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REVIEW ARTICLE

Gustatory Dysfunction in COVID-19: Solitary or Secondary?

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causing Coronavirus Disease 2019 (COVID-19) commonly presented with neurological and respiratory disorders. Among the neurological symptoms, headache, myalgia, dizziness, impaired consciousness, cerebrovascular accident (CVA), olfactory dysfunction (OD), and gustatory dysfunction (GD) are typical. GD and OD have been included as new symptoms of COVID-19 infection by the World Health Organization (WHO). Taste disorders varied from dysgeusia to ageusia. Similarly, OD or smell disorder severity went from microsomia or hyposmia to anosmia. The merit of these neurological disorders is an early screening criterion for a COVID-19 patient, especially where the diagnostic resources are limited. Most of the published articles demonstrate these two dysfunctions together. Our concise review aimed to determine whether GD in COVID-19 is a solitary (independent) symptom or a secondary (associated) symptom of OD. Besides, we were looking at the possible transmission pathways of SARS-CoV-2, if it can be an early diagnostic symptom, a predictor of severity, and a prognostic factor for impaired outcome. We have limited our study to publishing articles in English only. Therefore, further evaluation might be recommended to include studies published in other languages.

INTRODUCTION

The current global long-term health crisis is Corona Virus Disease 2019 (COVID-19), caused by a novel virus, Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2). It claimed to become a pandemic after being started in Wuhan, China, in the middle of December 2019. On 11 March 2020, the World Health Organization (WHO) declared the infection a pandemic (Cucinotta et al., 2020). Until November 2021, the deadly virus killed over five million lives worldwide and infected around 260 million people. Early diagnosis is another challenge in COVID-19. The expensive diagnostic kits are also not affordable in many countries. Moreover, the virus changes its character with time, and some new strains have been found in a few countries. In this circumstance, to save lives, besides vaccination and treatment, it is essential to prevent infection through early diagnosis, isolation, and maintaining health hygiene by following the standard operating procedure (SOP) strictly in every sector. Preventive measures will benefit countries that cannot do adequate vaccination for their citizens. Early screening based on the clinical presentation of COVID-19 could be the most cost-effective preventative measure.

Initially, fever, unproductive cough, myalgia, and tiredness are considered early symptoms. The severe symptoms are shortness of breath or breathing difficulty. COVID-19 is commonly presented with respiratory and neurological symptoms. Among the neurological symptoms, headache, myalgia, dizziness, impaired consciousness, and cerebrovascular accident (CVA) have been recorded. Olfactory dysfunction (OD) and gustatory dysfunction (GD) are quite established presentations claimed by many articles and have been included as the new most common symptom of COVID-19 infection by the World Health Organization by June 2021 (WHO Health Topics, 2021). The GD in the quality of life of COVID-19 patients imposed a significant impact reported in clinical practice (Bigiani et al., 2020). It will be helpful if these two symptoms can be scientifically established as early symptoms of COVID-19. Screening of patients will be faster and easier.

Furthermore, it will help ease the isolation of the patient, save expenses, and reduce the rapid spread of this deadly disease. It will be conducive for countries with poor infrastructure of health facilities. It could even be a self-assessment tool for an individual to rush for early expert help. Most of the published articles described both symptoms together. Our primary aim in this short review was to find if the GD in COVID-19 is a solitary (independent) symptom or a secondary (associated) symptom due to OD. In addition, we looked at the possible transmission pathways of SARS-CoV-2 in GD and OD; and whether it can be an early diagnostic symptom, a predictor of disease severity, and an indicator of prognosis for the impaired outcome.

