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Pathogenesis of dysgeusia in COVID-19 patients: a scoping review

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Abstract. – OBJECTIVE: The novel coronavirus disease-19 (COVID-19) pandemic had intense social and economic effects. Patients infected with COVID-19 may present with a series of conditions. A considerable number of patients express taste and smell disturbances as a prodromal, coexistent, or as the only manifestation of COVID-19 infection. The objective of the present review is to review the hypothetical mechanisms of action and etiopathogenesis of dysgeusia in COVID-19 patients.

MATERIALS AND METHODS: Multiple scientific databases were explored, including PubMed, Medline, Scopus, Cochrane-library, LILACS, Livivo and OpenGrey. All types of articles that discussed the pathogenesis of dysgeusia were included, while articles that described dysgeusia without detail about its mode of action were excluded.

RESULTS: A total of 47 articles, with different designs, were included in this review. These articles suggested direct viral neural invasion to olfactory and gustatory nerves, viral cytotoxicity to taste buds, angiotensin II imbalance, augmented pro-inflammatory cytokines, and disturbances in salivary glands and sialic acid. COVID-19 induced-dysgeusia was also associated with systemic diseases, medications, zinc, chemicals, and disinfectants.

CONCLUSIONS: The most likely cause of transient dysgeusia in COVID-19 is peripheral neurotropism and direct toxicity to taste buds or olfactory epithelium. Other factors may also play a contributory role in dysgeusia, such as a defect in the quality and quantity of saliva, pro-inflammatory cytokines, angiotensin II accumulation, systemic diseases, hypozincemia, and excessive use of chemicals.

Key Words:
COVID-19, Dysgeusia, SARS-CoV-2, Taste, Pathogenesis.

Introduction

The coronavirus disease 19 (COVID-19) is an ongoing viral pandemic that emerged in Wuhan, the capital of Hubei, China, in December 2019. COVID-19 has had a tremendous impact on human lives and caused serious economic losses globally. As of November 17, 2020, a total of 54,301,156 confirmed cases of COVID 19, with 1,316,994 deaths, have been reported worldwide[1]. The typical symptoms of the novel coronavirus disease include fever, dry cough, shortness of breath, and fatigue[2]. Less common signs include diarrhea, hemoptysis, sore throat, headache, nasal congestion, acute conjunctivitis, myalgia, anosmia, and dysgeusia[3]. Various studies have reported olfactory and taste disturbances in patients with COVID-19, with the prevalence ranging from 68% to 85% and 71% to 88.8%, respectively[4,5]. Taste disturbances range from complete ageusia or partial hypogeusia (loss of taste sensation) to dysgeusia (altered taste sensation). Based on a few studies, infected patients may present with only taste alterations, without any other significant symptoms[5].

Dysgeusia is a general terminology that identifies all types of impaired taste sensation, whether qualitative or quantitative. Quantitative taste impairment sensations include ageusia and hypogeusia, which result in either total loss or a partial decrease of the ability to taste, respectively. At the other end of the spectrum, hypergeusia refers to an extreme acuteness of the sense of taste.

Dysgeusia also includes quantitative taste disorders, such as parageusia and phantogeusia, that cause distorted or hallucinatory taste sensations in the presence or absence of external stimuli, respectively[6].

Considering the community spread, as well as the volume of cases in each country, we require early detection of the disease through proper understanding of the early recognizable symptoms, such as dysgeusia. The aim of the present study is to review the possible hypotheses for

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how COVID-19 infection may induce dysgeusia, in order to help with early diagnosis and prompt treatment.

Materials and Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[7], while the International Prospective Register of Systematic Reviews (PROSPERO) registration was not performed.

In the present review, multiple scientific research databases were employed, such as PubMed, Medline, Scopus, Cochrane-library, LILACS, Livivo and OpenGrey. Moreover, we conducted a manual search across reference lists of the included articles. The following MESH terms and keywords were used: "COVID -19 AND dysgeusia", "COVID-19 AND dysgeusia" OR "SARS-CoV-2 AND dysgeusia". The searches were conducted between 15 and 18 November 2020. All search results were imported into endnote online, where duplicates were removed. Articles that fulfilled the selection criteria of this review were included, while irrelevant articles were excluded.

The inclusion criteria followed in this review were all types of reported cases and published articles that suggested or identified possible mechanisms by which COVID-19 infection induces dysgeusia. The PICOS requirements of the review were as follows.

Population: patients diagnosed with COVID-19 and showing dysgeusia (loss of taste sensation).
Intervention: all kind of medical treatments or protocols, including patients in quarantine.
Comparison: control patients not diagnosed with COVID-19 but showing or not showing dysgeusia.
Outcome: suggestion of the mechanistic pathogenesis of dysgeusia in COVID-19 patients.
Study design: published case reports, case series, clinical investigations (trials, cohort, case control ... etc.), conference abstract, animal *in-vivo* studies, *in-vitro* studies, editorial letters, reviews, and meta-analysis. Studies written in languages other than English were excluded.

Three authors (MM, AB, and HA) independently performed the preliminary databases searches. Titles and abstracts of all search results were initially evaluated. All articles were incorporated into a table. Information about articles, such as the author's name, country of origin of the article, study type, subject number and gender (if indicated), presence or absence of dysgeusia and other oral symptoms, objective of the study, main outcome of the study, and discussed mechanisms of dysgeusia, were collected. The articles were then evaluated according to the inclusion and exclusion criteria by all reviewing team members. After evaluating the articles, the table was separated into two. The characterization of each included article was described in Table I by extraction of the stated objective and major outcome. The suggested mechanism/s of dysgeusia in each included article was described in Table II. Preparation of the final tables was performed by HM and AB, respectively. Discussion and detailed descriptions of the suggested mechanism/s of dysgeusia in each included article were accomplished by MM, DK, AK, and MM.

Results

The database search process resulted in 335 articles. After removal of duplicates, the number was reduced to 155 articles. Titles and abstracts of all articles were reviewed to check whether they were relevant to the current review; 28 articles were excluded in this phase. The remaining 128 articles were then evaluated according to the inclusion criteria, and 47 articles were included in the review. Articles written in any language other than English were excluded[8-12]. In addition, articles that included dysgeusia as a manifestation without details about its mechanism of action were excluded[3,13-61]. Articles that included details about anosmia without description of the pathogenesis of dysgeusia were excluded[62-75]. Articles that described only the general features of dysgeusia, such as prevalence or incidence, which are linked with age, population, gender, and systemic conditions, without discussing its mechanism of action, were excluded[76-87]. Figure 1 demonstrates the selection process followed in this review. A meta-analysis was not conducted in this study due to heterogeneity in the designs of the included articles.

