

SPECIAL ISSUE REVIEW

Disinfectants role in the prevention of spreading the COVID-19 and other infectious diseases: The need for functional polymers!

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Funding information

MAOF Fellowship from the Council for Higher Education, Israel; European Union's Horizon 2020 Research and Innovation Programme; EIT Health

Abstract

The spreading of coronavirus through droplets and aerosols of an infected person is a well-known mechanism. The main protection methods from this virus are using disinfectants/sanitizers, face masks, keeping social distance, and vaccination. With the rapid mutations of the virus accompanied by its features and contagions changing, new advanced functional materials development is highly needed. The usage of disinfectants/sanitizers in excess generates poisonous effects among the general public. Effective and simultaneously, human-friendly sanitizers or disinfectants are required to prevent the poisoning and the associated issues. They minimize the toxic effects of the currently available materials by rapid action, high potential, long-term stability, and excellent biocompatible nature. Here, we summarize the available antiviral materials, their features, and their limitations. We highlight the need to develop an arsenal of advanced functional antiviral polymers with intrinsic bioactive functionalities or released bioactive moieties in a controlled manner for rapid and long-term actions for current and future anticipated viral outbreaks.

KEYWORDS

antimicrobial polymers, COVID-19, disinfectants, surface coatings

1 | INTRODUCTION

Coronavirus infection among humans was discovered and reported early in 1960. Later, the virus has emerged several times worldwide, including two significant outbreaks in Asia in 2003 and in Saudi Arabia in 2012.^{1,2} A novel strain of the coronavirus has emerged in recent times, named severe acute respiratory syndrome coronavirus 2, SARS-CoV-2. The disease caused by the virus, known as COVID-19, has spread in China at the end of 2019. The World Health Organization (WHO) has declared COVID-19 as a Pandemic on March 11, 2020,

which means the disease has spread in most countries around the world by that time. Acute respiratory disease, with varying severity, is giving rise to the mortality rate from 1% to 5% of patients. Almost 6 months later (1.09.2020, 9:00 GMT), 24,468,031 confirmed cases of the disease and 871,166 deaths worldwide (Figure 1A). The toll passed over 400 million confirmed cases and more than 5.8 million deaths recently.

The infectious patient could be categorized into two groups: symptomatic and asymptomatic.³ Due to the symptoms, symptomatic patients with severe respiratory issues are usually diagnosed and

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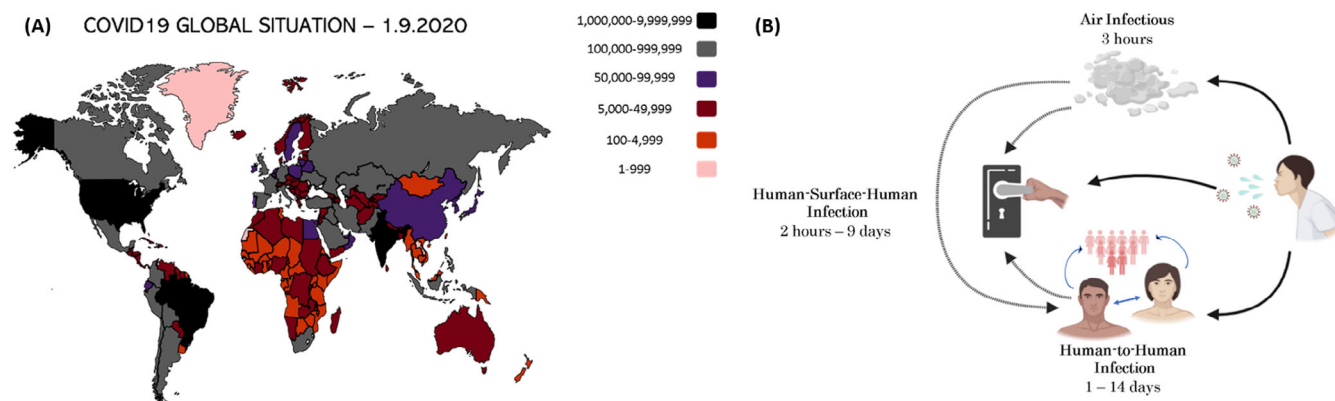


FIGURE 1 (A) SARS-CoV-2 (COVID-19) spreading status around the globe on September 1, 2020. The toll passed over 400 million confirmed cases and more than 5.8 million deaths recently. (B) An illustration of the possible infection mechanisms and the spreading potential of a single infecting individual and the persistence of the virus among each element. Source: Created with [BioRender.com](https://www.biorender.com)

treated carefully at hospitals. Unfortunately, sometimes these patients may infect other people previous to their diagnosis. On the other hand, since asymptomatic people do not experience any abnormalities, their diagnosis tends to be missed and they may spread the disease as well.³ Both symptomatic and asymptomatic populations carried the disease and transmitted it worldwide.

