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Review Article

# IODINE AS A POTENTIAL FRONT-LINE DEFENSE AGAINST COVID-19: A LITERATURE REVIEW

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**ABSTRACT**

The novel coronavirus disease, first identified in 2019 known as COVID-19, is caused by a new strain of severe acute respiratory syndrome coronavirus (SARS-CoV or SARS-CoV-1), named SARS-CoV-2. Recent studies showed that the virus may be airborne and spreads through small respiratory droplets of saliva in aerosols, indirect or direct physical contact with the affected individual, in a similar way to the cold and influenza. Emerging studies also demonstrate the importance of the throat along with salivary glands as sites of viral replication and transmission in early COVID-19 infection. The most common route of entry of SARS-CoV-2 is the upper respiratory tract (nasopharynx) that slowly reaches the lower respiratory tract to infect the epithelial cells within the lungs which can cause lung damage and severe respiratory symptoms, if not treated immediately. Averting colonization of the virus in the nasopharynx could be one of the best options to reduce the incidence of severe infection. It has been well-documented that iodine is one of the most effective of all antimicrobials available. Hospitals and medical facilities worldwide use povidone-iodine (PVP-I) as a standard of care in infection control. Several research studies during the ongoing COVID-19 pandemic showed the *in vitro* and *in vivo* efficacy of iodine-containing solutions such as PVP-I (Betadine), Iodine-V (Essential Iodine Drops) etc. and other iodine complexes to effectively kill the SARS-CoV-2 virus within few seconds to hours. Few commercially available iodine-containing gargling, mouthwash, and nasal spray solutions have been recommended to use in humans against SARS-CoV-2 infection by experts to prevent viral spread, especially among health workers. The present article aims to summarize these studies and highlights the rationale, safety and recommendations of use of iodine as an effective method to decrease the viral load during the early COVID-19 infection.

**Keywords:** COVID-19, SARS-CoV-2, Iodine, Povidone-Iodine, Iodine-V, Iodine complex.

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## INTRODUCTION

The novel coronavirus disease in 2019 (COVID-19), initially referred to as nCov19, is caused by a new severe acute respiratory syndrome coronavirus (SARS-CoV-1) strain, known as SARS-CoV-2 [1]. The COVID-19 epidemic which was first detected and reported in December 2019 in Wuhan, China, and has been declared a public health emergency of international concern by the World Health Organization (WHO), has progressed to a pandemic that caused substantial morbidity and mortality in different waves [2,3]. Millions of people from different countries in the world have documented COVID-19 infection; millions more are suspected of undocumented cases including asymptomatic cases and globally over 3 million people have died. Airborne aerosol transmission has been recently recognized by the WHO, Centers for Disease Control and Prevention,and the world scientific community as a significant mode of SARS-CoV-2 transmission [4-10]. These transmission dynamics are particularly concerning to the rhinologic provider in light of the evidence of high viral loads within the upper respiratory tract among both symptomatic and asymptomatic patients [2]. Till the mass vaccination had been successfully implemented globally, non-pharmaceutical interventions (NPIs) were the only proven measures to mitigate the transmission of COVID-19. Preventive measures such as lockdowns, masking, social distancing, washing hands frequently, and eye protection have already been adopted to reduce the transmission of SARS-CoV-2 [11]. However, the outbreak has been challenging to contain, as new case clusters continued to emerge and surged in numbers even after the initial quarantine measures, as seen in India and other countries. Several waves of the COVID-19 pandemic, due to the emergence of different new variants of SARS-CoV-2, has been observed. Besides NPIs, additional pharmacological interventions such as use of anti-parasitic drugs such as hydroxychloroquine, ivermectin, and antimicrobial agents such as povidone-iodine (PVP-I), zinc, vitamin C, chlorhexidine, cyclodextrins, and hydrogen peroxide against SARS-CoV-2 were explored to reduce and control the spread of the virus [12,13]. Several lines of scientific investigations on this front also showed that iodine-containing mouthwash, gargling or nasal spray may be the simplest and most cost-effective therapeutic antidote against COVID-19 [14]. Iodine has been well documented as one of the most effective of all antimicrobials available (Fig. 1). Even though COVID-19 is waning at present, the application of iodine holds promise for many other infectious diseases including COVID-19.

