

REVIEW

Oral manifestations of Covid-19-A literature review

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Summary

Initially, it was reported that coronavirus 2019 disease (Covid-19) affects respiratory, gastrointestinal and neurological systems, but the oral, olfactory and integumentary systems are also involved. This review discusses various oral manifestations of Covid-19 reported in the literature along with possible underlying mechanisms. The reported manifestations include taste impairment, oral mucosal changes (petechiae, ulcers, plaque-like lesions, reactivation of herpes simplex virus 1 (HSV1), geographical tongue and desquamative gingivitis) and dry mouth. The prominent location for mucosal lesions are tongue, palate and labial mucosa. The exact pathogenesis of these oral symptoms is not known. Angiotensin-converting enzyme 2 (ACE2) cell receptors are expressed in abundance on oral mucosa allowing severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) to infect them. Gustatory impairment along with olfactory changes is now listed as a symptom of Covid-19 by the World Health Organization, but further research is needed to confirm a link between reported additional oral symptoms and Covid-19. Dental professionals may encounter individuals with Covid-19 and be called upon to identify various oral manifestations of this disease.

KEYWORDS

Covid-19, dry mouth, gustatory changes, mucosal lesions, oral manifestations

1 | INTRODUCTION

'Wuhan Pneumonia of unknown origin' was identified as a novel coronavirus, the seventh member of the coronavirus family, by Chinese researchers through sequencing its genome.¹ On 30 January 2020, the World Health Organization (WHO) declared this outbreak a Public Health Emergency of International Concern (PHEIC) due to its spread across 18 countries till that date. WHO named this disease as 'Covid-19', which is short for 'coronavirus disease 2019'.² The virus was named severe acute respiratory virus syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses.³

Coronavirus comprises a single plus strand of RNA (+ssRNA). SARS-CoV-2 is a β -CoV and mainly infects the respiratory,

gastrointestinal, and central nervous systems of humans and mammals. It is transmitted through respiratory droplets, aerosols, contact and fomites.⁴ Bilateral lung ground-glass opacity on computed tomography is found in many patients infected with this virus. Fever, dyspnea, body aches and dry cough are common presenting symptoms, whereas sputum production, hemoptysis, diarrhea and headache are less common symptoms.^{5,6} Along with these symptoms, this virus can affect other organs including skin, olfactory system and oral cavity.^{7,8} Various manifestations in the oral cavity such as mucosal lesions, taste changes and gingivitis are reported in the literature.⁹⁻¹¹ Oral lesions can be an inaugural sign of Covid-19 or a warning sign of peripheral thrombosis.^{7,12} To avoid more serious complications arising as a result of peripheral thrombosis, it is suggested to start

Abbreviations: HSV1, herpes simplex virus 1; PHEIC, Public Health Emergency of International Concern; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; TNF, tumour necrosis factor; WHO, World Health Organization; CN, Cranial Nerve; PCR, Polymerase Chain Reaction; RT-PCR, Reverse transcription- polymerase chain reaction; HSV-1, Herpes Simplex Virus type 1.

anticoagulant therapy as soon as possible after emergence of these oral lesions.¹²

As dental practices throughout the world have opened or are preparing to open, it is quite possible that dentists may encounter oral manifestations of Covid-19 in their patients. The objective of this review is to report various oral manifestation of Covid-19 described in the literature. This will help dental professionals to focus on detailed intraoral examination before initiating any dental treatment on Covid-19 suspected or confirmed patients.

2 | METHODOLOGY

2.1 | Search strategy

Online database PubMed was searched for all publications related to oral manifestation of Covid-19 with a combination of following keywords:

1. 'Covid-19' or '2019 novel Coronavirus' or '2019-nCoV' or 'SARS-CoV-2',
2. and 'oral manifestation'
3. (1) and 'oral sign and symptoms'
4. (1) and 'oral mucosal changes'
5. (1) and 'taste impairment'
6. (1) and 'gustatory changes'

2.2 | Inclusion criteria

1. Publications in English language only.
2. Publications from January 2020 to February 2021.
3. Type of publications (letter to the editors, correspondence, case report, case series, observational studies, clinical studies, clinical trials and reviews).