Bats are most likely the initial agent for coronavirus.⁴ The possible potential intermediate host for the transmission of SARS-CoV-2 to humans from bats is likely pangolins.⁴ The human-to-human transmission is possible via the respiratory droplets that might appear when the diseased person is coughing or sneezing and on top of contaminated hands. Moreover, there are reports describing the indirect transmission of the disease by commonly shared public places via surface contamination.⁵ Another possibility of surface contamination is by asymptomatic infected persons.⁶ Although some variations were found in the aerosol transmission of this virus, environmental contamination could not be neglected. Air exhausts, toilet rooms, hospitals' facilities, or objects touched by patients are hotspots for spreading the disease⁷⁻⁹ (Figure 1B).

The disease COVID-19 has started at the end of 2019, and within a few weeks, it has quickly spread throughout the world by various pathways (Figure 1B). In one report, it was mentioned that the virus is active in the air almost for 3 h, and also the virus persists on different surfaces such as plastic, stainless steel, metal, and glass for up to 3–9 days.^{5,10,11} In another report by the US Centers for Disease Control and Prevention (CDC), SARS-CoV-2 was identified on various surfaces in the cabins of the Diamond Princess cruise ship up to 17 days after infected passengers vacated.¹² The virus high persistence ability makes it difficult to control its spreading, along with the struggle to find an immediate and appropriate treatment for the infected patients.¹³ Generally, viruses tend to mutate rapidly, changing their features, including stability and ability to be transmitted. As for SARS-CoV-2, the mutation rate is high, starting with Alfa up to Omicron strains.¹⁴ Due to the increased spreading ability of coronavirus, most countries around the world have put severe restrictions on people's movement and public gatherings, which is eventually affecting the

social life of human beings. Also, it obstinately affects the economy since most of the business has been on hold several times during this ongoing pandemic and still wreaking economic havoc. Although several types of vaccines are available now, the emerging mutations of coronavirus force the manufacturers to adapt every time newer versions of vaccines. This procedure takes even more time and effort to establish the newer versions of the vaccine plus conducting stability studies. Also, no specific therapy is available for this virus that can address all variants and mutants at once. Early prevention of further spreading is crucial to control the infectious network. Thus, in parallel to treatment and advanced vaccine development for various variants of the virus, efforts to prevent the infection must be prioritized. Here, we cover those preventative methods and materials and the urgent need to develop a new arsenal of stable antiviral polymeric materials for addressing both ongoing and anticipated viral outbreaks in the future.

2 | IMPORTANCE OF PERSONAL AND SURFACES HYGIENE

Limited knowledge is available on the COVID-19 infection cycles, especially with the increase of new mutants, which eventually have led to many unanswered questions regarding the usage of the sanitizers and disinfectants applied in the prevention of the spreading of the disease.¹⁵ The most efficient way to prevent the transmission of this disease is to keep social distancing, although it has social and economic drawbacks, which were mentioned before. Therefore, basic and nearby environmental hygiene is necessary to prevent spreading this disease. Frequent handwashing with soap for at least 20 s is essential. Alternatively, cleaning hands with alcohol-based sanitizers is also effective. Soap and alcohol-based sanitizers work in a similar mechanism: they break down the lipid layer of the virus envelope. During the initial period of spreading the coronavirus worldwide, the Food and Drugs Administration (FDA) has given specific guidelines about the usage of hand sanitizers. Alcohol-based or benzalkonium

chloride-based sanitizers are destined to be used topically. Ethanol or isopropyl alcohol-based sanitizers are primarily available in the form of wipes and alcohol gels. They can be readily usable in various institutional, residential, and health care places. The concentration of alcohol in the sanitizers is very important. It evaporates very quickly and as the contact with the contamination should last for a minimal time to be effective. Mixing an appropriate amount of water will enhance the surface contact for about 30 s, which effectively kills the virus. However, benzalkonium chloride-based sanitizers can be used as alternatives to alcohol-based sanitizers since they are non-toxic at a lower concentration, causing less irritation to the skin and are non-flammable.¹⁶