## COVID-19 INFECTION AND TRANSMISSION

SARS-CoV-2 is an enveloped, single-stranded RNA virus that belongs to the same class of beta-coronaviruses such as SARS-CoV and Middle East Respiratory Syndrome (MERS)-CoV, the viruses responsible for the SARS 2003 and MERS 2012 epidemics, respectively [15,16]. It is spherical and is surrounded by a lipid bi-layer envelope (E), into which the spike glycoproteins (S1 and S2) required for infection are inserted (Fig. 2) [17]. Initial studies showed that SARS-CoV-2 occupies host cells mainly through the host receptor angiotensin-converting enzyme 2 or ACE2 which is one of the important receptors on the cell membrane of the host cells [18-20]. More recent studies have found that viral invasion can also be mediated through other alternative routes like CD147 (also known as Basigin or EMMPRIN) receptor [21,22] and GRP78 (also known as Heat shock protein family A member 5 or HSPA5) receptor [23]. CD147 is a transmembrane protein, highly glycosylated of the immunoglobulin superfamily which acts as the main upstream stimulator of matrix metalloproteinases [20]. GRP78 or HSPA5 also referred to as immunoglobulin heavy chain-binding protein, is a member of the heat-shock protein-70 family and is widely known for its role in the degradation of misfolded proteins and the unfolded protein response [24]. Virus spike protein (S1 and S2) binds to ACE2, CD147 and/or GRP78 receptors on the host cell, mediating viral invasion and spreading to other cells [18-23]. Therefore it can be assumed that in case of SARS-CoV-2, early interactions between its host

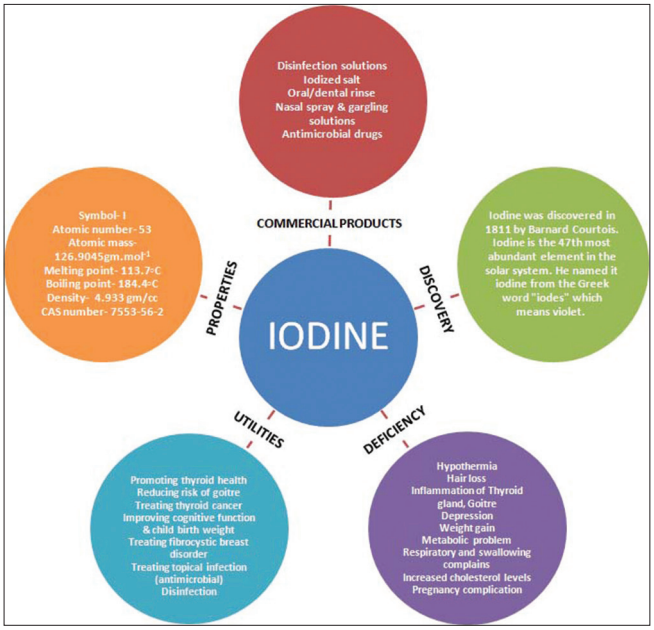


**Fig. 1: Discovery, properties and utilities of Iodine**

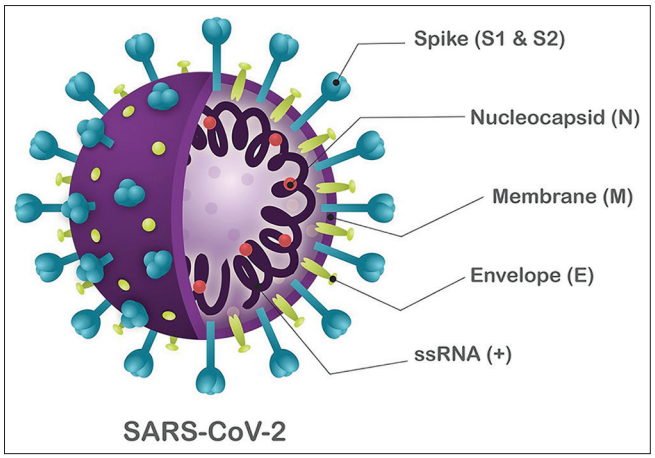


**Fig. 2: Schematic structure of SARS-CoV-2 (adapted from Santos *et al.* 2020 [17] article)**

receptor and the spike protein S domains are the initiating event in the establishment of human host infection.