2.3 | Exclusion criteria

1. The publications addressing Covid-19 symptoms in general or challenges in dentistry without reference to oral manifestations or oral symptoms.
2. The studies presenting oral mucosal changes without reference to Covid-19.
3. In cases, where both the review and research articles present in that review were retrieved, a review article was selected instead of individual studies (Duplication removal).

2.4 | Article selection

Publications screening and selection was divided into two phases: an initial screening of titles and abstracts, and final screening of full-text

publications. Authors (Huma Farid, Madiha Khan, Shizrah Jamal) independently screened the titles and abstracts of retrieved publications from the initial search strategy. In this stage, articles were included if they reported the above-mentioned keywords in title or abstract. Full-text reading was carried out at initial screening stage only if the content of the title/abstract was unclear or abstract was not provided.

The initial screening phase was followed by full-text publication screening. In this phase, publications were screened and selected on the basis of pre-determined inclusion and exclusion criteria. There was no disagreement between the authors during screening process.

Except for the taste impairment, all other oral manifestations were mostly reported in the form of cross sectional studies, letters to the editors, case reports or short communications. Due to scarcity of literature on this topic, we were not able to report a systematic review. Still to make a structured narrative review and ensured standardization, PRISMA flowchart was followed for literature search and selection (Figure 1: Literature search flowchart).

3 | RESULTS

Using the described search strategy, a total of 86 publications were retrieved. After removing the duplicate publications, the total number reduced to 62. These 62 publications underwent titles and abstract screening and 30 were selected for full-text screening. On full-text review, 11 publications were excluded. In addition to the above-mentioned exclusion criteria, at this stage, the studies that did not distinguish between olfactory and gustatory impairment and considered them one entity were excluded. Similarly, a publication with hypothesized oral manifestations that can arise as a result of Covid-19 was excluded. A total of 19 publications were selected. Among these, there was one systematic review and meta-analysis on gustatory changes associated with Covid-19. For the remaining oral manifestations, mostly case report, case series, letters to the editors and short communications were found. The summary of included publications including type of study, demographics of patients (age and gender), oral manifestations, treatment provided, duration of symptoms and Covid-19 confirmation status is presented in Table 1. The reported oral manifestations are briefly discussed under the discussion section.

4 | DISCUSSION

4.1 | Gustatory changes or taste impairment

Gustatory and olfactory changes can be the only symptom in mild cases of Covid-19 or the initial symptom in patients who ultimately present with more severe respiratory failure. The reported gustatory changes associated with Covid-19 are hypogeusia, dysgeusia and