All included studies described multiple mechanisms by which COVID-19 induces dysgeusia. Neural invasion of the virus to the olfactory and gustatory nerves (neurotropism) was the most reported mechanism. The cytotoxic effect of the virus and its direct injury to taste buds was also

Table I. Characteristics of included studies.

No.	Reference	Country	Study type	Stated study objective and major findings
1.	Bellocchio et al[102]	France/Romania/ Italy/Albania/ Vietnam	Review	**Objective:** To summarize neurological symptoms and complications associated with COVID-19. **Major findings:** Multiple neurological symptoms and complications were linked with COVID-19 including headache, dizziness, encephalopathy, delirium, cerebrovascular accidents, Guillain-Barré syndrome, acute transverse myelitis, and acute encephalitis. They should be considered as a part of the clinical features of this novel global pandemic.
2.	Sheng et al[106]	Taiwan	Prospective	**Objective**: To investigate the characteristics of dysosmia and dysgeusia among 217 patients diagnosed with COVID-19 in Taiwan. **Major findings:** Dysosmia and/or dysgeusia are common symptoms and clues for the diagnosis of COVID-19, particularly in the early stage of the disease
3.	Risso et al[6]	Italy/USA	Review	**Objective:** To review the main causes of alteration, reduction, and loss of taste and their potential repercussion on dietary habits and health, with a special focus on the recently developed hypotheses regarding the mechanisms through which SARS-CoV-2 might alter taste perception. **Major findings:** Taste impairments are not life-threatening conditions. However, It should be given more consideration to understand their underlining mechanisms in COVID-19 patients.
4.	Almeria et al[93]	Spain	Cohort	**Objective:** To evaluate the impact of COVID-19 on neurocognitive performance in 35 patients. **Major findings:** Neurologic manifestations in COVID-19 patients such as cognitive impairments are frequent and associated with anxiety and depression.
5.	Panda et al[116]	India	Prospective cohort	**Objective:** To study the spectrum of ENT manifestations in mild and asymptomatic COVID-19 and observe the natural course of anosmia and dysgeusia consequent to SARS-Cov-2 infection in 225 patients. **Major findings:** The incidence of anosmia and dysgeusia in this study parallels the rates in other Asian countries. Structured reporting of all ENT manifestations especially smell and taste disturbances is recommended.
6.	Kadiane-Oussou et al[123]	France	Retrospective	**Objective:** to compare the clinical characteristics and outcome of 114 COVID-19 patients with and without pneumonia. **Major findings:** Pneumonia affects more often older male patients with comorbidities and can worsen to respiratory failure and acute respiratory distress syndrome, while COVID-19 patients without pneumonia are more often women, complaining of quite specific neurologic symptoms such as anosmia and dysgeusia.
7.	Eshraghi et al[119]	USA	Letter	**Objective:** N/A **Major findings:** N/A
8.	Sinjari et al[133]	Italy	Observational	**Objective:** To determine the oral manifestation of the hospitalized patients for 20 patients with COVID-19. **Major findings:** Oral manifestations such as xerostomia, low oral hygiene, impaired taste, burning sensation, and swallowing difficulty were reported.
9.	Ho et al[88]	USA	Case series	**Objective:** To clarify the prevalence of gastrointestinal and oral symptoms in interviewed 7 patients. **Major findings:** gastrointestinal symptoms frequency is high relative to currently available epidemiological reports.

Continued

Table I *(Continued)*. Characteristics of included studies.

No.	Reference	Country	Study type	Stated study objective and major findings
10.	Capocasale et al[136]	Italy	Review	**Objective:** To collect all findings from literature about oral signs and symptoms of COVID-19. **Major findings:** Detecting oral signs and symptoms of COVID-19 could be useful to perform a better preliminary triage in dental setting, and in recognizing possible early manifestations of the disease.
11.	Jarrahi et al[91]	USA	Review	**Objective:** To summarize the central nervous system effects of SARS-CoV-2 and discuss several potential targets for therapeutic development. **Major findings:** SARS-CoV-2 produces wide-ranging and often unpredictable neurological symptoms, ranging from anosmia to encephalitis to increased stroke risk
12.	Fantozzi et al[94]	Italy/USA	Retrospective	**Objective:** To evaluate the prevalence and characterize specific symptoms associated with COVID-19 in 326 patients. Major findings: Xerostomia, gustatory and olfactory dysfunctions may present as a prodromal or as the sole manifestation of COVID-19.
13.	Harikrishnan[97]	England	Letter	**Objective:** N/A **Major findings:** N/A
14.	Sato et al[115]	Japan	Experimental	**Objective:** To elucidate the underlying histological mechanisms of the aerodigestive disorders caused by SARS-CoV-2. **Major findings:** A wide range of organs have been speculated to be affected by SARS-CoV-2 depending on the expression levels of ACE2 and transmembrane protease serine 2 (TMPRSS2). Differential distribution of TMPRSS2 in the lung indicated the COVID-19 symptoms to possibly be exacerbated by TMPRSS2 expression.
15.	Brandão et al[125]	Brazil/USA	Case series	**Objective:** To report a series of 8 cases of COVID-19 infection, with oral necrotic ulcers and aphthous-like ulcerations which developed early in the course of disease after the development of dysgeusia and affected the tongue, lips, palate, and oropharynx. **Major findings:** Etiopathogenic mechanisms between ACE2 and SARS-CoV-2 may contribute in the oral manifestations of COVID-19 patients.
16.	Cazzolla et al[100]	Italy	Observational	**Objective:** To correlate interleukin-6 levels in COVID-19 patients with olfactory or gustatory dysfunctions and to investigate the role of IL-6 in the onset of these disorders in 67 COVID-19 patients. **Major findings:** Interleukin-6 levels in COVID-19 patients in relation to olfactory or gustatory disorders were correlated from the time of their admission to the time of swab negativization. Statistically significant correlations were obtained between the decrease of interleukin-6 levels and the improvement of smell and taste functions at swab negativization.
17.	Agyeman et al[137]	Australia	Systematic Review and Meta-analysis	**Objective:** To estimate the prevalence of olfactory and gustatory dysfunctions (OGDs) among patients infected with novel coronavirus disease 2019 (COVID-19). Major findings: There is a high prevalence of OGDs among patients infected with COVID-19. Routine screening for these conditions could contribute to improved case detection in the ongoing COVID-19 pandemic.
18.	Lozada-Nur et al[134]	USA/UK	letter	**Objective:** N/A **Major findings:** N/A

Continued

Table I *(Continued)*. Characteristics of included studies.

