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Potential pharmacologic treatments for COVID-19 smell and taste loss: A comprehensive review

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ABSTRACT

The acute loss of taste and smell following COVID-19 are hallmark symptoms that affect 20–85% of patients. However, the pathophysiology and potential treatments of COVID-19 smell and taste loss are not fully understood. We searched the literature to review the potential pathologic pathways and treatment options for COVID-19 smell and taste loss. The interaction of novel coronavirus with ACE-2 receptors expressed on sustentacular cells and taste buds results in direct damage to the olfactory and gustatory systems. Also, the invasion of the virus to the olfactory neurons and consequent local inflammation are other proposed mechanisms. Therefore, COVID-19 patients with smell or taste loss may benefit from neuroprotective, anti-inflammatory, or depolarizing agents. Based on the current evidence, phosphodiesterase inhibitors, insulin, and corticosteroids can be promising for the management of COVID-19 smell and taste loss. This review provided crucial information for treating COVID-19-related smell and/or taste loss, urging to perform large clinical trials to find optimum treatment options.

1. Introduction

Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), more than 210 million cases and 4 million deaths have been reported worldwide. Despite the considerable progress in treatment tools of the disease, effective therapies for managing the long-lasting complications of the novel coronavirus disease (COVID-19) are still lacking. It is now clear that COVID-19 is not just a respiratory disease and affects other parts of the body. The common manifestations of COVID-19 are fever, cough, and fatigue, which are nonspecific and make the diagnosis challenging (Huang et al., 2020). The acute loss of taste and smell are key diagnostic criteria supposed to be used as screening tools based on the National Institute on Deafness and Other Communication Disorders (NIDCD), and the Global Consortium for Chemosensory Research (GCCR) reports (Gerkin et al., 2021; Lovato et al., 2020; National Institute on Deafness and Other Communication Disorders, 2021; Parma et al., 2020).

Anosmia and ageusia are categorized as neurological complications of the SARS-CoV-2 infection. Previous studies revealed that approximately 20–85% of COVID-19 patients experienced olfactory and gustatory dysfunctions (Bilinska and Butowt, 2020; Mao et al., 2020). Although the clear causes of these complications are not fully understood, angiotensin-converting enzyme 2 (ACE2) expression and local inflammation have been considered key mechanisms (Giacomelli et al., 2020; Lechien et al., 2020; Spinato et al., 2020). Other suggested mechanisms were infecting olfactory non-neuronal cells and sensory neurons (Brann et al., 2020; de Melo et al., 2021).

Given to paramount findings of COVID-19 smell and taste loss and lack of effective treatments, we aimed to review the potential treatments of COVID-19 smell and taste loss based on clinical pharmacology principles.

2. Pathophysiology of anosmia

Numerous probable mechanisms have been suggested for the COVID-19-related anosmia, such as nasal obstruction and rhinorrhea, olfactory cleft syndrome, local cytokine storm, damage to the olfactory centers in the brain, direct damage of olfactory receptor neurons (ORNs), also called olfactory sensory neurons (OSNs), or sustentacular cells (SUSs). However, most of them have been ruled out subsequently.

2.1. Damages to SUS and ORNs

In the normal olfactory system, odorant particles bind to the

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olfactory receptors; the ORN sends the smell sensation signal through the cribriform plate (bone) to the olfactory bulb, where they synapse to the dendrites of mitral and tufted cells. The normal function of ORNs depends on sustentacular cells (SUSs) of the olfactory epithelium (OE). In this regard, SUSs protect the ORNs through metabolizing volatile chemicals via expressing the cytochrome P450 family enzymes. Besides, SUSs could endocytose the complexes of odorant-binding proteins−odorant after initiation of signal transduction at the neurons' cilia to let the next series of odorants bind to the receptors. Lastly, SUSs supply ORNs cilia with additional glucose, where olfactory receptors are found (Heydel et al., 2013; Villar et al., 2017).

It is well-known that SARS-CoV-2 infectivity depends on the binding of spike (S) proteins to the host cells receptors of ACE2 and transmembrane protease serine 2 (TMPRSS2). After interaction with host cells receptors, the S proteins of the SARS-CoV-2 undergo conformational changes that lead to viral cell entry.

It has been shown that SUSs express ACE2 and TMPRSS2 that could result in the SARS-CoV-2 entry and consequential damages to the SUSs. Whereas ORNs do not express the entry proteins for the virus. Therefore, the direct damage to the SUSs could result in olfactory dysfunction without transfer to ORNs due to the functional and anatomical link between SUSs and ORNs. Moreover, Brann et al. showed that SARS-CoV-2 infection of non-neuronal cell types leads to olfactory dysfunction in COVID-19 patients (Brann et al., 2020; Fodoulian et al., 2020).

Recently, in a study by de Melo et al., olfactory mucosa sampling revealed that SARS-CoV-2 invades both ORNs and SUSs in human and Syrian hamster models with COVID-19-related anosmia and ageusia. By investigating cell death in the olfactory neuroepithelium, this study considered the apoptosis of mature ORNs as the most relevant cause of anosmia in COVID-19 patients. Notably, they found that SARS-CoV-2 presents in the ORNs of COVID-19 patients with long-lasting anosmia even after six months from diagnosis. Although this study supported the ORNs damage and possible neuroinvasion as anosmia causes, further studies should precisely determine the olfactory bulb dysfunction using larger sample sizes and control groups (de Melo et al., 2021).

