INTRODUCTION

The rapid global spread of novel coronavirus, SARS-CoV-2, has resulted in unprecedented mobilisation of local and national governments, public health officials, paramedical personnel, basic scientists and clinicians, not only to treat patients, but also to thwart the spread of this efficient and virulent pathogen. In severe cases, SARS-CoV-2 induces liberation of cytokines and chemokines, such as interleukins (IL), interferons (IFN) and tumour necrosis factors (TNF), causing cytopathic effects as well as “cytokine” storm leading to organ failure—a phenomena similar to overwhelming bacterial sepsis, which increases pro-inflammatory cytokines such as TNF and interleukin-6 (IL-6). While it is vital to decrease viral basic reproductive potential (R0), it is also important to find specific therapies for this novel coronavirus, as treatment essentially is supportive in critically ill patients. Convalescent plasma infusion, the antiviral, remdesivir and the immunomodulatory agents, chloroquine and hydroxychloroquine are among current therapeutic candidates for SARS-CoV-2, although there are cardiotoxicity concerns for chloroquine agents. However, agents that are inexpensive, relatively nontoxic and readily available, which blunt the severity of established infection would be welcomed worldwide. Two potential agents include indomethacin, which has been shown in experimental models to decrease canine coronavirus levels in dogs and exhibit antiviral activity against several other viruses and the polyphenol, resveratrol, a potent antioxidant that has shown antiviral activity against several viruses.
activity in vitro against severe acute respiratory syndrome coronavirus (SARS-CoV) in monkey VERO cells as well as in vivo activity at relatively low doses (1 mg/kg) against canine coronavirus (CCoV) in dogs.5 The authors concluded that indomethacin possesses direct antiviral activity for SARS-CoV and CCoV by blocking viral RNA synthesis (>1000-fold reduction in virus yield in CCoV infected dogs), independent of anti-inflammatory effects.3

Several in vitro and in vivo studies in animals have also demonstrated varying degrees of antiviral activity of indomethacin. Indomethacin has been shown to interrupt the viral life cycle of various herpesviruses, and may diminish latent infections by inhibiting prostaglandin synthesis, which is blocked by indomethacin and other nonsteroidal drugs.5 Ray et al demonstrated that COX-2 transcription increased after herpes simplex virus type I and pseudorabies virus infection of embryonic rat cells and that COX inhibitors decreased growth of the pseudorabies virus.7,8 Cytomegalovirus induces accumulation of COX-2 and indomethacin decreased cell-to-cell spread of CMV in cultured fibroblasts in vitro.9 Bahrami and colleagues reported that indomethacin 25 mg three times a day eradicated hepatitis B virus DNA in seven human patients.10 Other studies have shown that indomethacin-induced inhibition of COX and antagonised mouse vesicular stomatitis virus encephalitis growth in vitro and in vivo.11 As a final example, indomethacin reduced rotavirus infection in human intestinal Caco-2 cells, by inhibiting viral protein synthesis.12 Although the activity of indomethacin in the above scenarios is mainly in vitro or in animal models, there is compelling data that indomethacin may be therapeutic in certain viral infections. Furthermore, this agent is available with predictable toxicity profiles and may be an option to consider in combatting human SARS-CoV-2.

Indomethacin, however, can induce side effects such as gastritis, renal dysfunction and platelet dysfunction,4 that could be detrimental to patients with severe SARS-CoV-2 infection, especially if they have multiorgan dysfunction resulting from cytokine storm. Furthermore, some authors have reported that NSAIDS such as ibuprofen may be detrimental in patients with novel coronavirus, causing more severe infection or lead to later complications such as empyema, prolonged hospital stay or lung caviation, as has been reported in patients with bacterial pneumonia.13,14 However, the WHO recently did not recommend against ibuprofen use for infection with SARS-CoV-2.15

Studies have shown ibuprofen to decrease sputum IL-6 in cystic fibrosis patients16 and synovial fluid IL-6 in patients with knee osteoarthritis,17 which demonstrates that NSAIDS can lower IL-6 in human fluids. This lends biologic plausibility that COX inhibition with indomethacin could lower IL-6 levels in nasopharyngeal–respiratory tract secretions.