3 | ACTIVE INGREDIENTS OF HOUSEHOLD DISINFECTANTS AGAINST CORONAVIRUS

Although we do not yet understand some aspects of the SARS-CoV-2, based on the genetic and morphologic similarity of SARS-CoV-1 and Middle East Respiratory Syndrome (MERS), disinfectants spraying can be helpful to eradicating the coronavirus from the surfaces.¹⁷ The Environmental Protection Agency (EPA) from the USA has made a list of disinfectants for coronavirus elimination. They were proved to work against this virus similarly on other types of enveloped viruses. Based on this list, most commercially available formulations can be used to disinfect various public and residential sites/places.¹⁸ Active ingredients of commercially available disinfectants against coronavirus or other similar viruses on various areas/places are

discussed in the following sections. The main categories of these disinfectants belong to quaternary ammonium; bleaches such as sodium hypochlorite, hypochlorous acid; peroxides of hydrogen peroxide and peroxyacetic acid; alcohols such as ethyl alcohol, isopropyl alcohol; natural-based compounds such as citric acid, thymol, lactic acid, others such as phenols, sodium chlorite, etc. The disinfectants mentioned in the EPA list are available either as one active ingredient or a combination of them, as they vary in their mechanism of action (Figure 2).

Quaternary ammonium (QA) containing disinfectants are available as household cleaning agents for killing viruses. There are more than 220 products available that contain QA moiety in the EPA List N for use as disinfectants or preventing the spreading of the COVID-19. These disinfectants are primarily used in the health care and food service sector. QA disinfectants affect the protein and lipid structures of the coronavirus and restrict the spreading of the virus.^{19,20} QA functionalities are permanently positively charged, and thus they can attract the partially negatively charged virus and destabilize it up to detachment of the envelope. Most of the commercially available formulations contain small molecule-based quaternary ammonium compounds. The EPA approved two Lysol disinfectant sprays for killing the coronavirus based on the lab test results.²¹

Sodium hypochlorite or regular household bleach is another commonly used disinfectant mentioned in the EPA List N. A dilution (0.1%) of household bleach was sprayed in various public places since the exact viral load on the inanimate surfaces is unknown.²² However, the stability of the sodium hypochlorite is very poor under UV/Sunlight. Due to this drawback, frequent spraying is required to

