Editorial

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Focusing on development of novel sampling approaches and alternative therapies for COVID-19: Are they still useful in an era after the pandemic?

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SUMMARY The different viral characteristics of the Omicron variant of SARS-CoV-2 have fundamentally changed people's view concerning COVID-19. Many alternative sampling approaches and therapies have been developed that may be better suited to the Omicron variant, such as a saline gargle to detect SARS-CoV-2 and nasal irrigation with chlorine dioxide. The mechanisms of these methods of sampling and alternative therapies are briefly summarized here. Development of novel alternative sampling/therapeutic approaches for COVID-19 is crucial due to the uncertain future of emerging respiratory viruses, and their efficiency/safety needs to be verified in a post-pandemic era since viral infections of the respiratory tract have a similar route of transmission as SARS-CoV-2.

Keywords SARS-CoV-2, COVID-19, alternative therapy, sampling approach, viral infections of the respiratory tract

Since the COVID-19 pandemic started in 2019, several variants of SARS-CoV-2 have emerged from time to time. Undoubtedly, at present (the end of 2022) Omicron and its subvariants have become the predominant variant in terms of patients with COVID-19 due to its rapid spread and lower lethality. Unlike previous variants, the Omicron variant has peculiar clinical and epidemiologic characteristics: *i*) It tends to cause severe disease less often. The Omicron variant is less likely to induce pro-inflammatory cytokines and thereby cause a "cytokine storm". Hence, lung function is seldom diminished. *ii*) Upper respiratory symptoms such as a cough, fatigue, and a stuffy or runny nose are most commonly reported. *iii*) Most patients are asymptomatic or have mild symptoms (*1*). Although patients infected with Omicron are less likely to develop severe illness in comparison to previous variants, Omicron remains a danger in older people, and particularly in the unvaccinated (*2*). Moreover, the Omicron variant exhibits stronger immune evasion than previous strains, and easier to cause reinfection. Accordingly, the dangerousness of Omicron infection is far from being completely ignored and or underestimated. Taking measures to control the transmission of the Omicron variant remains an important public health task for global healthcare administrators.

Based on the nature of its potent infectivity and the existence of asymptomatic cases, conducting mass, frequent, and repeated sampling to identify asymptomatic patients is crucial to controlling viral transmission. The commonly reported methods of sampling are nasopharyngeal swabs (NPS), oropharyngeal swab (OPS), saliva and gargle (Figure 1A). The advantages and disadvantages of these sampling methods are listed in Table 1. Since the Omicron variant mainly affects the upper respiratory tract, saliva or gargle sampling might be a satisfactory solution compared to conventional methods. Qiao *et al*. conducted a pilot study to verify the efficiency of a saline gargle sampling at detection of the Omicron variant. Their sample was small, but they found that saline gargle sampling was no less efficient than an NPS. Interestingly, they found that saline gargle sampling might have better sensitivity at identifying asymptomatic patients. This was the first study to verify the efficiency of a saline gargle as a sampling method in the context of Omicron.

Another important issue is alternative therapy for the Omicron variant. Thus far, there is no specific treatment for COVID-19. The main treatments for COVID-19, such as corticosteroids and antivirals (remdesivir, lopinavir, ritonavir, *etc*.), vitamin supplements (vitamin D, vitamin C, vitamin E, and zinc), and antibiotics, are commonly used to treat patients infected with a previous variant, and particularly for those patients with severe disease (*3*). Patients who are asymptomatic or who have mild symptoms account for the majority of patients

infected with Omicron. Accordingly, few patients infected with the Omicron variant require treatments like corticosteroids and antibiotics. In contrast, many patients prefer convenient, simple, and low-cost alternative therapies. Mechanisms of these reported alternative therapies include: *i*) *Directly killing the virus*: Such methods usually use a disinfectant directly administered into the upper respiratory tract, such as nasal irrigation of one nostril with povidone-iodine (*4*), to achieve "physical killing". Nebulization of ozone (O_3) also falls under this type (*3*). *ii*) *Removal of the local virus*: Several studies have reported using non-disinfectants such as saline (*5*) and triamcinolone acetonide (*6*) for nasal irrigation.