ACE2 receptor has been reported to be expressed in the liver, lung, stomach, kidney, ileum, and colon however current evidence supports low expression of this receptor in the human respiratory system. This raises questions about the exact role of the ACE2 receptor in SARS-CoV-2 infection and has given rise to the hypothesis that co-receptors/attachment factors or putative alternative receptors, such as CD147 and GRP78, could be involved in the entry of SARS-CoV-2 and contribute to tropism [25,26]. Several studies also point out a possibility of local replication of the virus followed by systemic involvement, especially in cases of droplet or aerosol transmission through the ocular route [27-31]. It was speculated that the upper respiratory tract infection occurs due to the binding of SARS CoV-2 with either ACE2 or CD147 receptor in ocular tissues then drains into the nasal cavity through nasolacrimal duct [20,21,28,32].

Emerging data emphasize the major role played by the upper and lower respiratory tract in SARS-CoV-2 virus replication and transmission [2,33]. The oropharynx and nasopharynx of the upper respiratory tract are targeted by the virus initially that subject to high numbers of infective copies of the virus [34]. A gradient of expression of these receptors exists within the respiratory tract with the greatest density, expressed in the ciliated epithelial and goblet cells of the nose and fading expression in the distal alveolar and bronchiolar regions [35,36]. These upper respiratory tract cells likely serve as a primary host site for viral replication and eventual dissemination [37]. Because of preferential receptor density, it has been speculated that the nasal surfaces represent a dominant initial site of infection and that seeding of the deeper lung from the nose may be responsible for the heterogeneous manifestations of severity of COVID-19 disease [38]. These findings serve to illuminate both the role the eye and nose may play as a potential portal of infection and the risks associated with viral particle translocation to the pulmonary system.

Human-to-human transmission of COVID-19 occurs primarily through respiratory droplets from coughs or sneezes and/or physical contact in the community [4,5]. Contaminated surfaces are known to be significant vectors in the transmission of infections in the hospital setting as well as the community via touch transfer. Recent studies suggest the potential for airborne transmission of the virus through aerosols formed either due to coughing and sneezing by an affected individual in the community or due to during medical and dental procedures in the healthcare settings [4-10]. These transmission dynamics are particularly concerning to the rhinologic provider in light of the evidence of high viral loads within the upper respiratory tract among both symptomatic and asymptomatic patients [2]. Averting colonization of the virus in the nasopharynx could be one of the best options to reduce the incidence of transmission.

## IODINE-BASED SOLUTIONS

Iodine-based solutions have been utilized as antiseptics for many years, particularly in the head and neck region as a topical disinfectant on nasal, oral, cutaneous and ocular surfaces [39]. It has been well documented that iodine is one of the most effective of all antimicrobials available (Fig. 1).

### PVP-I

Hospitals and medical facilities worldwide use PVP-I, which is polymer polyvinylpyrrolidone (PVP-I), as a standard of care in infection control even though it contains very small amounts of iodine. An *in vitro* study by Moskowitz and Mendenhall [39] showed a 100 ppm molecular iodine oral rinse (Formula 100-S molecular iodine from Iotech International, Boca Raton, Florida) can inactivate the SARS-CoV-2 virus completely in 30 s with no associated cytotoxicity [40]. Along with 100-S molecular iodine, the study also showed robust efficacy of PVP-I to inactivate the virus when compared with other oral rinses containing chlorhexidine gluconate and hydrogen peroxide. This study opened the door for further research and the need to review the past and current research about the efficacy of iodine as an antiviral therapeutic agent. The development of a topical intranasal virucide against SARS-CoV-2 became a highly desirable goal to mitigate the evident risk of aerosol-based transmission in both the outpatient clinic and operating room [41].