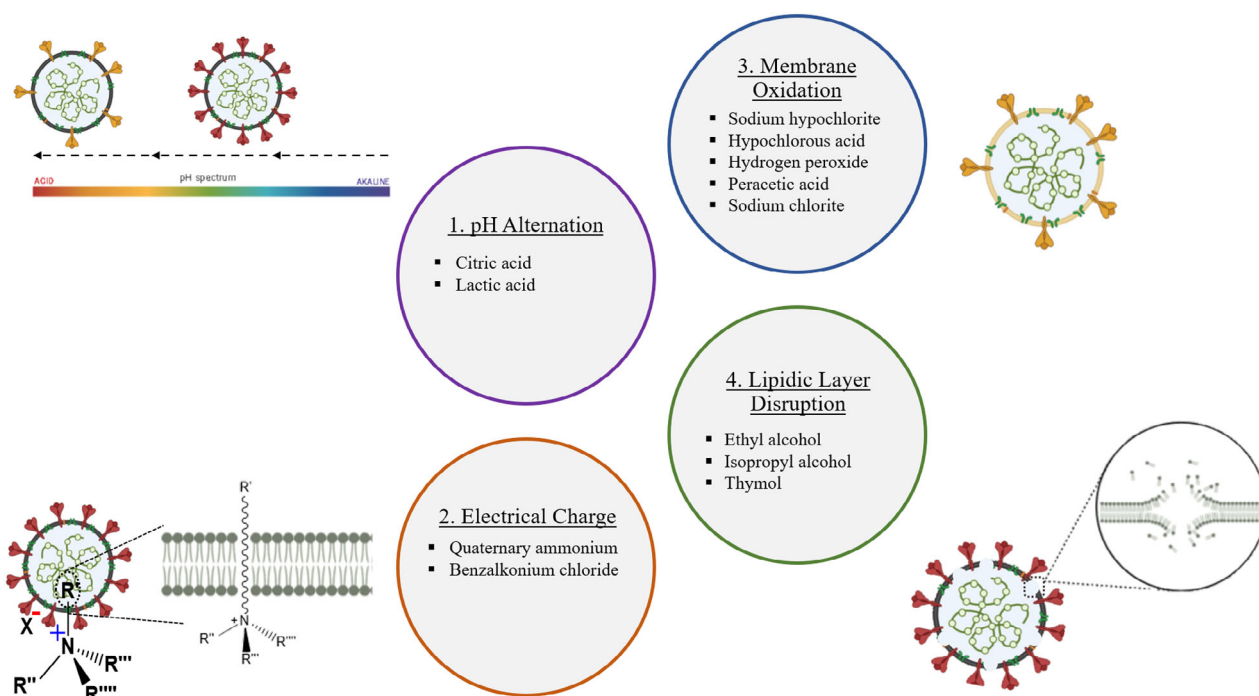


FIGURE 2 Disinfectant divided by action mechanisms: (1) inactivation through the alternation of pH, (2) inactivation through electrical charge disruption and instability, (3) membrane oxidation, and (4) disruption of the membrane lipidic layer. Source: Created with BioRender.com

maintain the effect. Other bleach-releasing formulations based on hypochlorous acid and sodium chlorite have been mentioned in the EPA List N as surface disinfectants.

Hydrogen peroxide is a useful disinfectant and is available in various commercial formulations mentioned in EPA List N against the prevention of spreading the COVID-19. A 3% concentration of hydrogen peroxide can inactivate different viruses, including coronavirus, within 1–10 min, addition to the advantage of less harmful effects on human health. Moreover, it can oxidize the membrane proteins, enzymes, and nucleic acids, which lead to the inactivation of the virus.^{23,24}

Another synthetic reagent mentioned in the various formulations of the EPA List used in the health care sector and food and beverage industries is peracetic acid. There are also natural-based substances such as citric acid, thymol, lactic acid, sodium bisulfate, and dodecylbenzenesulfonic acid that have been mentioned in the EPA List N. The usage of these materials may be safer. It can be effective in killing the virus on surfaces.

4 | ADDRESSING THE SHORT-TERM ACTIVITY AND TOXICITY ISSUES OF DISINFECTANTS WITH ENVIRONMENTAL-FRIENDLY LONG-LASTING ANTIVIRAL POLYMERS

COVID-19 high transmission requires thorough cleaning. Therefore, re-spraying of disinfectants is one of the high valued options to seize the spreading of the disease.²⁵ Using disinfectants and sanitizers during the current COVID-19 situation should not generate any poisoning effect on public health. In the recent report released by CDC, there were incidents of poisoning by disinfectants.²⁶ One such example was an adult woman who watched TV news about the washing of groceries purchased from the supermarket before utilizing them due to the spreading of the coronavirus. The woman filled the sink with bleach along with hot water and vinegar. While disinfecting the groceries, she could not breathe and called the emergency health care services. In another example, a preschooler ingested the alcohol-based sanitizer and was admitted to the hospital. Although the adult woman and preschooler were eventually safe, the usage of these disinfectants has raised an imposed risk on the consumer's health. Also, the improper use of sanitizers and disinfectants leads to the pollution of the environment. Therefore, the usage must be as instructed in detail on the labels of the sanitizer or disinfectant containers. Moreover, improper mixing could lead to chemical hazards. Thus, it is essential to identify the materials which are effective against coronavirus in achieving the necessary disinfection activity with maximized safety to the public and environment.

The most common disinfectant categories are bleach molecules, quaternary ammonium compounds, peroxides and a combination of these molecules, covering more than 70% among available disinfectants. However, they pose some user risks that should be noted. Bleach has been classified as asthmagen, as even the lower levels of exposure cause respiratory problems. Carcinogenic byproduct chloroform will be generated from the bleach after disinfecting the places.²⁷

One frequently used quaternary ammonium is benzalkonium chloride, which causes dermatitis.²⁷ Peroxides at higher concentrations cause acute toxicity.²⁷

Overall, these products provide effective treatment of a contaminated surface. However, they are effective only at the time of application and are not long-term rather momentary solutions. The surface can get recontaminated immediately, remaining a potential source of infection transmission until the next cleaning period. To overcome this, increased frequency of spraying the disinfectants has been the applied solution. However, this solution is impractical. So, there is a need to find an effective, long-lasting method to constantly reduce the number of viruses and/or microbes living on the surfaces in their spaces. The lack of the arsenal of long-lasting materials in facing the COVID-19 pandemic is clearly evidenced. Continuous disinfection of the various surfaces is required, usually performed with small molecules-based surface decontamination, known for their instability.

