Review

Treatments of COVID-19-Associated Taste and Saliva Secretory Disorders

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Treatments of COVID-19-Associated Taste and Saliva Secretory Disorders

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Abstract: Since the worldwide spread of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), treating taste and saliva secretory disorders associated with coronavirus disease 2019 (COVID-19) has become one of the most critical issues in the COVID-19 era. The aim of the present study was to update information on treatments being applicable to such oral symptoms and discuss their pathogenic mechanisms. Promising treatments include different types of methods using tetracycline, corticosteroid, zinc, stellate ganglion block, phytochemical curcumin, traditional herbal medicine, nutraceutical vitamin D, photobiomodulation, antiviral drug, malic acid sialagogue, chewing gum, acupuncture, and/or moxibustion. At present, however, fully validated treatments are still lacking for COVID-19-associated ageusia/dysgeusia/hypogeusia and xerostomia/dry mouth/hyposalivation. An appropriately selected treatment and oral healthcare should be provided to COVID-19 patients and survivors suffering from taste and saliva secretory disorders. Understanding of currently available treatment options is required for dental professionals because they not only experience patients who were infected with SARS-CoV-2 or recovered from COVID-19 but first become aware of their abnormal taste and salivary secretion. By doing so, dentists and dental hygienists can play a crucial role in managing COVID-19-associated oral symptoms and contribute to improving the oral health-related quality of life of the relevant dental patients.

Keywords: COVID-19; taste disorder; saliva secretory disorder; treatment; pathogenic mechanism

1. Introduction

As of 10 March 2023, over 676.6 million individuals were globally infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and over 6.8 million patients with coronavirus disease 2019 (COVID-19) had died in the world according to the Johns Hopkins University and Medicine Coronavirus Resource Center [1]. Worldometer, a reference website of live world statistics [2], indicates over 685.0 million COVID-19 cases and over 657.8 million recovered cases as of 10 April 2023. Over three years have passed since the first emergence of COVID-19 in Wuhan, China, and it has become apparent that SARS-CoV-2 infection produces a wide range of manifestations varying from asymptomatic presentation to respiratory distress syndrome and death in a critical case. In addition to typical symptom fever, cough, dyspnea, myalgia, cardiomyopathy, etc. in the early stage of SARS-CoV-2 infection, COVID-19 is characterized by oral symptoms consisting of ageusia (taste loss), dysgeusia (taste impairment), or hypogeusia (taste reduction) [3] and xerostomia, dry mouth (subjective complaint of oral dryness), or hyposalivation (objective reduction of salivary flow) [4]. Up to 93% of COVID-19 patients present with taste disorders: prevalence of 3–67% for ageusia, 19–48% for dysgeusia, and 35% for hypogeusia [5–9]. Saliva secretory disorders are also reported by 42–77% of COVID-19 patients [6–8,10,11]. Even after complete vaccination (Pfizer/BioNTech, AstraZeneca, Moderna, and Johnson & Johnson vaccines), 54% of patients who developed symptomatic COVID-19 complain of oral symptoms [12].

COVID-19 oral symptoms had been initially considered to be transient and eventually disappear without treatment. However, there is increasing evidence that taste and saliva secretory disorders persist in subjects who recovered from COVID-19 as well as other sequelae such as fatigue, dyspnea, cough, headache, neurocognitive impairment (or brain fog), hair loss, etc. A significant number of COVID-19 survivors report persistent taste disorders when followed up 1–12 months after symptom onset, disease diagnosis, or hospitalization [13,14]. The prevalence is 39% for dysgeusia at 8-month

follow-up [11], 19% for ageusia at 12-month follow-up [15], and 22% for taste or smell impairment at 12-month follow-up [16]. According to follow-up studies [11,17,18] and comprehensive symptom reviews [13,19], xerostomia, dry mouth, and hyposalivation persist in COVID-19 survivors with prevalence of 9–29% at 1–8 months follow-ups. Parageusia (wrong taste elicited by a taste stimulus) and phantogeusia (feeling taste in the absence of a taste stimulus) are also observed in 23.5% and 17.6%, respectively, of subjects followed up 2 months after negativity of the reverse transcription-polymerase chain reaction (RT-PCR) test [20].

Although taste and saliva secretory disorders are not life-threatening, ageusia/dysgeusia/hypogeusia and xerostomia/dry mouth/hyposalivation, especially their persistence, not only reduce the oral health-related quality of life of COVID-19 patients and survivors [21] but adversely affect their nutrition by decreasing appetite [22], and even elevate the risk of depression and suicidal ideation [23]. Reduction of salivary secretion is linked to the increased incidence of dental caries, periodontal disease, oral infection, and halitosis, and to difficulty of mastication, swallowing, and speaking [24]. Therefore, treating COVID-19-associated taste and saliva secretory disorders has become one of the most critical issues in the COVID-19 era. The aim of the present study was to update information on treatments being applicable to such oral symptoms in the early stage of SARS-CoV-2 infection and after recovery from the disease and to discuss the pathogenic mechanisms underlying them. In order to achieve this aim, a literature search was performed in PubMed, LitCovid, ProQuest, and Google Scholar.

Neta et al. [25] and Khani et al. [26] recently reviewed pharmacological approaches to potential treatments of smell and taste disorders in COVID-19 patients. Although gustation is adversely affected when there is an abnormality in olfaction, taste disorders are more prevalent than smell disorders as reported by several COVID-19 symptomatology studies [27–30], and COVID-19 ageusia is not necessarily accompanied by anosmia associated with nasal obstruction and rhinitis [31]. Taste disorders are observed in almost all of COVID-19 patients with smell disorders, whereas only 30% of abnormal taste cases show smell disorders [32]. Taste disorders could be referred to as an independent symptom rather than one of COVID-19 symptoms closely associated with olfactory dysfunction [33]. Taste disorders frequently co-occur with saliva secretary disorders in COVID-19 patients and survivors [11,13], while taste disorders are more prevalent [7,34] or less prevalent than saliva secretory disorders [6,35]. The present study focused on both oral symptoms and their treatments applied to human subjects. Neither animal experiments nor in silico studies were covered.

2. Treatment Strategy

Specific treatments for taste and saliva secretory disorders can be designed and developed through understanding their pathophysiology. However, only hypotheses have been proposed so far to explain how SARS-CoV-2 infection causes ageusia, dysgeusia, or hypogeusia and xerostomia, dry mouth, or hyposalivation [3,4,10,27,36,37]. While it is very likely that COVID-19 oral symptoms are the result of local or systemic etiology or both, their pathogenic mechanisms remain largely unclear. The treatment strategy consists of (1) targeting SARS-CoV-2 that can enter, replicate in, and cause damage to cells responsible for taste perception and salivary secretion; (2) alleviating, reducing, or protecting against SARS-CoV-2 infection-induced pathological conditions such as inflammation, cytokine storm, pyroptosis, neuropathy, zinc dyshomeostasis, and dysautonomia; (3) symptomatic therapies for taste and saliva secretory disorders; and (4) alternative medicines to be expected from the clinical outcomes of applied studies.

3. Treatments of COVID-19-Associated Taste Disorders

Diverse treatment approaches have been tried for ageusia, dysgeusia, or hypogeusia caused by SARS-CoV-2 infection. In the following Sections, different types of treatments being applicable to COVID-19-associated taste disorders are reviewed together with discussing their pathogenic mechanisms and treatment rationales. They are summarized in Table 1 with used methods, patients or subjects, clinical outcomes, and references.

Table 1. Treatments being applicable to COVID-19-associated taste disorders.