No.	Reference	Country	Study type	Stated study objective and major findings
19.	Khan et al[131]	France	Review	**Objective:** To correlate COVID-19, reduced oro-naso-Sensory (ONS) perception, and obesity. **Major findings:** SARS-CoV-2 infection will install (or aggravate) an inflammatory state both in the lingual and nasal epithelia. Obese subjects are at high risk for SARS-CoV-2 infection as they already exhibit a low ONS capacity for different taste modalities.
20.	DosSantos et al[96]	Brazil	Review	**Objective:** To review the current literature that indicates that SARS-CoV-2 can invade the nervous system and to describe the neural circuits those are potentially affected by the virus and their possible role in the progress of COVID-19. **Major findings:** The effects of COVID-19 on the human NS have been inadequately explored.
21.	Azim et al[92]	USA/Pakistan, Aruba/Saint Kitts and Nevis	Review	**Objective:** To delineate the possible mechanisms of nervous system invasion and damage by SARS-CoV-2 and subsequent consequences. **Major findings:** Coronavirus may alter the neuronal mechanism either directly, or may exaggerate a preexisting condition.
22.	Lechien et al[135]	France	Letter	**Objective:** N/A **Major findings:** N/A
23.	Freni et al[95]	Italy	Prospective	**Objective:** To investigate transversally Ear Nose Throat (ENT) symptoms COVID-19 infection correlated and to study the neurotropism and neuroinvasiveness of the virus in the head-neck district through the investigation of the sense of smell, taste, tearing, salivation and hearing in 50 patients. **Major findings:** There was an alteration of the sense of taste, of the sense of smell, dry eyes and of the oral cavity and an auditory discomfort, symptoms probably linked to the neurotropism of the virus.
24.	Mehraeen et al[89]	Iran	Review	**Objective:** To review current evidence on olfactory and gustatory dysfunctions caused by COVID-19. **Major findings:** SARS-CoV-2 may infect oral and nasal tissues and cause olfactory and gustatory dysfunctions.
25.	Kang et al[121]	Republic of Korea.	Review	**Objective:** To review articles about for COVID-19 or other viral infection and olfactory and/or gustatory dysfunctions. **Major findings:** Olfactory dysfunctions, even without other upper respiratory infection or otolaryngologic symptoms, might be the early signs of COVID-19.
26.	Qiu et al[122]	China/France/ Germany/USA	Multicenter case series.	**Objective:** To evaluate the prevalence and characteristics of olfactory or gustatory dysfunction in 394 COVID-19 patients. **Major findings:** Olfactory and/or gustatory disorders may represent early or isolated symptoms of severe acute SARS-CoV-2 infection, which serve as a useful additional screening criterion.
27.	Mariz et al[127]	Brazil	Letter	**Objective:** N/A **Major findings:** N/A
28.	Maurier et al[105]	France	Case report	**Objective:** To describe a COVID-19 patient with phrenic paralysis inducing pulmonary failure without any cardiac, pleural, parenchymal or vascular pulmonary abnormalities. **Major findings:** Direct peripheral neurological involvement of phrenic nerves is suggested. The possibility of neurological assault by SARS-CoV-2 on peripheral nerves, especially the vagus nerve, should be determined.

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Table I *(Continued)*. Characteristics of included studies.

No.	Reference	Country	Study type	Stated study objective and major findings
29.	Sayin et al[110]	Turkey	Comparative	**Objective:** To identify the taste and smell impairment in COVID-19-positive subjects and to compare the findings with COVID-19-negative subjects using the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) Anosmia Reporting Tool. **Major findings:** COVID-19-positive subjects are strongly associated with smell/taste impairment.
30.	Lee et al[111]	Canada	Cross-sectional	**Objective:** To evaluate the self-reported symptoms among adults (over 18 years old) who underwent COVID-19 tests (1,345 patients) at an ambulatory assessment center. **Major findings:** Smell and taste loss may be key symptoms of COVID-19, which is helpful in the clinical diagnosis of COVID-19.
31.	Román et al[108]	Global	Review	**Objective:** To comprehensively review of the neurological disorders reported during the current COVID-19 pandemic. **Major findings:** SARS-CoV-2 affects the central nervous system (CNS), the peripheral nervous system (PNS) and the muscle.
32.	Boscolo-Rizzo et al[120]	Italy/UK	Cross-sectional	**Objective:** To estimate the prevalence of smell or taste impairment in household contacts of mildly symptomatic home-isolated SARS-CoV-2-positive 214 patients. **Major findings:** Smell or taste impairments are quite common in not-tested household contacts of mildly symptomatic home-isolated SARS-CoV-2-positive patients.
33.	Liguori et al[98]	Italy	Prospective	**Objective:** To prospectively assess subjective neurological observationalsymptoms in 103 patients with SARS-CoV2 infection. **Major findings:** Patients with SARS-CoV2 infection frequently present with subjective neurological symptoms. These symptoms are present from the early phases of the disease.
34.	Paderno et al[124]	Italy/Sweden	Cross-sectional	**Objective:** To assess the prevalence of olfactory and gustatory dysfunction in 508 COVID-19 patients. **Major findings:** Olfactory and gustatory dysfunctions are more prevalent in home-quarantined subjects, and they are independently associated with younger age and emale gender.
35.	Pellegrino et al[101]	USA/Germany	Review	**Objective:** To gather insights on the relationship between the changes in chemosensory ability and COVID-19 and to highlight the similarities and differences with the symptomatology reported in other human coronaviruses and viral infections known to cause olfaction and taste disturbances. **Major findings:** Further studies are needed to quantify olfaction and taste disturbances associated with SARS-CoV-2 infection, compared to those of other viral and respiratory infections, to understand the relation between smell, taste, and chemesthesis disturbances in COVID-19, and to understand how persistent these disturbances are after the infection has resolved.
36.	Aziz et al[126]	USA	Systematic Review & Meta-Analysis	**Objective:** To assess the presence of ageusia/dysgeusia among patients with COVID-19. **Major findings:** There is weak evidence if the taste or smell changes could prognosticate COVID-19–related severity and mortality. More epidemiological studies are needed to assess the prevalence of ageusia/dysgeusia in patients with COVID-19, as well as comparing mild to moderate and severe cases.

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Table I *(Continued)*. Characteristics of included studies.

