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DENTAL HEALTH STATUS AND ORAL PIGMENTATION OF EAST BELITUNG REGENCY RESIDENTS (STUDY ON COMMUNITY SERVICE PROGRAM "MERAJUT NUSANTARA 2018)

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ABSTRAK

Latar Belakang: prevalensi karies di Indonesia sebesar 57,6% dan 45,9% khususnya di Provinsi Bangka Belitung menurut Riskesdas 2018. Provinsi Bangka Belitung terkenal dengan sumber daya alam berupa timbal. Penambangan timbal mempengaruhi lingkungan termasuk air. Sebagian besar penduduk di Bangka Belitung sering mengkonsumsi air tanah. **Tujuan**: mengumpulkan status kesehatan gigi dan pigmentasi rongga mulut warga, data level logam dan keasaman air minum 3 desa di Kabupaten Belitung Timur pada saat diselenggarakan Kuliah Kerja Nyata 2018. **Metode**: deskriptif dengan pendekatan potong lintang dengan memeriksa DMFT, pigmentasi rongga mulut, kadar Pb, Fe, F, Cd dan pH air minum. **Hasil**: 98 penduduk memiliki usia rata-rata 18.949±13.626 tahun. Rerata kadar Pb dan Cd air minum di 3 desa lebih tinggi dari batas maksimum, sedangkan kadar Fe dan F lebih rendah dari batas maksimum, pH lebih rendah dari 7, nilai rata-rata DMFT adalah 5,59±4,20, 8 penduduk memiliki pigmentasi fisiologis. Berdasarkan Analisis korelasi non parametrik *Spearman* antara konsentrasi Pb, Fe, F, Cd dan pH air minum dengan skor DMFT sangat buruk. **Kesimpulan**: kesehatan gigi penduduk kabupaten Belitung Timur sangat rendah, frekuensi pigmentasi oral rendah. Terjadinya karies gigi dan pigmentasi oral tidak dipengaruhi oleh kandungan logam pada air minum.

Kata kunci: DMFT, pigmentasi, Timbal, Besi, Fluorida, Kadmium, pH air.

ABSTRACT

Background: the prevalence of caries in Indonesia is 57.6% and 45.9% in Bangka Belitung Province according to the Riskesdas 2018. Bangka Belitung Province is known for its natural resources in the form of lead. Lead mining affects the environment including water. Most of the population in Bangka Belitung consume groundwater. **Purpose:** to collect dental health status, oral pigmentation of residents, score of metal, acidity of drinking water of 3 villages East Belitung District at Kuliah Kerja Nyata 2018. **Method:** descriptive cross-sectional conducted by examine DMFT, macula, concentration level of Pb, Fe, F, Cd and pH of drinking water. **Results**: the average age of 98 residents was 18,949±13,626 years. The mean level of Pb and Cd in drinking water were higher, while Fe and F were lower than the maximum limit, pH <7, the mean score of DMFT was 5.59±4.20, 8 residents had physiological pigmentation. Analysis of Spearman's non parametric correlation between concentration of Pb, Fe,F, Cd, pH of drinking water and DMFT score were very poor. **Conclusion:** the dental health of the residents of East Belitung district is very low, low frequency of oral pigmentation, dental caries and oral pigmentation are not influenced by the metal contents in drinking water.

Keywords: DMFT, pigmentation, Lead, Iron, Fluoride, Cadmium, pH of water.

INTRODUCTION

Bangka Belitung Province is well known for its metal resources in the form of lead. Mineral mining affects the environment including water and remains a significant pollutant after being abandoned. The majority of Bangka Belitung Islanders suffer from tooth decay and they often consume groundwater.[1,2]

The prevalence of caries in Indonesia is 57.6% and 45.9% particularly in Bangka Belitung Province according to the Riskesdas 2018.[3] Riset Kesehatan Dasar (Riskesdas 2013) reported the prevalence of dental and oral disease problems in Indonesia increased from 23.2% in 2007 to 25.9% in 2013. The Decay, Missed, Filled Tooth (DMFT) Index of Bangka Belitung Province was 8.5 which means that tooth decay is 850 teeth per 100 people. The number of dentists in the province of Belitung has not yet reached the healthy indicator target of Indonesia. The ratio of dentists serving in Bangka Belitung is only 5 dentists per 100,000 population with an ideal number of 11 dentists per 100,000 population.[4]