Surface cleaning techniques include continuous high-intensity blue light emission,²⁸ antimicrobial active metal plating, and antimicrobial polymeric coatings. Yet, constant exposure to high-intensity blue light emission alters the human cellular functions.²⁹ Antimicrobial active metal plating for the surfaces is another considerable surface decontamination method, although its effectiveness is unclear.³⁰ Metal-based surface coatings, especially silver-based biocides including silver nanoparticles, have been widely used in medical applications. However, identifying silver-resistant genes in several bacteria has created awareness to monitor frequently for resistant bacteria.³¹ Thereby continuous efforts are required to have new and powerful biocides. To overcome the limitations associated with small molecules and other previously mentioned surface decontamination techniques, polymers are considered as one of the alternatives.

Antimicrobial polymers are attractive macromolecules with bioactive functionalities.³² The majority of these polymers show activity against bacteria, but very selective polymers are active against viruses.³³ The polymers can act either as carriers for bioactive molecules to be released in a controlled fashion or possess functional groups as intrinsic antiviral moieties. The last-mentioned class has better antiviral functionality. They can be formulated or can be cast into various forms as necessary. Various antiviral polymer classes according to their mechanism of action are given in Figure 3.

The majority of antiviral/antimicrobial polymers are charged, containing a positive charge in the form of quaternary ammonium functionality.^{34–41} Quaternary ammonium on the polyethyleneimine (PEI) backbone interacts with the lipid membrane of the virus. Cationic and zwitterionic PEI polymers showed virucidal activity within 5 min.⁴² A similar kind of mechanism is anticipated for antiviral pyridinium polyvinyl pyrrolidones.⁴³ Quaternary phosphonium-based polymers are utilized for non-enveloped viruses, which do not contain any lipid membrane. They can perform inactivation as an alternative strategy for the non-enveloped virus.⁴⁴

In another work, about 14 polymers containing anionic functionalities such as carboxylates, phosphates/phosphonates, and sulfonates with various hydrophobic backbones were synthesized.⁴⁵ These 14 polymers were studied against 11 viral pathogens, including SARS to understand the structure–activity relationship.⁴⁵ The authors have