Bryche et al. have evaluated the effects of SARS-CoV-2 infection on the olfactory system in golden Syrian hamsters' model. They observed considerable damage to the OE and loss of smell after two days of nasal instillation of the virus. However, they showed that, unlike the SUSs, the virus did not affect olfactory neurons and olfactory bulbs. They suggested that infiltrated immune cells in the OE may lead the OE to be desquamated and damaged. The restoration of the OE was achieved within 14 days after infection. Thus, this in-vivo study supported that sudden anosmia results from infected SUSs, leading to extended and quick damage to the OE and lamina propria due to immune cells (Bryche et al., 2020).

Meinhardt et al. investigated the brain samples of 32 patients who died of COVID-19. This study suggested that the virus affects the ORNs. However, by single immunocytochemical imaging, especially in old samples that were taken lately after death, the differentiation between neuronal and non-neuronal cells cannot be performed obviously. Moreover, the ribonucleic acid (RNA) of the virus was detected in only 3 of the olfactory bulb samples that did not strongly support the viral diffusion to the brain by the olfactory nerve. Also, lacking data about which patients experienced anosmia limits the interpretation of the results (Meinhardt et al., 2021).

2.2. Inflammation

Along with the damage to the SUSs, a rapid immune response in microvillar cells (MVCs) and a subset of ORNs leads to activation and infiltration of macrophages and lymphocytes into the OE, the release of pro-inflammatory cytokines, and occurrence of cytokine storm, which all may explain the sudden anosmia in patients with COVID-19. Notably, it seems that progenitor/stem cell infection is responsible for COVID-19 induced long-term dysosmia. It has been shown that a local excessive immune response and cytokine storm could lead to olfactory dysfunction even in patients with a milder form of the disease. Of note, to date, no adequate data support the rapid harm to the olfactory cortical areas in the brain; therefore, it is unlikely that excessive systemic immune response and inflammation in the brain have an essential role in the anosmia development (Baxter et al., 2021). In a study by Torabi et al., the direct role of inflammatory cytokines in acute olfactory dysfunction has been highlighted. In this study, the levels of tumor necrosis factor-alpha (TNF-α) in the OE were significantly higher in COVID-19 patients compared to the control group, whereas interleukin-1-beta (IL-1β) levels were similar between groups.

Furthermore, in other studies, SARS-CoV-2-induced infiltration of immune cells, including macrophages and granulocytes, into the OE has been reported (Bryche et al., 2020; Meinhardt et al., 2021; Torabi et al., 2020). Also, de Melo et al. considered local inflammation a key factor in COVID-19 patients with long-lasting olfactory dysfunction. They showed a high IL-6 expression and myeloid cells in the olfactory mucosa of these patients (de Melo et al., 2021).

2.3. Other probable mechanisms

Nasal obstruction and rhinorrhea, which could block nasal air-flow, are suggested to be much less common and have been ruled out as a cause of SARS-CoV-2 induced anosmia (Salmon Ceron et al., 2020). The interaction of SARS-CoV-2 with sialic acid receptors expressed in nasal mucosa can be another entry pathway other than ACE2 receptors, which might have a role in the complications of the virus, such as anosmia (Kuchipudi et al., 2021; Milanetti et al., 2020).

The virus infiltration to the brain is another suggested mechanism in which the OSN is considered a direct route to the brain through anterograde axonal transport (Fenrich et al., 2020). Also, the reports of meningitis and encephalitis in some COVID-19 patients could support the idea that SARS-CoV-2 might invade the central nervous system (CNS). Magnetic resonance imaging could provide information about the olfactory bulb and possible CNS invasion of the virus. The olfactory bulb volume was normal in the first report of olfactory bulb magnetic resonance imaging in a patient with COVID-19-related anosmia (Galougahi et al., 2020). However, further studies showed changes in the volume and shape of the olfactory bulb in COVID-19 patients with anosmia (Altundag et al., 2020; Kandemirli et al., 2021; Politi et al., 2020).

3. Ageusia pathophysiology

Due to the close connection between olfactory and gustatory functions, it might be possible that the concomitant presence of olfactory dysfunction adversely influences the ability of taste perception in COVID-19 patients. However, different pathways have also been suggested, including direct damage to taste buds and salivary glands, binding to sialic acid receptors, and inflammation.

It has been shown that the taste buds and salivary glands have a high number of ACE2 receptors (Doyle et al., 2021; Song et al., 2020). Furthermore, the essential role of the renin-angiotensin-aldosterone system (RAAS) in the perception of flavors has been confirmed previously. Similarly, the cases of gustatory dysfunction have been reported in patients receiving angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers in a dose-dependent manner. It has been suggested that ACE2 inhibitors inactivate the G protein-coupled proteins and sodium-ion channels located in the taste receptors. Similarly, it has been suggested that SARS-CoV-2-induced ACE2 down-regulation and the consequent RAAS impairment are associated with gustatory dysfunction in patients with COVID-19 (Luchiari et al., 2021). Also, early detection of SARS-CoV RNA in saliva before lung injury confirms that salivary glands might be the initial target for the virus.

Previously, it has been shown that the Middle East respiratory syndrome coronavirus (MERS-CoV) binds to the sialic acid receptors, the

pathway that has also recently been indicated for SARS-CoV-2 (Milanetti et al., 2020; Park et al., 2019). Sialic acid is a substantial factor of the salivary mucin and has protective effects on glycoproteins that transport taste molecules inside taste pores from early enzymatic metabolism (Witt and Miller, 1992). Thus, SARS-CoV-2 could block the binding sites of sialic acid on the taste buds, increasing the destruction rate of the taste molecules and cause ageusia.