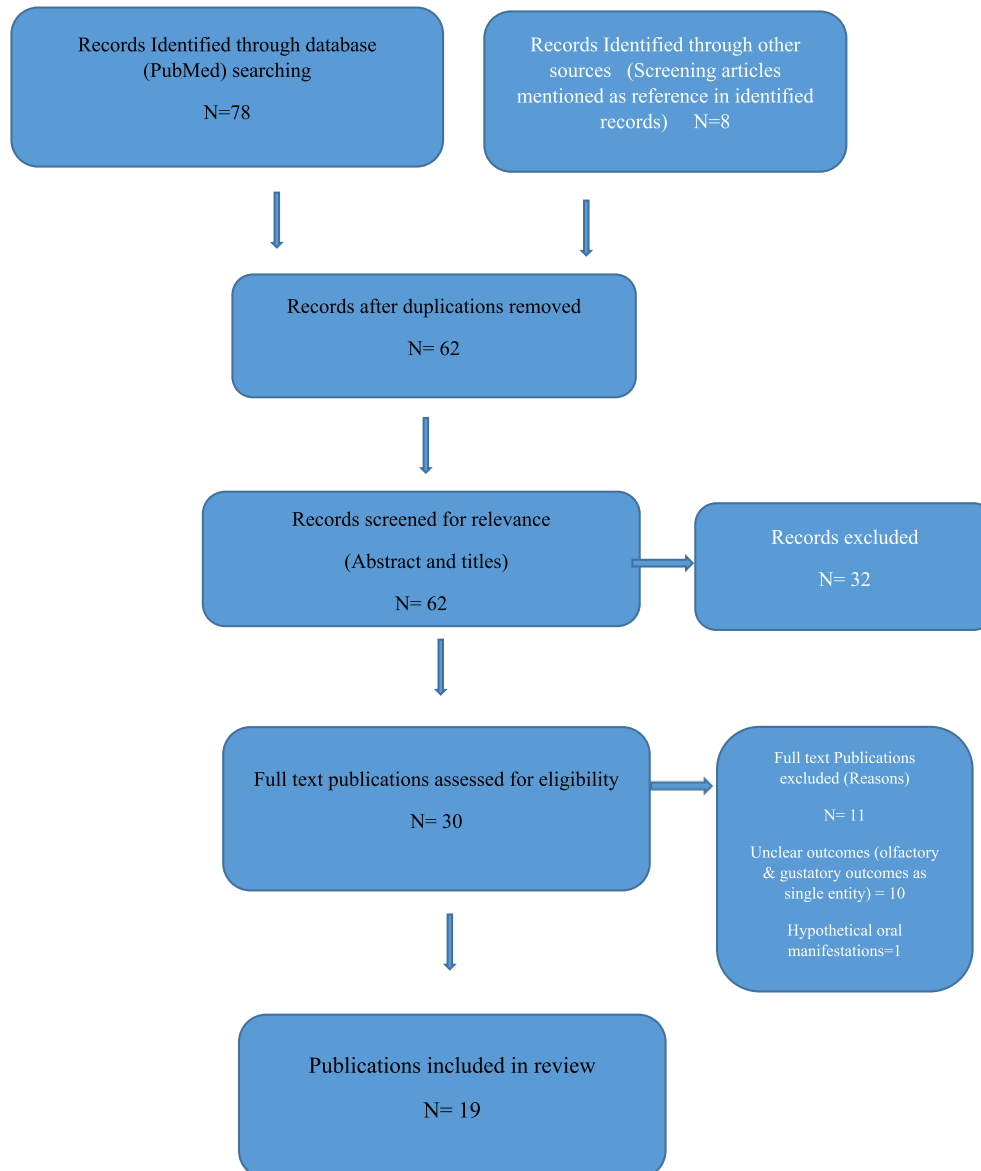


FIGURE 1 Literature search flowchart

ageusia.^{10,13–17} The exact pathogenesis of SARS-CoV-2 and olfactory and gustatory dysfunction is not known. It is reported that angiotensin-converting enzyme 2 (ACE2) cell receptors are expressed in abundance on respiratory epithelium and oral mucosa especially tongue.^{16,18} SARS-CoV-2 has a great affinity for these receptors.^{19,20} Direct damage to nasal and oral epithelium and neuroinvasive nature of this virus can result in olfactory and gustatory disorders. It is reported that 95% of the cases with taste disturbances are secondary to olfactory dysfunction.²¹ Olfactory dysfunction should be considered as a primary cause if patient complaints of both smell and taste disturbances. Most of the studies had considered smell and taste disturbances as a single entity rather than two separate entities.^{22–24} In fact, it is often very difficult for the patient to delineate between taste and smell dysfunctions. There is a need to highlight Covid-19 cases presented with gustatory

dysfunction (hypogeusia, dysgeusia and ageusia) in the absence of olfactory changes. Investigations such as whole mouth and spatial taste tests can be employed to identify the presence of gustatory dysfunctions along with localization of area of impairment and threshold sensitivity to a particular taste.²⁵ Different mechanisms proposed in the literature for taste alterations are shown in the Figure 2.

Based on the frequent presence of these symptoms in Covid-19 positive and suspected patients, the American Academy of Otolaryngology recommended the addition of anosmia, hyposmia, and dysgeusia to the list of screening tools for COVID-19 in asymptomatic individuals.²⁶ The US Centers for Disease Control and Prevention officially added olfactory and gustatory dysfunctions as an important Covid-19 symptom whereas the WHO listed them as less common symptoms of Covid-19.^{27,28}

