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POSSIBLE MECHANISMS OF TASTE IMPAIRMENT AS A CRUCIAL SYMPTOM OF COVID-19

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ABSTRAK

Latar Belakang: Pandemi *Coronavirus Disease* –19 (COVID-19) adalah sindrom pernafasan akut yang parah, disebabkan oleh *Severe Acute Respiratory Syndrome Corona Virus*–2 (SARS-CoV-2) dan berdampak di seluruh negara. Penyakit ini menyebar terutama melalui jalur pernapasan. Gangguan rasa pengecapan adalah salah satu gejala awal COVID-19. SARS-CoV-2 menyerang tubuh manusia melalui reseptor *Angiotensin – Converting Enzyme* 2 (ACE2). Populasi sel dengan peningkatan kadar ACE2 yang diekspresikan pada sel epitel paru, jantung, usus, ginjal, pembuluh darah, otak, dan mukosa mulut akan menjadi paling rentan terkena infeksi virus. Adhesi protein *spike* SARS-CoV-2 ke ACE2 menyebabkan penurunan regulasi ACE2, yang mengakibatkan peningkatan Angiontensin II (Ang II). Ang II memiliki efek menurunkan respon terhadap rasa pengecapan dan mengatur amiloride – garam sensitif dan reaksi terhadap rasa manis. **Tujuan:** Menyoroti, mengeksplorasi dan menjelaskan kemungkinan mekanisme penurunan rasa pengecapan pada infeksi SARS-CoV-2. **Metode**: Menganalisis jurnal dari database Google *Scholar*, Perpustakaan Nasional Republik Indonesia, *Science Direct*, EBSCO, dan PubMed dari tahun 2011 sampai dengan tahun 2021. **Kesimpulan**: Patogenisitas dan kemampuan SARS-CoV-2 dalam gangguan rasa pengecapan melalui ACE2 yang mengarah akumulasi Angiotensin II dan mengakibatkan terjadinya penekanan respons rasa, namun masih dibutuhkan investigasi lebih lanjut untuk memastikan mekanisme yang pasti.

Kata kunci: COVID-19, SARS-CoV-2, gangguan pengecapan, ACE2, Ang II, amiloride

ABSTRACT

Background: Corona virus disease – 19 (COVID-19) pandemic is a syndrome caused by infection of severe acute respiratory syndrome corona virus–2 (SARS-CoV-2) and impacting all over the countries. Gustatory impairment is one of early illness and signs in COVID-19. The SARS-CoV-2 invades the person body via angiotensin – converting enzyme 2 (ACE2) receptors. Cell populations with elevated level of expressed ACE2 (epithelial cells of the pulmonary, cardiac, intestinal, renal, blood vessels, brain and oral mucosa) will be most vulnerable from viral infection. The adhesion of SARS- CoV-2 spike protein to ACE2 caused ACE2 downregulation, result in an enhancement of Angiontensin II (Ang II). Ang II has suppressive effects on gustatory responses and regulates amiloride – sensitive salt and sweet sense reactions. **Purpose:** Highlights and explores the possible mechanisms of the taste impairment of SARS-CoV-2 infection. **Method**: Journal analysis from Google Scholar, National Library of the Republic of Indonesia, Science Direct, EBSCO, and PubMed databases from 2011 to 2021. **Conclusion** The pathogenicity and capability of SARS-CoV-2 in taste impairment via ACE2 leading to Angiotensin II accumulation and as a consequence of suppressive effects on taste responses. Further investigation to ascertain its mechanism is needed.

Keywords: COVID-19, SARS-CoV-2, taste impairment, ACE2, Ang II, amiloride

INTRODUCTION

Corona virus disease - 19 (COVID-19) is a novel coronavirus infection inflicted by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and infected most people throughout the world. People infected with the

COVID-19 virus will suffer many symptoms from mild to moderate respiratory disorders. The World Health Organization (WHO) declared it as a global epidemic only 2 and a half months after the outbreak of the disease.[1] Oral health worker may be exposed to variety of bacteria, viruses, fungi and protozoan from many sources in a highly infected condition.[2]