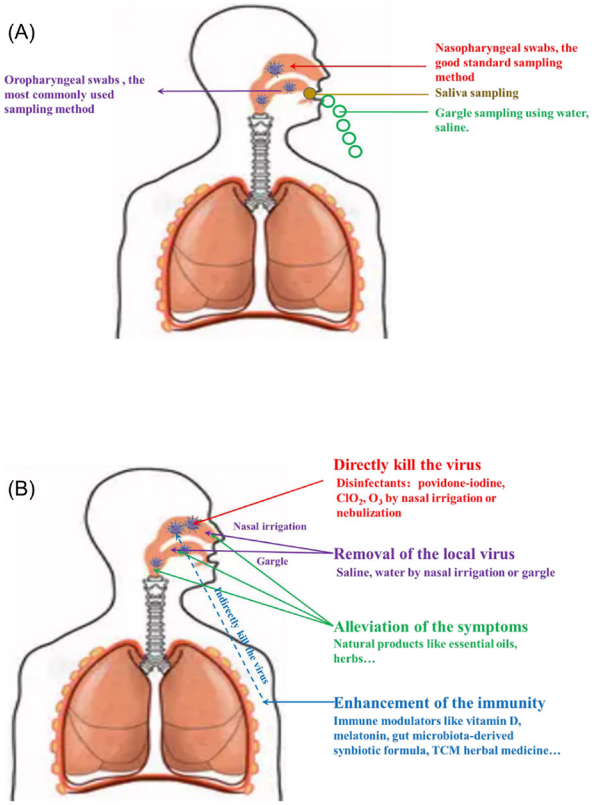

Figure 1. Mainstream sampling approaches and alternative therapies for SARS-CoV-2. (A), The reported sampling approaches to detect SARS-CoV-2. **(B)**, Mechanisms of the available alternative therapies to treat COVID-19.

They contend that such nasal irrigation may "wash out the nasal cavity", helping to reduce the viral load in the upper respiratory tract and thereby ameliorating COVID-19-related symptoms. Studies in Mexico even orally administered chlorine dioxide (ClO_2) in a low dose to prevent/treat COVID-19-related symptoms in relatives living with COVID-19 patients (*7,8*). *iii*) *Alleviation of symptoms using natural products*: This scenario includes a number of natural products such as Indonesian herbal compounds (*9*), Iran herbal medicine (*10*), propolis and honey (*11*), Indian herbs (*12*), essential oils (*13*), and traditional Chinese medicine (TCM) (*14-16*). Although all of these studies contend that these natural products "are efficacious and safe", these products are not amenable to becoming generally accepted therapeutics worldwide due to regional and cultural characteristics. Moreover, more rigorously designed randomized controlled trials need to be conducted to provide more compelling evidence regarding the safety and efficacy of these natural products. *iv*) *Enhancement of immunity by supportive treatment*: Naturopathic treatment (*17*), negative pressure therapy (*18*), and neurological music therapy (*19*) have also been cited as efficacious against COVID-19. Cao *et al*. discussed the possibility of using ClO_2, a safe and highly effective disinfectant, as a potential agent for nasal irrigation. In comparison to povidone-iodine that was previously used, ClO_2 seems to have better antiviral action and cause less irritation. Nasal irrigation with ClO_2 might be a more satisfactory solution to the Omicron variant of SARS-CoV-2. Hence, their final results are eagerly anticipated.

The Omicron variant has, in fact, markedly changed how people view SARS-CoV-2 as well as COVID-19. However, no one knows when the pandemic will finally abate. Moreover, no one knows what new variants of SARS-CoV-2 and what emerging respiratory viruses will emerge in the future. Coinfection with COVID-19 and the other respiratory viruses such as influenza might be a potential threat to public health (*20*). Viral infections of the respiratory tract have a similar route of transmission, so measures being taken against SARS-CoV-2 might also be potentially effective against other emerging viral infections that mainly affect the respiratory system. Thus,

Table 1. Advantages and disadvantages of the reported methods of sampling

Items	Advantages	Disadvantages
Nasopharyngeal swabs (NPS)	Gold standard with the best sensitivity	Uncomfortable, might be resisted by some individuals, not suitable for some patients, requires an experienced tester, might cause sneezing, which is risky for the tester.
Oropharyngeal swabs (OPS)	Acceptable sensitivity and acceptable comfort; the most commonly used method of sampling. Easier to perform than an NPS.	Lower sensitivity than OPS, is also risky because it might cause a cough.
Saliva	Convenient, easy to perform, allows self-sampling.	Not easy to standardize, lower sensitivity than NPS and OPS.
Gargle	Convenient, easy to perform, allows self-sampling. Easy to standardize.	Lower sensitivity than NPS and OPS for non-Omicron variants.

development of novel alternative sampling/therapeutic approaches for COVID-19, and verification of their efficiency/safety, is crucial in a post-pandemic era.