TABLE 1 Publications regarding oral manifestations associated with COVID 19

Type of study	Author, year	No. of patients, age & gender	Oral manifestation	Covid-19 confirmed/suspected	Treatment provided	Symptoms resolved
Letter to the editor	Chaux-bodard ⁷ 2020	1 patient 45 years female	Irregular ulcer on the dorsal side of the tongue	Confirmed at 8 days (RT-PCR)	Not mentioned	Healing of ulcer without scar after 10 days
Case series	Martin Carreras-Presas C ¹⁰ 2020	3 patients 56 years Male 58 years Male 65 years Female	*Dysgeusia, *Multiple ulcers on palate and internal lip *Mucosal blisters, *Desquamative gingivitis, *Pain in tongue.	1 confirmed 2 suspected	Valaciclovir 500 mg every 8 h for 10 days, and topical antiseptics with chlorhexidine and hyaluronic acid, Predinolone	Within 7–10 days
Letter to the editor	Patel J, Woolley J ¹¹ 2020	1 patient 35 years Female	*Severe halitosis, *Generalized erythematous and edematous gingivae, *Necrotic interdental papillae in both the maxillary and mandibular labial sextants.	Suspected	400 mg metronidazole three times daily for 5 days and 0.12% chlorhexidine mouthwash twice daily for 10 days.	Complete resolution of oral and Covid-19 symptoms after 5 days
Cross-sectional study	Favia G ¹² 2021	123 patients 70 male 53 female Median age = 72 years	*Geographic tongue (5) *Fissured tongue (4) *Ulcerative lesion (51) *Blisters (14)	Confirmed-PCR	Hyaluronic acid gel and chlorhexidine 2% mouthwash or gel (twice a day) for 14 days in patients with ulcero-erosive lesions Miconazole nitrate twice a day in patients with cytological diagnosis of candidiasis tranexamic acid for local hemorrhages	Days of appearance of symptoms mentioned. No information regarding resolution of symptoms.

TABLE 1 (Continued)

Type of study	Author, year	No. of patients, age & gender	Oral manifestation	Covid-19 confirmed/suspected	Treatment provided	Symptoms resolved
Case report	Zarch et al. ¹³ 2021	1 patient, 56 year old female	(Patients were classified as moderate, severe and critical form of Covid-19)	Confirmed (PCR)	Azithromycin, levofloxacin Anti-inflammatory and antiasmathic drugs (montelukast, naproxen and acetaminophen)	7 days
			*Hyperplasia of papillae (33)			
			*Angina bullosa (8) *Candidiasis (18) *Ulceronecrotic gingivitis (1) *Petechiae (4) *Above 80% of patients in each form of Covid-19 presented with taste disorders			
Case series	Riad et al. ¹⁴ 2020	26 patients mean age = 37 Male = 9 Female = 17	*Ageusia = 3 *Painful tongue ulcers (all cases)	Confirmed (PCR)	Chlorhexidine, paracetamol	21 patients = 7 days 5 patients = 14 days
Systematic review	Tong JY & colleagues ¹⁵ 2020	1390 patients (9 studies)	626 reported gustatory dysfunction	Majority were hospitalized & RT-PCR was done	Not mentioned in review	Not mentioned in review
Case report	Hjelmæsæth J, Skaare D ¹⁶ 2020	2 patients male in sixties	Ageusia for 9 days	Confirmed (RT-PCR)	No treatment for taste disturbance	On 10 days, sweet & sour flavor was detected On 13 th day umami flavor was detected
			Dysgeusia			
Case report	Santos JA dos et al. ¹⁷	1 patient	*White plaque and multiple tiny yellow ulcers on dorsum of the tongue (resemble to late stage of herpetic recurrent oral lesions associated with candidiasis)	Confirmed (RT-PCR)	*Intravenous fluconazole (Zoltec® 200 mg/100 ml, one bag a day for 10 days) and oral nystatin (100,000 IU/ml, 8/8h, for 30 days), but no regression was observed. Then	Complete lesion of white lesion after 14 days of oral examination

(Continues)

TABLE 1 (Continued)