The transmissions of SARS–CoV-2 is basically via aerosol, small drops of saliva or emanation from the upper respiratory tract when a contagious person coughs or sneezes causing an aerosol.[3] Meanwhile, the virus also has been detected in asymptomatic persons. Based on People's Republic of China (PRC) information, the international WHO mission report confirms as far as 75% of initially asymptomatic cases will progress to clinical disease, causing the true asymptomatic infection rather rare (estimated at 1-3%).[4] Patients with SARS-CoV-2 infection often have main illness such as fever, dry cough and fatigue, and subordinate illness i.e. pharyngeal pain, abdominal pain, diarrhoea and conjunctivitis.[5,6,7]

The British Rhinological Society and ENT UK reported anosmia in 10 – 15% SARS-CoV-2 infected patients, in Republic of Korea, about 30% of cases with confirmed COVID-19 test experienced olfactory disorder as a major presenting symptom.[8] While in German, about 66% over 100 patients who had an interview reported loss of smell and taste lasting for several days and 50% occurred after the earliest respiratory symptoms. According to the American Academy of Otolaryngology, patient with positive Covid-19 experienced anosmia or hyposmia and ageusia although had no other symptoms.[9] SARS-CoV-2 is able to persist active and contagious in aerosols for period of time and on superficies until few days (determined by the inoculum shed).[10]

As an oral health care worker, dentist must aware with these symptoms especially dental patient with smell and taste impairment who had an emergency dental condition, and anticipate with referral to the medical doctor for testing for COVID-19 according to local health regulation.

METHOD

This review was made based on reference sources or references obtained from articles, journals, textbooks, and websites accessed through the Google Scholar database, Science Direct, EBSCO, PubMed and searched for the keywords COVID-19, SARS-CoV-2, taste impairment, gustatory impairment, ACE2, Ang II, amiloride. The reference journals were taken in the form of research and descriptive journals published from 2011-2020.