As the entranceway of SARS-CoV-2 to the host cells, ACE2 receptors are also present in the oral mucosa. By binding to these receptors, inflammation and consequent cytokine signaling pathways in taste buds might affect the sense of taste. As in acute respiratory distress syndrome, this pathway could be induced through the interaction between Toll-like receptors and the virus. Also, inflammatory cytokines such as interferons can cause apoptosis and alter the turnover of taste buds (Wang et al., 2009; Xu et al., 2020).

4. Potential therapeutic agents against olfactory and gustatory dysfunctions

We categorized the literature according to the American College of Cardiology/American Heart Association Clinical Practice Guidelines Recommendation Classification System (Halperin et al., 2016). This system evaluates medications based on the strength of recommendation (strong = I, IIa = moderate, IIb = weak, and III = moderately no benefit or strongly harmful) and quality of evidence (A = high quality randomized clinical trials, B-R = moderate-quality randomized clinical trial, B-NR = moderate-quality non-randomized clinical trial, C-LD = limited data, and C-EO = expert opinion). The summary of the promising agents against COVID-19-related smell and/or taste loss is shown in Table 1 and Fig. 1.

4.1. Pentoxifylline (IIb/B-NR)

Signal transduction begins while an odorant binds to the receptors of an ORN. The odor-receptor complex results in the intracellular activation of type 3 adenylate cyclase by a G protein, leading to an elevated intracellular cyclic adenosine monophosphate (cAMP). An increased level of intracellular cAMP leads to calcium influx and depolarization of the neuron, consequently. Of note, it has been confirmed that in patients suffering from anosmia and ageusia, the salivary and nasal mucus growth factors, including cAMP and cyclic guanosine monophosphate (cGMP), were lower than healthy individuals (Henkin and Velicu, 2008, 2011). In the cilia of OSNs, cAMP is metabolized by phosphodiesterase 1C2 (Henkin et al., 2007; Nakamura, 2000). Pentoxifylline is a methylxanthine derivative that acts as a phosphodiesterase inhibitor. Thus, it could be reasonable to consider that pentoxifylline-induced inhibition of phosphodiesterase 1C2 can increase intracellular cAMP levels. Also, pentoxifylline reduces TNF-α and other inflammatory cytokines such as IL-1, leading to immunomodulatory effects (Hassan et al., 2014). The effect of pentoxifylline on olfactory function has been evaluated in Gudziol and Hummel's (2009)prospective post-marketing surveillance. A total of 19 patients were included in the study. Of them, 15 patients were assigned to receive 200 mg of pentoxifylline intravenously, two times per day, and 4 patients received 200 mg of pentoxifylline orally 3 times per day. The mean (SD) of the age of patients was 51 (19.9), and 52.6% of them were female. Data analysis showed a significant reduction in odor threshold after treatment with pentoxifylline ($P = 0.01$). This reduction was markedly more in younger patients than in older patients ($P = 0.001$). However, the nasal airflow did not significantly change by pentoxifylline ($P = 0.84$). Of note, although the oral pentoxifylline has smaller bioavailability, of 4 patients who received the oral forms, half of them showed a clinically significant reduction in odor threshold (Gudziol and Hummel, 2009). The prospective design and small sample size of this study increase the risk of bias for accurate

Table 1
Categorization of the proposed medications for COVID-19 smell and taste loss.

Medication	Mechanism of action	Outcomes (study design)	Class of recommendation/ Level of evidence	References
Pentoxifylline	PDE inhibitor	Promising results in smell loss (post-marketing surveillance study), No beneficial effects in patients with post-traumatic anosmia (case series)	IIb/B-NR	(Gudziol and Hummel, 2009; Whitcroft et al., 2020)
Caffeine	PDE inhibitor, Adenosine receptors antagonist	Direct correlation between coffee consumption and smell scores in patients with Parkinson's disease (retrospective cohort), 65 mg of caffeine showed no beneficial effects in patients with hyposmia related with upper respiratory tract infection or sinus node dysfunction (RCT)	IIb/B-R	(Meusel et al., 2016; Siderowf et al., 2007)
Theophylline	PDE inhibitor	Improved the smell and taste dysfunction caused by various diseases (two non-RCT)	IIb/B-NR	(Henkin et al., 2009, 2012)
Intranasal insulin	Neuroprotective	Beneficial effects in olfactory dysfunction caused by infection (non-RCT), COVID-19 (non-RCT), and other diseases (RCT)	IIa/B-R	(Mohamad et al., 2021; Rezaeian, 2018; Schöpf et al., 2015)
Statins	Neuroprotective, anti-inflammatory	Improved anosmia in mice models (two animal studies)	IIb/C-EO	(Kim et al., 2010, 2012)
Minocycline	Neuroprotective	Inhibit apoptosis of OSNs in rat models (Histological analysis)	IIb/C-EO	Kern et al. (2004b)
Zinc	Trace element, growth factor	Reports of anosmia with intra-nasal zinc gluconate, No beneficial effects of zinc sulfate in chemotherapy-induced taste and smell loss (RCT)	III/B-R	(Davidson and Smith, 2010; Lyckholm et al., 2012)
Intranasal vitamin A	Anti-neurodegenerative	Beneficial effects in post-infectious smell dysfunction (retrospective cohort study)	IIb/C-LD	Hummel et al. (2017)
Omega-3	Neuroprotective	Beneficial effects in olfactory loss caused by tumors (RCT)	IIb/B-R	Yan et al. (2020)
Intranasal mometasone	Anti-inflammatory	No beneficial effects in COVID-19 smell loss (RCT)	III/B-R	Abdelalim et al. (2021)
Intranasal fluticasone	Anti-inflammatory	Beneficial effects in COVID-19 smell loss (non-RCT)	IIa/B-NR	Singh et al. (2021)
Oral triamcinolone paste	Anti-inflammatory	Beneficial effects in COVID-19 dysgeusia (non-RCT)	IIa/B-NR	Singh et al. (2021)
Melatonin	Neuroprotective, anti-inflammatory	Inhibit apoptosis of OSNs in rat models (animal study)	IIb/C-EO	Koc et al. (2016)

PDE, phosphodiesterase; RCT, randomized clinical trial.