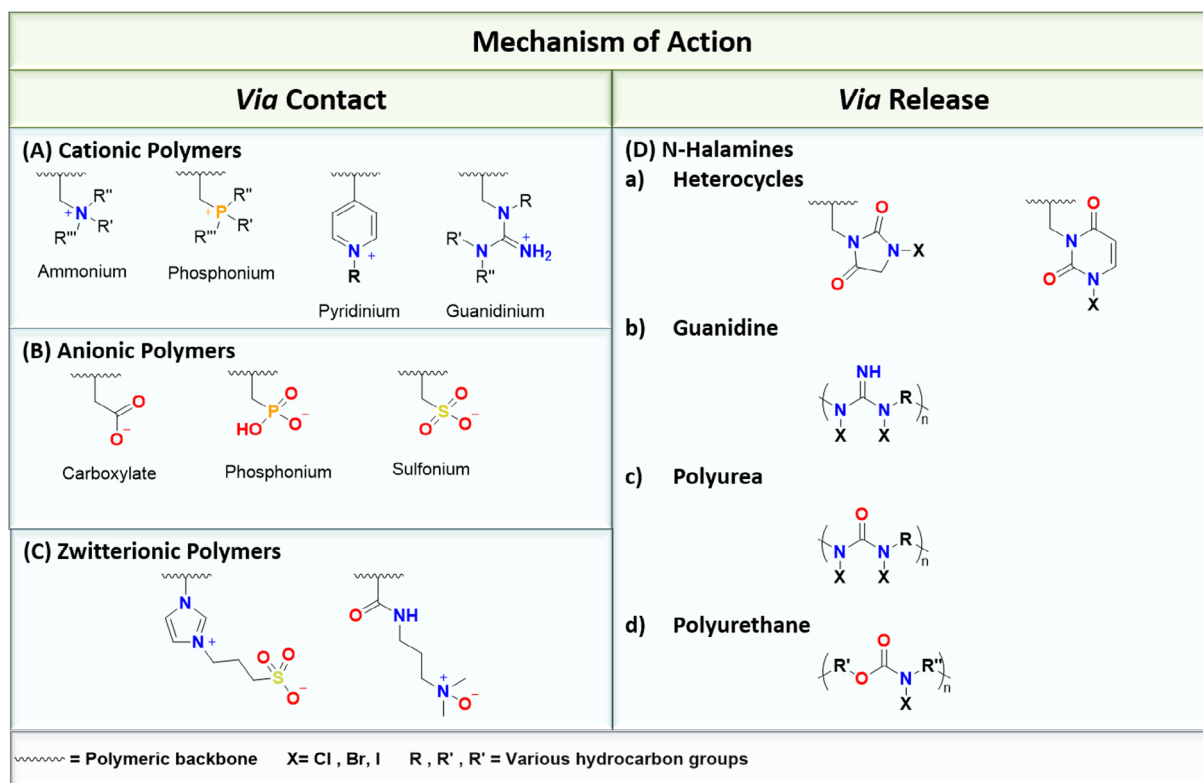


FIGURE 3 Various antiviral polymeric classes based on their mechanism of action

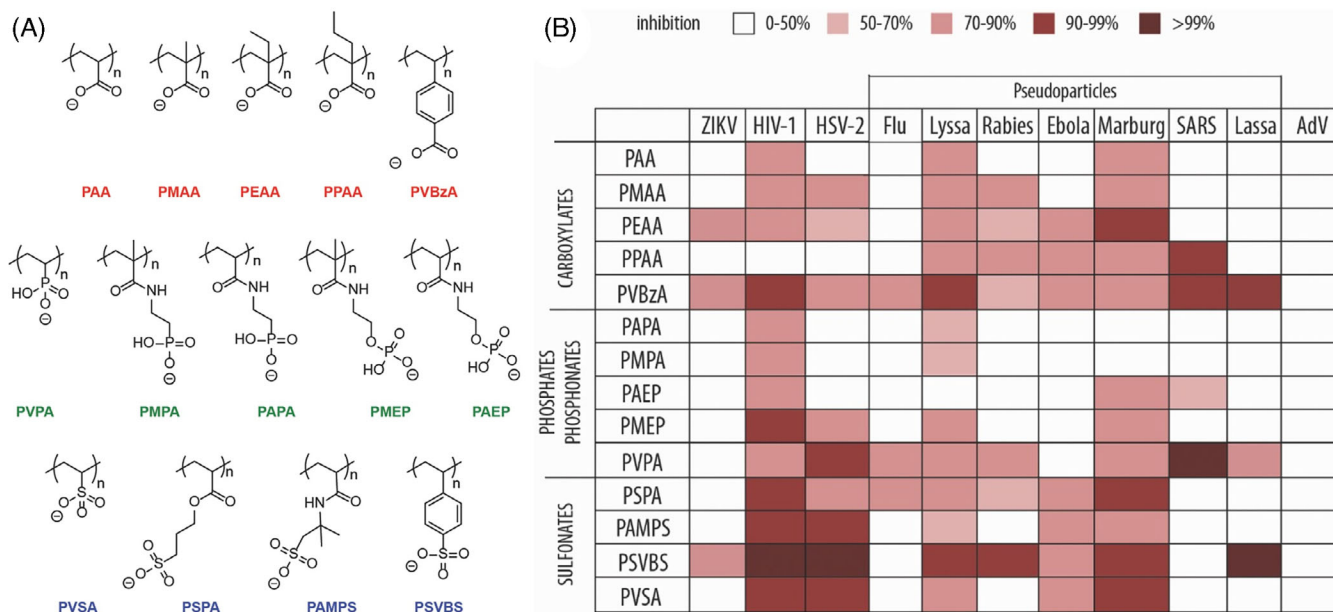


FIGURE 4 (A) Chemical formulas of the polymers used in this study. Carboxylates (in red): poly(acrylic acid), PAA; poly(methacrylic acid), PMAA; poly(ethylacrylic acid), PEAA; poly(propylacrylic acid), PPAA, poly(vinylbenzoic acid), PVBzA. Phosphates/phosphonates (in green): poly(vinylphosphonic acid), PVPA; poly([2-methacrylamidoethyl]phosphonic acid), PMPA; poly([2-acrylamidoethyl]phosphonic acid), PAPA; poly([2-methacrylamidoethyl]phosphate), PMEP; poly([2-acrylamidoethyl]phosphate), PAEP. Sulfonates (in blue): poly(vinylsulfonic acid), PVSA; poly(3-sulfopropyl acrylate), PSPA; poly(2-acrylamido-2-methyl-1-propanesulfonic acid), PAMPS; poly(vinylbenzenesulfonate), PSVBS.⁴⁵ (B) Summary of the maximum antiviral activities of tested polyanions.⁴⁵ Source: Adapted from Reference [45], copyright 2017, WILEY-VCH Verlag GmbH & Co. KGaA, Weinhei