PVP-I formulations have been previously shown to be active against SARS-CoV and MERS-CoV viruses [42-44]. From the start of the COVID-19 pandemic to this date there were several *in-vitro* clinical investigations performed by the researchers, to show the anti-virulent efficacy of PVP-I against SARS-CoV-2 [14,45-52]. Few *in-vivo* randomized clinical trial studies were also performed, showing PVP-I throat/nasal spray or oral rinse solutions are effective to kill the virus and reduce the transmission [12,53-58]. A major pharma company Cipla has recently rolled out an anti-viral nasal spray called Naselin, which contains PVP-I (0.5% W/V in 15 mL) to protect against coronavirus and respiratory tract infections. The spray acts by killing the disease-causing viruses and bacteria in the nose [59]. Melbourne-based biotech company Firebrick Pharma, founded in 2012, by Betadine throat gargle creator Dr. Peter Molloy, has also developed another similar nasal spray Nasodine (0.5% PVP-I) that could be capable of reducing the amount of detectable coronavirus by almost 100% in 60 s (*in vitro* study) [58]. A pilot *in vivo* study performed with 14 laboratory-confirmed Reverse transcription polymerase chain reaction, COVID-19 positive subjects with COVID-19 symptoms (within

5 days of onset), showed promising results of antivirulent activity of the 0.5% PVP-I nasal spray, warranted for further larger scale confirmatory trials. Nasodine is yet to be approved for commercial use by any global regulators and the authors have undertaken a large double-blinded randomized controlled trial to confirm if repeated application of 0.5% PVP-I nasal spray over a longer period could be useful in suppressing viral shedding and transmission risk in COVID-positive patients [58].

PVP-I elicit potent antiviral activity by blocking viral attachment to the host cell receptors and inhibition of viral release from infected cells [60]. After dilution in an aqueous solution PVP-I complex releases free iodine which oxidizes fatty acid of the viral cell wall and deactivates the essential viral enzymes, thereby blocking the viral release from the host cells, preventing further spread of the virus to the host cell receptor and inhibits the inflammation of host tissue [61-63]. In addition, PVP-I also inhibit viral hemagglutinin, resulting in the blockade of attachment to the host cell receptor [14].

PVP-I is well tolerated by majority of the patients. Recent *in vitro* studies showed that iodine is not cytotoxic at concentrations greater than 100 times higher than that found in PVP-I [64]. Allergenic dermatitis and significant toxicity after prolonged skin contact with PVP-I have been reported to be rare complications [65,66]. Meanwhile, 0.5% PVP-I application on ciliated human nasal epithelial cells did not demonstrate any damage [67]. Gargled PVP-I solution like betadine is well tolerated when compared with other gargled antiseptics [68]. It is expected that other approved commercially available PVP-I gargle and mouthwash solutions such as Cipladine (Cipla Ltd.), Wokadine (Dr Reddy's Laboratories Ltd.), Pyodine (Brookes Pharma Ltd.), and Biodine (Biochem Pharmaceutical Industries) will also show the similar tolerance level like betadine. The daily use of PVP-I mouthwash either for 4 times for a short period (2 weeks) or once for a prolonged period (24 weeks) was not found to affect thyroid function [69,70]. Below 0.5% PVP-I gargle once or twice a day up to 6 months showed no alteration in thyroid hormone levels (serum T3/T4 and free T4) but a small increase in thyroidstimulating hormone (TSH) levels within the normal range [71]. However, increased serum TSH concentrations may occur after prolonged use. Therefore, PVP-I should be used carefully in those with thyroid problems. Short-term use of PVP-I has not been shown to irritate healthy or diseased oral mucosa or exhibit adverse effects, such as discoloration of teeth and tongue or change in taste [72]. PVP-I was found to be favorably tolerated by children receiving PVP-I for dental conditions, however, recommended not to be used in pediatric patients of below 6 years [14,72,73]. Some researchers and clinicians suggested that, in hospital settings in case of suspected or confirmed COVID-19 patients, 0·5% PVP-I solution (0·55 mg/mL available iodine) can be applied to the oral, oropharyngeal and nasopharyngeal mucosa of patients with the healthcare personnel in close contact to prevent cross infection [73]. 0.2% povidone-iodine may reduce the risk of ventilator pneumonia [67,74,75].

Few well-designed studies have established the efficacy of Betadine eye drops in viral conjunctivitis [76]. In case of conjunctivitis with COVID-19, this preparation may help to reduce the viral load due to its action against a wide range of viruses. Burning and irritation is a significant side effects of the drug, which can be effectively reduced by diluting 1 mL of 5% Betadine with 4 mL of Benzalkonium chloride (BAK) containing lubricant drops [77]. This formulation will have the advantage of dual antiviral action with BAK and Betadine with patient comfort [76-78]. It can help in decreasing the risk for contamination due to accidental eye exposure or contact, at a remarkable level.