Pathophysiology

The exact mechanism of entry of SARS-CoV-2 into the central nervous system (CNS) is not yet evident. Neurological symptoms are common in COVID-19 patients', but no evidence is found regarding the direct invasion of intracranial inflammation by SARS-CoV-2 (Kabir et al., 2021). Possible explanations are hematogenous spread from systemic circulation (Baig et al., 2020) and trans-synaptic transfer through the cribriform plate and olfactory bulb (Netland et al., 2008). The evidence of spreading to the brain was found in the previous study on SARS-CoV and Middle East Respiratory Syndrome Corona Virus (MERS-CoV), the neurotransmitter pathways, specifically through the serotonergic dorsal raphe system. The study also suggested spreading a virus through the Virchow-Robin spaces (Li et al., 2016). However, research is required if the same theory applies to the spread of SARS-CoV-2. In an observational study, Mao et al. (2020) demonstrated that 36.4 % of COVID-19 patients presented with neurological symptoms. Xiao-Wei et al.

(2020) claimed in their study that 8.9 % of COVID-19 patients presented with symptoms of peripheral nervous system disorder, among which hypogeusia and hyposmia were remarkable with hypoplasia and neuralgia. The SARS-CoV-2 has an affinity for CNS targets (Montalvan et al., 2020). In the nucleus of the ventrolateral medulla and tractus solitarius, a high virus expression was observed (Doobay et al., 2007; Palace et al., 2018). The virus is known to present a particular affinity to nerve tissue, neurotropism, which may contribute to OD and GD (Lechien et al., 2020). The area near the olfactory bulbs in the brain, known as the frontobasal region, is considered the overlapping area between taste and the olfactory system. The vascular pericytes contain angiotensin-converting enzyme 2 (ACE2) receptors. The SARS-CoV-2 has a high binding affinity to this ACE2. Any damage to this brain area by SARS-CoV-2 infection can alter gustatory and olfactory function (Lechien et al., 2020; Walls et al., 2020). Delayed or lack of recovery from GD and OD in many COVID-19 patients also supports the neurological damage due to severe inflammation by SARS-CoV-2. The taste renin-angiotensin system (RAS) can be involved in the GD of COVID-19 patients (Bigiani et al., 2020). An experimental study showing the expression of ACE2 in the taste organs of mice suggested that it may influence the development of GD in COVID-19 patients (Lechien et al., 2020). A previous animal study on rhesus monkeys showed that the early target of SARS coronavirus is the epithelial cells lining salivary gland ducts (Liu, 2020). As both SARS-CoV and SARS-CoV-2 have phylogenetic similarity, alteration of taste function is possible in the COVID-19 patient. ACE2 has been identified as the cellular receptor for SARS-CoV-2 (Zhou et al., 2020). Diffuse expression of the ACE2 receptor was found on the mucous membrane of the tongue and the whole oral cavity (Xu et al., 2020). So, based on this hypothesis, viral infection can disrupt the composition of saliva, the usual transduction of taste, or the continuous normal taste bud renewal process (Wang et al., 2009). Volume and composition alteration of saliva can also disrupt taste sensation (Matsuo, 2020). Numerous studies highlighted the action of ACE2 in regulating taste perception after analysing the chemo-sensitive side effects of angiotensin II blockers and ACE2 inhibitors. The mechanism of action is not yet precise regarding ACE2 inhibitors causing taste dysfunction, but it is not related to the zinc level in serum or saliva (Suliburska, 2012; Tsuruoka et al., 2005). SARS-CoV-2 occupies the binding sites of sialic acid on the taste buds and could accelerate the degradation of the gustatory particles. It may have the ability to bind with sialic acid receptors (Milanetti et al., 2021), which was observed in the MERS-CoV Previously (Park et al., 2019). The fundamental component of salivary mucin is sialic acid. It prevents the premature enzymatic degradation of the glycoproteins inside the taste pores (Witt et al., 1992). Reducing salivary sialic acid increases the gustatory threshold (Pushpass et al., 2019). It is also possible that OD can influence GD. OD can block the perception of the flavour of food due to the intimate relationship between these two chemosensory systems. A chemosensory network called a flavour network is formed by the orbitofrontal cortex, frontal operculum, anterior insula, and anterior cingulate cortex in the chemosensory regions of the brain. The interaction of this network with other heteromodal regions, including the ventrolateral prefrontal and posterior parietal cortex, is responsible for flavour perception (Small et al., 2005). Independent GD cases were reported in 10.2-22.5% of patients (Giacomelli et al., 2020; Lechien et al., 2020; Yan et al., 2020).