found a broad spectrum of antiviral activity for these polymers (Figure 4). They also observed virus-specific antiviral activity for some of the polymers in this study. This study suggested hydrophobicity of the polymer influences the antiviral activity of the polymer under investigation. Among the 14 polymers, poly(vinylbenzoic acid), PVBzA was active against all the enveloped viruses studied in this report.⁴⁵ This polymer might be considered as a useful antiviral agent for the development of disinfectants after clinical studies. The antiviral lead polymers of this study can be projected as microbicides to prepare formulations of creams, gels, coatings and paints, sprays, etc., for various medical and non-medical applications.⁴⁵

Sulfated polysaccharides are another type of anionic polymers that have been frequently used as antiviral polymers. These polymers including heparin, carrageenan, and dextran sulfate, have been reported for their antiviral activity.⁴⁶ Alternative to the natural sulfated polysaccharides, synthetic sulfated polysaccharides were developed recently as a powerful arsenal of antiviral materials for a broad spectrum of virus inactivation.⁴⁷

Small molecule-based guanidine functionality showed remarkable antiviral activity as it inhibits the virus from entering host cell.⁴⁸ Based on this result, polymers containing guanidine functionality have been developed for the exploration as antiviral polymers.⁴⁹⁻⁵²

N-halamine (*N*-X; X = Cl/Br/I) functionality containing polymers is gaining popularity among antiviral polymers. The polymers containing *N*-halamine functionality release halonium ions, which have a positive charge function as an antiseptic oxidizing agent.⁵³⁻⁵⁵ In a recent study from the Domb group, polyurea and polyguanidines were

converted to *N*-halamine linkages to study their antiviral activity against T4 bacteriophage and tomato brown rugose fruit virus. The halonium ions linked to these polymers, such as chloronium/bromonium, were released in a controlled manner as studied for 4 weeks.⁵⁵ This study paved the way for the development of industrial polymers as disinfectants for the release of bioactive for long-term antiviral activity in agricultural science.

Advanced functionalized and environmental-friendly polymers will play a significant role in treating coronavirus and other viral infections. They have the potential to limit the spreading of the virus, serving in the preparation of face and mouth protection to various disinfectants and long-lasting surface coatings. Moreover, polymers possessing targeted gene delivery can have incapacitate the coronavirus. Different intrinsic polymeric biocides such as polycations, macromolecular prodrugs, and other polymeric drug delivery systems can have an impact on the virus and related diseases. It is anticipated that the development of new antiviral polymers towards clinical treatment shortly will be possible.

5 | OUTLOOK, THE ROLE OF ADVANCED POLYMERS, AND FUTURE PERSPECTIVES RELATED TO THE DISINFECTANTS

Infection through surfaces is a very serious threat, especially in public places, since coronavirus can persist on various surfaces for an extended period. Since there is no ultimate therapy or an ideal vaccine