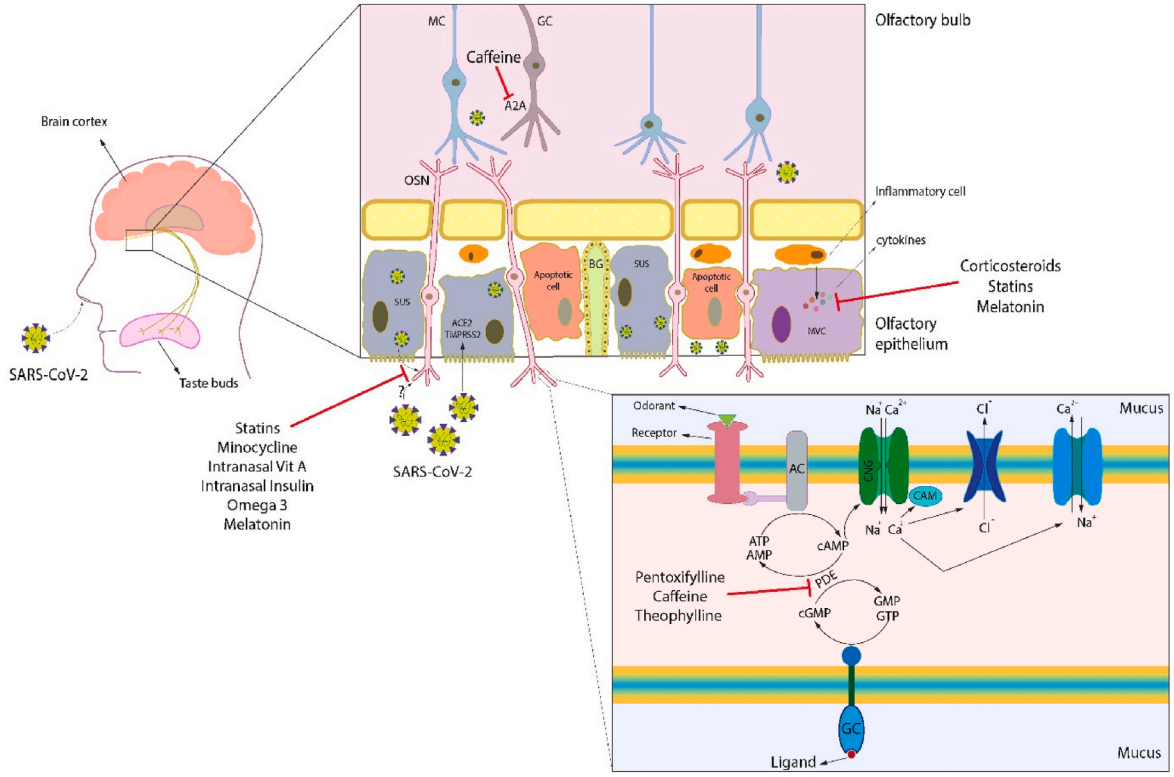

Fig. 1. The potential mechanistic pathways and treatments suggested for COVID-19-related smell loss. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters nasal epithelium, particularly with angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) receptors on sustentacular cells (SUSs). Damage to the olfactory sensory neurons (OSNs) could lead to a decrease in cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate cGMP levels, which can be inhibited by phosphodiesterase inhibitors (pentoxifylline, caffeine, and theophylline). Neuroprotective agents such as statins, minocycline, intranasal vitamin A, intranasal insulin, omega-3, and melatonin could regenerate olfactory receptor neurons (ORNs). Also, the inflammatory effects of the virus in the nasal epithelium can be blocked by corticosteroids, statins, and melatonin. BG, bowman's gland; GC, granule cell; MC, mitral cell; MVC, microvillar cell.

interpretation of these results. Furthermore, the patients in this study have diseases other than COVID-19 that led to olfactory loss. Conversely, a case series of 6 patients with post-traumatic anosmia showed that administration of oral pentoxifylline (200 mg 3 times daily for 3 weeks) did not significantly improve the odor threshold, discrimination, and identification scores (P-values = 0.3, 0.06, and 0.1, respectively) (Whitcroft et al., 2020). Due to the different results, conducting larger double-blinded clinical trials, which directly evaluate the pentoxifylline role in COVID-19 patients with olfactory or gustatory dysfunctions, is recommended.

4.2. Caffeine (IIb/B-R)

Caffeine is a CNS stimulant that belongs to the methylxanthine class. The pharmacologic effects of methylxanthine derivatives can be caused by phosphodiesterase inhibition and blocking of adenosine receptors. Particularly, caffeine could affect the CNS by antagonizing different subtypes of adenosine (A1, A2A, A2B, and A3) receptors in the brain (Ribeiro and Sebastião, 2010). Previously, it has been shown that in rodents, the genes of the adenosine A2A receptors are highly expressed in the granular cells of the accessory olfactory bulb (Abraham et al., 2010; Kaelin-Lang et al., 1999; Nunes and Kuner, 2015).