DISCUSSION

The GD alters the perception of the taste: sweet, sour, bitter, and salty. In a COVID-19 patient, alteration of the gustatory function could be related to the spread of SARS CoV-2 into the nerve ending of taste buds. Most of the time, the GD is self-reported. Only 5% of pure taste disorders were evaluated in specialized smell

and taste consultation (Bigiani et al., 2020). The prevalence of self-reported taste dysfunction could reach 56.4% of patients (Lechien et al., 2020). COVID-19 patients presented with GD, OD, and other neurological disorders even though the respiratory symptoms were most common (Mao et al., 2020; Wang et al., 2020). COVID-19-related GD is mainly self-reported, which could be unreliable and often confused with loss of perception of aroma due to olfactory dysfunction (Soter et al., 2008). A few recent studies investigated taste function assessment using electrophysiological or psychophysical tools. Even unreliable, based on self-reporting cases hypothetically, it can be assumed that half of the COVID-19 patients should have intact GD (Lechien et al., 2020). The outcome of current studies on self-reported GD in COVID-19 patients suggested the need for future studies to be conducted using electrophysiological or psychophysical taste evaluation. At least evaluation using taste strips or electrogustometry will be reliable (Bigiani, 2020; Pavlidis et al., 2014; Soter, 2008; Vaira et al., 2020).

A systematic review and meta-analysis were conducted, and 24 studies involving 8,438 confirmed diagnostic patients infected with SARS-CoV-2 from 13 countries. Agyeman et al. (2020) described the pooled prevalence of OD and GD were 41.0% and 38.2%, respectively. Of the 24 studies, only five (21%) used objective assessments, and 19 (79%) were self-reported cases. In addition, the author reported the prevalence of GD in 5,649 patients involved in 15 studies, of which only two (13%) used objective assessments and the remaining 13 (87%) based on self-reports. The reported prevalence of GD ranged from 5.6% to 62.7%, and the pooled prevalence was 38.2%.

Lechien et al. (2020), in a multicentre European study involving 417 diagnosed SARS CoV 2 infected patients with mild to moderate symptoms, reported OD and GD in 85.6% and 88.8% of patients, respectively. OD of different severity levels was reported in 357 patients (85.6%), among which anosmia was reported in 284 (79.6%) and hyposmia in 73 (20.4%) patients. The relationship between the appearance of OD with general nasal symptoms was 11.8%, 65.4%, and 22.8% before, after, and simultaneous, respectively. GD was reported by a total number of 342 (88.8%) patients. Among them, 78.9% had reduced taste function, and 21.1% had a distorted ability to taste flavours. Thirty-two patients were confused if they had GD. Twenty out of 43 patients reported OD who did not have GD. The remaining 19 have neither GD nor OD. 53.9% and 22.5% of cured patients reported having residual isolated OD and GD, respectively. Both OD and GD persisted among 23.6% of them. The association between these two disorders was significant ($p<0.001$).

Twenty-four studies from 13 countries with data from 8,438 confirmed COVID-19 patients were included in a study by Agyeman et al., 2020. In their systematic review and meta-analysis, 41.0% of patients presented with OD and 38.2% with GD. Carrillo-Larco et al. (2020) in a systematic review included six studies (n = 2,757) from the UK (n = 1,702), China (n = 214), US (n = 262), Iran (n = 120), Israel (n = 42); in which only two studies reported the association between OD and GD in COVID-19 patients; the review also included data from four European countries (n = 417), chosen from 31 related reports. In their analysis, the range of anosmia was found to be between 22 – 68%. The GD was described as a variable between dysgeusia (33%), ageusia (20%), and taste distortion (21%). There were six-fold and ten-fold higher odds of being COVID-19 positive among the patients who reported OD and GD, respectively.