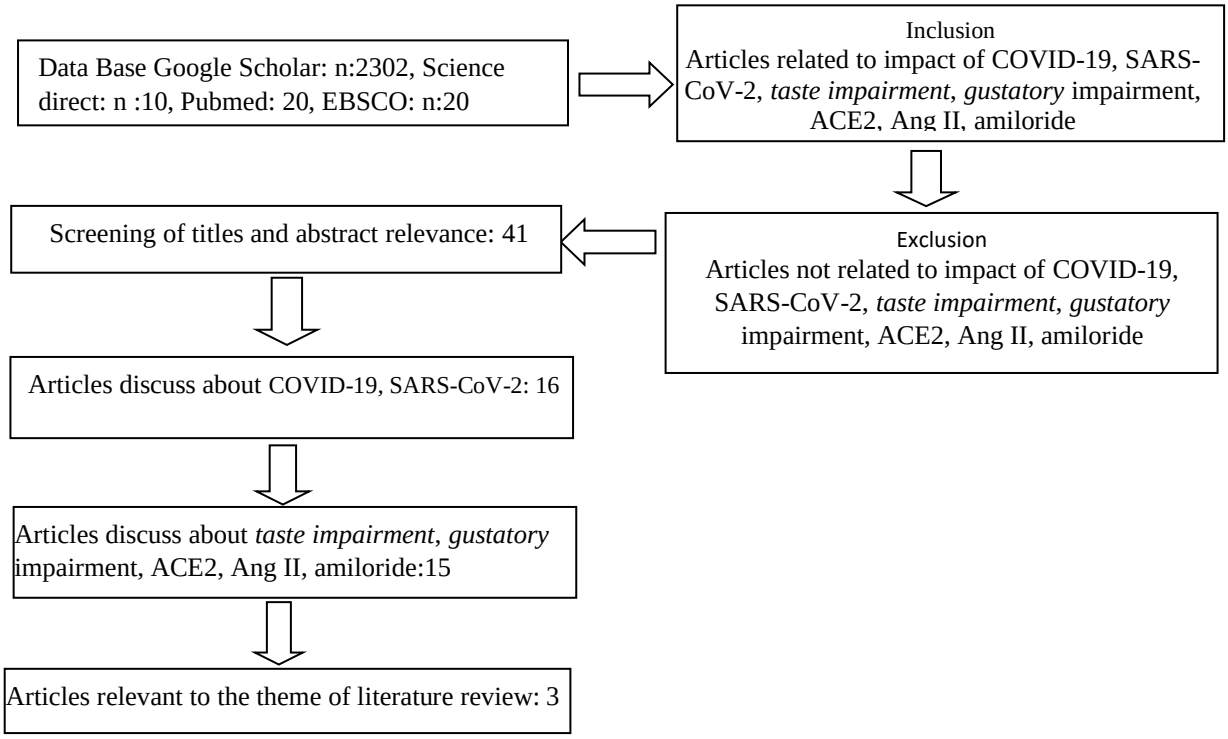

Figure 1. Publishing flowchart of all databases

RESULT

Total of 2.352 articles were collected, titles and abstracts of all articles were reviewed and checked for the relevancy to the inclusion criteria, only articles in English language was included. Figure 1 demonstrates the selection process in this review. Articles which included details about its mechanism of action Ang II and amiloride in taste impairment of SARS CoV-2 infection were included. After data extraction process, a total of 3 articles relevant to the theme of literature review were accepted and included. Table 1 shows the result of research on taste impairment as a crucial symptom of COVID-19.

Singer-Cornelius T et al. study confirmed a total of the 41 patients complained subjective olfactory and gustatory disorders followed Brief Smell Identification Test, and taste strips test. Impartially, all of the symptomatic patients had reduced senses of taste (hypogeusia or ageusia) according to sum scores accomplished on Burghart test. No statistic significant was found among symptomatic and asymptomatic gustatory disorder in patients when being tested with taste qualities.[11]

Lechien JR et al. reported 154 males out of a total of 417 mild-to-moderate Covid-19 patients with the most common manifestations comprised of tussis, muscle pain and anorexia. A total of 85.6% and 88.0% of patients complained olfactory and gustatory dysfunctions. These dysfunctions were significantly associated and olfactory disorder emerged prior to the other manifestations (11.8% of the patients). The initial olfactory improvement rate was 44.0%. Females were significantly more influenced by olfactory and gustatory dysfunctions than males ($p = 0.001$).[12]

Yan CH et al informed that more than half of the Covid-19 patients had olfactory and gustatory impairment and inversely proportional to only quarter of non-Covid-19 patients ($\chi 2$ test $p < 0.001$). Less than half of COVID-19 patients had improvement of smell and taste that provisionally not correlated with clinical resolution of disease.[13]

Table 1. Results of Research on Taste Impairment as a Crucial Symptom of COVID-19.

References	Aims	Methods	Sample	Result
Singer-Cornelius T et al. (2020)[11]	To know the frequency of olfactory and gustatory impairment in virulence of SARS-CoV-2	Questionnaire and Brief Smell Identification Test (BSIT) and Burghart taste strip test	n=41	A significant loss of sour (33.3% (13/39)) and salty taste (17.9% (7/39)); 10.3% (4/39) had a reduction in sweet and bitter taste. 9.8% (4/41) showed a deficit relative to younger age in the BSIT
Lechien JR et al. (2020)[12]	To evaluate the prevalence of smell and taste impairment in definitive COVID-19 humans	smell and taste questionnaires	n=417	Significant association between smell and taste impairment with female predilection to suffer taste and smell disorders than males. p<0.001.
Yan CH et al. 2020[13]	To evaluate symptoms of olfactory and gustatory impairment for patient underwent testing for COVID-19	stated symptoms with a centered on altered olfactory and gustatory function	n = 1480	Olfactory and gustatory disruption were strongly related with COVID-19 positivity (anosmia: [aOR] 10.9; 95% CI, 5.08-23.5; ageusia: aOR 10.2; 95% CI, 4.74-22.1)

DISCUSSION

Systemic Symptoms

SARS-CoV-2 infection causes Severe Acute Respiratory Syndrome with primary symptoms and illness such as febrile, tussis, muscle pain, or weakness and secondary symptoms such as sputum secretion, cephalgia, hemoptysis, and diarrhoea.[5,6] SARS-CoV-2 also has implicated various neurological symptoms comprising of the implication of the systema nervosum consist of the brain and spinal cord (lightheadedness, cephalgia, defective cognition, acute cerebrovascular disease, loss of full control of bodily movement and seizures), peripheral nervous system (flavor, smell, and eyesight defect and also nerve pain) andskeletomuscular injury.[5] All of neurological symptoms can indicate the potency of neurotropism and neurovirulence of of SARS-CoV-2.[14]