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References

1. Tian D, Sun Y, Xu H, Ye Q. The emergence and epidemic characteristics of the highly mutated SARS-CoV-2 Omicron variant. J Med Virol. 2022; 94:2376-2383.
2. Fall A, Eldesouki RE, Sachithanandham J, Morris CP, Norton JM, Gaston DC, Forman M, Abdullah O, Gallagher N, Li M, Swanson NJ, Pekosz A, Klein EY, Mostafa HH. The displacement of the SARS-CoV-2 variant Delta with Omicron: An investigation of hospital admissions and upper respiratory viral loads. EBioMedicine. 2022; 79:104008.
3. Setyo Budi D, Fahmi Rofananda I, Reza Pratama N, Sutanto H, Sukma Hariftyani A, Ratna Desita S, Zinedinita Rahmasari A, Pudy Asmarawati T, Agung Waskito L, Dyah Kencono Wungu C. Ozone as an adjuvant therapy for COVID-19: A systematic review and meta-analysis. Int Immunopharmacol. 2022; 110:109014.
4. Baxter AL, Schwartz KR, Johnson RW, Kuchinski AM, Swartout KM, Srinivasa Rao ASR, Gibson RW, Cherian E, Giller T, Boomer H, Lyon M, Schwartz R. Rapid initiation of nasal saline irrigation to reduce severity in high-risk COVID+ outpatients. Ear Nose Throat J. 2022; 1455613221123737.
5. Huijghebaert S, Hoste L, Vanham G. Essentials in saline pharmacology for nasal or respiratory hygiene in times of COVID-19. Eur J Clin Pharmacol. 2021; 77:1275-1293.
6. Yildiz E, Koca Yildiz S, Kuzu S, Gunebakan C, Bucak A, Kahveci OK. Comparison of the healing effect of nasal saline irrigation with triamcinolone acetonide versus nasal saline irrigation alone in COVID-19 related olfactory dysfunction: A randomized controlled study. Indian J Otolaryngol Head Neck Surg. 2022;74(Suppl 2):3022-3027.
7. Aparicio-Alonso M, Domínguez-Sánchez C, Banuet-Martínez M. Chlorine dioxide as an alternative treatment for COVID19. J Infec Dis Ther. 2021; 9:1-8
8. Aparicio-Alonso M, Domínguez-Sánchez CA, Banuet-Martínez M. A retrospective observational study of chlorine dioxide effectiveness to COVID19-like symptoms prophylaxis in relatives living with COVID19 patients. Int J Multidiscip Res Anal. 2021; 4:1062-1071.
9. Erlina L, Paramita RI, Kusuma WA, Fadilah F, Tedjo A, Pratomo IP, Ramadhanti NS, Nasution AK, Surado FK, Fitriawan A, Istiadi KA, Yanuar A. Virtual screening of Indonesian herbal compounds as COVID-19 supportive therapy: Machine learning and pharmacophore modeling approaches. BMC Complement Med Ther. 2022; 22:207.
10. Dehghan M, Ghanbari A, Ghaedi Heidari F, Mangolian Shahrbabaki P, Zakeri MA. Use of complementary and alternative medicine in general population during COVID-19 outbreak: A survey in Iran. J Integr Med. 2022; 20:45-51.
11. Dilokthornsakul W, Kosiyaporn R, Wuttipongwaragon R, Dilokthornsakul P. Potential effects of propolis and honey in COVID-19 prevention and treatment: A systematic review of in silico and clinical studies. J Integr Med. 2022; 20:114-125.
12. Kumar B, Misra A, Singh SP, Dhar YV, Rawat P, Chattopadhyay D, Barik SK, Srivastava S. In-silico efficacy of potential phytomolecules from Ayurvedic herbs as an adjuvant therapy in management of COVID-19. J Food Drug Anal. 2021; 29:559-580.
13. Damiescu R, Lee DYW, Efferth T. Can essential oils provide an alternative adjuvant therapy for COVID-19 infections and pain management at the same Time? Pharmaceuticals (Basel). 2022; 15:1387.
14. Hao D, Liu C. Chinese herbal medicines will illuminate the post-epidemic era. Chin Herb Med. 2022; 14:169-170.
15. Xia Y, Qi W, Li X, Yang Y, Cao J. Clinical efficacy and safety of Qingshu Yiqi decoction as a complementary and alternative therapy for COVID-19 with Delta variant: A protocol for systematic review and meta-analysis. Medicine (Baltimore). 2021; 100:e28184.
16. Yang Z, Liu Y, Wang L, Lin S, Dai X, Yan H, Ge Z, Ren Q, Wang H, Zhu F, Wang S. Traditional Chinese medicine against COVID-19: Role of the gut microbiota. Biomed Pharmacother. 2022; 149:112787.
17. Barber MS, Barrett R, Bradley RD, Walker E. A naturopathic treatment approach for mild and moderate COVID-19: A retrospective chart review. Complement Ther Med. 2021; 63:102788.
18. Soler-Silva A, Sanchez-Guillen L, Rodriguez-Arias FL, Arroyo A. Negative pressure therapy as a safe alternative in the treatment of massive subcutaneous emphysema in critically ill patients COVID-19. Heart Lung. 2022; 52:190-193.
19. Vinciguerra C, Federico A. Neurological music therapy during the COVID-19 outbreak: Updates and future challenges. Neurol Sci. 2022; 43:3473-3478.
20. Li T, Asakawa T, Liu H, Chu C, Lu H. The role of influenza in the era of COVID-19: Can we forget it? Biosci Trends. 2022; 16:374-376.

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