No.	Reference	Country	Study type	Stated study objective and major findings
37.	Tong et al[107]	USA	Systematic Review and Meta-analysis	**Objective:** To determine the pooled global prevalence of olfactory and gustatory dysfunction in patients with COVID-19. **Major findings:** Olfactory and gustatory dysfunctions are common symptoms in patients with COVID-19 and may represent early symptoms in the clinical course of infection.
38.	Zanin et al[99]	Italy	Case Report	**Objective:** To describe the case of a COVID-19 patient admitted for interstitial pneumonia and seizures **Major findings:** Sudden neurological impairment with seizures in COVID-19 patients may be sustained by CNS involvement and demyelinating lesions.
39.	Keyhan et al[109]	Iran	Letter	**Objective:** N/A **Major findings:** N/A
40.	Lechien et al[5]	France/Belgium/ Spain/Canada/ Italy/Switzerland	Prospective	**Objective:** To investigate the occurrence of olfactory and gustatory dysfunctions in 417 patients with laboratory-confirmed COVID-19 infection. **Major findings:** Olfactory and gustatory disorders are prevalent symptoms in European COVID-19 patients, who may not have nasal symptoms. The sudden anosmia or ageusia need to be recognized by the international scientific community as important symptoms of the COVID-19 infection.
41.	Finsterer et al[103]	Austria	Letter	**Objective:** N/A **Major findings:** N/A
42.	Parma et al[113]	Global	Prospective	**Objective:** to assess self-reported quantity and quality of perception in three distinct chemosensory modalities (smell, taste, and chemesthesis) before and during COVID-19. **Major findings:** COVID-19-associated chemosensory impairment is not limited to smell, but also affects taste and chemesthesis.
43.	Lechien et al[114]	France/ Belgium/ Czech Republic/ Italy/Canada/UK	Prospective	**Objective:** To study the clinical presentation of COVID-19 in Europe. **Major findings:** The clinical presentation of mild-to-moderate COVID-19 substantially varies according to the age and the sex characteristics of patients. Olfactory dysfunction seems to be an important underestimated symptom of mild-to-moderate COVID-19.
44.	Altin et al[117]	Turkey	Prospective	**Objective:** To report the results from comprehensive olfactory and gustatory testing in a series of 81 hospital patients. **Major findings:** Olfactory and gustatory dysfunctions are strongly associated with SARS-CoV-2 infection. Hyposmia with or without hypogeusia is potentially a reliable indicator of latent COVID-19
45.	Zayet et al[118]	France	Retrospective	**Objective**: to compare the clinical features of COVID-19 and influenza in 124 patients. **Major findings:** Several clinical differences between COVID-19 and influenza were described, which can help the clinicians during the co-circulation of influenza and SARS-CoV-2.
46.	Biadsee et al[90]	Israel	Case series	**Objective**: To report the olfactory and oral disorders in 140 COVID-19 patients. **Major findings:** Considerable number of patients presented with olfactory and oral disorders. Women presented with a different cluster of symptoms than men.
47.	Abalo-Lojo et al[112]	Spain	Letter	**Objective**: N/A **Major findings:** N/A

Table II. Suggested mechanisms of dysgeusia discussed in the included studies.

No.	Reference	Mechanism discussed
1.	Bellocchio et al[102]	• CNS damage secondary to SARS-CoV-2 virus invasion. • CNS damage secondary to inflammation after SARS-CoV-2 virus.
2.	Sheng et al[106]	• Inflammation of the olfactory epithelium and mucosal epithelial cells of the oral cavity secondary to entry of the virus via ACE2 receptors may explain dysosmia and/or dysgeusia observed in COVID-19 patients.
3.	Risso et al[6]	• ACE2 and TMPRSS2 receptors give an access to SARS-CoV-2 virus to the target cells and lead in the loss of taste and smell. • Direct infection of the taste bud cells, inflammation secondary to infection, or direct damage of cranial nerves are possible mechanisms for taste disturbance. • Changes in the cellular zinc homeostasis in oral gustatory cells (hypozincemia) may result in dysgeusia.
4.	Almeria et al[93]	• Neurological manifestations such as loss of smell and taste may be related to the invasion of SARS-CoV-2 virus into CNS.
5.	Panda et al[116]	• SARS-Cov-2 enters epithelial cells by binding to ACE-2 on the cell surface and subsequently cause taste disturbance.
6.	Kadiane-Oussou et al[123]	• High expression of ACE2 the oral mucosa may be responsible for some frequent symptoms as dysgeusia during COVID-19 infection.
7.	Eshraghi et al[119]	• Increased levels of pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-6 in COVID-19 patients may impair the maturation of taste buds and subsequently lead to dysgeusia. • Binding of the virus with COVID-19 receptors such as ACE2 downregulates ACE2 expression and a corresponding increase in inflammatory angiotensin II may be related to dysgeusia and anosmia.
8.	Sinjari et al[133]	• Taste alteration may be related to impairment of salivary flow due to viral invasion into salivary glands of COVI1D19 patients.
9.	Ho et al[88]	• Sensory symptoms including anosmia/hyposmia, ageusia, and dysgeusia may be related to: – SARS-CoV-2 may cause a demyelinating reaction in olfactory neurons, and/or causes an inflammatory process that mediates neural injury – Neuro-invasion ability of SARS-CoV-2 virus into brain – Inhibition of ACE or entrance of the virus into the epithelial cells *via* ACE receptors.
10.	Capocasale et al[136]	• Taste alteration is associated with viral invasion into tongue and salivary glands of COVI1D19 patients via ACE2 receptors.
11.	Jarrahi et al[91]	• Olfactory and gustatory deficits might be related to the invasion of the SARS-CoV-2 virus into CNS
12.	Fantozzi et al[94]	• Dysgeusia, hyposmia/anosmia and xerostomia secondary to the COVID-19 may be associated with either: – Invasion of SARS-CoV-2 virus into olfactory/trigeminal and salivary gland cells via ACE2 receptors – Invasion of SARS-CoV-2 virus into CNS via olfactory/trigeminal bulb.
13.	Harikrishnan[97]	• Entry of SARS-CoV-2 virus in taste buds' region and tongue epithelium via ACE2 receptors may affect taste sensation. • Conversion of angiotensin enzyme in taste buds is affected by the ACE2 receptor - SARS- CoV-2 binding, which may alter taste sense in COVID-19 patients. • Imbalance angiotensin II expression may play a role in taste dysfunction. • Loss of taste may result from degradation of taste stimulating molecules bonding by SARS-CoV-2 to Sialic acid. • Binding of SARS-CoV-2 RNA with the Toll-like receptors (TLRs), abundantly expressed on taste bud cells, may lead to inflammation in taste bud cells and consequently change in the taste sense. • Loss of taste could be secondary to loss of smell, due to the close functional relation between these two chemosenses

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Table II *(Continued)*. Suggested mechanisms of dysgeusia discussed in the included studies.

