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# Investigating hypothiocyanite against SARS-CoV-2

L. Cegolon[a,b]

[a] Local Health Unit N.2 "Marca Trevigiana", Public Health Department, Treviso, Veneto Region, Italy
[b] Institute for Maternal & Child Health, IRCCS "Burlo Garofolo", Trieste, Italy

Sustained human-to-human transmission of the novel coronavirus SARS-CoV-2, the etiologic agent of COVID-19, has been documented across the world, with COVID-19 declared a global pandemic affecting 209 countries as of April 6, 2020 (World Health Organization, 2020a; Coronavirus, 2020).

The median incubation period of this novel coronavirus has been estimated to be 5–6 days (range: 0–14 days) (World Health Organization, 2020b). According to the World Health Organization (WHO) the respective base reproductive number (Ro) of SARS-CoV-2 is 1.95, although a recent metanalysis estimated it to fall in the range of 2–3, with a mean of 3.28, a median of 2.79 and an interquartile range of 1.16. (Liu et al., 2020), close to SARS-CoV' (Ro = 2–5), although much higher than MERS-CoV's (Ro = 0.5) (Liu et al., 2020; Poletto et al., 2014; Kucharski and Althaus, 2015). A Ro > 1 signifies self-sustaining outbreak unless control measures are taken to curb or stop the transmission of the infection (Imai et al., 2019).

With no antiviral drugs or vaccines available, prevention of COVID-19 should rely upon prompt detection and isolation of symptomatic cases, in addition to infection prevention and control (IPC) measures (Imai et al., 2019; Lu, 2020).

The main actions recommended to prevent and control the spread of COVID-19 are (World Health Organization, 2020c, 2020d; Fischer and Heymann, 2020):

- stay home and avoid crowdy places;
- early detection and isolation of presumed and confirmed COVID-19 cases;
- quarantine for close contacts;
- identifying and containing any transmission from animal reservoirs;
- precautionary measures against risk of droplet infection, using surgical masks and maintaining interpersonal distance of at least 1–2 m;
- Frequent hand washing and disinfection of fomites with Alcohol Based Rub Hand (ABRH, containing at least 60% ethanol);
- precautionary measures against risk of airborne infection, particularly with the use of FFP2 and FFP3 filters.

These preventative measures should stop >60% viral transmission to be capable to effectively block the COVID-19 epidemic (Imai et al., 2019; Lu, 2020).

As other common respiratory viruses like cold (which also belongs to the coronaviridae family) and influenza, SARS-CoV-2 seems to spread from human-to-human by 3 recognized ways for transmission (Centre for Disease Prevention and Control, 2020; Tellier, 2007; Brankston et al., 2007; Lemieux et al., 2007; Aitken and Jefferies, 2001; Boone and Gerba, 2005; Heymann and Shindo, 2020):

- droplets (talking, sneezing, coughing);
- fomites (hand touching);
- airborne (breathing).

While the risk of droplet transmission can be contained by social distancing and the employment of simple respiratory barriers (surgical masks), hand washing is the primary preventive measure against fomites contagion (Fischer and Heymann, 2020; Heymann and Shindo, 2020). Nonetheless, airborne infection seems the most important channel to transmit respiratory viruses amongst humans (Herfst, 2012). Albeit recommended to reduce the aerosol risk of viruses, FFP2/FFP3 masks may not provide enough protection (Weber and Stilianakis, 2008), since they are often improperly fitted and donned, and sometimes may render breathing difficult (Cummings et al., 2007).

The hypothiocyanite ion ($OSCN-$), product of the lactoperoxidase/ $H2O2/SCN-$ ($LPO/H2O2/SCN-$) complex of central airways, is part of the human natural protective system against infectious agents (Cegolon et al., 2014). The lack of LPO/H2O2/SCN- system in nasal and eye secretions of humans may explain the survival, proliferation and environmental shedding of some bacteria and viruses as influenza from mucosal secretions of the nose and the conjuctiva (Tenovuo et al., 1986; Marcozzi et al., 2003; Mastrangelo et al., 2005, 2009; Schaffer et al., 1976; Couch, 1995).