A study by Prediger et al. aimed to assess the efficacy of caffeine on age-related olfactory deficiency in rats. This study demonstrated that caffeine could improve olfactory dysfunction with doses of 3, 10, and 30 mg/kg through blocking A2A receptors (P = 0.001) (Prediger et al., 2005). Furthermore, cAMP and cGMP have substantial effects on olfactory function. Thus, increasing the intracellular levels of cAMP and cGMP by phosphodiesterase inhibitors with less adverse effects can be suggested as potential treatment approaches for anosmia and ageusia/dysgeusia.

Several studies have evaluated the association between caffeinated coffee consumption and various clinical outcomes. For example, a retrospective cohort on 173 patients with Parkinson's disease (mean age = 58.1 years, 69% female) showed that higher coffee consumption significantly improved the scores of smell test with means of 30.4, 32.6, 33.1, and 34.4 for consuming <1, 1, 2 to 3, and ≥4 cups daily (P = 0.009); this improvement was more noticeable among men. Also, this study showed that the rate of hyposmia is greater among patients whose daily coffee consumption was ≤1 cup compared to patients with more than 1 cup of coffee consumption (26% versus 8%; OR = 0.026; 95% CI, 0.10, 0.67; P = 0.007) (Siderowf et al., 2007). Although these results were adjusted for some confounding factors, the study's observational design still cannot confirm the exact role of coffee consumption on hyposmia.

A double-blinded, placebo-controlled study was carried out on 76 patients with hyposmia due to either upper respiratory tract infection (n = 48) or sinus node dysfunction (n = 26) to evaluate the effects of caffeine on olfactory dysfunction. The mean age of patients was 57 years, with a mean duration of 14 months for olfactory loss. Patients were assigned to receive 65 mg caffeine in one cup of espresso (n = 39) or a placebo (n = 38). The evaluations before and 45 min after intervention could not support the beneficial effects of coffee in patients suffering hyposmia (odor discrimination: t = 0.03, P = 0.97; odor threshold: t = 0.05, P = 0.96; discrimination and threshold combination score: t = 0.79, P = 0.83) (Meusel et al., 2016). This study only evaluates the short-term effects of coffee on olfactory dysfunction; however, the result may differ with a longer duration of coffee consumption or higher

dose. Another limitation was the small sample size of the study that can increase the risk of bias. Despite several types of studies about the role of caffeine in olfactory and gustatory dysfunctions, lacking data on COVID-19 patients makes it difficult to define whether it improves anosmia or ageusia. However, coffee consumption might be a safe way to resolve these complications in patients without caffeine sensitivity.

4.3. Theophylline (IIb/B-NR)

As previously discussed, cAMP and cGMP have key roles in the normal olfactory and gustatory functions (Henkin et al., 2007). As a phosphodiesterase inhibitor, theophylline administration has been evaluated on 312 patients with smell loss. Based on the measurement prior to the study, the reason for patients' smell loss was related to the lower levels of cAMP and cGMP in the nasal and salivary mucus. In this study, patients received 200–800 mg of theophylline orally for 2–8 months. The results showed that the administration of theophylline was associated with smell function improvement in 50.3% of patients. The doses of 600 and 800 mg showed better results than 200 or 400 mg. Therefore, high doses of oral theophylline are required to elevate cAMP and cGMP levels; however, the high doses might result in increased adverse events such as tachycardia, tremor, restlessness, and gastrointestinal disorders. Also, theophylline has a life-threatening narrow therapeutic window that needs regular blood level monitoring (Henkin et al., 2009; Skinner, 1990).

Therefore, another trial evaluated the intranasal theophylline effects on 10 patients from 312 patients of the previous study; these patients were selected due to their lower than expected response for oral theophylline or experiencing adverse effects. The mean age of patients was 64 years. They had a smell or taste loss for several reasons: post-viral olfactory dysfunction, allergic rhinitis, head trauma, and congenital olfactory dysfunction. While the serum level of theophylline became unmeasurable after 3–12 weeks of the oral drug discontinuation, the intranasal theophylline was administered with a dose of 20 μg daily for 4 weeks. The improvement of smell and taste perception has occurred in 8 patients after intranasal administration, which was greater than the oral theophylline. Moreover, no adverse effects were observed after the intranasal theophylline administration (Henkin et al., 2012). However, it should be noted that this trial was primarily conducted to assess the safety of intranasal theophylline use. Thus, the studies with a larger sample size and the placebo group should evaluate the efficacy of intranasal theophylline.

4.4. Intranasal insulin (IIa/B-R)

The intranasal pathway is a well-known drug delivery system for the CNS; particularly for insulin, the mechanism of brain delivery was fully understood. In mice models, fluorescent and electron microscopy imaging of olfactory tissues showed that intranasal insulin affects the brain through the olfactory nerve pathway (Renner et al., 2012). Insulin can be involved in olfactory function through receptors presented on MCs of the olfactory bulb. Furthermore, it has neuroprotective effects and could regenerate the olfactory mucosa (Fadool et al., 2011; Lacroix et al., 2011). In a study bySchopf et al. (2015), 10 patients with post-infectious olfactory loss were included to receive 20 units of insulin in each nostril (a total of 40 units). The function of the olfactory system was assessed 30 min after insulin administration. After a year from the first intervention, the patients were asked to receive 0.4 ml of intranasal saline as a placebo. The mean age of patients was 46.5 years, and the mean body mass index for them was 27.1 kg/m^2. According to the measurements of olfactory functions, 60% and 28.5% of patients showed an improvement in odor threshold and sensitivity after intranasal insulin and saline administration, respectively. The intensity of the odor perception was significantly higher after insulin application than the placebo ($P = 0.04$). Of note, the higher body mass index resulted in significantly better odor identification after insulin administration ($P < 0.01$) (Schöpf et al., 2015). However, the small sample size and non-randomized design of this study limited the interpretation of results.