There are other approved iodine-based solutions, often used in the treatment of inflammation of gums and tonsillitis, pharyngitis, and throat congestion due to common cold or flu infection. These solutions have used different formulations which are alternatives to PVP-I.

**Glycoseptol**

Glycoseptol, an alcohol-based (Surasar Q.S.) antiseptic gargle, and mouthwash, manufactured by Jupiter Pharmaceutical Ltd., Kolkata, has used a formulation that contains key antimicrobial agents like Cetylpyridinium Chloride (CPC) and iodine along with ayurvedic components as active ingredients, commonly used to fight against tropical common cold symptoms [79]. CPC is a cationic biocide, widely used as a disinfectant in dentistry and also as a mouthwash in different formulations with other active ingredients. The application of CPC has been postulated as a supplementary strategy to fight the transmission of viruses such as Influenza [80,81] or Herpesviruses [82], where the oral cavity plays an important role in spreading the virus, however, more clinical studies are required to confirm this. Although the underlying mechanism of the antiviral activity of the CPC molecule and mouth rinses containing CPC remains to be determined, it is potential viral membrane degradation mechanism, by which mouth rinses inhibit the spread of SARS-CoV-2, have been hypothesized and shown by *in vitro* experiments [83-88]. A recent *in vitro* study showed that the concentrations of 0.05% CPC (w/v) commonly used in mouthwash preparations are sufficient to rupture the membranes of SARS-CoV-2 virus-like-particles [88]. Two clinical trials have been documented, the first is a randomized controlled clinical trial, in which it was concluded that commercial mouthwashes formulated with CPC could reduce the viral load of SARS-COV-2 more consistently than other mouthwashes [56], uncovering the potential role of CPC in the control of COVID-19 transmission. The second clinical trial, a pilot study, which also showed the efficacy of mouthwashes containing CPC and zinc, as a risk-mitigation step to help to reduce the oral viral load of SARS-CoV-2 among COVID-19-positive patients [89]. The combination of CPC and iodine formulation in glycoseptol along with alcohol that makes the solution evaporative could be a safe alternative to PVP-I throat/nasal spray, that warrants the need of further clinical studies to confirm its efficacy against SARA-CoV-2.

**ioRinse ITU**

ioTech International, a Florida-based antimicrobial company, has developed and patented a stable aqueous formulation of iodine (ioRinse ITU) which contains over 100 times of available iodine as compared to PVP-I while limiting the other non-bioactive iodine species from 30,000 ppm to just a few hundred ppm [90]. This dramatically increases efficacy while drastically minimizing overall toxicity. The need for polyvinylpyrrolidone has been eliminated in this formulation [91]. IoRinse was tested at the Antiviral Research Institute of Utah State University [92]. Its *in-vitro* efficacy was compared with 1.5% hydrogen peroxide rinse, 0.2% povidone-iodine rinse and 0.12% chlorhexidine gluconate rinse against SARS-CoV-2. Only IoRinse was observed to be completely effective in deactivating the virus within 30 seconds [92]. This outcome suggests that this new formulation has the potential to become a safer alternative to PVP-I as a frontline defense against the COVID-19 pandemic [93].

**Iodine-V**

A recent study by Köntös, a researcher from IOI Investment Zrt., in Budapest, Hungary, evaluated the *in vitro* virucidal activity of aqueous solution of Iodine-V, a clathrate complex formed by elemental iodine and fulvic acid as in Essential Iodine Drops (EID) against SARS-CoV-2 to ascertain whether it is a better alternative to PVP-I [94]. It was found that Iodine-V, in EID formulation, inactivated 99% of SARS-CoV-2 after 60 and 90 s. These results were similar to PVP-I, which has previously been reported to inhibit 99.99% of SARS-CoV-2 at 60 s [40,47]. Moreover, it can be a better and safer alternative to PVP-I, as the significantly lower amount of iodine present in this formulation is compared to that which is found in PVP-I. The study showed that an aqueous solution of Iodine-V containing 200 micrograms (μg) of elemental iodine/milliliter (mL) is comparable to 1–5% PVP-I, which often contains 1000–5000 μg/mL iodine. Furthermore, EID is formulated with Iodine-V without excipients unlike PVP-I, and therefore, has a potentially better virucidal activity against SARS-CoV-2 virus. PVP-I excipient has been reported, in rare cases, to induce immediate type 1 hypersensitivity reactions in children [95]. In addition to the therapeutic benefits of EID against SARS-CoV-2, the Iodine-V in EID also serves as a mineral supplement that can maintain a healthy thyroid functioning. Thus the Iodine-V is likely to have better stability and an enhanced potency *in-vivo* when compared with PVP-I against SARS-CoV-2 and can be potentially applied intranasally or orally to reduce SARS-CoV-2 transmission in known or suspected COVID-19 patients [94,96]. Further