Type	Mechanism	Method	Subject	Outcome	Reference
Tetracycline	Antiviral Anti-inflammatory Neuroprotective Anti-apoptotic	Oral administration of either doxycycline (100 mg/day or 100 mg twice a day) or minocycline (50 mg/day, 100 mg/day, or 100 mg twice a day)	COVID-19 patients (n = 38, female: 52.6%, age: 21–67 years) with the mild disease quarantined at home	Ageusia disappeared in all patients within 7 days after treatment.	Gironi et al. [60]
Corticosteroid	Anti-inflammatory	Local application of triamcinolone oral paste (0.1% triamcinolone acetonide)	COVID-19 patients (n = 60, female: 25.0%, mean age: 50.9 years)	Sweet, bitter, salty, and sour taste were improved in 83.3–91.7% of patients on day 5 of treatment.	Singh et al. [64]
		Oral administration of corticosteroid (10 mg/day for the first week and reduced to 5 mg in the second week)	COVID-19 patients (n = 34, female: 55.9% and n = 33, female: 57.6%; grouped according to the different duration of taste disorders)	At weekly follow-ups up to 3 months, all patients recovered from ageusia at the end of treatment without no side-effects.	Gamil et al. [67]
Zinc	Compensation for deficient zinc	Supplementation with 220 mg zinc sulfate (corresponding to elemental zinc of 50 mg) twice a day	COVID-19 patients (n = 49) with different disease severity	When followed up until the pharyngeal swabs became negative, the duration of tase function recovery was shortened compared with control subjects (n = 56).	Abdelmaksoud et al. [81]
		Taking lozenges of zinc citrate (corresponding to elemental zinc of 23 mg), zinc citrate/zinc gluconate (23 mg), or zinc acetate (15 mg) every 2–4 hours	COVID-19 outpatients (n = 4)	All patients showed symptomatic and objective improvements.	Finzi [82]

		Supplementation with elemental zinc of 25 mg twice a day for 15 days	Ambulatory and hospitalized COVID-19 patients (n = 231, female: 47.6%, mean age: 54.6 years)	The symptom duration was shortened.	Ben Abdallah et al. [83]
		Taking 6–12 lozenges of zinc gluconate/citrate (corresponding to elemental zinc of 23 mg) or zinc acetate (corresponding to elemental zinc of 15 mg) once a day	COVID-19 patients (n = 28, female: 60.7%, mean age: 40 years)	Symptoms including ageusia were improved 7 days after treatment and zinc gluconate was better tolerated than zinc acetate.	Finzi and Harrington [84]
		Supplementation with a combination of zinc, magnesium, and calcium	COVID-19 pregnant patients (n = 74)	Ageusia/anosmia was reported by 41.9% of patients with zinc treatment, but by 57.2% of patients without zinc treatment.	Citu et al. [85]
Stellate ganglion block	Treatment of dysautonomia	Right-sided stellate ganglion block with a local anesthetic and left-sided stellate ganglion block 2 days later	COVID-19 patient, a 42-year-old female who recovered from the disease but had continued to suffer from dysgeusia and anosmia	Immediately after treatment, dysgeusia and anosmia were improved and taste/smell functions were normal at 2-week follow-up.	Liu and Duricka [91]
		Right-sided stellate ganglion block, followed by left-sided stellate ganglion block on the next day	COVID-19 patient, a 44-year-old female with taste and smell loss who contracted the disease approximately 8 months ago	Within minutes after treatment, dysgeusia was drastically improved and taste function was normal at 60-day follow-up.	Liu and Duricka [91]

		Right-sided stellate ganglion block with 4 ml of 0.25% bupivacaine and left-sided stellate ganglion block after 3 days	COVID-19 patient, a 48-year-old female who recovered from the disease before 4 months but had altered taste to various types of foods	Taste disorders were improved a few days after treatment.	Chauhan et al. [92]
Phytochemical: Curcumin	Antiviral Anti-inflammatory Neuroprotective Anti-apoptotic Antioxidant	Oral administration of capsule containing 1000 mg turmeric extract (95% curcuminoids) and 10 mg black pepper extract	COVID-19 patient, a 25-year-old male with ageusia persisting for 46 days	The patient experienced the complete recovery of taste function 10 min after treatment.	Chabot and Huntwork [102]
		Oral administration of capsule containing 1000 mg turmeric extract (95% curcuminoids), 15 mg black pepper extract, and 1000 mg *Boswellia serrata* plant extract	COVID-19 patient, a 28-year-old male complaining of ageusia	Taste sensation was improved 12 hours after treatment and completely restored 3 days later.	Chabot and Huntwork [102]
Traditional herbal medicine: Ayurveda	Antiviral Anti-inflammatory	Oral administration of one tablet of 900 mg *Dasamoolkaduthrayam Kashaya* and one tablet of 600 mg *Guluchyadi Kwatham* 12-hourly after meal for 7 days in addition to the Standard of Care as the Indian Council of Medical Research guidelines	COVID-19 patients (n = 60, mean age: 44.0 years) with ageusia due to the mild to moderate disease	The ageusia prevalence of 75% on day 1 was reduced to 25% on day 3 and 3.3% on day 7, whereas 35.9% on day 3 and 25.6% on day 7 in the control group (n = 39, mean age: 41.6 years) who received only the Standard of Care.	Wanjarkhedkar et al. [103]
Vitamin D	Nutraceutical supplementation	Oral administration of either 5000 IU vitamin D3 or 1000 IU vitamin D3 once a day for 2 weeks	COVID-19 patients with the mild to moderate disease: 5000 IU vitamin	When received 5000 IU vitamin D3, the time to recovery from ageusia was	Sabico et al. [108]

			D3 for patients (n = 36, female: 41.7%, mean age: 46.3 years) or 1000 IU vitamin D3 for patients (n = 33, female: 60.6%, mean age: 53.5 years)	significantly reduced to mean 11.4 days compared with mean 16.9 days for 1000 IU vitamin D3.	
		Oral administration twice a day of 1000 IU vitamin D, 40 mg β-caryophyllene, 40 mg pregnenolone, 30 mg dehydroepiandrosterone, 416 mg bromelain, 150 mg St. John's Wort extract, 100 mg *Boswellia serrata* gum/resin extract, 40 mg quercetin, and 12 mg zinc picolinate	COVID-19 patients (n = 51, female: approximately 67%, age: 21–73 year) suffering from various symptoms including ageusia for at least 3 months after SARS-CoV-2 infection	Taste/smell loss became significantly milder after 2 weeks and the symptoms were further improved in 72–84% of subjects after 4 weeks.	Gaylis et al. [109]
Photobiomodulation	Stimulation of cell proliferation and differentiation Anti-inflammatory Increase of neurogenesis Immune modulation Apoptosis inhibition Promotion of tissue repair	Illumination of 3 laser beams (680 nm) and 3 laser beams (808 nm) for 2 min on the back of the tongue and the skin surface of the cheeks, consisting of 10 sessions: Performed over 25 days with a minimum interval of 48 hours between sessions	COVID-19 patient, a 34-year-old female with ageusia	Taste function was improved with each session and back to normal after the last session.	de Souza et al. [115]

3.1. Tetracycline

3.1.1. Viral Cellular Entry, Inflammatory Cell Death, and Neuropathy

For SARS-CoV-2 to enter host cells, its spike protein binds to a cellular receptor angiotensin-converting enzyme 2 (ACE2) through the receptor binding domain (RBD), followed by the viral and cellular membrane fusion that is mediated by cellular protein convertase (Furin) and transmembrane serine protease 2 (TMPRSS2) [38]. ACE2 and TMPRSS2 are richly distributed in taste buds and taste

bud-embedded papillae of humans [39]. Each taste bud consists of 50–100 packed specialized epithelial cells, taste receptor cells, that include distinct types of cells such as type-I cells (glia-like supporting cells) to respond to salty stimuli, type-II cells (G-protein coupled receptors) to respond to sweet, bitter, and umami stimuli, and type-III cells (ion channels) to respond to sour stimuli. Lingual papillae are classified into circumvallate, fungiform, and foliate papillae, all of which contain taste buds, and filiform papillae being devoid of taste buds but involved in texture perception of foods. Doyle et al. [40] revealed that ACE2 receptors are expressed in taste receptor type-II cells within taste buds buried in circumvallate and fungiform papillae and that replicating SARS-CoV-2 is present in type-II cells of fungiform papillae biopsied from COVID-19 patients with taste disorders. The specific expression of ACE2 and the presence of SARS-CoV-2 are consistent with the characteristics of taste disorders that sweet, bitter, and umami taste are more frequently impaired in moderate COVID-19 [41] but salty taste is less significantly affected by COVID-19 [42]. SARS-CoV-2 can also enter host cells by binding to toll like receptor (TLR) and transient receptor potential vanilloid type 1 (TRPV-1) that are expressed in taste buds (highly in type-II cells) and oral epithelia (tongue and palate), respectively. Since SARS-CoV-2 interacts with multiple receptors (ACE2, TLR, and TRPV-1), it is conceivable that cytopathic SARS-CoV-2 damages taste buds and taste receptor cells to cause their dysfunctions in the process of viral cellular entry [43,44]. Since the viral shedding is found for extended periods after recovery from COVID-19, the long-lasting presence of SARS-CoV-2 in taste buds could cause the persistence of taste disorders in COVID-19 survivors.