Taste Mechanism

Gustatory bulbs contain gustatory receptors and innervated by the seventh, ninth and tenth cranial nerves. For salted and acid sensations, these sensations are assured which pore forming

membrane proteins on taste cells act as receptors.[12,15] The taste receptors have seven transmembrane domains[15]. Hidrogen ion ($H^{+)}$ and Sodium (Na^{+}) ions are streaming through the channels into taste cell. G-protein coupled receptors (GPCRs) attach taste group of chemically bonded atoms in a kind of enzyme and the substrate interaction with specific complementary geometric shape technique. A family of three GPCRs, well known as taste receptor family I member 1 (T1R1), T1R2, and T1R3, perform parallelly (T1R1 + T1R3 for umami, and T1R2 + T1R3 for sweet) to recognize group of chemically bonded atoms transmitting flavor qualities for sweet, umami, and bitter tastes. The acrid sense organs, the T2Rs, constitute a fundamentally comprehensive cluster of GPCRs, consist of 25 elements.[15,16]

The gustatory differentiated structure of body has several main constituents of renin angiotensin system (RAS), specifically renin, angiotensinogen, and angiotensin converting enzyme 1 (ACE1), which enable the regional outcome of Ang II in gustatory bulbs. The RAS constituents are co-expressed with α epithelial natrium channel (αENaC) or T1R3 in a subdivision of gustatory cells. Reactive result of immunohistochemistry of Renin was located at the apex sections of gustatory cells and significantly up regulated in response to water deprivation. The distinctive alleviation of amiloride-sensitive salt taste sensibility and elevation of sugary taste sensibility can be interceded by pair local-generated Ang II (temporal feed forward propagation) and circling Ang II (sustained balancing feedback propagation).[17]

ACE, a zinc metalloendopeptidase which serves qua a carboxyldirected dipeptidase, tranforms Ang I to Ang II.[18] ACE2 is a type 1 integral membrane glycoprotein[19] and resistant to ACE inhibitors.[18] Ang II has an effect on peripheral amiloride-sensitive salt and sweet sensation reactions calculated by Chorda Timpani (CT) nerve recording. Ang II selectively withholds amiloride-sensitive salt taste perceptions, increases sweet taste perceptions. Ang II serves to regulate amiloride-sensitive salt and sweet sensation feedback autonomously through two different subdivisions of taste cell-expressing ENaC and T1r3, correlatively.[20]

Route of Transmissions

Transmission via pulmonary droplets and exposure with the mucous membranes is the major paths of transmission of SARS- CoV-2. Virus and its RNA could be discovered within digestive tract and human feces.[5] Moreover, aerosol with prolonged exposure in a relatively closed environment such in dental clinic and fomite transmission of SARS-CoV-2 is reasonable. Patient can be a source of dental aerosol and depends on site and type of treatment procedure. Saliva, nasal and throat discharge, blood, dental biofilm, plaque and calculus with associated periodontal diseases influence the amount and composition of dental aerosol.[2]

Gustatory disorder in COVID-19 patients was more often occur in female compare with male patient according to study held by Liechen et al [12], while study conducted by Yan et al. did not diverse among gender. The mechanism of gender diversity still remains unclear.[11,12] Gustatory and olfactory disorders can be divides into three main types of absences: transport; sensory, and neural absences. Sensory absences are caused by destruction of the sensory tissues for instance as in viral infection which decrease cell alteration or directly convert cells, which can impair taste and smell function. [11,21] Neural absences as results of destruction of the peripheral nervous system which interceded gustatory and flavor info or to the brain and spinal cord.[21]

The peplomer(s) protein facilitates SARS-CoV-2 to analyze protein on the surface or interior of cell which has an affinity for ACE2 in the stratified epithelial cells of mucosa preferentially in mouth and penetrate human cells, would spread to the other part of body through the vascular system and conduce a cytokine storm if favor by clinical conditions and not arrested by an efficient immune response.[5,22,23,24]

The similarity among three studies is the subjects of these studies was mild-to-moderate COVID-19 patients, defined as patients without need of intensive cares. The difference among these studies is objective examination for taste impairment which was done by Cornelius TS et al.[11] The taste qualities “sour” (33.3%) and “salty” (17.9%) were significantly reduced in outpatient cohort[11] while chemosensory impairments were at least 10-fold more common in COVID-19–positive cases compare with COVID-19–negative individuals, both presenting with similar influenza-like symptoms.[12]