clinical trials among confirmed COVID-19 patients and healthy controls with iodine-V in EID formulation, will be helpful to determine the actual *in-vivo* efficacy of this drug and any other safety concerns.

## IODINE-BASED COMPLEXES

### CupriDyne

In another study, the antiviral activity of CupriDyne, an iodine complex surface disinfectant solution was evaluated against SARS-CoV-2 [97]. CupriDyne® iodine complex, made by Odor-No-More, Inc., a subsidiary of California-based life sciences company BioLargo, Inc., is a novel iodine complex solution that produces high local concentrations of iodine without causing the safety and staining issues associated with Lugol's iodine or PVP-I respectively. CupriDyne uses a proprietary chemical solution to produce aqueous elemental iodine and cuprous iodide in equilibrium. The study showed that this iodine complex solution was able to inactivate the SARS-CoV-2 virus in both time and concentration-dependent manner, reducing the virus titers by 99% and reducing the virus titers below the detection limit after 60 min [97]. The CupriDyne iodine complex contains ingredients that were tested safe for human exposure and not known to be associated with poor environmental outcomes (e.g., aquatic toxicity and skin sensitivity). It has been recommended to be used only as an alternative surface disinfectant to bleach or alcohol-based products that have disadvantages for widespread use including skin sensitivity, inhalation risks, and poor environmental outcomes [97].

### Renessans

In a recent study the antiviral efficacy of an oral iodine complex Renessans, was evaluated against SARS-CoV-2 [98]. Renessans capsule (containing 200 mg iodine) and syrup (containing 10 mg/ml iodine), known as an antiviral drug, manufactured by MTI Medical Pvt. Ltd., Lahore, Pakistan, were used in this *in-vitro* study. The cytotoxicity assay confirmed that up to 50 μg/mL concentration of Renessans was nontoxic to the VERO cells. The VERO cells were exposed to SARS-CoV-2 with and without different non-toxic concentrations of Renessans capsule and syrup. The results showed dose-dependent antiviral behavior of both Renessans syrup and capsule against SARS-CoV-2. At 1.5 μg/mL concentration, the viral titers were significantly reduced as compared to infected non-treated control cells. There was no virus detected at concentration of 3.1–50 μg/mL of Renessans after 72 h. This study indicates that Renessans, containing iodine, have potential activity against SARS-CoV-2 which needs to be further investigated in human clinical trials [98]. The authors also evaluated the efficacy of Renessans against SARS-CoV-2, in non-human primates [99]. The study showed complete recovery of Renessans-treated monkeys within 2–3 weeks of post-infection as compared to the untreated monkeys. Gross pathological leisons in different organs was also determined in Renessans treated and untreated monkeys, showed less severe lesions in treated monkeys, suggesting that Renessans did have antiviral activity and helped in the early recovery of SARS-CoV-2 infected monkeys. Based on these findings, it was concluded that Renessans has an *in vivo* SARS-CoV-2 activity and may result in early clearance of the virus, that provides a basis for the clinical trial of the drug in SARS-CoV-2 patients and reveal its anti-SARS-CoV-2 potential [100]. As per the latest update, a controlled randomized ongoing trial is being conducted to evaluate the effectiveness of this iodine complex for clinical and radiological improvements in patients affected with mild to moderate COVID-19 in Pakistan [100,101].