In a randomized clinical trial by Rezaeian (2018), the role of intranasal insulin in olfactory function has been assessed in patients with mild to severe hyposmia that lasts more than 6 months. Totally, 38 patients underwent randomization to receive either 40 units of intranasal protamine insulin ($n = 19$) or 20 mL of normal saline as a placebo ($n = 19$) two times per week for 4 weeks. The mean age of patients and the mean duration of hyposmia in the insulin and placebo groups were 37.3 versus 35.7 years and 2.3 versus 3.0 years, respectively. The mean (±SD) score of the insulin-treated group was significantly higher than the placebo group (5.0 ± 6 0.7 versus 3.8 ± 6 1.0, $P = 0.01$) (Rezaeian, 2018). Recently, Mohamad et al. (2021) formulated intranasal insulin films to evaluate their effectiveness in managing SARS-CoV-2 induced anosmia. Of 40 patients who underwent randomization, 20 patients were assigned to receive intranasal insulin films, and 20 were assigned to the placebo group. The comparison of the olfactory function between the two groups showed better scoring test results for the insulin-treated group regarding both odor detection (7.9 ± 1.2 versus 3 ± 0.8) and discrimination (6.7 ± 0.5 versus 2.8 ± 1). Moreover, comparing scores before and after intervention showed that, unlike the placebo group, insulin administration resulted in significantly higher scores after intervention (Mohamad et al., 2021).

4.5. Statins (IIb/C-EO)

Statins are known as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors that are widely used in cases of hypercholesterolemia. Besides their lipid-lowering activity, they have multiple beneficial properties, including anti-inflammatory, immunomodulatory, and neuroprotective effects (Saee di Saravi et al., 2017). Previously, it has been shown that statins could improve the proliferation and neurogenesis of injured OE through immunohistochemical staining investigations. In this study, statin-treated (10 mg/kg for 4 weeks) rats showed a higher rate of OE proliferation and better regeneration of neurons than both prednisolone-treated (1 mg/kg for 2 weeks) or control groups (Kim et al., 2010). In another study on anosmia using mouse models, the improvement of the olfaction system was observed among 75% of mice with oral administration of 10 mg/kg atorvastatin versus 16.6% of control groups ($P = 0.004$) (Kim et al., 2012). These studies show the neuroprotective and anti-inflammatory effects of statins to improve the COVID-19 related anosmia. Of note, the adverse effects of the statins such as arthralgia and hepatotoxicity should be taken into account, and the pros and cons of treatment should be evaluated cautionary.

4.6. Minocycline (IIb/C-EO)

Minocycline belongs to the tetracycline class of antibiotics approved to manage a wide variety of infections such as skin, respiratory tract, and sexually transmitted infections. Furthermore, minocycline exerts several effects, including anti-inflammatory, anti-apoptotic, and anti-angiogenesis activities. The interference with apoptosis, particularly in neurons, makes minocycline the most neuroprotective agent among tetracycline derivatives. The beneficial effects of minocycline have been indicated in several neurodegenerative disorders such as Huntington's disease, Parkinson's disease, Alzheimer's disease, and degeneration of photoreceptor cells. Besides, the beneficial effects of minocycline against olfactory dysfunction have been reported. Histological analysis of animal olfactory tissue showed that minocycline could inhibit apoptosis of OSN in rat models with bulbectomy (Kern et al., 2004b). The balance between OSN apoptosis and regeneration is vital in maintaining a normal sensory function (Kern et al., 2004a). Thus, this may be a rationale for raising the number of OSNs by inhibiting apoptosis by using well-tolerated medication minocycline.

4.7. Zinc (III/B-R)

Zinc is a trace element that contributes as one of the growth factors in taste and smell function. It has been shown that growth factors activate stem cells in both taste buds and olfactory epithelial cells. Zinc is a constituent of the salivary enzyme carbonic anhydrase VI, which plays a vital role in the maintenance of taste and smell function. Therefore, zinc deficiency could result in anosmia and dysgeusia (Komai et al., 2000; Wrobel and Leopold, 2004). Also, Equils et al. (2021)suggested that a reduction of nasal zinc level is a common nasal immune reaction to acute viral infections such as SARS-CoV-2 and involves the pathogenesis of anosmia.

Moreover, they proposed that patients with zinc deficiency have long-lasting anosmia and severe COVID-19 (Equils et al., 2021;Ozlem Equils, 2020). Previously, several reports of anosmia caused by the zinc-containing nasal product (Zicam) forced the U.S. Food and Drug Administration (FDA) to recall them. Moreover, Davidson and Smith (2010) suggested that intranasal zinc gluconate can cause anosmia or hyposmia in patients (Davidson and Smith, 2010). Also, intranasal zinc sulfate (5%) is well known to induce anosmia in animal models (Cancalon, 1982; McBride et al., 2003). In a double-blinded, placebo-controlled, randomized clinical trial, administration of 50 mg elemental zinc sulfate two times per day showed no significant improvements in chemotherapy-induced taste and smell dysfunctions in comparison with the placebo group. However, the small sample size (n = 58), lacked standard methods to evaluate sensory variations, and various concurrent medication used in patients increased the risk of bias in this study (Lyckholm et al., 2012).