The central nervous system (CNS) would become a potential target because has ACE2 receptors which have been located over neuroglia and nerve cells. The movement of the SARS-CoV-2 to the CNS through the lamina cribirosa of the ethmoid bone adjacent to the *bulbus olfactorius* could be a supplementary route which allow the virus to gain and influence the CNS. Consecutive asexual reproduction of the virus fragments from the capillary endothelial cells and injury to the endothelial basement membrane could facilitate

entry of virus to the CNS. Once inside the surroundings of the neuroglial cells, its reciprocal action with ACE2 receptors manifested in neurons commence a sequence of viral budding coexist with neuronal injury in the absence of significant immune system's natural response to cellular injury as has been noticed with episodes infection of SARS-CoV-1 in 2004. Additionally, this discoveries like a changed odor of smell or hyposmia in a non - life threatening early stage of covid-19 must be studied completely for CNS association and implication. [11,12,22]

Moreover, protein on the surface or interior of cell which has an affinity for ACE 2 is exploited by SARS-CoV-2 to attach as well as invade the cell, parallel with ACE2 is extensively manifested in the oral mucosal epithelial cells.[11] The degree of ACE2 representation in cavum oris tissues was more prominent and excessive in *lingua* than buccal or gingival tissues. These reports indicated *cavum oris* tissues could be regarded as possibly high risk for SARS-CoV-2 infectious awareness[25] and pathogenesis of taste impairment.

It is assumed also that SARS–CoV-2 are presented in oral fluid and capable to bond with gustatory sense differentiated body structure and hence disrupt the perception of sweet and acrid tastes. Study showed sensations of Na^+ and acid are obtained by ion channels (NaCl; amiloride-sensitive epithelial NaCl channel, acid; amiloride-sensitive epithelial Na channels and H+-activated cation channels).[23] The salivary SARS–CoV-2 might inhibit ion channels and disrupt salt and acid tastes. The further studies must be achieved in order to identify SARS–CoV-2 contained in saliva and several oral fluids followed with its metabolite.

In rodent specimen, specific adherence of SARS-CoV peplomer(s) protein to ACE2 induce reduction of ACE2 sensitivity, causing to an enhancement of Ang II.[11,17] ACE2 is a crucial counterrally catalytic protein complex that breakdown angiotensin II into angiotensin-(1–7). Covid-19 infected patients emerged to experience increased degree of plasma angiotensin II and local RAAS activation.[26]

Ang II has suppressive effects on taste responses. the decline of CT nerve reaction and perception to sodium chloride by Ang II may be consequence of modulation of ENaC activity by cAMP in taste cells. On contrary, Ang II enhanced sweet taste. responses via endocannabinoids and GLP-1. GLP-1 signaling escalates sweet and sour sensation reactivity. Endocannabinoids specifically increase reactivity of sweet sensation via CB1 receptors on the sweet taste cells expressing T1r3. The CB1 receptors are trans-activated by Angiotensin II receptor type I (AT1). Ang II and sweet taste compounds normally turn on the phospholipase C signaling pathway by AT1 and T1r2 +T1r3 receptors, successfully, which intensifies discharge of inositol-1,4,5, trisphosphate and diacylglycerol (DAG). DAG lipase breaks water from DAG in order to generate an endocannabinoid [2-arachidonoylglycerol (2-AG)]. If any sequence of chemical transformations occurs in taste cell for AG2, discharged 2-AG can serve as a boost autocrine signaling for CB1 receptors on sweet taste cells.[20]

Ang II regulates amiloride – sensitive salt and sweet sensation reactions and feedback. The influence of Ang II on gustatory perceptions is by AT1 receptors.

The gustatory differentiated structure is suggested as a recently comprehend auxiliary objective of Ang II's processes, and the particular alleviation of amiloride-sensitive salt response receptivity by Ang II can assist to increased natrium absorption. Ang II works on AT1 and AT2 mayor subtypes receptors. AT1 receptors are extensively circulated alongside the body and capable for mediating sodium reabsorption. Ang II receptors are detected in peripheral taste cells while Ang II which circulate will additionally respond in modulating amiloride – sensitive salt feedback which in turn hypothesized causing taste impairment.[11,20]

CONCLUSION

The pathogenicity and capability of SARS-CoV-2 in taste impairment via ACE2 leading to Angiotensin II accumulation and as a consequence of suppressive effects on taste responses. Further investigation to ascertain its mechanism is needed with structured questionnaires, level of serum Ang II, and objective tests in order to differentiate of salty, sweet, sour, bitter and umami taste and qualities.

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