No.	Reference	Mechanism discussed
14.	Sato et al[115]	• Co-expression of ACE2 and TMPRSS2 receptors in the taste buds of the tongue and nasal epithelium can lead in the loss of taste and smell.
15.	Brandão et al[125]	• Interaction between SARS-CoV-2 and ACE2 receptors in epithelial cells of salivary glands and tongue might be involved in the loss of taste.
16.	Cazzolla et al[100]	• Loss of taste may result from degradation of taste stimulating molecules bonding by SARS-CoV-2 Sialic acid. • Loss of taste could be secondary to loss of smell, due to the close functional relation between these two chemosenses • Invasion of SARS-CoV-2 in the CNS might be involved in the loss of taste and smell. • Increased level of cytokine (IL-6) can be associated with taste or smell disturbances.
17.	Agyeman et al[137]	• SARS corona virus targets epithelial lining of salivary glands and this may alter the volume and composition of saliva and, subsequently affect taste sense.
18.	Lozada-Nur et al[134]	• Dysgeusia may result from interaction between SARS-CoV-2 and ACE2 receptors in salivary gland, which may result in gland damage gland and subsequent salivary flow impairment • Gustatory and olfactory functions are closely related, an impairment of the olfactory system can affect the taste sensation. • Virus may cause dysgeusia either by direct damage of any of the cranial nerves responsible for gustation or through direct damage of taste buds expressing ACE2 receptors. • Binding of virus and ACE2 receptors in oral mucosa may trigger an inflammatory response could alter taste sensation. • Tissue hypoxia in patients with COVID-19 may result in oral tissue injury leading to disturbance in taste • hypozincemia because of infection by SARS-CoV-2 may affect cellular zinc homeostasis of oral gustatory cells and subsequent taste disturbance.
19.	Khan et al[131]	• Binding of SARS-CoV-2 RNA with the Toll-like receptors (TLRs), abundantly expressed on taste bud cells, may lead to inflammation in taste bud cells and consequently change in the taste sense. • Overproduction of IL-6 and IFN-γ inflammatory markers in gustatory epithelium may impact taste perception. • Invasion of different brain areas might be involved in the loss of taste and smell
20.	DosSantos et al[96]	• Olfactory and taste disorders such as anosmia, hyposmia, ageusia, and dysgeusia might be related to the involvement of cranial nerves. • Dysgeusia can be secondary to brainstem involvement. • SARS-CoV-2 virus can affect CNS through invasion of PNS causing los of smell and taste senses. • Expression of ACE2 and TMPRSS2 in oral and nasal epithelia cells may result in virus invasion and lead to olfactory and gustatory alterations.
21.	Azim et al[92]	• High expression of ACE2 receptors on the oral mucosa and tongue, raising the possibility of virus invasion and may lead to gustatory dysfunction.
22.	Lechien et al[135]	• Spread of SARS-CoV-2 virus into the nerve ending of the taste buds may cause gustatory dysfunction. • Inflammation following the binding between the ACE2 receptors in the tongue and the virus may lead to change in the saliva composition, normal taste, and affect the continuous renewal of taste buds. • SARS-CoV-2 is a neurotropism, which may cause olfactory and gustatory dysfunction. • Inflammatory and neurological damages of olfactory and oral epitheliums secondary to SARS-CoV-2 infection may alter both smell and taste senses
23.	Freni et al[95]	• Invasion of SARS-CoV-2 virus into CNS is probably associated with alteration in taste and smell sensitivities, dry mouth, and hearing discomfort.

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Table II *(Continued)*. Suggested mechanisms of dysgeusia discussed in the included studies.

No.	Reference	Mechanism discussed
24.	Mehraeen et al89	• Invasion of SARS-CoV-2 into CNS via olfactory nerves or peripheral trigeminal may harm the trigeminal and olfactory nerves and lead to dysosmia and dysgeusia symptoms in COVID-19 patients. • COVID-19 disease may decrease the sensitivity of sensory neurons reflexes and causes dysosmia and dysgeusia. • Consumption of chemicals and disinfectants may cause alternation in smell and taste sensitivities. • Isolation of SARS-CoV-2 from cerebrospinal fluid may indicate the neuroinvasiveness of the virus.
25.	Kang et al[121]	• Microinvasion of SARS-CoV-2 via ACE2 receptor, which is expressed on the olfactory bulb and the epithelial cell of oral mucosa, may be associated with olfactory and gustatory dysfunctions of COVID-19 patients.
26.	Qiu et al[122]	• High expression of ACE2 receptors on the oral mucosa and tongue, raising the possibility of virus invasion and may lead to gustatory dysfunction.
27.	Mariz et al[127]	• Accumulation of degraded Angiotensin II by ACE2 (expressed in the oral cavity) in taste buds during COVID-19 infection may be associated with dysgeusia.
28.	Maurier et al[105]	• Dysgeusia and anosmia were thought to result from direct viral attack to olfactory nerve cells. However, evidence showed that SARS-CoV-2 may play a role in COVID-19 symptoms development.
29.	Sayin et al[110]	• Expression of ACE2 and TMPRSS2 in non-neural cells may result in an inflammatory response that damage of the olfactory epithelium and cause smell impairment
30.	Lee et al[111]	• Interaction between ACE2 receptor and SARS-CoV-2 in the olfactory epithelium may cause apoptosis of mature sensory neurons and disordering smell sensation. • Dysgeusia/ageusia can be secondary to loss of smell sensitivity in COVID-19 patients.
31.	Román et al[108]	• ACE2 receptor is responsible for the pathogenesis of SARS-CoV-2 neurotropism and its effect on smell and taste.
32.	Boscolo-Rizzo et al[120]	• Binding of SARS-CoV-2 to ACE2 receptors expressed in different cells may be related to loss of smell and taste.
33.	Liguori et al[98]	• CNS invasion by SARS-CoV-2 through hematogenous or non-hematogenous routes may be related to neurological symptoms such as hyposmia and dysgeusia • Interaction between SARS-CoV-2 and ACE2 receptors expressed in multiple tissues in CNS may be associated with neurological symptoms such as hyposmia and dysgeusia • SARS-CoV-2 infection triggered inflammatory response that may associate with neurological symptoms such as hyposmia and dysgeusia.
34.	Paderno et al[124]	• Interaction between SARS-CoV-2 and ACE2 receptors expressed in the epithelial cells of the tongue may be related to post-viral gustatory dysfunction.
35.	Pellegrino et al101	• Taste loss may be secondary to olfactory impairment. • Drugs prescribed for COVID-19 disease may impact the taste function. • Virus may directly affect the taste sensation.
36.	Aziz et al126	• Interaction between SARS-CoV-2 and ACE2 receptors expressed on tongue and oral cavity may cause ageusia/dysgeusia
37.	Tong et al[107]	• Interaction between SARS-CoV-2 and ACE2 receptors in both nasal and olfactory epithelial cells may be associated with gustatory and olfactory disturbance.
38.	Zanin et al[99]	• Invasion of SARS-CoV-2 into brain through olfactory tract and then penetration of the virus into the neural via ACE receptors expressed on endothelial cells may lead to anosmia and dysgeusia.

Continued

Table II *(Continued)*. Suggested mechanisms of dysgeusia discussed in the included studies.