4.8. Intranasal vitamin A (IIb/C-LD)

The active metabolite of vitamin A, retinoic acid, participates in various biological situations, including olfactory system embryogenesis, cell growth, and differentiation. Also, retinoic acid has immunomodulatory properties that might improve cell turnover and protection, mainly in the OE, which is susceptible to several inflammatory particles. Due to the regenerative and immunomodulatory effects of Vitamin A on ORNs, some studies were conducted to evaluate intranasal vitamin A effects on olfactory dysfunction (Rawson and LaMantia, 2007).

In a retrospective cohort study, 170 patients with post-infectious and post-traumatic smell complaints were treated with smell training and topical vitamin A (n = 124) or smell training alone (n = 46). Of note, patients with other causes of olfactory dysfunction such as congenital anosmia and/or aged younger than 18 years were not included in this study; the dose of intranasal vitamin A drop was 10 000 units per day for 2 months. Also, smell training was carried out for 3 months. The mean ± SD of the age of patients was 55 ± 14 years, and approximately 59% of them were female. After nearly 10 months of follow-up, the rise of smell distinction score was markedly higher in the vitamin A group than the control group (P = 0.008). In patients with post-infectious olfactory dysfunction, 37% and 23% were clinically improved in the vitamin A and control groups, respectively (P = 0.03). The comparison of the groups in the post-traumatic patients showed no significant changes in the olfactory function (P = 0.29) (Hummel et al., 2017). Although this study supported the beneficial effects of vitamin A in infection-induced olfactory dysfunction, further studies are required to directly evaluate the efficacy and safety in SARS-CoV-2 induced olfactory dysfunction. Also, the duration and the dose of vitamin A administration in this study were based on expert opinion. Moreover, the possible adverse events were not indicated in this study.

4.9. Omega-3 (IIb/B-R)

Omega-3 polyunsaturated fatty acids are vital parts of membrane phospholipids that have substantial effects on gene expression. The low levels of docosahexaenoic acid (DHA), an essential omega-3 fatty acid found in fish oil, exert signs of olfactory dysfunction (Greiner et al., 2001). A multi-institutional, prospective, randomized controlled trial has evaluated the effects of omega-3 administration on olfaction. This trial included 110 patients with sellar or parasellar tumors who underwent endoscopic resection were assigned to receive either nasal saline irrigations (n = 55) or nasal saline irrigations combined with omega-3 supplements with a total dose of 2000 mg per day (n = 55). According to the results, omega-3 administration was found to have beneficial effects on olfactory loss after controlling for multiple confounding variables (odds ratio [OR] 0.05; 95% CI 0.003–0.81; P = 0.03) (Yan et al., 2020). This study did not declare whether patients used other medications with potential benefits on olfactory function, such as corticosteroids, limiting the interpretation. Moreover, it is noteworthy that omega-3 supplements should be used with caution in patients with fish allergy, hepatic failure, and bleeding risk, particularly in patients on concomitant antiplatelet or anticoagulant medications.

4.10. Corticosteroids (mometasone: III/B-R; fluticasone: IIa/B-NR; oral triamcinolone paste: IIa/B-NR)

Corticosteroids could combat the local inflammatory response in the nasal area and taste buds, which may occur during the anosmia and ageusia caused by COVID-19. In addition, corticosteroids could directly improve the olfactory function by modifying the sodium-potassium adenosine triphosphatase (Na/K-ATPase) present on ORNs. Na/K-ATPase is also a key factor of the salivary glands, which is required for the secretion of saliva in the glandular acini, along with later alteration in the ducts (Catana et al., 2013; Kim et al., 2016).

Abdelalim et al. (2021) evaluated the use of mometasone nasal spray for the treatment of COVID-19-related anosmia in a randomized clinical trial. Patients with RT-PCR confirmed COVID-19 who aged 18 years or older and experienced recent anosmia and/or ageusia entered the study. Besides, previous use of systemic steroids and pregnancy were exclusion criteria of the study. Patients in the intervention group (n = 50) received mometasone furoate nasal spray with a dose of 100 μg per day for three weeks plus olfactory training. In comparison, patients in the control group (n = 50) were managed by olfactory training alone. The median age of patients was 29.0 years, and 54% were men; mostly (94%) suffered from mild or moderate COVID-19 symptoms. The comparison of smell scores showed no significant difference between the groups after 1, 2, and 3 weeks of treatment (P = 0.10, 0.08, and 0.16, respectively). Also, the duration of anosmia was statistically similar between both groups, with the mean (SD) of 26.41 (7.99) days versus 26.15 (5.07) days for the intervention and control groups, respectively (P = 0.88) (Abdelalim et al., 2021). Although the results of this study did not support the beneficial effects of topical steroids in anosmia caused by COVID-19, the small sample size and unblinded design of the study should be taken into account in the interpretation of the results. Also, some patients received systemic steroids during the study period, which may affect the results.

Another clinical trial in COVID-19 patients assessed the efficacy of topical fluticasone and triamcinolone on anosmia and taste dysfunction, respectively. Of the 120 patients enrolled in the study, 60 patients received two puffs of fluticasone nasal spray for anosmia and triamcinolone paste three times daily for dysgeusia. On day five of the intervention, the smell and taste perceptions were significantly improved compared to the first day (Singh et al., 2021). In this study, saline irrigations or gargles were also administered that might affect the results. Also, the limited sample size and non-randomized design of the study increased the risk of bias.