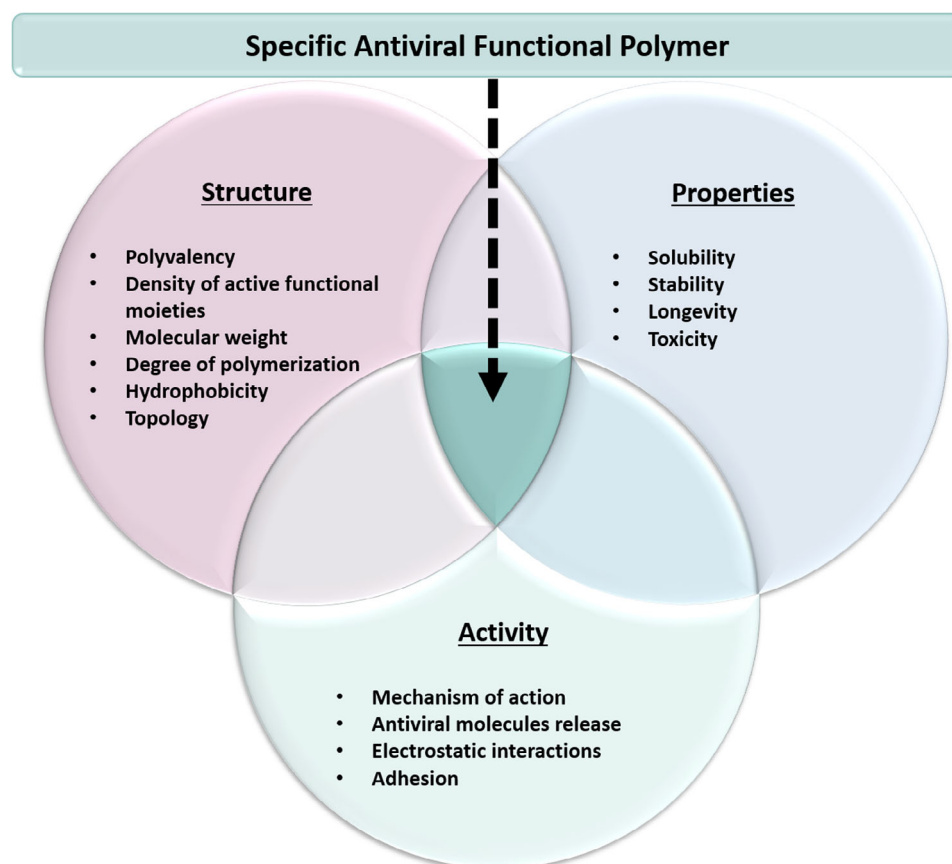


FIGURE 5 To obtain specific antiviral functional polymer, libraries of functional polymers with the mentioned structure–property–activity relationship should be prepared and evaluated

available for COVID-19, disinfection measures including common surfaces is with great importance to prevent the spreading of the coronavirus and its variants, as it is a highly contagious disease. Different classes of disinfectants are available for the inactivation of coronavirus. It is evident that disinfecting agents such as sodium hypochlorite, small-molecule quaternary ammonium compounds, and peroxides eradicate coronavirus, but their toxicities, short-term activity, and surface damaging effects limit their application on different surfaces. To prevent toxicity and related accidents, one should act by the regulations made for the usage of disinfectants. Bleaches and other disinfectants should not be used to clean food products, vegetables, fruits, etc. Sanitizers containing alcohols and surfactants will be effective on the envelop disintegration of the coronavirus; however, this depends on the exposure time of the sanitizers. Alcohol-based sanitizers always should be kept away from children.

Effective and at the same time, human-friendly sanitizers or disinfectants are required to prevent the poisoning and the associated issues. These will minimize the poisonous effects of the currently available materials by rapid action, high potential, long-term stability, and showing excellent biocompatible nature. Polymers are one of the important classes of disinfectants that might receive significant attention towards developing novel disinfectants for coronavirus disinfection and other microorganism-based outbreaks. Moreover, thanks to their universal mechanism of action, they also have the potential to be suited for future pandemics that are probably expected. Polymers can have intrinsic bioactive functionalities, release active agents in a controlled manner and possess long-term stability with immediate effect on the microorganisms. They also could serve as carriers, enhancing the stability of relevant substances. Furthermore, the variety of applications that polymers could be used for is great: antiviral polymers can be prepared as disinfectant coating materials. They can also be used as additives in everyday household products showing long-term inactivation capacities towards the coronavirus and other microorganism-based outbreaks. Therefore, polymers may generally offer a high-potential solution for disinfecting application, especially for COVID-19. To obtain effective and a virus-specific functional antiviral polymer, libraries of polymers should be prepared based on the structure–property–activity relationship (Figure 5), where each aspect should be studied and evaluated. We strongly believe that such studies, not only will result with superior antiviral polymers but also with virus specific functional polymers, that is, against SARS-COV-2.

ACKNOWLEDGMENTS

This review article is part of an activity, COVID-19 Rapid Response Innovation Project (Grant No. 20878) on Long-Lasting Antiviral Polymers that has received funding from EIT Health. EIT Health is supported by the European Institute of Innovation and Technology (EIT), a body of the European Union receives support from the European Union's Horizon 2020 Research and Innovation Programme. The Neubauer Family Foundation is thanked for its generous funding and support. S.F. was supported by MAOF Fellowship from the Council for Higher Education, Israel.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Kunduru KR, Kutner N, Nassar-Marjiya E, Shaheen-Mualim M, Rizik L, Farah S. Disinfectants role in the prevention of spreading the COVID-19 and other infectious diseases: The need for functional polymers!. *Polym Adv Technol*. 2022;33(11): 3853-3861. doi:[10.1002/pat.5689](https://doi.org/10.1002/pat.5689)