At micromolar concentration, the reactive mixture LPO/H2O2/OSCN- already proved effective cidal activity against a range of bacteria (Gram positive as well as Gram negative) (Moskwa et al., 2007; Conner et al., 2007; Carlsson et al., 1984; Thomas and Aune, 1978; Ihalin et al., 1998; Reiter et al., 1976), fungi (Candida albicans and Candida krusei) and viruses as HIV, herpes-simplex virus (HSV-1), adenovirus, echovirus, respiratory syncytial virus (RSV) and 12 different strains of infuenza virus (Patel et al., 2018; Lenander-Lumikari, 1992; Mikola et al.,

E-mail address: l.cegolon@gmail.com.

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1995; Pourtois et al., 1990),.

The cidal activity of hypothiocyanite has been mostly tested blending OSCN- with components of the catalytic reaction which enables its continuous production (Pruitt and Reiter, 1985; Shin et al., 2005). In order to reduce the risk of allergic reactions in humans, Alaxia (Lyon, France) licensed ALX-009, a compound combining enzyme-free OSCN- with lactoferrin, a multifunctional protein capable to inactivate/kill bacteria (Alaxia. ALX-009, 2020). A Phase 1 clinical trial is ongoing on healthy volunteers and patients affected by cystic fibrosis and bronchiectasis, challenging OSCN-, lactoferrin and combined OSCN-/lactoferrin separately (Alaxia. ALX-009, 2020).

A recent laboratory experiment challenged enzyme free OSCN- against A/H1N1 2009 pandemic influenza virus, showing a clear dose-dependent viricidal activity, fully devoid of any cytotoxic effect (Cegolon et al., 2014).

By oxidizing free thiol radicals of proteins and creating disulfide bonds (Alaxia. ALX-009, 2020), OSCN- seems capable to alter the surface proteins of respiratory viruses, contrasting their binding with the airways epithelium. It is also argued that OSCN- might interfere with the synthesis and assemblance of viral proteins and nucleic acids, thereby hampering the release of viruses from infected cells (Cegolon et al., 2014). Because OSCN− is effective against a vast range of viruses and micro-organisms, a general cidal effect seems implicated, not directed at specific proteins. This would suggest a wide potential application of OSCN-, possibly also against SARS-CoV-2, with low risk of resistance due to viral mutations (Cegolon et al., 2014). Moreover, the lack of toxicity in vitro of enzyme-free OSCN- is encouraging, considering also the human airways epithelium has an intensive turnover and is protected by a mucus layer (Cegolon et al., 2014).

Unlike SARS-CoV, SARS-CoV-2 seems able to replicate efficiently in the upper airways epithelium, with large amounts of viruses released by infected subjects during the incubation period, which as mentioned earlier can stretch up to 14 days (World Health Organization, 2020b; Heymann, 2020). This renders the spread of SARS-CoV-2 much easier than SARS-CoV's, which conversely exhibited contagion risk only when infected individuals were critically ill, but not during the prodromal stage (Peiris et al., 2003).

Front-line health care workers are at high risk of being infected from SARS-CoV-2 when managing confirmed or suspected COVID-19 cases, especially if IPC measures are not adopted (Heymann, 2020). These health care staff can then become disease carriers for other patients, their household contacts and the general population too (Heymann, 2020).

Latest evidence suggests that SARS-CoV-2 can remain infectious for up to 9 days on inanimate surfaces at indoor environmental temperatures (Kampf et al., 2020). Whilst recommended products as 62–71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite may be effective to disinfect fomites within 1 minute, they cannot be used for air sanitation due to their intrinsic toxicity, especially for short term airborne prophylaxis (Kampf et al., 2020).

In view of the above, considering the importance of asymptomatic individuals in the communicability of the infection, it seems interesting and worth testing OSCN- in vitro against SARS-CoV-2. If proven effective against SARS-CoV-2 in vitro, OSCN- could be tested in vivo with the aim of providing a potentially effective disinfectant for mucosae in the form of aerosol (for nose and upper airways) and eye drops (for the conjunctiva). Another useful application of hypothiocyanite could be as a spraying disinfectant for public places, transports, fomites.

In addition to new anti-virals drugs, an effective vaccine against SARS-CoV-2 and animal surveillance (Fischer et al., 2020; Daszak et al., 2020), research on disinfection of mucosae, public places and transports, using efficacious and well tolerated products should be pursued, with a view of providing short-term prevention against the spread of COVID-19 among humans.

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## Declaration of competing interest

None to declare.

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