No.	Reference	Mechanism discussed
39.	Keyhan et al[109]	• Dysosmia and dysgeusia can be attributed to olfactory nerve and trigeminal nerve damage in COVI-19 patients. • Dysosmia and dysgeusia might be caused by excessive exposure to chemicals and disinfectants commonly used during epidemic.
40.	Lechien et al[5]	• Dysgeusia results from olfactory and gustatory dysfunctions caused by SARS-CoV-2 invasion of the olfactory bulb and, therefore, the central nervous system.
41.	Finsterer et al[103]	• Mechanism of gustatory dysfunction could be related to CNS or peripheral nerves involvement • Gustatory and olfactory dysfunction could be inter-related • Role of drugs and systemic diseases in dysgeusia
42.	Parma et al[113]	• In relation to dysgeusia in COVID-19 the gustatory and olfactory dysfunction are not related to each other
43.	Lechien et al[114]	• The relation between olfactory and gustatory dysfunction in COVID-19 • Gustatory dysfunction is not dependent on olfactory one • The recovery of olfactory function is not linked to the recovery of taste
44. 45.	Altin et al[117] Zayet et al[118]	• High expression of ACE2 in the tongue may be responsible for gustatory loss in COVID-19 infection. • High expression of ACE2 receptors in the oral mucosa may play a role in the observation of frequent dysgeusia during COVID-19 infection.
46.	Biadsee et al[90]	• Dysgeusia may be secondary to xerostomia • Neurological involvement due to SARS-CoV-2 infection may lead to dysgeusia and xerostomia.
47.	Abalo-Lojo et al[112]	• The virus damages the gustatory and olfactory cells by binding to the ACE2 receptor.

suggested. Other mechanisms included an imbalance in angiotensin II, triggering of pro-inflammatory cytokines, viral associated-changes in saliva and salivary glands, and sialic acid. The pathogenesis of dysgeusia was also linked with systemic diseases, medications, zinc, chemicals, and disinfectants. These mechanisms are described and discussed in detail.

Discussion

Neurotropism

Neurotropism is one of the commonly noted features of COVID-19, with suggested neuro-invasive properties of the olfactory or gustatory nerves[6,88-90]. This has also been proven in SARS-CoV-2, MERS-CoV, HCoV-229E, HCoV-OC43, and porcine hemagglutinating encephalomyelitis coronavirus (PHE)[91]. The neurological manifestations of COVID-19 are generally classified into three sections: manifestations of first skeletal muscular injury; CNS manifestations such as acute cerebrovascular disease, headache, or dizziness; and peripheral nervous system manifestations such as impaired taste, smell, or vision[92]. Impairment of smell and taste, in the form of hyposmia, dysgeusia, or changes in chemesthesis, which is the ability to sense chemical irritants, have been considered as common neurological symptoms of the coronavirus disease caused by SARS-CoV-2[5,89]. Several hypotheses[6,88,93-98] have been considered in relation to the neural mechanism of the sensory taste/smell disturbance in SARS-CoV-2. One of them claimed that the olfactory/gustatory sensory involvement is central in origin. This hypothesis suggested that SARS-CoV-2 can affect the blood-brain barrier, attacking the nervous system through the cerebral microcirculation and binding to ACE2 receptors in the nervous system, which are highly expressed in the brain endothelial cells, glial cells, and neurons[91,99,100]. Additionally, the virus RNA can be detected in the cerebrospinal fluid (CSF) of SARS-CoV-2 infected patients[98], or it can pass through the olfactory epithelium directly through the cribriform plate to reach the CNS[101]. Moreover, some COVID-19 positive patients have experienced CNS manifestations such as coma, seizures, and neck stiffness[102]. Others have presented with meningitis and encephalitis[103].

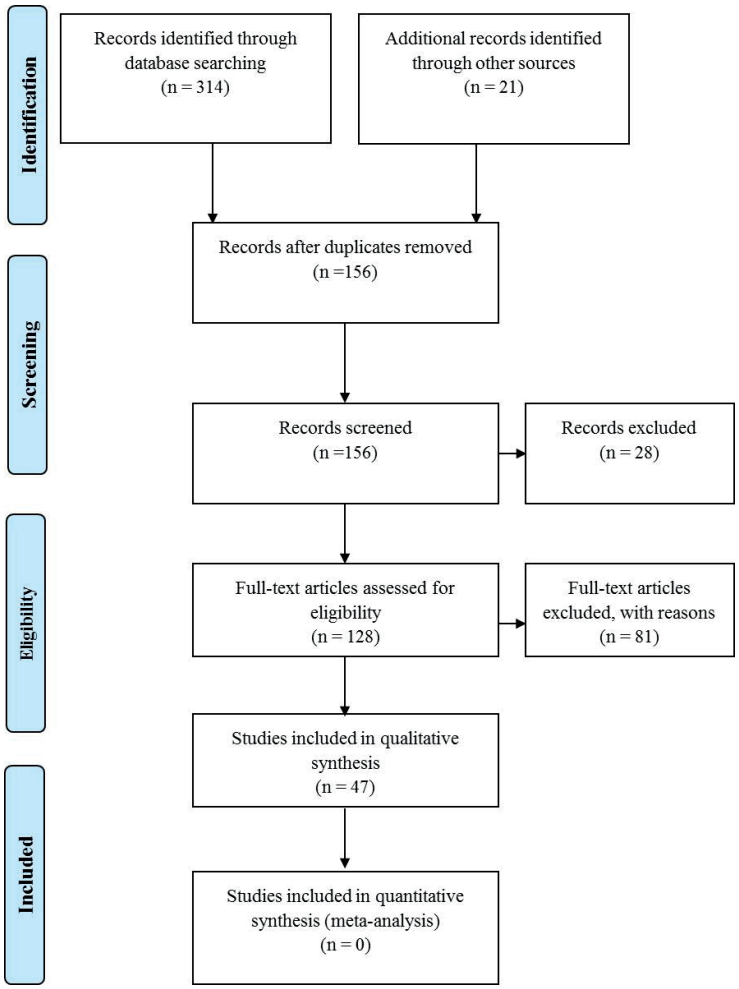

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

This neural invasion of the gustatory and olfactory nerves could be supported by the lack of recovery of both taste and smell after weeks or months in some COVID-19 patients, which may be due to neurological damage caused by extensive inflammation in these regions[5]. However, in disagreement of this assumption, the taste/smell abnormalities are usually transient, with a maximal duration of 21 days. Additionally, SARS-CoV2-associated CNS involvement is rare compared with smell/taste abnormalities, which are frequent. Thus, the cerebral origin of sensory disturbances is thought to be unlikely[103]. Another hypothesis suggested that gustatory dysfunction mainly originates from peripheral nerve involvement. In support of this claim is the peripheral nerve involvement in other viral infections, such as VZV in Ramsey Hunt syndrome[104], and the selective involvement of the specific cranial nerves I, VII, IX, and X in SARS-Cov2 in some patients, while others experience selective involvement of visual impairment (cranial nerve II), double vision (cranial nerve III,IV,VI), hypoacusis (cranial nerve VIII), dysphagia, or dysarthria (cranial nerves IX, X)[103].