4.11. Melatonin (IIb/C-EO)

Melatonin is recognized as an anti-inflammatory, antioxidative, and immune-enhancing medication with a great safety profile. Due to melatonin's small size and amphiphilic properties, it has high cell diffusion

ability and permeability through biological compartments, including the blood-brain barrier (BBB). Melatonin renovates BBB homeostasis preventing microvascular hyperpermeability and thus making it a favorable agent to combat SARS-CoV-2 induced neuroinvasion. Also, the neuroprotective effects of melatonin on OSNs were previously indicated in rat models (Koc et al., 2016; Romero et al., 2020). However, more clinical data are needed to explore the role of melatonin in smell and taste loss following COVID-19.

5. Discussion

The current study has reviewed the suggested pathways for the anosmia and ageusia caused by SARS-CoV-2 infection and summarized some of the agents to treat them based on pharmacology principles. This summary can be used in designing further clinical trials in the era of COVID-19.

The anosmia and ageusia caused by SARS-CoV-2 have some important properties. First, the notable proportions of COVID-19 patients experience these symptoms that can be the only features of the disease. Second, the symptoms suddenly start and mostly persist for a short period of time. Third, mostly they are not associated with nasal congestion (Butowt and von Bartheld, 2020; Lechien et al., 2020). These symptoms are not life-threatening; however, they affect the quality of life and are associated with depression, anxiety, and increased suicidal thoughts(Elkholi et al., 2021; Yom-Tov et al., 2021). The precise pathophysiology of anosmia and ageusia is unclear, but several studies suggest multiple causations. Among the suggested mechanisms, direct damage in the SUSs and the local inflammation are the most likely causations for the SARS-CoV-2 induced anosmia. Previously, neuronal damage, including direct damage to ORNs is considered as the least probable reason from two reasons: first, ACE2 and TMPRSS2 are not expressed in ORNs; second, the time required for clinical recovery is faster than the regeneration of ORNs in most cases (Printza and Constantinidis, 2020). However, nasal samples and magnetic resonance imaging results showed that ORN infection and CNS invasion play a key role in COVID-19-related anosmia. The neuronal damage should be particularly taken into account in COVID-19 patients with long-lasting anosmia (Boscolo-Rizzo et al., 2020; Butowt and von Bartheld, 2020; de Melo et al., 2021; Kandemirli et al., 2021; Meinhardt et al., 2021; Politi et al., 2020). Considering the correlation between olfactory and gustatory systems, the mechanistic pathways contributing to anosmia could also cause ageusia. However, some unique pathways have also been suggested for ageusia/dysgeusia. Similar to anosmia, among the suggested pathways for ageusia, the participation of the central nervous system looks less probable since the appearances of this participation, such as meningitis and encephalitis, are experienced rarely in COVID-19 (Butowt and von Bartheld, 2020; Finsterer and Stollberger, 2020; Luchiari et al., 2021).

Taken together, several medications have been suggested to treat anosmia and ageusia. Previously, olfactory training was recommended as an effective and safe way for olfactory dysfunction. However, there is no medication approved to treat olfactory dysfunction. Among the discussed medications, corticosteroids are the most studied in COVID-19. However, it should be noted that the use of systemic corticosteroids for the SARS-CoV-2-mediated olfactory and gustatory dysfunctions might have additional risks and could reduce the viral clearance from the body (Tlayjeh et al., 2020). Other medications mentioned in this review were mostly neuroprotective used for different causes of anosmia and/or ageusia.

Considering the involvement of the neuronal pathway in COVID-19-induced anosmia and/or ageusia, neuroprotective agents, including intranasal vitamin A, intranasal insulin, omega-3, statins, minocycline, and melatonin, might have beneficial effects in patients with long-lasting anosmia by inducing regeneration of the ORNs. Also, phosphodiesterase inhibitors can activate olfactory function through depolarization of the neurons. However, further studies are required to assess the effects of theophylline, pentoxifylline, and caffeine on SARS-CoV-2 induced anosmia and/or ageusia. Different formulations of zinc have also resulted in completely different results. Some of the zinc-containing products were recalled by the U.S. FDA since there were several cases with compliance of anosmia with them. The precise association between SARS-CoV-2 infection and zinc level, either in the systemic or in the local level, is not fully understood. There are hypotheses that low zinc levels are linked with anosmia and dysgeusia, and additional clinical trials are required for further consideration (Equils et al., 2021). Finally, the medications' safety issues, adverse reactions, contraindications, and drug interactions, should be considered before administration.

5.1. Limitation

Our study might have some limitations. First, due to the lack of data in the era of COVID-19 mediated anosmia and/or ageusia, the proposed medications have a low level of evidence to support their application in treating anosmia and ageusia following SARS-CoV-2 infection. Second, similar to most review articles, some studies may be missed to enter our review.

6. Conclusion

We searched the literature to review the potential mechanistic pathways and treatments in COVID-19-related anosmia and/or ageusia. According to available data, there are limited studies about possible treatments of COVID-19 taste and smell loss, which need further clinical trials. This review can provide basic information to direct future clinical trials according to clinical pharmacology principles.

Author agreement

We certify that all authors have seen and approved the final version of the manuscript (EJP-59088R1) being submitted to the European Journal of Pharmacology. We warrant that the article is the authors' original work, has not received prior publication, and is not under consideration for publication elsewhere.

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Data statement

None to declare.

Declaration of competing interest

None.

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