Whether using lower doses of indomethacin (eg, 25 mg three times daily) at first sign of infection (in outpatients after a positive nasopharynx swab) or for inpatients with adequate organ function and no evidence of cytokine storm is conjectural, but use of this agent along with gastric protective agents (eg, H2 blockers) may be prudent. Since cytokine storm is, at its root, an inflammatory response, well-timed blunting of this cascade with indomethacin could conceivably lower inflammatory mediators such as TNF and IL-6 as well as superoxide free radicals, which invoke cellular damage.5

Perhaps a clinical strategy would be to monitor IL-6 levels (or C-reactive protein [CRP] as a surrogate marker), upon admission in noncritical patients and start indomethacin when IL-6 (or CRP) begins to rise, and subsequently monitor levels daily. Indeed, well-timed anti-inflammatory agents such as NSAIDS and corticosteroids have been suggested to reduce systemic inflammation prior to the development of overwhelming systemic inflammation/cytokine storm.18 Indomethacin could be used alone or more likely as an adjunct to antiviral therapy such as remdisivir in noncritical patients. It would be interesting to monitor time to clearance of the antigen from upper respiratory secretion, antibody kinetics and duration of symptomatic disease in patients treated with indomethacin. Given the cost and availability of this agent, indomethacin may warrant study in outpatients or admitted patients with documented infection with SARS-CoV-2 without evidence of cytokine storm.

### 3 | RESVERATROL

Resveratrol, a natural polyphenol compound found abundantly in grapes, red wine, mulberry and peanuts, possesses antioxidant, antitumour, antiviral and free radical scavenging properties.19 Resveratrol belongs to the phytoalexin family of phytochemicals, which are antimicrobial-like compounds produced by plants in response to fungal infection or physiologic stress.20 Resveratrol modulates inflammation response in a pleiotropic manner and scavenges free radicals such as superoxide, and may interfere with infections by altering numerous cellular pathways.20,21

Resveratrol has been reported to exhibit antiviral properties against a variety of viral pathogens in vitro and in vivo.22 Lin et al demonstrated that resveratrol significantly inhibited Middle East Respiratory Syndrome Coronavirus (MERS-CoV) replication in vitro by inhibition of RNA production as well as other pleiotropic effects.23 Resveratrol inhibited viral replication and mortality in ducklings infected with duck enteritis virus.24 Zhao et al found that resveratrol was able to suppress pseudorabies virus (a herpesvirus affecting swine that causes fatal encephalitis as well as lung inflammation) in vitro by inhibiting intracellular viral multiplication.25 Piglets inoculated with pseudorabies virus, who were supplemented with resveratrol at different dose levels for seven days prior to infection, had significantly lower viral loads than the untreated group as well as significantly decreased death rates (90% survival in the resveratrol group, with no deaths in the higher dosed groups—30 mg/kg and 10 mg/kg had 100% survival; the low dose group of 3 mg/kg had 90% survival).25 Since resveratrol has limited oral bioavailability, some authors have suggested nanoparticle formulations or combination with modified beta-glucan in aqueous solutions may improve stability and absorption.21,26 Intranasal resveratrol and carboxymethyl-beta-glucan mixture administered to infants decreased symptoms of the common cold.26 As a final example of the biologic therapeutic plausibility for resveratrol for viral and/or SARS-CoV-2 infection, resveratrol...
added to the diet of piglets for 21 days, decreased TNF-alpha levels and diminished diarrhoea because of rotavirus.27 Although there are no data for using resveratrol in humans infected with SARS-CoV-2, the above studies demonstrate that this compound may be an adjunctive antiviral agent to consider, especially based on the data published by Linn et al showing activity against MERS-CoV in vitro.23 Although dosing in humans is unknown, resveratrol is considered safe when taken at supplemental doses.

4 | CONCLUSION

Although randomised trial data are not yet available for indomethacin and resveratrol for treatment of or slowing progression of SARS-CoV-2 infection, these agents should be considered by the medical community as potentially worthy of further study as therapeutic adjuncts, given the relative safety, accessibility and low cost.

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