribonucleic acid
RNA:	Ribonucleic acid
COPD:	Chronic obstructive pulmonary disease
HCPs:	Healthcare professionals
HCoVs:	Human coronaviruses
MERS-CoV:	Middle East Respiratory-Corona Virus
UV:	Ultraviolet
SARS-CoV-1:	Severe acute respiratory syndrome corona virus-1
SARS-CoV-2:	Severe acute respiratory syndrome corona virus-2
TGEV:	Transmissible gastroenteritis coronavirus of pigs, a SARS-CoV surrogate
MHV:	Mouse hepatitis virus
CCoV:	Canine coronavirus
ATCC:	American Type Culture Collection
PVP-I:	Polyvinylpyrrolidone
EMC:	Erasmus Medical Center
QACs:	Quaternary ammonium compounds

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