Following the cellular entry of SARS-CoV-2, the relevant cells undergo a highly inflammatory cell death, pyroptosis, that triggers the generation and secretion of pro-inflammatory cytokines and chemokines, promoting further inflammation [45]. SARS-CoV-2 infection induces inflammation of taste receptor cells and taste buds to impair taste perception. Their inflammatory responses could cause damage to cells responsible for multiple tastes (sour, salty, sweet, bitter, and umami taste) [41]. While mammalian caspases are classified into apoptotic and inflammatory caspases, caspase-1 belonging to the latter is activated to induce pyroptotic cell death and release pro-inflammatory cytokines [46]. Inflammatory cytokines also trigger apoptotic cell death, resulting in the abnormal turnover of taste buds.

Since neurotropic SARS-CoV-2 has the neuro-invasive potential, the viral infection-induced neuropathy is pathogenically related to COVID-19-associated taste disorders [47]. Taste signals are transmitted to the brain stem through taste bud-innervating cranial nerves. The facial nerve (cranial nerve VII), the glossopharyngeal nerve (cranial nerve IX), and the vagus nerve (cranial nerve X) innervate the anterior two-thirds of the tongue, the posterior one-third of the tongue, and the epiglottis region, respectively, to transmit information on tastants. Among them, the facial nerve is most commonly affected by COVID-19, followed by the glossopharyngeal nerve and the vagus nerve [48]. A possible link has been indicated between COVID-19 and facial nerve paralysis [49]. Taste disorders are also accompanied by neurodegeneration occurring in COVID-19 cases [50] and COVID-19 promotes neurodegenerative changes [51]. While a significant proportion of COVID-19 patients present with persistent taste disorders even after two consecutive negative nasopharyngeal swabs [52], such long-term sequelae could be related to neural damages due to SARS-CoV-2 infection.

Drug repurposing is a strategy to use existing and approved drugs for the novel therapeutic purpose, which has the advantage of reducing cost and time needed for developing new drugs and using drugs with the confirmed safety and commercial availability. One of repurposed drugs for COVID-19 is tetracyclines that exhibit viral cellular entry-suppressing, viral replication-inhibiting, anti-inflammatory, neuroprotective, and anti-apoptotic activity in addition to the antibiotic activity. Tetracyclines have antiviral effects on SARS-CoV-2 that could enter taste cells, replicate in them, and affect their functions [53]. Tetracyclines have so high affinity for the RBD of SARS-CoV-2 that they inhibit the binding between viral spike protein and ACE2 receptor [54]. In in vitro experiments using Vero E6 cells infected with SARS-CoV-2, doxycycline inhibited the viral entry and replication at low micromolar concentrations [55]. Doxycycline also possesses the anti-inflammatory property to inhibit pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α [56]. Minocycline is able to inhibit the expression and activation of caspase-1 expressed by SARS-CoV-2

infection and counteract cytokine storm inflammation in COVID-19 [57]. Tetracyclines, especially the second-generation minocycline and doxycycline, are expected to be effective in treatment of taste disorders associated with inflammatory responses to SARS-CoV-2 infection. In addition to antiviral and anti-inflammatory effects, tetracyclines exhibit the anti-apoptotic activity that is protective against neurological disorders [58]. Minocycline and doxycycline also have multimodal neuroprotective effects [59].

3.1.2. Treatment with Tetracyclines and Outcome

Gironi et al. [60] conducted a multicenter prospective observational study to evaluate the effects of tetracyclines on COVID-19 symptoms. They orally administered either doxycycline (100 mg once a day (n = 10) or 100 mg twice a day (n = 15)) or minocycline (50 mg once a day (n = 8), 100 mg once a day (n = 3), or 100 mg twice a day (n = 2)) to COVID-19 outpatients (n = 38, female: 52.6%, age: 21–67 years). Ageusia reported by 23.7% of the patients disappeared in the first week of treatment. Other symptoms, including fatigue and dyspnea, were also resolved in all patients within 10 days.

3.2. Corticosteroid

3.2.1. Inflammation of Taste Buds and Papillae

SARS-CoV-2 infection induces pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α. Among them, IL-6 acts on taste receptor cells to cause inflammation and there is a close relation between IL-6 increase and taste disorder occurrence [61]. Multiple tastes are impaired to cause ageusia in COVID-19 patients with high IL-6 levels [41]. While inflammation activates the interferon (INF) signaling pathway in taste bud cells, viral infection induces INFs that not only impair the function of taste buds to disturb taste transduction but cause the apoptotic cell death of taste buds to affect the turnover and renewal of different types of taste cells [62]. Henin et al. [63] performed morphological and histopathological examinations of the tongues collected from cadavers. Their RT-PCR analyses indicated that SARS-CoV-2 is present in circumvallate and foliate papillae, both of which showed severe inflammation (infiltrate and fibrosis) with the destruction of taste buds. They speculated that ACE2 and INF-γ mediate inflammatory damages to these papillae. Circumvallate and foliate papillae could be invaded by SARS-CoV-2 to produce inflammation with the subsequent damage to taste buds, resulting in taste disorders.

Since SARS-CoV-2 infection is related to inflamed taste buds and papillae, anti-inflammatory cortcosteroid is usable for treating COVID-19-associated taste disorders.

3.2.2. Treatment with Corticosteroid and Outcome

In a prospective interventional study of Singh et al. [64], COVID-19 patients (n = 60, female: 25.0%, mean age: 50.9 years) complaining of dysgeusia and anosmia due to the mild to moderate disease were subjected to local application of triamcinolone oral paste, which commonly contains 0.1% triamcinolone acetonide. Taste sensation of the patients was tested by applying different tastant solutions to the anterior two-thirds of the tongue. Control subjects (n = 60, female: 28.3%, mean age: 51.2 years) did not receive any interventions. All study participants in both groups had dysgeusia. Sweet, bitter, salty, and sour taste were improved in 91.7%, 83.3%, 83.3%, and 86.6% of patients, respectively, on day 5 of treatment, whereas taste disorders of control subjects further worsened on day 5 compared with day 1. Triamcinolone used in this study acts only on the site of application with minimal systemic side-effects [65]. The use of triamcinolone oral paste could be one of treatment options for COVID-19-associated taste disorders [66].

Gamil et al. [67] conducted a prospective cohort study to confirm the effect of systemic corticosteroid on COVID-19-associated taste disorders. Among a total of 80 study participants (female: 51.3%, age: 18-67 years), 67 COVID-19 patients who were diagnosed by the RT-PCR test and presented with ageusia were recruited. All patients were prescribed with 10 mg corticosteroid once a day in the early morning for the first week and then oral corticosteroid was reduced to 5 mg in the second week to withdraw a drug gradually. They were weekly followed up for 3 months. According

to the duration of taste disorders, patients were assigned into two groups: early group (within 1 week; n = 34, female: 55.9%) and late group (> 1 week; n = 33, female: 57.6%). All patients recovered from ageusia at the end of treatment and reported no side-effects of corticosteroid. While the recovery time was different between early and late group, systemic administration of corticosteroid is effective for treatment of COVID-19 ageusia as well as local application.

From a perspective of inflammation suppression, non-steroidal anti-inflammatory drugs may be applicable to COVID-19-associated taste disorders. However, their use has not been recommended because of the possibility of aggravating COVID-19 symptoms [68]. In a case report, an adult male COVID-19 patient with reactive arthritis and ageusia orally took ibuprofen of 400 mg twice a day [69]. Consequently, his arthritis-relating symptom was resolved 2 days after treatment, but ageusia remained.

3.3. Zinc

3.3.1. Zinc Deficiency Induced by SARS-CoV-2 Infection

Zinc plays an important role not only in physiological functions at a level of taste buds and taste stimulus-transmitting nerves but in the regeneration and maintenance of taste cells. Since maintaining the appropriate concentration of intracellular zinc is essential for the functional and morphological normality of cells, zinc deficiency makes an adverse impact on papillae, taste buds, and taste receptor cells to decrease their number and size [70]. COVID-19 patients show hypozincemia [13,71], in which zinc is redistributed from blood to the liver at the expense of zinc in peripheral tissues and cells as obserbed in infection-induced systemic inflammation [72]. SARS-CoV-2 infection disturbs zinc homeostasis or causes zinc dyshomeostasis in cells responsible for taste perception [73]. Taste disorders are pathogenically related to zinc deficiency resulting from SARS-CoV-2 infection [13]. Among different isozymes of zinc-metalloenzyme carbonic anhydrases, carbonic anhydrase VI is localized in taste buds and secreted into saliva from parotid and submandibular glands [74]. Carbonic anhydrase VI is a trophic factor to promote the growth, development, and maintenance of taste buds and papillae. Henkin et al. [75] suggested that a decrease of carbonic anhydrase VI in parotid saliva is associated with a pathological change of taste buds. COVID-19 patients with ageusia or hypogeusia show significantly low levels of salivary zinc, which are elevated with recovering from taste disorders [76]. When patients suffering from taste disorders were supplemented with 100 mg zinc once a day for 4–6 months, they showed significant increases of salivary zinc and carbonic anhydrase VI together with the morphological recovery of taste buds and the resolution of taste disorders [77]. Zinc-binding metallothionein-3 is also expressed in taste buds [78]. The formation and development of taste buds depend on afferent nerves and sensory neurite growth [79]. If SARS-CoV-2 infection upregulates the expression of metallothionein-3, cellular metallothionein-3 would increase and affect taste buds because it has the ability to inhibit neurite formation.