Drinking water consumed must fulfill chemical, physical and health requirements. Teeth are a good indicator of exposure to heavy metals in the environment, especially in drinking water.[5,6] Teeth that are exposed to heavy metals such as lead can undergo changes in tooth structure which results in being more susceptible to caries,[5,7,8] iron can decrease caries development teeth.[9] In adults, the most common cause of increased levels of heavy metals is through occupational exposure to heavy metal vapors. In children, possible sources of

exposure include water or paint containing lead.[10]

Studies of the dental health status, oral pigmentation of people in East Belitung Regency, Indonesia and also level of iron, lead, cadmium, fluoride and acidity of drinking are still scarce, therefore the aim of this is to collect the dental health status and oral pigmentation of residents, level of lead (Pb), iron (Fe), fluoride (F), Cadmium (Cd), the acidity (pH) of drinking water, of East Belitung District when Kuliah Kerja Nyata 2018 was held.

METHOD

A cross-sectional study was performed in 3 districts of East Belitung regency (Baru Village, Buku Limau Island, Manggar city) on February 2018. This study was approved by the University of Prof Dr Moestopo (Beragama) Research Ethics Board. The sample of this study is the participants of community service program of Merajut Nusantara 2018. Data were collected on a large number of variables including demographics, education, socioeconomic, dietary, frequency of smoking, oral hygiene routine and utilization of dental services. Participants were given written informed consent before joining the survey and intraoral examination.

The intraoral examination included recording of decay, missing and fillings (DMFT) in permanent teeth, Löe and Sillness's gingival index and oral pigmentation. Teeth were dried before the dental caries assessment followed by detection of macula and inflammation of gingiva by probing on buccal gingiva of first maxilla molar teeth, lingual gingiva of first mandibular molar teeth, labial gingiva of maxilla and mandibular of central incisor. The quality control was maintained by various procedures including training and calibration of staff, the use of a standard examiner, and ongoing monitoring of interexaminer reliability and consistency with the standard examiner. [7,11]

The collection of drinking water samples from 20 different locations in 3 districts for laboratory analyses in Jakarta to detect a concentration of Pb, Fe, F, Cd and pH of drinking water in accordance to standard analytic practices guidelines set forth in ISO 17025:2005. All the data were entered into an Excel database and analyzed including descriptive statistics and Mann-Whitney analyses, a p value $\leq$ 0.05 was statistically significant.

RESULTS

Total of 98 residents were recruited, the mean age of all residents was 18.949±13.626 years. Most of the residents were male, with 63.3% of them were students. Only 4 residents had a frequent visit to dentist, while 66 of the them never visited dentist. Table 1 presents descriptive information about residents.

Table 2 presents the result of intra oral examination of the participants including DMFT and gingivitis score, the mean DMFT score was 5.59±4.20 (mean of decay was 3.74 and missing teeth was 1.83) and gingivitis score was 0.79 ± 0.74. Eight residents have generalized gingival pigmentation and 11 residents have dark brown pigmentation on anterior gingiva (Picture 1).

Table 1. Characteristics of Residents of East Belitung District (Merajut Nusantara 2018)

Characteristics of residents	**n**	**%**
Mean Age (years) ± SD	18,949 ± 13,626	
Sex		
Male	52	53,1
Female	46	46.9
Village		
Baru	31	31.6
Manggar	30	30.2
Buku Limau	37	37.8
Educational Background		
No education	2	2
Drop out / currently studying elementary school	63	64.3
Complete elementary school	20	20.4
Complete junior high school	5	5.1
Complete senior /vocational high school	5	5.1
Complete bachelor	3	3.1
Occupation		
Student	62	63.3
Housewife	12	12.2
Fisherman	19	19.4
Security officer	1	1
Honorary worker	3	3.1
Goverment employees	1	1
Frequency of visits to dentist		
6 – 12 month	4	4.1
1 – 2 year	15	15.3
2 – 5 year	8	8.2
> 5 year	5	5.1
Never	66	67.3
Reason for visit the dentist		
Consultation	4	12.5
Pain / dental / gum problems	28	87.5
Wear denture		