Other hypotheses[89,96,105-107] suggested olfactory nerve neurotropism plays a role in COVID-19 associated dysgeusia, since smell disturbance could affect the taste sensation. It is well known that taste, smell, and chemesthesis are collaborators in stimulating the perception of flavor in the oral cavity. A major spectrum of volatile food odors is recognized retro-nasally by the olfactory sensory neurons (OSNs), while the taste collection is restricted to non-volatile salt, sweet, sour, bitter, and umami stimuli that directly initiate taste perception in the taste buds on the tongue. However, the spicy taste of chili peppers and the coolness of mint are neither odors nor tastes, but rather stim-

ulate the sensory neurons of chemesthesis, which innervate the oral epithelium[6]. It can be concluded that the neural function of the olfactory nerve is altered both directly and indirectly. The direct route occurs due to central involvement as a result of vascular infection, by direct invasion of the SARS-CoV-2 virus into the olfactory and trigeminal nerve cells via ACE2 receptors[108,109], or by a demyelinating reaction in olfactory neurons[88]. The indirect route occurs by invasion of the olfactory epithelium as peripheral supporting cells of the olfactory nerve, where ACE2 and TMPRSS-2 are highly expressed[100,110-112]. In contrast, it has been suggested that taste and smell may be distressed separately in COVID-19 patients. In these studies, Parma et al[113] stated that 60% of the involved participants experienced taste loss of one certain taste quality, such as the salty taste, while distinguishing changes in flavor, while Lechien et al[114] reported that gustatory dysfunction is not dependent on olfactory dysfunction, and the recovery of olfactory function was not significantly linked to the recovery of taste.

Cytotoxicity and Direct Injury of Taste Buds

It is well known that our sense of taste arises from the sensory information generated after compounds in the oral cavity activate receptor cells situated on the taste buds; this produces the perception of sweet, bitter, salty, sour, or umami stimuli[115]. Many researchers have suggested that direct inflammation of the oral cavity mucosa and damage to the taste buds may be the underlying mechanism which causes dysgeusia associated with COVID-19[106,116-118]. Angiotensin converting enzyme2 (ACE2) receptors are attached to the cell membranes of many tissues and play a crucial role in the renin-angiotensin-aldosterone system (RAS) pathway, which controls many biological processes such as blood pressure, wound healing, and inflammation[115,119,120]. It has been claimed that the ACE2 receptor is responsible for the cellular entry of SARS-CoV2, by binding of the spike glycoprotein on the viral envelope of the virus to the ACE2 receptor on the target host cells[121]. After binding of the virus to the ACE2 receptor, the viral entry to the host cell is facilitated by the trans-membrane protease serine 2 (TMPRSS2) of the host cells, which cleaves the viral spike protein, allowing fusion between the viral envelope and endosomal compartment of the host cell[6,96,115,121]. The binding between COVID-19 and ACE2 leads to downregulation of ACE2, which in turn leads to an increase in inflammatory angiotensin II via unopposed ACE and a decrease in anti-inflammatory angiotensin (1-7)[9]. This imbalance in inflammation may include the nasal passages, tongue, and oral cavity, leading to increased inflammation and damage to the taste buds[88,92]. Exploration of ACE2 expression in the oral cavity found that the ACE2 receptor is expressed in the oral cavity and is highly enriched in epithelial cells. Additionally, among different oral sites, ACE2 expression is higher in the tongue than in the buccal and gingival tissues[122-124]. In a recent immunohistochemical study[115] to investigate the expression of ACE2 and TMPRSS2 proteins in the aerodigestive tract, including the tongue, hard palate with partial nasal tissue, larynx with hypopharynx, trachea, esophagus, and the lungs of rats, both ACE2 and TMPRSS2 proteins were co-expressed in the taste buds, and they attributed this co-expression to be the cause of the high incidence of ageusia or dysgeusia in patients with SARS-CoV-2 infection. In another recent case study from Brazil, including eight cases proven to be COVID-19 positive by polymerase light chain reaction (PCR), all the cases showed oral manifestations ranging from aphthous ulcers up to widespread necrotic ulcers during the active period of the disease, and dysgeusia was present in six out of the eight patients included in the study. Moreover, the oral lesions were more diffuse and severe with more severe COVID 19 infection. The authors suggested that the interaction between the ACE2 receptor and SARS-COV-2 might disrupt the oral keratinocytes, leading to dysgeusia[125]. The direct interaction between SARS-CoV-2 and tastebud receptors could lead to cytotoxicity of these gustatory receptors, which in turn causes taste disturbance[119,126].

Role of the Renin-Angiotensin-System (RAS) and Angiotensin II Imbalance

Dysgeusia is considered an adverse event of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers[127]. It has already been proven[128] that ACE2 is highly expressed in the oral cavity, in the mucosa and mainly on the taste buds. It has also been found that angiotensin II is a pro-inflammatory, pro-fibrosis, and active vasoconstrictor. During COVID-19 infection its level is elevated due to the downregulation of ACE2 receptors; on the other hand, the angiotensin-(1-7) level, which has an anti-inflammatory and vasodilatory action, will be reduced. Angiotensin II accumulation is claimed to play a role in SARS-CoV-2 associated dysgeusia through two

different mechanisms; evoking of an inflammatory response which in turn causes cytotoxicity of the taste buds[129], and secondly through an imbalance in the RAS system, which is involved in the normal taste sensation pathway[119].

Pro-Inflammatory Cytokines and Taste Loss

Due to the down-expression of ACE2 receptors and subsequent inflammatory reaction, various proinflammatory cytokines are released. As the serums of confirmed COVID-19 patients have high level of TNF-a, IFN-g, and IL-6, it is rational to assume that these pro-inflammatory cytokines can result in dysgeusia[119]. Prior studies have indicated that pro-inflammatory cytokines could directly affect the activity of taste buds, contributing to taste dysfunction[130]. It has been found that serum measurements of interleukin (IL-6) and lactose dehydrogenases (LDH) are strongly associated with taste loss. Moreover, major associations have been also identified between a higher level of IL-6 and the level of olfactory and gustatory dysfunction. Patients with both conditions had higher IL-6 levels[131]. Taste bud cells have an average life span of 10 days and they undergo continuous renewal from the oral epithelium stem cells. However, in COVID-19, the stem cell proliferation and active process of taste bud renewal could be inhibited by the high levels of proinflammatory cytokines IL-6 and TNF-α, that can impede stem cell proliferation and may also reduce the lifespan of mature taste bud cells by activation of the apoptotic pathway[119]. IL6 can also act centrally by targeting the thermo-regulatory center in the hypothalamus during COVID-19 infections. This can affect the nearby thalamus, where both the gustatory and the olfactory pathways converge. The temporary rise in IL-6 induced by microglial cells and astrocytes in the central nervous system can affect the gustatory and olfactory nerves, causing dysgeusia[100]. Additionally, Toll-like receptors (TLRs), which are expressed on taste buds, are activated by viral pathogens and can trigger type I and II interferon (IFN) pathways. This mechanism may also cause taste disorder by interfering with taste bud regeneration and taste transduction with dysgeusia in COVID-19[97,131].