Type of study	Author, year	No. of patients, age & gender	Oral manifestation	Covid-19 confirmed/suspected	Treatment provided	Symptoms resolved
	2020	67 years Male	*asymptomatic geographical tongue *Lower lip nodule (reactive reaction) *Hypogeusia		*Antifungals, chlorhexidine digluconate (0.12%), 1% hydrogen peroxide.	Over the time recession in size of geographical tongue
Correspondence	J Jimenez-Cauhe et al. ²⁹	Total 4 patients Oral manifestations in 3 Mean age 66.75 years all female	Palatal macules and petechiae	Confirmed (PCR)	Systemic corticosteroids	Within 2–3 weeks.
Case series	Orcina F et al. ³⁰ 2021	4 patients, 52 year old male 32 year old male 30 year old female 29 year old male	Apthous ulcers	Confirmed (PCR)	Phtalox mouth wash	12 h–4 days
Case report and narrative review	Hockova et al. ³¹ 2021	Total = 210, 23 female 62 male	*Perioral pressure ulcers = 179 *Intraoral candidiasis = 27, *Other intraoral ulcers = 3 *macroglossia = 1,	Confirmed (PCR)	Dressings, position adjustment, antifungals, antivirals, and surgical interventions, full thickness excisions	Healed after 1–2 weeks
Prospective, observational study	Fidan et al. ³² 2021	74 patients 49 males, 25 females	*Apthous ulcers = 27 *Erythema = 19 *Lichen planus = 12	Confirmed (PCR)	Not reported	Not reported
Descriptive cross sectional study (Questionnaire based)	C. Galván Casas et al. ³⁹ 2020	Total 375 cases Oral manifestation in 2 Age and gender not specify	Maculopapular eruption on palatal and lower lip mucosa	1 confirmed 1 suspected (Method of Covid-19 confirmation not mentioned)	Not available	Not mentioned

TABLE 1 (Continued)

Type of study	Author, year	No. of patients, age & gender	Oral manifestation	Covid-19 confirmed/suspected	Treatment provided	Symptoms resolved
Descriptive cross sectional study (Web based questionnaire)	Biadsee A ⁴¹ 2020	Total 128	*Impaired sense of taste = 67	Confirmed (RT-PCR)	Not mentioned	Not mentioned
		Mean age 36.25	*Dry mouth = 72			
		58 male	*Facial pain = 18			
		70 female	*Masticatory muscles pain = 15			
			*Change in tongue sensation = 20			
			*plaque-like changes in the tongue = 9			
			*Swelling in the oral cavity = 9			
			*Swelling in palate = 4			
			*Swelling in tongue = 4			
			*Swelling in gums = 2			
Prospective Cohort study	M Hedou et al. ⁴² 2020	Total 103 patients	Oral herpes simplex virus-type 1 (HSV-1) reactivation	Confirmed (PCR)	Not available	Cutaneous manifestations disappeared with median time of 48 h (from 24 h to 6 days). Oral manifestation disappearance not mentioned.
		Oral manifestation in 1				
Descriptive, cross sectional study (in two phases) Active phase (A) and 15 days after RT-PCR - (B)	Freni F et al. ⁴³ 2020	50 patients	*Gustatory disorders	Confirmed (Autoimmune RT-PCR)	Not mentioned	15 days after RT-PCR became negative, Gustatory disorder in 4 Xerostomia in 1 patient
		Mean age 37.7	A = 35			
		30 male	B = 4			
		20 female	*Xerostomia A = 16 B = 1			

(Continues)

TABLE 1 (Continued)

Type of study	Author, year	No. of patients, age & gender	Oral manifestation	Covid-19 confirmed/suspected	Treatment provided	Symptoms resolved
Case report	Villalba LN et al. ⁴⁴ 2020	2 patients 1 with oral manifestations 80 years female	5-days history of taste loss preceding smelling problems and fatigue.	Confirmed (PCR)	Asymptomatic treatment and an oxygen supply.	Not mentioned
Letter to editor	Ansari et al. ⁴⁵ 2020	2 patients with oral manifestations	*Painful, red ulcerations on hard palate = 1 *Several small painful ulcers on the anterior tongue = 1	Confirmed (PCR)	Diphenhydramine, dexamethasone, tetracycline, and lidocaine	Healed after 1 week

4.2 | Oral mucosal lesions

Many oral mucosal lesions are reported in Covid-19 confirmed and suspected individuals. They include ulcers, erosions, blisters, plaque-like lesions, reactivation of herpes simplex virus 1(HSV1), and geographical tongue.^{10,13,14,29-33} Oral mucosal lesions are presented along with common symptoms of Covid-19 or with other cutaneous manifestations. The lesions appear either before or along with systemic manifestations of Covid-19. A clear relationship between Covid-19 and oral mucosal lesions has yet to be established. It is stated in few publications that only oral symptom associated with Covid-19 is taste impairment and other oral lesions arise as a result of decreased immunity due to viral infection, opportunistic or secondary infection or treatment for Covid-19.^{8,14,32,34,35} Oral mucosal lesions are reported to disappear (6 days–2 weeks) or regress in size with time.^{7,17,29} Different possible mechanisms proposed in the literature for oral mucosal lesions are shown in Figure 3. Following is the brief description of different oral mucosal lesions as reported in the literature.