Given the SARS-CoV-2 infection-induced disturbance of zinc homeostasis to cause zinc deficiency in taste buds and papillae, zinc supplementation to compensate for deficient zinc is expected as one of treatments for COVID-19-associated taste disorders [13,80]. Zinc is also able to inhibit viral replication, which should contribute to increasing the efficacy of zinc supplementation.

3.3.2. Supplementation with Zinc and Outcome

Abdelmaksoud et al. [81] assessed the effects of zinc on chemosensory disorders associated with COVID-19. COVID-19 patients (n = 49) with different disease severity orally received 220 mg zinc sulfate (corresponding to elemental zinc of 50 mg) twice a day and followed up until pharyngeal swabs became SARS-CoV-2 negative. The patients showed the shorter duration of recovery of tase and smell functions than control subjects (n = 56) without zinc supplementation, although further detailes were not mentioned about taste improvement.

In a case report of Finzi [82], COVID-19 outpatients (n = 4) were orally supplemented with zinc citrate (corresponding to elemental zinc of 23 mg), zinc citrate/zinc gluconate (23 mg), or zinc acetate

(15 mg), which were taken as lozenges every 2–4 hours by dissolving on the tongue over 20–30 min. Such zinc supplementations showed symptomatic and objective improvements in all patients. However, this report did not refer to detailed effects on oral symptoms.

Ben Abdallah et al. [83] performed a randomized double-blind controlled trial, in which ambulatory and hospitalized COVID-19 patients (n = 231, female: 47.6%, mean age: 54.6 years) orally received elemental zinc of 25 mg twice a day for 15 days. They revealed that zinc supplementation shortens the symptom duration, but did not mention in detail its effect on taste disorders.

Finzi and Harrington [84] performed a retrospective study, in which 21 and 7 COVID-19 patients (a total of n = 28, female: 60.7%, mean age: 40 years) orally received zinc gluconate/citrate-containing lozenges (corresponding to elemental zinc of 23 mg) and zinc acetate-containing lozenges (corresponding to elemental zinc of 15 mg), respectively, at a total dosage of 2–2.5 mg/kg/day by taking 6–12 lozenges once a day depending on weight. COVID-19 symptoms, including taste and smell loss, were assessed by scoring. The symptom scores were significantly decreased 7 days after zinc supplementation and the symptomatic improvement began mean 1.6 days after treatment. Zinc gluconate was found to be better tolerated than zinc acetate.

Citu et al. [85] assessed the effects of mineral supplementation during pregnancy. In a cohort of 448 pregnant patients with COVID-19, 74 patients were supplemented with a combination of zinc, magnesium, and calcium. Consequently, ageusia and anosmia were reported by 41.9% of subjects with zinc supplementation, but by 57.2% of subjects without zinc supplementation.

On the other hand, one randomized clinical trial suggested that supplementation with high-dose zinc gluconate, ascorbic acid, and their combination are not effective in decreasing the duration of symptoms of COVID-19 ambulatory patients compared with the standard care [86].

3.4. Stellate Ganglion Block

3.4.1. Dysautonomia

Patients who recovered from COVID-19 frequently complain of long-lasting neurological symptoms such as fatigue, headache, cognitive impairment, and taste/smell disorders. Many of these symptoms are observed in patients with dysautonomia, the overactivity of sympathetic or parasympathetic components of the autonomic nervous system. Familial dysautonomia is characterized by a high incidence of perception failures of sweet, bitter, and salty taste [87]. Since the excessive activity of the sympathetic nervous system is implicated in comorbidities of COVID-19 [88,89], it is conceivable that dysautonomia pathophysiologically underlies taste disorders [90].

Stellate ganglion block, which is performed by injecting local anesthetics (lidocaine, bupivacaine, etc.) into or around the stellate ganglion, effectively blocks the activity of the cervical sympathetic chain innervating post-ganglionic neurons. It has been used for the purpose of treating sympathetically-mediated pathological conditions and its safety has been well established. Given the possibility that COVID-19-associated taste disorders are due to dysregulation of the sympathetic nervous system, stellate ganglion block is expected as one of treatment options for them.

3.4.2. Stellate Ganglion Block and Outcome

In a case series of Liu and Duricka [91], a 42-year-old female, who recovered from COVID-19 but had continued to suffer from taste and smell disorders, underwent right-sided stellate ganglion block with a local anesthetic (the used drug, not described). Ipsilateral dysgeusia and anosmia were improved immediately after treatment, but the disorders persisted contralaterally. Therefore, she underwent left-sided stellate ganglion block 2 days later. Taste and smell functions were restored to a normal state at 2-week follow-up. Another 44-year-old female with taste and smell loss, who contracted SARS-CoV-2 approximately 8 months ago, underwent right-sided stellate ganglion block, followed by left-sided stellate ganglion block on the next day. Within minutes of each treatment, she reported the drastic improvement of ipsilateral dysgeusia and anosmia. Restored taste and smell functions were confirmed at 60-day follow-up.

Chauhan et al. [92] carried out stellate ganglion block with 4 ml of 0.25% bupivacaine for a 48-year-old female who recovered from COVID-19 before 4 months but had complained of altered taste to various types of foods. She underwent right-sided stellate ganglion block and then left-sided stellate ganglion block 3 days later. Consequently, her taste disorders were improved a few days after treatment.

3.5. Phytochemical

3.5.1. Multiple Pathogenic Mechanisms

As described in Section 3.1 and Section 3.2, COVID-19-associated taste disorders are pathogenically interpreted by multiple mechanisms: viral cellular entry by interacting with ACE2, TMPRSS2, TLR, and TRPV-1 expressed in taste buds and papillae, damages to taste buds and papillae in the process of viral cellular invasion, viral infection-induced inflammation of taste buds and papillae, and viral neuropathy of taste bud-innervating cranial nerves. Persistent inflammation is also related to the weakened antioxidant defense or the imbalanced antioxidant system of COVID-19 patients.

Phytochemicals, bioactive plant components, have antiviral [93], anti-inflammatory [94], neuroprotective [95], and antioxidant activity [96], which are implicated in managing COVID-19 neurological symptoms. SARS-CoV-2 main protease (M^{pro}) is essential for the cleavage of viral nonstructural polypeptides into individual functional proteins, therefore M^{pro} plays an important role in viral replication. A molecular docking study has suggested that phytochemicals such as curcuminoid (curcumin), flavonoid (rutin, hesperidin, (–)-epigallocatechin gallate, (–)-epigallocatechin, quercitrin, etc.), and capsaicinoid (capsaicin) inhibit SARS-CoV-2 M^{pro} [97].

Since phytochemicals have diverse anti-COVID-19 potentials, they are usable for treating COVID-19-associated taste disorders. Koyama et al. [98] recently reported a very excellent review on the possible use of phytochemicals for recovery from anosmia and ageusia induced by COVID-19.

3.5.2. Treatment with Curcumin and Outcome

Curcumin derived from the rhizome of turmeric (Curcuma longa) has high binding affinity for SARS-CoV-2 spike protein, host cell ACE2 receptor, and RBD/ACE2 complex [99], suggesting that curcumin may inhibit the cellular entry of SARS-CoV-2. Curcumin also shows virucidal effects independently of SARS-CoV-2 variants and inhibitory effects on the release of pro-inflammatory cytokine IL-1b, IL-6, and IL-8 [100]. Curcumin of subtoxic concentrations is also effective in neutralizing SARS-CoV-2 in Calu-3 cells (human lung cancer cell line) and Vero E6 cells (African green monkey kidney cells) [101].