Salivary Glands and Taste Change

Salivary glands play an important role in taste sensation as they produce saliva, which is the main fluid part of the external media surrounding the taste receptor cells. It could affect taste sensitivity in different ways, such as through dissolving of the taste substances and subsequent diffusion to taste receptors, chemical interaction of taste substances, stimulation of taste receptors, and protection of taste receptors[132]. A high expression of ACE 2 receptors has been reported in the salivary gland epithelium in humans. Moreover, it has been reported that the epithelial cells of the salivary glands, which express ACE2, are an early target of SARS-CoV-2 in rhesus macaques. Hence, it is possible that human salivary glands may be affected early by SARS-CoV-2 infection[94,133]. The binding of SARS-CoV 2 to the ACE2 receptors present on the salivary gland epithelium will evoke an inflammatory reaction, which in turn will cause damage to the glands and their ducts. The damage of the salivary glands by the inflammatory process will lead to impairment in their function, with subsequent disturbance in salivary flow and abnormalities in the saliva, both in quantity and quality. This may lead to dysgeusia in patients with COVID-19[134,135]. These findings are supported by Xu et al[128], who compared the ACE2 receptor expression in different tissues. A higher expression of ACE2 was found in the epithelial cells of the salivary glands compared to the lung cells, suggesting that salivary glands may be a possible target for COVID-19. Owing to the destruction of the salivary glands and their ducts, a comparatively high proportion of COVID-19 patients have been found to have dry mouth (xerostomia). These alterations in salivary production are responsible for taste alterations and oral symptoms[136]. The salivary glands, affected early by SARS-CoV-2, may cause changes in consistency and quantity of salivary secretion, thereby resulting in dysgeusia. This could become an early indicator in asymptomatic COVID-19 patients[134,137].

New research has highlighted hyposalivation in patients to be a greater risk factor for being exposed to COVID-19, due to the absence of certain antiviral proteins in the saliva[138]. The change in saliva also includes salivary flow, and the salivary composition may be responsible for SARS-CoV-2 associated taste changes[137,139].

Sialic Acid and Dysgeusia

In infection with SARS-CoV-2, sialic acid binding the S1 spike protein is necessary for the virus to involve host cells[97]. Sialic acid is an integral component of salivary mucin and protects against premature enzymatic degradation of the glycoproteins that transmit gustatory molecules in the

pores of the taste buds. Reduced sialic acid is associated with an increase of the taste threshold in the saliva[97,100]. SARS-CoV-2 might thus occupy the sites that bind sialic acid in the taste buds, and accelerate gustatory particle degradation[97]. Interruption of taste transduction triggered by changes in salivary constituents is responsible for oral sensory symptoms and loss of taste sensation[140]. The deleterious influence on sensory neurons or other elements of the peripheral gustatory system should also be considered, due to the direct impact of SARS-CoV-2 infection. Thus, salivary gland infection and resultant salivary flow and composition alterations may be among the potential causes of SARS-CoV-2 associated taste changes[139].

Systemic Diseases and Drugs

SARS-CoV-2 infection is especially serious in people aged over 50 and with related comorbidities, including asthma, cardiovascular disorders, nervous system diseases, and psychological disorders, such as depression and anxiety[93]. Salivary flow is believed to decline with increasing age. In addition, hyposalivation is also associated with diabetes and medications for chronic systemic diseases. Folic acid deficiency anemia is associated with poor oxygen transport, which may develop and has been shown to result in dysgeusia in SARS-CoV-2. Moreover, the tissue hypoxia in patients with COVID-19 who are clinically conscious and in a functional state may result in tissue injury that leads to the reported disturbance in taste[134]. Insufficient oral hygiene or microbial imbalances and therapeutic drugs in the management of COVID-19, including antibiotics or antipyretics, could also impair smelling/tasting[101,134].

Role of Zinc

Another probable mechanism in dysgeusia may be related to zinc metabolism, which is considered to play a role in taste perception[6]. Since zinc could have a role in antiviral immune responses, utilizing zinc in the SARS CoV-2 inflammatory process could lead to hypozincemia or localized cellular zinc homeostasis, which when it occurs in gustatory cells, may result in taste impairment[134]. Presently, there is great interest in using zinc supplements for prevention during the current pandemic.

Excessive Exposure to Chemicals and Disinfectants

Due to the unprotected anatomical location of the olfactory neurons and taste buds they are often in intimate contact with environmental agents, hence they are susceptible to damage from acute and chronic toxic exposures[109]. There is not yet any definite medication or vaccine available to treat SARS-CoV-2 infection, and only protective measures and a healthy lifestyle are recommended for fighting and staying safe from SARS-CoV-2 by the World Health Organization (WHO). Therefore, it can be suggested that excessive use of chemicals and disinfectants during the SARS-CoV-2 outbreak may have played an important role in the mechanism of dysgeusia associated with COVID-19 infection[89,109].

Conclusions

Dysgeusia is considered a temporary and early manifestation of COVID-19. This review identified and collected multiple suggested mechanisms of dysgeusia in COVID-19 patients. (A) Peripheral neurotropism in the gustatory or olfactory nerves, which is more likely than central nervous system invasion. (B) Direct taste bud cytotoxicity, as they are rich in ACE2 receptors that support viral fusion and subsequent inflammation. (C) Imbalance in angiotensin II might occur in COVID-19, which has an impact on taste sensation. (D) Interleukin-6 may be involved in dysgeusia since it could act on the thermo-regulatory center, which affects the nearby thalamus and eventually both the gustatory and olfactory nerve pathways. (E) Salivary glands with high ACE2 expression could be a target for SARS-CoV-2, causing xerostomia with subsequent dysgeusia. (F) Defective sialic acid function could accelerate gustatory particles degradation. (G) Other factors such as hypozincemia, excessive exposure to chemicals and disinfectants, systemic diseases, and certain drugs taken by COVID-19 patients could play a role in the etiology of dysgeusia.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

MM, AB, and HA designed the review and preformed the preliminary databases searches. MM, DK, AK, HA, and AB analyzed the collected data and critically appraised it. MM, DK, and AK wrote the draft of the manuscript. HA, AB, and MM reviewed and edited the draft and prepared the tables. All authors had full access to all the study data. All authors reviewed, wrote, and approved the final version.

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