4.2.1 | Ulcers and erosions

One of the most common oral complication associated with Covid-19 confirmed or suspected individuals is ulcerative lesions of the oral cavity.^{7,13,14,17,29,32,36-38} The site, pattern and presentation varies in different reported papers. Tongue (dorsum and lateral boarder) is the most common reported site followed by hard palate and buccal mucosa. Irregular and painful ulcers either appear alone (single ulcers) or in the form of multiple tiny ulcers. Clusters of ulcers either resemble herpetiform ulcers or multiple aphthoid ulcers with diffuse erythematous base. These multiple aphthoid ulcer later on coalesce to form large ulcers with yellowish fibrin covering them, resembling erythema multiform-like disease.¹² Ulcers, erosions and blood crust on labial mucosa along with palatal and gingival petechiae are also reported in one study.³⁸

4.2.2 | Vesicobullous lesions

These lesions mostly appear in association with cutaneous manifestations and show a range of presentation such as blisters, petechiae, erythematous lesions and erythema multiform-like lesions.^{10,17,29,31,36,38-40} Tongue and palate (soft and hard) are the most common reported location of these lesions. Erythema multiform-like lesions are most commonly reported lesions accompanied by skin target lesions.²⁹

4.2.3 | Plaques (white or red)

Candidal plaque-like lesions are also observed in association with Covid-19. Both red and white plaques were observed. They are located on the dorsum of the tongue and palate. They were also