In a case series of Chabot and Huntwork [102], a 25-year-old male with COVID-19 diagnosed by the RT-PCR test took a capsule containing 1000 mg turmeric extract (95% curcuminoid) and 10 mg black pepper extract. Although the patient had suffered from ageusia persisting for 46 days, he experienced the complete recovery of taste 10 min after treatment. Another 28-year-old male COVID-19 patient complaining of ageusia took a capsule containing 1000 mg turmeric extract (95% curcuminoids), 15 mg black pepper extract, and 1000 mg Boswellia serrata plant extract. His taste sensation was improved 12 hours after treatment and completely restored 3 days later. These outcomes suggest that oral administration of curcumin with the extract of black pepper is effective for treatment of COVID-19-associated taste disorders. Piperin, a phytochemical component in black pepper, is considered to enhance the bioavailability of curcumin.

Besides curcuminoid, phytochemicals belonging to flavonoid and capsaicinoid interact with SARS-CoV-2 spike protein, host cell ACE2 receptor, RBD/ACE2 complex, and viral M^{pro}, and exhibit antiviral, anti-inflammatory, neuroprotective, and antioxidant activity. In the literature, however, they have not been applied to the treatment of taste disorders of COVID-19 patients.

3.6. Herbal Medicine

3.6.1. Multiple Pathogenic Mechanisms

Different classes of phytochemicals have antiviral [93], anti-inflammatory [94], neuroprotective [95], antioxidant [96], and SARS-CoV-2 M^{pro} inhibitory potential [97], which support the rationale for herbs to be used for treating COVID-19-associated taste disorders.

3.6.2. Treatment with Herbal Medicine and Outcome

Ayurveda is an alternative medicine with historical roots in India. Ayurvedic treatments include a combination of natural healing methods and herbs. Wanjarkhedkar et al. [103] assessed the efficacy of an Ayurveda regime containing Dasamoolkaduthrayam Kashaya and Guluchyadi Kwatham, ingredients of which possess antiviral and anti-inflammatory potentials [104]. Patients (n = 60, mean age: 44.0 years), who presented with ageusia due to mild to moderate COVID-19 diagnosed by the TR-PCR test, orally received one tablet of 900 mg Dasamoolkaduthrayam Kashaya (consisting of extracts prepared from root, rhizome, or fruit of 14 different herbs) and one tablet of 600 mg Guluchyadi Kwatham (consisting of extracts prepared from stem, heartwood, stembark, or fruit of 5 different herbs) 12-hourly after meal for 7 days in addition to the Standard of Care as the Indian Council of Medical Research guidelines. The prevalence of ageusia was reduced from 75% on day 1 to 25% on day 3 and 3.3% on day 7, whereas 35.9% on day 3 and 25.6% on day 7 in control subjects (n = 39, mean age: 41.6 years) who received only the Standard of Care.

Although traditional herbal medicines have been used for COVID-19 treatment in individual countries/regions, their clinical applications to taste disorders of COVID-19 patients and survivors remain little known except for the Ayurveda regime.

3.7. Nutraceutical

3.7.1. Association with Disease Severity and Multiple Pathogenic Mechanisms

There is evidence that low levels of nutraceuticals, especially vitamin D, are closely related to COVID-19 severity [105]. Vitamin D enhances ACE2 expression to restore the SARS-CoV-2 infection-disrupted balance between ACE/ACE2 and angiotensin II/angiotensin-(1-7), decreases pro-inflammatory cytokines, and increases anti-inflammatory cytokines [106]. In addition, vitamin D has a potent neuroprotective effect linked to the regulation of neurotrophins that are responsible for the differentiation and maintenance of nerve cells [107]. Therefore, supplementation with vitamin D is expected to alleviate COVID-19-associated taste disorders.

3.7.2. Supplementation with Vitamin D and Outcome

Sabico et al. [108] assessed the effects of vitamin D3 supplementation on COVID-19 symptoms by a multi-center randomized clinical trial. They orally administered 5000 IU vitamin D3 and 1000 IU vitamin D3 once a day for 2 weeks to patients (n = 36, female: 41.7%, mean age: 46.3 years) and patients (n = 33, female: 60.6%, mean age: 53.5 years), respectively, who had mild to moderate COVID-19 diagnosed by the RT-PCR test. The group of 5000 IU vitamin D3 showed the significantly shorter time to recover from ageusia (mean 11.4 days) compared with the group of 1000 IU vitamin D3 (mean 16.9 days). Decreases of IL-6 levels in blood were also found in both groups.

Gaylis et al. [109] designed the formula of a nutraceutical supplement to treat persistent COVID-19 symptoms. In their clinical application, subjects (n = 51, female: approximately 67%, age: 21–73 year), who had suffered from different symptoms including ageusia for at least 3 months after SARS-CoV-2 infection, orally received a supplement twice a day for 2 and 4 weeks. The nutraceutical formula consisted of vitamin D (1000 IU), β-caryophyllene (40 mg), pregnenolone (40 mg), dehydroepiandrosterone (30 mg), bromelain (416 mg, 2400 gelatin digesting unit/g), St. John's Wort extract (150 mg), Boswellia serrata gum/resin extract (100 mg), quercetin (40 mg), and zinc as zinc picolinate (12 mg). Taste/smell loss of COVID-19 survivors became significantly milder 2 weeks after treatment and the symptoms were further improved in 72–84% of subjects after 4 weeks.

3.8. Photobiomodulation

3.8.1. Multiple Pathogenic Mechanisms

Photobiomodulation uses light-emitting diodes or low-level lasers to produce the red or near-infrared light, which are locally illuminated on the tissues. Laser illumination without observed side-effects has been suggested to stimulate the proliferation and differentiation of cells, decrease pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α, increase neurogenesis and synaptogenesis, promote the tissue repair, modulate the immune system, and inhibit apoptosis [110–112]. Therefore, photobiomodulation could be one of treatment options for COVID-19 neurological symptoms [113]. Its applicability to COVID-19-associated taste disorders may be supported by a case report that photobiomodulation was effective for treatment of dysgeusia of a cancer patient [114].

3.8.2. Photobiomodulation and Outcome

de Souza et al. [115] conducted a photobiomodulation therapy for a 34-year-old female who was infected with SARS-CoV-2 and developed ageusia. The patient was illuminated with 3 laser beams (680 nm) and 3 laser beams (808 nm), which were applied for 2 min on the back of her tongue and the skin surface of her cheeks with the mouth slightly open to permit the light to reach the sides of her tongue and the inner mucosae of her cheeks. The treatment consisted of 10 sessions performed over 25 days with a minimum interval of 48 hours between sessions. Her taste was improved with each session and back to normal after the last session.

3.9. Alternative Medicine

3.9.1. Multiple Pathogenic Mechanisms

Acupuncture is an ancient practice of traditional Chinese medicine. It involves the insertion of extremely thin, solid, metallic needles into intradermal or subdermal loci by sticking the needles in specific points (acupuncture points). Since acupuncture exhibits an anti-inflammatory effect and restores the imbalanced autonomic nervous system, it may be an alternative medicine for COVID-19-associated taste disorders. Acupuncture is expected as an effective and safe treatment, especially for long-term persistent COVID-19 symptoms as reviewed by Williams [116]. Acupuncture is used alone or in combination with another traditional medicine, moxibustion. Moxibustion is a heat therapy that usually bakes acupoints, specific sites on or very near the surface of the skin, by burning dried plant mugwort called "*moxa*". Its therapeutic mechanism is related to thermal, radiation, and pharmacological (due to phytochemicals derived from moxa) effects [117].

3.9.2. Acupuncture and Moxibustion and Expected Outcome

Chao et al. [118] reported the meta-analysis about the efficacy and safety of acupuncture in treatment of post-COVID-19 taste disorders by collecting randomized controlled trials of acupuncture. They described that acupuncture is effective for taste disorders, but there is still no sufficient evidence to support its treatment efficacy in sequelae of taste dysfunction. Luo et al. [119] conducted the systematic review and meta-analysis of traditional Chinese medicine combined with moxibustion for treatment of COVID-19 sequelae including taste disorders. They claimed that more large-scale high-quality trials should be carried out to confirm the efficacy and safety. While both studies suggested that acupuncture and moxibustion may be applicable to COVID-19 survivors or long-lasting COVID-19 symptoms (so-called “long COVID”), they mentioned no detailes about ageusia/dysgeusia and clinical outcomes.