Yes	5	5.1
No	93	94.9
Tooth brushing		
Tooth brush + tooth paste	95	96.94
Tooth brush	2	2.04
Never	1	1.02
Frequency of tooth brusing / day		
0	1	1
1x/day	5	5.1
2x/day	77	78.6
3x/day	15	15.3
Smoking		
Yes	20	20.4
No	78	79.6

Table 2. Result of Intra Oral Examinations

Intra Oral Examinations		**n**	**%**
DMFT		5.59 ± 4.20	
Criteria of Gingivitis			
Normal		32	32.7
Mild		29	29.6
Moderate		35	35.7
Severe		2	2
Score of Gingivitis			
Mean ± SD		0.79 ± 0.74	
Pigmentation			
Labial	Maxilla	2	2
	Mandible	2	2
Dorsum of tongue		2	2
Gingiva	Generalized	8	8.2
	Upper and Lower Anterior	11	11.2
	None	79	80.6

Table 3. Laboratory Result of Metal Concentration and Acidity in Drinking Water

Parameter	**Mean**	**Maximum Limit**
pH	5.56	6.5 - 8.5
Fe (mg/L)	< 0.01	0.3
Pb (mg/L)	<0.1	0.01
F (mg/L)	0.053	1.5
Cd (mg/L)	<0.01	0.003

Picture 1. Dark brown oral pigmentation on anterior gingiva (a,b,c) and dorsum of tongue (d)

Only 2 participants had free caries, 34 of them had lost their teeth, only 5 participants had wear dentures, 5 participants had normal gingiva according Löe dan Silness gingivitis criteria. The mean concentration of Pb, Fe, F, Cd and pH in drinking water from 20 sources located in 3 villages can be seen in table 3. The concentration of Pb and Cd were above the allowed maximum limit of drinking water. Contrarily, the concentration of Fe and F were below the allowed maximum limit. Only the drinking water in Buku Limau had pH above 6.5 (the limit range is 6.5 – 8.5) while two other villages had pH above 6.5.

Bivariat analysis between incidence of caries and independent variables cannot be done because only 2 participants were free of caries. According to Mann-Whitney analysis, there is no significant difference obtained for all independent variables: completed/not completed junior high school, frequency of tooth brushing, smoking with DMFT score (0.212; 0.446; 0.140). Analysis of Spearman's non parametric correlation between concentration of Pb, Fe, F, Cd and pH of drinking water and DMFT score were very poor.

DISCUSSION

Male participants more contribute to this study compared with female in accordance with the ratio of the total population of men to more than women in East Belitung Regency. There are 9 dentists in Belitung Timur District and some dentists concurrently become structural employees.[12] The number of participants

who have never been to a dentist is 67.3%, but the reasons for not seeing a dentist were not asked. While study conducted by Sintawati in 2011 showed that majority of residents had toothache did not know of any dental health facilities that can provide dental health services. There was no dental restoration found in this study and most of the teeth were extracted because of extensive decay. These conditions probably were caused by delayed of dental treatment.[1] The awareness to examine, restore decayed tooth is low, if decayed tooth can be restored before become more extensive, extraction can be prevented.[13]

In this study, the mean level of lead and Cadmium are higher than maximum limit. Exposure to Lead and Cadmium from cigarette smoke, mining areas, vegetables can increase the risk of dental caries. Cadmium concentration can be checked through urine which is a marker of accumulation of cadmium in the body but no urine examination was performed in this study. Exposure to cadmium in studies of neonatal rats showed an increase in severe caries, salivary gland damage and cannot be eliminated by drinking water fluoridation.[8]