In a meta-analysis by Hajikhani et al. (2020), 3,739 COVID-19 patients from 15 studies were included. Among them, 1,729 reported GD and 1,354 with OD. The estimated prevalence rates of GD and OD were 49% and 61%, respectively. Dysgeusia and hypogeusia were more common than ageusia, and

similarly, hyposmia was more common than anosmia. Ibekwe et al. (2020) included 32 studies in their systematic review and meta-analysis, among which 27 studies containing data from 20,451 confirmed COVID-19 patients were analyzed, and the prevalence of OD, GD, or both was reported. Twenty-seven studies reported OD in 19,424 (48.47%) patients, 20 studies reported GD in 8,001 (41.47%) patients, and 13 studies reported both symptoms in 5,977 (35.04%) patients.

CONCLUSION

Most studies we reviewed hypothetically supported GD as an independent symptom of SARS-CoV-2 infection. We also noticed that most of the cases of GD in COVID-19 patients are self-reported. Therefore, further studies on taste function assessment using electrophysiological or psychophysical tools are required. Our concise review concludes that GD could indicate a disease-associated symptom. Neither the symptom nor the recovery period has been proven to be the indicator of the severity of the disease. SARS-CoV-2 does not cause permanent damage to gustatory function. Post-mortem forensic pathological analysis is crucial in patients who died of COVID-19 to understand GD's exact nature and location.

CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this article.

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REFERENCES

Agyeman, A. A., Chin, K. L., Landersdorfer, C. B., Liew, D., & Ofori-Asenso, R. (2020). Smell and taste dysfunction in patients with COVID-19: A systematic review and meta-analysis. *Mayo Clin Proc*, *95* (8), 1621 – 1631. https://doi.org/10.1016/j.mayocp.2020.05.030

Baig, A. M., Khaleeq, A., Ali, U., & Syeda, H. (2020). Evidence of the COVID-19 virus targeting the CNS: Tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci*, *11* (7), 995 – 998. https://doi.org/10.1021/acschemneuro.0c00122

Bigiani, A. (2020). Gustatory dysfunctions in COVID-19 patients: Possible involvement of taste renin-angiotensin system (RAS). *Eur Arch Otorhinolaryngol*, *277*, 2395. https://doi.org/10.1007/s00405-020-06054-z

Carrillo-Larco, R. M., & Altez-Fernandez, C. (2020). Anosmia and dysgeusia in COVID-19: A systematic review. *Wellcome Open Res*, *5*, 94. https://doi.org/10.12688/wellcomeopenres.15917.1

Cucinotta, D., & Vanelli, M. (2020). WHO declares COVID-19 a pandemic. *Acta Biomed*, *91* (1), 157 – 160. https://doi.org/10.23750/abm.v91i1.9397

Doobay, M. F., Talman, L. S., Obr, T. D., Tian, X., Davisson, R. L., & Lazartigues, E. (2007). Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. *Am J Physiol Regul Integr Comp Physiol*, *292* (1), R373 – 381. https://doi.org/10.1152/ajpregu.00292.2006

Giacomelli, A. Pezzati, L., Conti, F., Bernacchia, D., Siano, M., Oreni, L., Rusconi, S., Gervasoni, C., Ridolfo, A.L., Rizzardini, G., Antinori, S., & Galli, M. (2020). Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: A cross-sectional study. *Clin Infect Dis*, *71* (15), 889 – 890. PMID: 32215618; PMCID: PMC7184514. https://doi.org/10.1093/cid/ciaa330

Hajikhani, B., Calcagno, T., Nasiri, M. J., Jamshidi, P., Dadashi, M., Goudarzi, M., Eshraghi, A. A., & Mirsaeidi, M. (2020). Olfactory and gustatory dysfunction in COVID-19 patients: A meta-analysis study. *Physiol Rep*, *8* (18), e14578. PMID: 32975884; PMCID: PMC7518296. https://doi.org/10.14814/phy2.14578