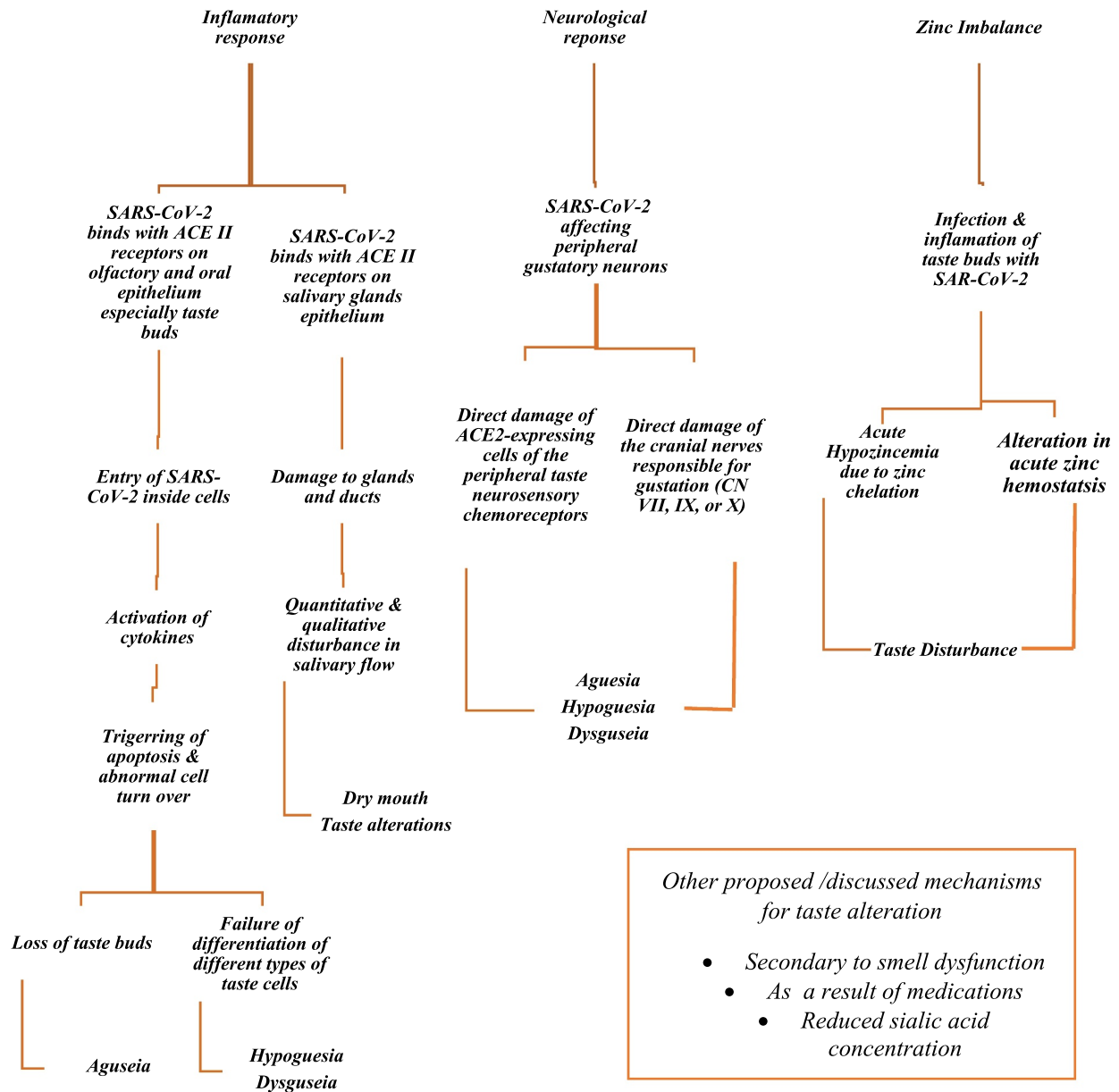


FIGURE 2 Proposed mechanisms for taste alteration in Covid-19. ACE2, angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory virus syndrome coronavirus 2

observed along with multiple tiny ulcers, taste changes, tongue and masticatory muscles pain.^{12,17,41} Immune system suppression as a result of antibiotic therapy, deteriorating general health and neglected oral hygiene can be possible causes of these plaques.

4.2.4 | Reactivation of Herpes Simplex 1(HSV 1)

Hedou et al. while reporting cutaneous manifestations of Covid-19 in 103 patients found reactivation of Herpes Simplex in one intubated patient in intensive care. Although cutaneous manifestations disappeared with median time of 48 h (from 24 h to 6 days), no

information regarding resolution of Herpes simplex is provided.⁴² Another study also reported multiple tiny yellow ulcers on dorsum of the tongue that resembled to late stage of herpetic recurrent infection along with geographical tongue. Both cases in above-mentioned studies were confirmed Covid-19.

4.2.5 | Angina bullosa

These blood filled blisters are observed on soft palate, tongue and cheek. They are brown-black single or multiple lesions and may appear after initiation of therapies for Covid-19.¹²