The limit of fluoride in drinking water that reduces caries is 1 mg / L, whereas more than 1.5 mg / L results in fluorosis. Fluorine contained in 3 drinking water sources in this study is very low namely 0.04, 0.05 and 0, 07mg / L. Fluorine and Calcium contained in drinking water reduce the value of DMFS. The degree of acidity of water sources that are used as drinking water has a pH below 7 which is acidic. Drinking water with a high degree of acidity (low pH) has a significant relationship with dental caries.[12,14]

Iron can reduce caries development in studies in rats and iron added to cariogenic foods can reduce the incidence of dental caries in animals and humans. Whereas children with low caries have low levels of ferritin, iron and hemoglobin.[8] On contrary with this study, the level of iron in drinking water is below maximum limit. Heavy metals such as lead are assimilated into enamel teeth during mineralization and after eruption. Lead is reported to be absorbed into baby teeth from 4 months prenatally to the time of tooth exfoliation.[6]

Dental caries is a multifactorial disease and environmental risk factors such as dental plaque, cariogenic food, insufficient exposure to fluoride, poor oral hygiene, cariogenic bacteria in large quantities, and inadequate salivary flow can affect the development of dental caries.[15,16]

Primary accumulation of metals in the body is found in the bones. Teeth are known to be the location of concentrations of heavy metal deposits associated with exposure at the time of dentin or enamel

formation and are biological markers for determining metal exposure. Epidemiologists showed an increased susceptibility of children's teeth to caries that live in highly contaminated areas of heavy metals.[17]

Email crystals are not deposited into the collagen matrix but grow along with the loss of most of the enamel matrix protein. The initial enamel crystal looks like a long thin band extending from the amelodentinal junction to the surface of the enamel. When the secretory phase has been completed, the matrix protein will be degraded, resorbed and replaced by liquid. This liquid is then substituted with minerals with an increase in crystallites that expand and widen. Email protein is responsible for the degradation of the organic matrix into low molecular weight proteins that will leave the matrix. Abnormal post-secretory protein matrix processes result in the hypomaturation and hypocalcification of amelogenesis imperfecta.[17]

Blood lead levels are a clear indication of near-term lead exposure, although they do not accurately indicate a history of lead exposure. Because the effect of lead resembles the effect of calcium in some ways joined in calcified tissue such as bones and teeth. Enamel and dentin generally do not undergo significant remodeling but lead levels in these tissues (particularly the circumpulpal dentin) are more frequently measured to assess lead exposure in children. Studies by Needleman et al on lead are related to psychological deficits and class-related learning abilities related to lead levels in dentin as a result of evidence of lead exposure.[18,19]

Lead affects bone cell function through changes of 1,2,5 dehydroxyvitamin D3; interferes with the cell's ability to respond to hormone regulation. Lead interferes with the cell's ability to synthesize bone collagen or sialoproteins and directly affects or substitutes calcium in the active location of calcium and the messenger cAMP system.[17] Lead in divalent conditions substitutes the isovalent calcium position in dentin hydroxyapatite. Exposure to lead and dental caries has a time relationship that is antenatal and early exposure which results in teeth being more susceptible to caries development.[7]

Iron is a cofactor for salivary lactoferrin protein (LTF), the main protein with antibacterial activity. This protein can bind very strongly with 2 iron atoms and bicarbonate, which enhances bacteriostatic by cariostatic ability by limiting the availability of iron for bacterial cells.[20]

Caries prevention is carried out through fluoridation of drinking water, fissure sealants, patient education, dietary advice, and visits dentist. Iron added to cariogenic foods can reduce the incidence

of dental caries. Iron ion is a strong inhibitor of the enzyme glucosetransferase, is karyostatic, protects teeth against the pathogenicity of *S. mutans* by forming a protective layer that binds to the tooth enamel as hydrous iron oxides and has a high affinity for organic material. Gel and crystals from hydrous iron oxides can absorb various ions (including calcium and phosphate) and various atoms of crystalline. Iron can have the ability to replace minerals dissolved during the acidic phase of the caries process. Iron ions also mediate the fixation of remineralization particles on the organic part of tooth enamel.[9]