Ibekwe, T. S., Fasunla, A. J., & Orimadegun, A. E. (2020). Systematic review and meta-analysis of smell and taste disorders in COVID-19. *OTO Open*, *4 (*3), 1 – 13. PMID: 32964177; PMCID: PMC7488903. https://doi.org/10.1177/2473974x20957975

Just, J., Puth, M. T., Regenold, F., Weckbecker, K., & Bleckwenn, M. (2020). Risk factors for a positive SARS CoV-2 PCR in patients with common cold symptoms in a primary care setting – A retrospective analysis based on a joint documentation standard. *BMC Fam Pract*, *21* (1), 251. https://doi.org/10.1186/s12875-020-01322-7

Kabir, S., Hossain, A. B. M. T., Hossain Parash, M. T., Lin, C.L.S., Murugaiah, C., Delwar, A. H. M., & Chowdhury, M. A. (2021). Olfactory dysfunction: A diagnostic symptom of COVID-19. *BJMS*, *15* (2), 3 – 9. https://doi.org/10.51200/bjms.v15i2.2637

Kaye, R., Chang, C. W. D., Kazahaya, K., Brereton, J., & Denneny, J. C. 3rd. (2020). COVID-19 anosmia reporting tool: initial findings. *Otolaryngol Head Neck Surg*, *163* (1), 132 – 134. https://doi.org/10.1177/0194599820922992

Lechien, J. R., Chiesa-Estomba, C. M., De Siati, D. R., Horoi, M., Le Bon, S. D., Rodriguez, A., Dequanter, D., Blecic, S., El Afia, F., Distinguin, L., Chekkoury-Idrissi, Y., Hans, S., Delgado, I. L., Calvo-Henriquez, C., Lavigne, P., Falanga, C., Barillari, M. R., Cammaroto, G., Khalife, M., Leich, P., Souchay, C., Rossi, C., Journe, F., Hsieh, J., Edjlali, M., Carlier, R., Ris, L., Lovato, A., De Filippis, C., Coppee, F., Fakhry, N., Ayad, T., & Saussez, S. (2020). Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): A multicenter European study. *Eur Arch Otorhinolaryngol*, *277* (8), 2251 – 2261. PMID: 32253535; PMCID: PMC7134551. https://doi.org/10.1007/s00405-020-05965-1

Lechien, J. R., Chiesa-Estomba, C. M., Hans, S., Barillari, M. R., Joufe, L., & Saussez, S. (2020). Loss of smell and taste in 2013 European patients with mild to moderate COVID-19. *Ann Intern Med*, *173* (8), 672 – 675. https://doi.org/10.7326/M20-2428

Lechien, J. R., Hsieh, J. W., Ayad, T., Fakhry, N., Hans, S., Chiesa-Estomba, C. M. & Saussez, S. (2020). Gustatory dysfunctions in COVID-19. *European Archives of Oto-Rhino-Laryngology*, *277*, 2397 – 2398. https://doi.org/10.1007/s00405-020-06154-w

Lechien, J. R., Cabaraux, P., Chiesa-Estomba, C. M., Khalife, M., Hans, S., Calvo-Henriquez, C., Martiny, D., Journe, F., Leigh, S., & Saussez, S. (2020). Objective olfactory evaluation of self-reported loss of smell in a case series of 86 COVID-19 patients. *Head & Neck*, *42,* 1583 – 1590. https://doi.org/10.1002/hed.26279

Li, K., Wohlford-Lenane, C., Perlman, S., Zhao, J., Jewell, A. K., Reznikov, L. R, Gibson-Corley, K. N., Meyerholz, D. K., & McCray, P. B Jr. (2016). Middle east respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. *J Infect Dis*, *213* (5), 712 – 722. https://doi.org/10.1093/infdis/jiv499