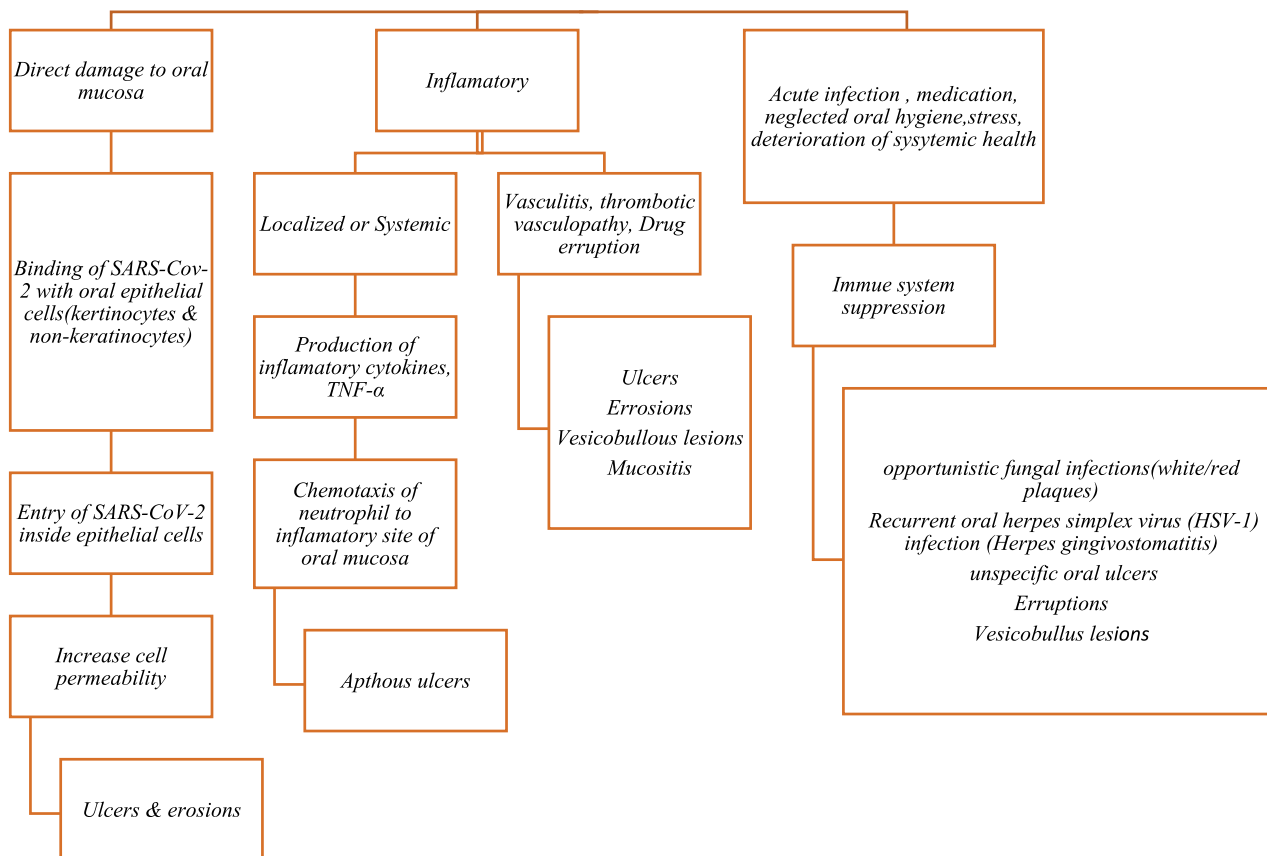


FIGURE 3 Proposed mechanisms of oral mucosal lesion due to Covid-19. SARS-CoV-2, severe acute respiratory virus syndrome coronavirus 2; TNF, tumour necrosis factor

4.2.6 | Gingival changes

Gingival changes such as generalized erythematous and edematous gingivae, gingivo-paradontal bleeding, necrotic interdental papillae and desquamative gingivitis are reported in the literature.¹⁰⁻¹² They are reported in critically ill patients with neglected oral hygiene. In a Covid-19 suspected patient symptoms disappeared within 10 days of antibiotics and topical antiseptic mouthwash usage.

4.3 | Dry mouth

Dry mouth is also reported in association with Covid-19 positive patients.^{13,41,43} In a study, 16 patients reported dry mouth along with other symptoms (PCR positive for Covid-19).⁴³ This number reduced to 1 when PCR for the disease became negative. In another cross-sectional study, 72 patients with Covid-19 reported dry mouth.⁴¹

4.4 | Other manifestations

Symptoms such as halitosis, tongue and masticatory muscle pain and swelling, geographical tongue, hyperplasia of papilla associated

with taste changes and macroglossia are also reported along with fatigue and major symptoms of Covid-19 in few case reports.^{11,31,43}

5 | CONCLUSION

This paper reports various oral manifestations associated with Covid-19 confirmed and suspected patients. Gustatory impairment along with olfactory changes is now listed as a symptom of Covid-19 by the WHO. Covid-19 patients may present with ulcerative, erosive, vesicobullous and plaque-like oral lesions. Further research is needed to confirm a link between reported mucosal lesions and Covid-19, as these lesions may be the first sign of the disease or secondary to medications, reduced immunity, vascular compromise, localized or generalized inflammation and neglected oral hygiene. Dental professionals should be aware of oral manifestations, predisposing factors and underlying mechanisms while examining and before initiating any treatment in patients.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION STATEMENT

Huma Farid presented the idea, conducted literature search and designed the first draft.

Madiha Khan and Shizrah Jamal conducted the literature search (independent screening and selection of publications).

Robia Ghafoor provided advice to improve the manuscript.

All authors have read and approved the submitted version.

DATA AVAILABILITY STATEMENT

This is a narrative review and data sharing is not applicable to this article as no new data was created in this study. The analyzed data (studies included in the review along with variable of interest are presented in the Table 1 whereas literature search flow chart in presented in Figure 1).

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