### Zinc iodide-DMSO

A hypothetical iodine complex containing Zinc Iodide and Dimethyl Sulfoxide (DMSO) has been proposed recently as a potential therapeutic agent to treat and prevent chronic and acute viral infections including SARS-CoV-2 infected patients [102]. The therapeutic compound might have strong synergetic efficacy in controlling symptoms, preventing and treating all types of viral infections including COVID-19 where zinc can act as an immunity booster agent, and Iodine and DMSO can act as antiviral agents [102]. Further clinical trials are needed to validate the effectiveness and develop an optimal therapeutic protocol for the possible application of Zinc Iodide-DMSO in patients with viral infections.

### Clyraguard

Recently, to protect workers and health-care professionals from infection by COVID-19, a Clyraguard copper iodine complex was tested for its ability to inactivate SARS-CoV-2 in solution [103]. Clyraguard spray, developed by Clyra Medical Technologies, Inc., CA, is a novel FDA-registered copper iodine complex designed to be used for decontaminating non-critical personal protective equipment (PPE). The formula has proven antimicrobial activity [104] and has been cleared for use on skin and wounds, in contrast to, other iodine-based products, such as Lugol's Iodine and PVP-I, that may cause staining and skin sensitivity. The data from this study showed that the undiluted Clyraguard is effective in reducing SARS-CoV-2 titers in a time-dependent manner, with the virus being reduced below the detection limits within 30 min. It suggests that Clyraguard may be an effective tool for mitigating cross-contamination of non-critical PPE that may come into contact with SARS-CoV-2 [103].

## DISCUSSION

Even though COVID-19 is waning at present and the vaccines have shown success, however, the efficacy of vaccines decreases with time and against variants [104-108]. More than 2 years have passed yet no cure for COVID-19 is available and most of the symptomatic treatment relies on supportive measures. Here, the role of iodine comes, as its solutions have been long used as anti-microbial agents and they offer appropriate safety profiles. Several clinical *in vitro* and *in vivo* studies, showed that patients treated with oral/nasal formulations of iodine, manifest better prognosis than the placebo, hence establishing its role in treating the disease [14,12,45-58,89,94,98,99]. These studies also showed that iodine-based products for mouthwash, gargle and nasal spray can effectively reduce nasopharyngeal viral load in patients with COVID-19. It has also been hypothesized that less number of deaths seen in Japan despite boosting a large number of old age population is because of the role of iodine in supporting innate immunity against viral pathogens since the Japanese are famous for taking higher amounts of iodine [109]. Since different formulations of iodine solutions and complexes have different concentration-dependent efficacy and side effects, more number of clinical trial studies will provide a better idea of optimal dosage with better efficacy and limited toxicity.

Apart from iodine's role against COVID-19 infection, it has also been proposed to act as an agent to limit post-vaccine adverse events [96]. Vaccines may trigger local and systemic inflammatory responses such as myocarditis and pericarditis after COVID-19 vaccination. Vaccines may also have toxic effects caused by the presence of synthetic nucleosides and delivery components [110]. Specifically, some COVID-19 mRNA vaccines [111,112] use lipid or polymer based nanoparticles to protect and stabilize the mRNA and improve uptake. The toxicity of mRNA, non-replicating viral vectors, and other vaccines can only be marginally assessed [96]. Iodine binds well to toxins. Iodine also binds to metals such as aluminum and mercury. Iodine also helps thyroid functions. It detoxifies toxic compounds and strongly increases the mRNA decay rate [113,114]. Therefore, iodine may be considered as a single substance, necessary to mitigate the adverse events from COVID-19 vaccines that could also help to fight against COVID-19 infection.

## CONCLUSION

In the absence of the clear understanding of medication known to be effective at preventing and treating this highly contagious disease that has challenged the traditional healthcare systems, iodine-containing solutions and complexes might be the candidates for fast-track measure as simple and inexpensive therapeutic compounds. Scientific evidence based on *in-vitro* and *in-vivo* studies already showed that iodine offers a great potential in the prevention of COVID-19 in patients, healthcare workers and general population. Now there is a need to conduct large-scale clinical trials with robust and standardized methodologies to confirm the effectiveness of these products.

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**AUTHORS' CONTRIBUTIONS**

1st author: Conceptualization, literature search, critical drafting, revision of manuscript.
2nd author: Conceptualization and revision of manuscript.
3rd author: Conceptualization, critical drafting, and approval of the final manuscript.

**CONFLICT OF INTERESTS**

The authors have no conflict of interest.

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