Liu, L., Wei, Q., Alvarez, X., Wang, H., Du, Y., Zhu, H., Jiang, H., Zhou, J., Lam, P., Zhang, L., Lackner, A., Qin, C., & Chen, Z. (2020). Epithelial cells lining salivary gland ducts are early target cells of severe acute respiratory syndrome coronavirus infection in the upper respiratory tracts of rhesus macaques. *J Virol*, *85* (8), 4025 – 4030. https://doi.org/10.1128/jvi.02292-10

Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Miao, X., Li, Y., & Hu, B. (2020). Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*, *77* (6), 683 – 690. https://doi.org/10.1001/jamaneurol.2020.1127

Matsuo, R. (2000). Role of saliva in the maintenance of taste sensitivity. *Crit Rev Oral Biol Med*, *11* (2), 216 – 229. https://doi.org/10.1177/10454411000110020501

Milanetti, E., Miotto, M., Di Rienzo, L., Nagaraj, M., Monti, M., Golbek, T. W., Gosti, G., Roeters, S. J., Weidner, T., Otzen, D. E., & Ruocco, G. (2021). In-silico evidence for a two receptor-based strategy of SARS CoV-2. *Front Mol Biosci*, *9* (8), 690655. https://doi.org/10.3389/fmolb.2021.690655

Montalvan, V., Lee, J., Bueso, T., De Toledo, J., & Rivas, K. (2020). Neurological manifestations of COVID-19 and other coronavirus infections: a systematic review. *Clin Neurol Neurosurg*, *194*, 105921. https://doi.org/10.1016/j.clineuro.2020.105921

Netland, J., Meyerholz, D. K., Moore, S., Cassell, M., & Perlman, S. (2008). Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol*, *82* (15), 7264 – 7275. https://doi.org/10.1128/jvi.00737-08

Palasca, O., Santos, A., Stolte, C., Gorodkin, J., & Jensen, L. J. (2018). TISSUES 2.0: An integrative web resource on mammalian tissue expression. *Database (Oxford),* 1, bay028. https://doi.org/10.1093/database/bay028

Park, Y. J., Walls, A. C., Wang, Z., Sauer, M. M., Li, W., Tortorici, M. A., Bosch, B. J., DiMaio, F., & Veesler, D. (2019). Structures of MERS-CoV spike glycoprotein in complex with sialoside attachment receptors. *Nat Struct Mol Biol*, *26* (12), 1151 – 1157. PMID: 31792450; PMCID: PMC7097669. https://doi.org/10.1038/s41594-019-0334-7

Pavlidis, P., Gouveris, C., Kekes, G., & Maurer, J. (2014). Changes in electrogustometry thresholds, tongue tip vascularization, density and form of the fungiform papillae in smokers. *Eur Arch Otorhinolaryngol*, *271* (8), 2325 – 2331. https://doi.org/10.1007/s00405-014-3003-9

Pushpass, R. G., Pellicciotta, N., Kelly, C., Proctor, G., & Carpenter, G. H. (2019). Reduced salivary mucin binding and glycosylation in older adults influences taste in an in vitro cell model. *Nutrients*, *11* (10), 2280. PMID: 31554163; PMCID: PMC6835954. https://doi.org/10.3390/nu11102280

Small, D. M., & Prescott, J. (2005). Odor/taste integration and the perception of flavor. *Exp Brain Res*, *166* (3 – 4), 345 – 357. PMID: 16028032. https://doi.org/10.1007/s00221-005-2376-9

Soter, A., Kim, J., Jackman, A., Tourbier, I., Kaul, A., & Doty, R. L. (2008). Accuracy of self-report in detecting taste dysfunction. *Laryngoscope*, *118* (4), 611 – 617. https://doi.org/10.1097/MLG.0b013e318161e53a

Suliburska, J., Duda, G., Pupek-Musialik, D. (2012). The influence of hypotensive drugs on the taste sensitivity in patients with primary hypertension. *Acta Pol Pharm*, *69* (1), 121 – 127. PMID: 22574515. https://pubmed.ncbi.nlm.nih.gov/22574515/