4. Treatments of COVID-19-Associated Saliva Secretory Disorders

Anecdotal reports have suggested that subjective sensation of mouth dryness is attributed to the prolonged mask wearing due to the COVID-19 pandemic. According to a recent assessment of changes in salivary secretion and oral conditions, however, there is no evidence that mask wearing

affects the flow rate of unstimulated whole saliva [120]. In addition to head and neck radiotherapy for cancer patients and autoimmune disorders like Sjögren's syndrome, certain medications are related to reduction of salivary secretion. Antiviral remdesivir, hydroxychloroquine, lopinavir, and ritonavir have been widely prescribed for COVID-19 patients, and antihypertensive drugs are used by COVID-19 patients with hypertension. Administration of these drugs is the primary reason to cause xerostomia. Xerostomia or dry mouth is also known as a symptom in diabetes mellitus, which is one of the most common comorbidities of COVID-19 patients. Apart from these causal factors, SARS-CoV-2 infection is closely associated with saliva secretory disorders.

Saliva in tongue film, a mucosal film covering the dorsum of the tongue, influences taste sensation by solubilizing, diluting, and modifying tastants. A significant number of patients infected with SARS-CoV-2 develop xerostomia, dry mouth, or hyposalivation along with ageusia, dysgeusia, or hypogeusia. Saliva secretory disorders are secondary to taste disorders and vice versa [121]. The combined taste and chewing function are associated with production and secretion of saliva, and reduced salivary secretion influences taste perception. The pathogenesis and possible treatment may be at least partly common to both taste and saliva secretory disorders in COVID-19. Diverse therapeutic approaches have been tried to treat xerostomia, dry mouth, or hyposalivation induced by SARS-CoV-2 infection. In the following Sections, different types of treatments being applicable to COVID-19-associated saliva secretory disorders are reviewed together with discussing their pathogenic mechanisms and treatment rationales. They are summarized in Table 2 with used methods, patients or subjects, expected clinical outcomes, and references.

Table 2. Treatments being applicable to COVID-19-associated saliva secretory disorders.

Type	Mechanism	Method	Subject	Outcome	Reference
Corticosteroid	Anti-inflammatory	Nystatin solution rinses 4 times a day for 15 days for intraoral lesions and ointments containing triamcinolone acetonide, neomycin, and nystatin for angular cheilitis	COVID-19 patient, a 78-year-old female who had suffered from mouth dryness, tongue and palate lesions, and angular cheilitis since hospitalization	Dry mouth and salivary secretion were improved along with disappearence of intraoral lesions.	Díaz Rodríguez et al. [130]
Zinc	Compensation for deficient zinc	Oral administration of zinc sulfate (300 mg/day) for 6 months	Non-COVID-19 patients (n = 93) with oral symptoms	Xerostomia and hypogeusia were relieved in 57.9–72.7% of patients.	Tanaka [132]
		Oral ingestion of 15 mg zinc acetate with milk every morning	Non-COVID-19 subjects (n = 10, female: 50%, age: 17–37 years)	After 5 weeks, the flow rate of stimulated parotid saliva was increased along with an increase of blood zinc levels.	Lane et al. [136]

		Taking 3 capsules (220 mg zinc sulfate) daily until the end of chemotherapy	Non-COVID-19 patients (n = 25, female: 48%, age: 18–70 years) undergoing chemotherapy	At 2–20 week follow-ups, the intensity of xerostomia was lower compared with control subjects.	Arbabi-kalati et al. [137]
		Mouth rinsing with 0.25% $ZnCl_2$ solution for 3 min	Non-COVID-19 patients (n = 29) with hyposalivation	Both unstimulated and mastication-stimulated saliva were increased.	Kim et al. [138]
Antiviral drug	Antiviral Inhibition of SARS-CoV-2 M^{pro}	Oral administration of Paxlovid (two 150-mg tablets of nirmatrelvir and one 100-mg tablet of ritonavir) 12-hourly for 5 days	COVID-19 hospitalized patient, a 79-year-old female with the moderate disease complaining of xerostomia due to infection with the Omicron variant BA.2.0 of SARS-CoV-2	Xerostomia was relieved on day 3 of treatment.	Zhang et al. [140]
Photobiomodulation	Stimulation of cell proliferation and differentiation Anti-inflammatory Increase of ducts and epithelial cell mitoses Increase of salivary gland protein synthesis Increase of salivary gland blood circulation Increase of salivary flow rate	Illumination of laser (808 nm) to 6 extraoral points on each parotid gland, 3 extraoral points on each submandibular gland, and 2 intraoral points on each sublingual gland: Illumination for 10 s per point with 2 laser sessions weekly during 3 months (a total of 24 sessions)	Non-COVID-19 patients (n = 29, female: 27.6%, age: ≥37 years) with persistent xerostomia after radiotherapy of head and neck cancer	Flow rates of both unstimulated and stimulated saliva were significantly increased.	Palma et al. [145]
Photobiomodulation	Stimulation of cell proliferation and differentiation Anti-inflammatory	External bilateral illumination of laser (810 nm) to the parotid gland on a continuous basis for 2.4	Non-COVID-19 patients (n = 30, female: 93.3%, mean age: 65.4 years) developing xerostomia due to drug use or	Xerostomia was significantly improved compared with control xerostomic subjects (n = 30, female: 100%,	Ferrandez-Pujante et al. [146]

	Increase of ducts and epithelial cell mitoses Increase of salivary gland protein synthesis Increase of salivary gland blood circulation Increase of salivary flow rate	min and to the submandibular gland on a continuous basis for 1.2 min: One weekly session carried out for a total of 6 weeks	Sjögren's syndrome	mean age: 68.4 years) with simulated treatments.	
Sialagogue: Malic acid	Promotion of salivary secretion	Topical application *of Xeros Dentaid® spray* (1% malic acid, 10% xylitol, and 0.05% sodium fluoride) on demand with a maximum of 8 doses per day for 2 weeks	Non-COVID-19 patients (n = 25, female: 56%, mean age: 54.3 years) with xerostomia induced by using antihypertensive **drugs**	Flow rates of both unstimulated and stimulated saliva were significantly increased compared with a placebo group (n = 20, female: 45%, mean age: 51.8 years).	**Gómez-Moreno et al. [149]**
Chewing gum	Mechanical stimulation of salivary glands	Chewing gum for 10 min 6 times a day and when feeling mouth dryness or thirsty	Non-COVID-19 patients (n = 22, female: 63.6%, mean age: 61.7 years) with chronic hemodialysis to cause xerostomia	At 3-month follow-up, xerostomia was alleviated and the flow rate of unstimulated saliva was increased compared with control subjects (n = 22, female: 36.4%, mean age: 61.4 years) who did not chew any gums.	Ozen et al. [154]
Alternative medicine: Acupuncture	Anti-inflammatory Activation of parasympathetic nerves Restoration of autonomic nervous balance Stimulation of salivary glands via the cranial nerves	Acupuncture performed by giving 24 treatments in 2 series (12 treatments in each series)	Non-COVID-19 patients (n = 70, female: 57.1%, age: 33–82 years) suffering from xerostomia due to Sjögren's syndrome (n = 25, female: 92.0%, age: 33–72 years), irradiation (n = 38, female: 31.6%, age: 37–82 years), and other causes (n = 7,	Flow rates of both unstimulated and stimulated saliva were increased after 6 months and the additional acupuncture maintained such effects for 3 years.	Blom and Lundeberg [156]

		female: 71.4%, age: 38–73 years)		
	Acupuncture applied to 3 auricular points and 1 digital point bilaterally	Non-COVID-19 patients (n = 18) with pilocarpine-resistant xerostomia due to radiotherapy	Xerostomia was relieved in some patients.	Johnstone et al. [158]

4.1. Corticosteroid

4.1.1. Viral Cellular Entry and Inflammation of Salivary Glands

SARS-CoV-2 cellular entry-relevant ACE2, TMPRSS2, and Furin are expressed in major salivary glands of humans [39]. ACE2 was found to be distributed in minor salivary glands of COVID-19 patients [122]. Biopsy specimens from patients who died of COVID-19 indicated that ACE2 and TMPRSS2 are localized in the ductal epithelia and serous acinar cells of parotid and submandibular glands and minor salivary glands, and that SARS-CoV-2 is present in ductal lining cell cytoplasm, acinar cells, and ductal lumens of submandibular and parotid glands [123]. SARS-CoV-2 infection was confirmed in parotid and submandibular salivary glands and minor salivary glands of COVID-19 patients [124]. Given the expression of viral cellular entry-relevant bio-factors and the high viral load in saliva, major and minor salivary glands are targeted for the direct infection and invasion of SARS-CoV-2, and saliva secreted from them richly contains SARS-CoV-2. Salivary glands are the potential reservoir for SARS-CoV-2 and droplets of saliva contaminated with SARS-CoV-2 is potentially one of causes for COVID-19 transmission [125]. After entering the relevant cells via the ACE2-, TMPRSS2-, and Furin-mediated pathway, cytopathic SARS-CoV-2 could cause damage to salivary glands. SARS-CoV-2 infection induces salivary gland inflammation, resulting in sialadenitis in the acute phase of COVID-18 and chronic sialadenitis by fibrosis repairment [126]. Parotitis and submandibular gland sialadenitis are associated with COVID-19 [127,128]. The turnover of salivary gland acinar cells ranges from 50 to 125 days and they are replaced in 6 months. Once salivary glands are damaged, they need several months to recover their secretory functions, resulting in the long-term persistence of xerostomia, dry mouth, or hyposalivation. SARS-CoV-2 also remains for a certain period in tissues of patients who recovered from COVID-19 as prolonged SARS-CoV-2 RNA shedding is observed for months after symptomatic relief [129].