Total pigmentation in gingiva was found in 8 participants who smoked, the majority smoked filters, and only 6 smokers without oral pigmentation. Physiological pigmentation is more common in people with dark skin. The color of pigmentation can vary from light brown to black.[10,21] Physiological pigmentation increases with age and the color intensity can be influenced by smoking, hormones, and systemic treatment.[21] The most common location of this pigmentation is in the attached gingiva but can be found in various locations of the mouth including the tip of the papillae filiform in the dorsum of the tongue.[10,21]

CONCLUSION

The dental health status of the population of East Belitung Regency is very low, with low drinking water acidity and the mean level of Pb and Cd in drinking water were higher, while Fe and F were lower than the maximum limit. We suggest because of lack of dentist and low frequency visit to the dentist could cause dental caries. The occurrence of dental caries is not influenced by the metal contents of drinking water. Further studies about the concentration of trace elements in enamel and dentine with other factors affect dental caries for example diet, microflora, the form, susceptible and arrangement of teeth, salivary flow and oral hygiene.

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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.

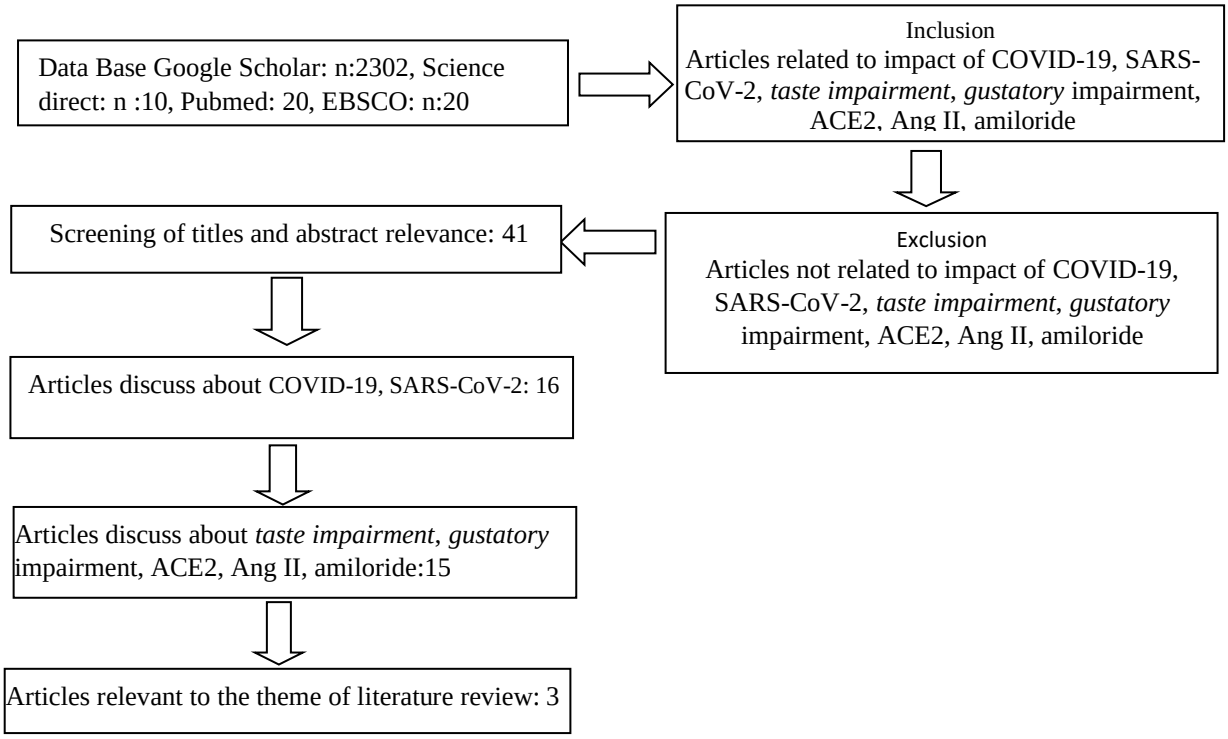

Figure 1. Publishing flowchart of all databases

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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