Tsuruoka, S., Wakaumi, M., Araki, N., Ioka, T., Sugimoto, K., & Fujimura, A.. (2005). Comparative study of taste disturbance by losartan and perindopril in healthy volunteers. *J Clin Pharmacol*, *45* (11), 1319 – 1323. PMID: 16239366. https://doi.org/10.1177/0091270005280445

Vaira, L. A, Hopkins, C., Salzano, G., Petrocelli, M., Melis, A., Cucurullo, M., Ferrari, M., Gagliardini, L., Pipolo, C., Deiana, G., Fiore, V., De Vito, A., Turra, N., Canu, S., Maglio, A., Serra, A., Bussu, F., Madeddu, G., Babudieri, S., Giuseppe Fois, A., Pirina, P., Salzano, F. A., De Riu, P., Biglioli, F., De Riu, G. (2020). Olfactory and gustatory function impairment in COVID-19 patients: Italian objective multicenter-study. *Head Neck*, *42* (7), 1560 – 1569; https://doi.org/10.1002/hed.26269

Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., & Veesler, D. (2020). Structure, function, and antigenicity of the SARS CoV-2 spike glycoprotein. *Cell*, *181* (2), 281 – 292, e6. https://doi.org/10.1016/j.cell.2020.02.058

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z., Xiong,. Y, Zhao, Y., Li, Y., Wang, X., & Peng, Z. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, china. *JAMA*, *323* (11), 1061 – 1069. https://doi.org/10.1001/jama.2020.1585

Wang, H., Zhou, M., Brand, J., & Huang, L. (2009). Inflammation and taste disorders: Mechanisms in taste buds. *Ann N Y Acad Sci*, *1170*, 596 – 603. https://doi.org/10.1111/j.1749-6632.2009.04480 .x

World Health Organization (WHO). (2021). Health topics, coronavirus disease (COVID-19), https://www.who.int/health-topics/coronavirus#tab=tab_3

Witt, M., & Miller, I. J Jr. (1992). Comparative lectin histochemistry on taste buds in foliate, circumvallate and fungiform papillae of the rabbit tongue. *Histochemistry*, *98* (3), 173 – 182. PMID: 1452451. https://doi.org/10.1007/bf00315876

Xiao-Wei, X., Xiao-Xin, W., Xian-Gao, J., Kai-Jin, X., Ling-Jun, Y., Chun-Lian, M., Shi-Bo, L., Hua-Ying, W., Sheng, Z., Hai-Nv, G., Ji-Fang, S., Hong-Liu, C., Yun-Qing, Q., & Lan-Juan, L. (2020). Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS Cov-2) outside of Wuhan, China: Retrospective case series, *BMJ*, *368,* m606. https://doi.org/10.1136/bmj.m606

Xu, H., Zhong, L., Deng, J., Peng, J., Dan, H., Zeng, X., Li, T., & Chen, Q. (2020). High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of the oral mucosa. *Int J Oral Sci*, *12* (1), 8. https://doi.org/10.1038/s41368-020-0074-x

Yan, C. H., Faraji, F., Prajapati, D. P., Boone, C. E., & DeConde, A. S. (2020). Association of chemosensory dysfunction and COVID-19 in patients presenting with influenza-like symptoms. *Int Forum Allergy Rhinol*, *10* (7), 806 – 813. PMID: 32279441; PMCID: PMC7262089. https://doi.org/10.1002/alr.22579

Zhou, P., Yang, X. L., Wang, X. G., Hu, B., Zhang, L., Zhang, W., Si, H. R., Zhu, Y., Li, B., Huang, C. L., Chen, H. D., Chen, J., Luo, Y., Guo, H., Jiang, R. D., Liu, M. Q., Chen, Y., Shen, X. R., Wang, X., Zheng, X. S., Zhao, K., Chen, Q. J., Deng, F., Liu, L. L., Yan, B., Zhan, F. X., Wang, Y. Y., Xiao, G. F., & Shi, Z. L. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, *579* (7798), 270 – 273. PMID: 32015507; PMCID: PMC7095418. https://doi.org/10.1038/s41586-020-2012-7