Given salivary gland inflammation through SARS-CoV-2 cellular entry and the consequent secretory dysfunction, anti-inflammatory corticosteroid is usable for treating COVID-19-associated saliva secretory disorders.

4.1.2. Treatment with Corticosteroid and Outcome

Díaz Rodríguez et al. [130] reported a clinical case of a 78-year-old female who was infected with SARS-CoV-2 and had suffered from very intense sensation of mouth dryness, tongue and palate lesions, and angular cheilitis since hospitalization. They prescribed nystatin solution rinses 4 times a day for 15 days for the intraoral lesions and ointments containing triamcinolone acetonide, neomycin, and nystatin for angular cheilitis. After treatment, not only the lesions disappeared but dry mouth was improved along with an increase of salivary secretion. Although concomitantly used nystatin has a pro-inflammatory property [131], triamcinolone is effective in alleviating COVID-19 symptoms.

4.2. Zinc

4.2.1. Zinc Deficiency Induced by SARS-CoV-2 Infection

Salivary secretion from submandibular and parotid glands is reduced in correlation with decreasing zinc levels in salivary glands [132]. Zinc deficiency decreases the activity of salivary gland carbonic anhydrase, which plays an important role in the production and secretion of saliva, and the

regulation of salivary pH [133]. Carbonic anhydrases are zinc-metalloenzymes with high binding affinity for zinc and activity depending on zinc. Among different isozymes, carbonic anhydrase VI is localized in the serous acinar and ductal cells of human parotid and submandibular glands, and is secreted into saliva from them [134]. In SARS-CoV-2 infection-induced hypozincemia, zinc is redistributed from blood to the liver at the expense of zinc in peripheral tissues [72], which would disturb intracellular zinc homeostasis or cause intracellular zinc dyshomeostasis in salivary glands. Zinc deficiency should make a negative impact on salivary secretion. Experimentally induced zinc deficiency in rats significantly decreases saliva secreted from submandibular glands with morphological changes [135]. When carbonic anhydrase VI-deficient patients orally received zinc of 100 mg once a day for 4–6 months, their parotid saliva showed significant increases of zinc and carbonic anhydrase VI [77].

Taken together, zinc supplementation to compensate for deficient zinc could be one of treatment options for COVID-19-associated saliva secretory disorders.

4.2.2. Supplementation with Zinc and Expected Outcome

Tanaka [132] orally administered 300 mg zinc sulfate once a day for 6 months to non-COVID-19 patients (n = 93) with xerostomia and hypogeusia. Consequently, oral symptoms were relieved in 57.9–72.7% of patients.

Lane et al. [136] assessed the effect of zinc supplementation on salivary secretion. Non-COVID-19 subjects (n = 10, female: 50%, age: 17–37 years) orally ingested 15 mg zinc acetate with milk every morning. After 5 weeks, the flow rate of stimulated parotid saliva was increased along with an increase of zinc levels in blood.

Arbabi-kalati et al. [137] performed a double-blind randomized clinical trial in which non-COVID-19 patients (n = 25, female: 48%, age: 18–70 years) undergoing chemotherapy took three capsules (220 mg zinc sulfate) daily until the end of chemotherapy. At 2–20 week follow-ups, the intensity of xerostomia was significantly lower compared with age- and gender-matched control subjects.

Kim et al. [138] measured the salivary flow rate of non-COVID-19 subjects (n = 29) with hyposalivation who rinsed the mouth with 0.25% $ZnCl_2$ solution for 3 min after resting for 5 min. The mouth rinsing increased secretion of both unstimulated and mastication-stimulated saliva.

Although zinc supplementation has not been clinically applied so far to COVID-19 patients, its successful outcomes in non-COVID-19 cases are considered to support the efficacy of treatment with zinc supplements for COVID-19-associated saliva secretory disorders, especially in patients with zinc deficiency induced by SARS-CoV-2 infection [139].

4.3. Antiviral Drug

4.3.1. Viral Invasion to Salivary Glands and Induced Inflammation

SARS-CoV-2 can directly invade major and minor salivary glands to cause damage to them because ACE2, TMPRSS2, and Furin essential for the viral cellular entry are expressed in salivary glands as described in Section 4.1. Acute and chronic inflammatory responses to SARS-CoV-2 infection occur in salivary glands [126] with the resultant impairment of their secretory functions.

When targeting cytopathic SARS-CoV-2 in salivary glands, the use of antiviral drugs is one of treatment options for COVID-19-associated saliva secretory disorders.

4.3.2. Treatment with Antiviral Drug and Outcome

In a case report of Zhang et al. [140], a 79-year-old female patient was hospitalized due to moderate COVID-19 that was caused by the Omicron variant BA.2.0 of SARS-CoV-2. While anecdotal reports have suggested that the Omicron variant causes oral symptoms with relatively low frequency compared with other SARS-CoV-2 variants like the Delta variant, she developed xerostomia together with cough. They orally administered Paxlovid, two 150-mg tablets of nirmatrelvir and one 100-mg tablet of ritonavir to the patient 12-hourly for 5 days. Paxlovid (Pfizer's blockbuster antiviral) is an

authorized oral prescription medicine consisting of nirmatrelvir and ritonavir, both of which show antiviral effects by inhibiting SARS-CoV-2 M^{pro}. On day 3 of treatment, xerostomia was relieved along with improvement of cough, lung exudation lesions, and inflammatory parameters. Although any side-effects of Paxlovid were not observed in this study, bad aftertaste is known for Paxlovid, so called "Paxlovid mouth". In addition, dysgeusia is more likely to be reported by patients receiving Paxlovid compared with patients receiving other protease inhibitors [141] and by pregnant or lactating COVID-19 patients prescribed with Paxlovid [142].

4.4. Photobiomodulation

4.4.1. Multiple Pathogenic Mechanisms

Through interaction with cellular entry-relevant ACE2, TMPRSS2, and Furin, SARS-CoV-2 can directly invade salivary glands as described in Section 4.1. Consequently, SARS-CoV-2 infection induces acute and chronic inflammation in salivary glands, parotitis and submandibular gland sialadenitis, which cause damage to salivary glands and affect their secretory functions.

Photobiomodulation stimulates cell proliferation and differentiation, inhibits inflammation, promotes tissue repair, enhances immunity, and prevents apoptosis [110–112]. Photobiomodulation acts on salivary glands to increase the number of ducts, the mitosis of epithelial cells, the protein synthesis and blood circulation, and the flow rate of saliva [143]. These effects are crucial for its use to treat COVID-19-associated saliva secretory disorders. Although no clinical applications to COVID-19 patients have been reported so far, successful outcomes for xerostomia and hyposalivation of non-COVID-19 patients suggest the efficacy of photobiomodulation in COVID-19 cases.

4.4.2. Photobiomodulation and Expected Outcome

Photobiomodulation is performed by illuminating the tissues with low-level lasers (usually ranging from 0.05 to 0.5 W at the source) of a red light-wavelength ranging from 630 to 685 nm and an infrared-wavelength ranging from 780 to 970 nm [143,144]. Palma et al. [145] evaluated the effect of photobiomodulation on persistent xerostomia of head and neck cancer patients (n = 29, female: 27.6%, age: ≥37 years) receiving radiotherapy. These non-COVID-19 patients were subjected to photobiomodulation with a diode laser (wavelength of 808 nm, power density of 0.75 W/cm^2, output power of 30 mW, illuminated area of 0.04 cm^2, mean dose per point of 7.5 J/cm^2, illumination time per point of 10 s, energy per point of 0.3 J, and energy per session of 6.6 J). Six extraoral points were illuminated on each parotid gland, 3 extraoral points on each submandibular gland, and 2 intraoral points on each sublingual gland. The patients underwent 2 laser sessions weekly during 3 months for a total of 24 sessions. Consequently, mean flow rates of both unstimulated and stimulated saliva were significantly increased.

Ferrandez-Pujante et al. [146] recruited non-COVID-19 patients (n = 60) who developed xerostomia due to drug use (n = 47) and Sjögren's syndrome (n = 13). The patients (n = 30, female: 93.3%, mean age: 65.4 years) underwent photobiomodulation and the resulting changes in salivary flow were compared with control subjects (n = 30, female: 100%, mean age: 68.4 years) who underwent simulated treatments. A diode laser (wavelength of 810 nm) was externally bilaterally illuminated to the parotid gland on a continuous basis at a dose of 6 J/cm^2 for 2 min and 24 s (24 cm^2 x 6 J/cm^2 = 144 s, total 1 W) and to the submandibular gland on a continuous basis at a dose of 6 J/cm^2 for 1 min and 12 s (12 cm^2 x 6 J/cm^2 = 72 s, total 1 W). One weekly session was carried out for a total of 6 weeks. As a result of photobiomodulation treatment, the patients showed a significant improvement of xerostomia compared with the control group.

4.5. Sialagogue

4.5.1. Promotion of Salivary Secretion

Given the parasympathetic innervation of parotid, submandibular, and sublingual glands, and minor salivary glands, stimulation of parasympathetic nerves should improve xerostomia, dry

mouth, and hypogeusia. Parasympathomimetic or muscarinic agonist pilocarpine and cevimeline stimulate salivary glands to increase saliva in patients with xerostomia [147]. However, these sialagogues are likely to cause side-effects such as nausea, vomiting, increased urinary frequency, and headache.

Salivary secretion is promoted in response to taste, especially sour taste [147]. Although acidic compounds stimulate salivary secretion, their long-term use increases the risk of tooth erosion. Low-concentration malic acid combined with xylitol and fluoride significantly was recently reported to reduce a dental erosion potential compared with conventional citric acid-based sialagogues [148].

4.5.2. Treatment with Malic Acid Sialagogue and Expected Outcome

Gómez-Moreno et al. [149–151] suggested the possibility that 1% malic acid topical sialagogue may be applicable to treatment of COVID-19-associated saliva secretory disorders. They conducted a randomized double-blind study to evaluate the efficacy of malic acid sialagogue in patients with xerostomia induced by using antihypertensive drugs [149]. Non-COVID-19 patients (n = 25, female: 56%, mean age: 54.3 years) received a topical sialagogue spray (*Xeros Dentaid® spray)* containing 1% malic acid, 10% xylitol, and 0.05% sodium fluoride. They were administered on demand with a maximum of 8 doses per day for 2 weeks. After treatment, flow rates of both unstimulated and stimulated saliva were significantly increased compared with the placebo group (n = 20, female: 45%, mean age: 51.8 years). In their following studies, a topical sialagogue spray of 1% malic acid used for 2 weeks promoted secretion of both unstimulated and stimulated saliva to improve antidepressant-induced dry mouth [150] and xerostomia of elderly people [151].

4.6. Artificial Saliva

4.6.1. Substitution for Saliva

The sensation of mouth dryness is perceived by insufficient mucosal wetness that is caused by a decrease of salivary film coating on oral tissue surfaces [152]. As a symptomatic therapy, artificial saliva is usable as a saliva substitute for patients with xerostomia, dry mouth, or hyposalivation.

4.6.2. Use of Artificial Saliva and Outcome

Eduardo et al. [153] prescribed artificial saliva for dry mouth of COVID-19 patients in an intensive care unit. Unfortunately, they memtioned neither treatment procedure nor clinical outcome in detail. However, their retrospective study provides a perspective on the use of artificial saliva for COVID-19-associated saliva secretory disorders.

4.7. Chewing Gum

4.7.1. Mechanical Stimulation of Salivary Glands

Mechanical stimulation of major salivary glands is expected to increase the amount of secreted saliva. Chewing gum, usually sugar-free or artificially sweetened, has been used for managing xerostomia, dry mouth, or hyposalivation as described in a review of Kapourani et al. [24], who also referred to commercially available chewing gums used for xerostomia and their characteristics.

4.7.2. Use of Chewing Gum and Expected Outcome

Xerostomia or dry mouth is induced in patients with chronic hemodialysis. Ozen et al. [154] conducted a prospective randomized controlled study in which non-COVID-19 patients receiving hemodialysis for at least 6 months were allocated to the chewing gum group and the control group. Patients (n = 22, female: 63.6%, mean age: 61.7 years) chewed gum (of various brands) for 10 min 6 times a day and when feeling mouth dryness or thirsty, and they were followed up for 3 months. Xerostomia was time-dependently decreased and the flow rate of unstimulated saliva was increased

compared with control subjects (n = 22, female: 36.4%, mean age: 61.4 years) who did not chew any gums.

4.8. Alternative Medicine

4.8.1. Multiple Pathogenic Mechanisms

Acupuncture has been attracting attention as an alternative medicine for xerostomia or dry mouth because it suppresses inflammation, activates parasympathetic nerves, restores the autonomic nervous balance, and stimulates salivary glands via the cranial nerves. All of these effects are useful for treatment of COVID-19-associated saliva secretory disorders, especially long-term persistent symptoms [116]. Acupuncture has been used in dentistry for managing various conditions such as dental pain, temporomandibular disorder, trigeminal neuralgia, and dry mouth [155].

4.8.2. Acupuncture and Expected Outcome

Blom and Lundeberg [156] conducted a retrospective study on patients (n = 70, female: 57.1%, age: 33–82 years) who had xerostomia due to primary and secondary Sjögren's syndrome (n = 25, female: 92.0%, age: 33–72 years), irradiation (n = 38, female: 31.6%, age: 37–82 years), and other causes (n = 7, female: 71.4%, age: 38–73 years). These non-COVID-19 patients were subjected to acupuncture given in 2 series (12 treatments in each series) and then their oral conditions were examined after 6 months and followed up for 3 years. Flow rates of both unstimulated and stimulated saliva were increased and such effects were maintained for 3 years by the additional acupuncture. As supported by a case report of multidisciplinary treatment [157], acupuncture also facilitates recovery from post-COVID syndrome (long-term effects of COVID-19). In a clinical trial of Johnstone et al. [158], non-COVID-19 patients (n = 18) with pilocarpine-resistant xerostomia following the radiotherapy of head and neck malignancies received acupuncture that was provided to 3 auricular points and 1 digital point bilaterally. After treatment, xerostomia was relieved in some patients. A systematic review and meta-analysis of Wu et al. [159] indicated that acupuncture combined with moxibustion produces better effects on radiotherapy-induced xerostomia.

While previous studies demonstrated the therepeutic effect in non-COVID-19 cases, evidence is still lacking for the clinical utility of acupuncture (combination with moxibustion) in COVID-19-associated saliva secretory disorders.

5. Conclusions

Different types of treatments are applicable to taste and saliva secretory disorders of COVID-19 patients and survivors. Their efficacy is supported by successful outcomes in COVID-19 cases and expected from non-COVID-19 cases. Promising treatments include the use of tetracycline, corticosteroid, zinc supplementation, stellate ganglion block, phytochemical curcumin, traditional herbal medicine, nutraceutical vitamin D, and/or photobiomodulation for COVID-19-associated taste disorders; and the use of corticosteroid, zinc supplementation, antiviral drug, malic acid sialagogue, chewing gum, acupuncture, and/or moxibustion for COVID-19-associated saliva secretory disorders. However, high-quality evidence is insufficient to support their routine use in clinical practice, requiring further well-designed studies with a greater variety of COVID-19 cases.

At present, fully validated treatments are still lacking for COVID-19-associated ageusia/dysgeusia/hypogeusia and xerostomia/dry mouth/hyposalivation in the early stage of SARS-CoV-2 infection and after recovery from the disease. Therefore, it is needed to use the most suitable treatment according to symptomatic and patient's characteristics. An appropriately selected treatment and oral healthcare should be provided to COVID-19 patients and survivors suffering from taste and saliva secretory disorders. Understanding of currently available treatment options is required for dental professionals because they not only experience patients who were infected with SARS-CoV-2 or recovered from COVID-19 but first become aware of their abnormal taste and salivary secretion. By doing so, dentists and dental hygienists can play a crucial role in managing

COVID-19-associated oral symptoms and contribute to improving the oral health-related quality of life of the relevant dental patients.

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