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Open Access Journal of Pulmonary & Respiratory Sciences
ISSN: 2642-1143

Soluble Angiotensin-Converting Enzyme 2 in Potential Therapy of Oral and Salivary Coronavirus Infection

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Research Article
Volume 6 Issue 1
Received Date: May 17, 2022
Published Date: July 15, 2022
DOI: 10.23880/oajprs-16000153

Abstract

A comprehensive search was carried out in mainstream bibliographic databases or Medical Subject Headings, including Science Direct, PubMed, Scopus, and ISI Web of Science. The search was applied to the articles that were published between 2004 and early 2022. With strict literature search and screening processes, it yielded 4 articles from 142 articles of initial literature database. In oral cavity, tongue has the highest angiotensin-converting enzyme 2 (ACE 2) expression and lesser amounts in the other oral tissues, oral mucosa, including the gingival tissue. By Pre-incubation with SARS-CoV-2 (COVID-19) RBD, CTB-ACE 2 activity was absolutely inhibited, offering a description for decreased saliva ACE 2 activity in COVID-19 patients. Through minimizing or debulking virus transmission, SARS-CoV-2 (COVID-19)-trapping proteins proposes an affordable strategy for protecting people from most oral re-infection, whereas newly evolving strains have higher viral load in saliva and greater transmission. Delta variant viral load in a patient is about 1,260 times higher than those infected with previous strains. In conclusion, ACE 2 fusion proteins or chewing gum can be used as the rapid methods of decreasing SARS-CoV-2 (COVID-19) from saliva and oral cavity of the infected patients for minimizing infection and transmission, diagnosis, inhibitors, vaccine development, and therapy of SARS-CoV-2 (COVID-19) disease.

Keywords: ACE 2; Angiotensin-Converting Enzyme 2; Chewing Gum; COVID-19; Oral; Salivary; SARS-CoV-2; Soluble

Abbreviations: ACE 2: Angiotensin-Converting Enzyme 2; AKI: Acute Kidney Injury; Ang II: Angiotensin II; AT 1,2: Alveolar Epithelial Cells Type 2; CKD : Chronic Kidney Disease; COVID-19: Coronavirus Disease-2019; CTB: Cholera Toxin B; DKD: Diabetic Kidney Disease; IC50: Inhibitory Concentration at 50 %; IgG : Immunoglobulin, mACE 2-Ig: Fusion protein Containing the ACE 2 Variants; RAS: Renin-Angiotensin System; RBD: Receptor-Binding Domain; SARS-CoV-2: Severe-Acute-Respiratory- Syndrome Coronavirus type 2; TMPRSS 2 : Transmembrane Protease Serine 2.

Objectives of the Study

To seek a comfortably novel method of SARS-CoV-2 (COVID-19) salivary and oral infection treatment that can prevent the disease progression.

Introduction

In oral cavity, tongue has the highest angiotensin-converting enzyme 2 (ACE 2) expression and lesser amounts

in the other oral tissues, oral mucosa, including the gingival tissue, in addition to other tissues of the human body, such as pulmonary alveolar epithelial cells type II (AT 2) or pneumocyte type II, myocardial cells (cardiomyocytes, expressed in myofibroblast and fibroblast in the stromal area spongiosa layer of the aortic valves), brush border of proximal renal tubular cells, urinary bladder urothelial cells, cholangiocytes (bile duct epithelial cells), ileum and colon enterocytes, and upper esophagus stratified epithelium [1]. Higher mean ACE 2 expression was identified in the minor salivary glands, in comparison to the lungs [1]. The SARS-CoV and SARS-CoV-2 spike protein 1 bind to ACE 2 that located on the host cytomembrane through transmembrane protease serine 2 (TMPRSS 2), a cytomembrane protease [2]. Two previous histological studies in Chinese rhesus macaques and rats have revealed the ACE 2 presence in salivary glands [3,4]. Nevertheless, clearly unexplored distribution details of the ACE 2 and TMPRSS 2 in human saliva, salivary gland, oral and nasal epithelium remain [5-7]. A recent study demonstrated that in vitro, exogenous ACE 2 and TMPRSS 2 can anchor and fuse to oral mucosa and SARS-CoV-2 spike protein can bind to ACE 2 in human salivary glands [5]. Several previous studies revealed that there was expression of ACE 2 and TMPRSS 2 in human salivary glands [8-11]. The majority of the previous studies on the clinical manifestations have not verified the COVID-19 patients' oral health status [12]. The alteration in the taste perception could be considered an early manifestation in COVID-19 patients although the mechanism for taste alteration is not clearly defined [13]. A previous study in American cohort of 305 COVID-19 patients, aged from 4 to 60 years revealed that the ACE 2 expression was lower among patients aged between 4 and 9 years, compared with adolescents and adults [14], while no cases of COVID-19 children with taste alteration have been reported [13], including the lower risk of pulmonary injury and inflammation among the younger COVID-19 patients [15,16]. In addition to SARS-CoV-2 (COVID-19) transmission via direct inhalation of microdroplets spread by coughing, speaking, sneezing, shouting, and singing, direct contact with virus contaminated surfaces by self-dissemination via oral, nasal, and ophthalmic mucosa [17]. A recent study on oral health among COVID-19 patients during hospitalization demonstrated that 25% of cases had taste impairment, 20% of cases had swallowing difficulty, and 15 % of cases reported burning sensation of the tongue and oral cavity (present only in female patients) [18]. A previous study in rodents revealed that gender- and age-dependent pattern of ACE 2 expression, with a more rapid decline with age in males, in comparison to females [19]. Additionally, 25% of patients presented thyroid disorders (hyperthyroidism or hypothyroidism), 15% of patients presented diabetes, and 15 % of patients presented obesity [18]. There were no statistically significant results on the onset of some manifestations emerged between age and sex in this study [18].

Method of the Study

Search Strategy and Inclusion Criteria

A comprehensive search was carried out in mainstream bibliographic databases or Medical Subject Headings, including Science Direct, PubMed, Scopus, and ISI Web of Science. The search was applied to the articles that were published between 2004 and early 2022. Our first involved performing searches of article abstract/keywords/title using strings of [("SARS-CoV-2" or "COVID-19", "Angiotensin-Converting Enzyme 2" or "ACE 2", "Soluble", "Therapy", "Salivary " or "Saliva", "Oral")]. After a first approach of search, published articles focusing on soluble ACE 2 therapy on oral and salivary COVID-19 infection were retained and the information on soluble ACE 2 in chewing gum and salivary and oral COVID-19 infection was extracted for having a crude knowledge involving their themes. Another round of publication search was conducted for adding the missing published articles that were not identified by the first round.

All keywords combinations from ACE 2, angiotensin-converting enzyme 2, chewing gum, COVID-19, oral, salivary, soluble, and SARS-CoV-2, to bind the population of cases were under consideration. Search string for disease groups include ["SARS-Cov-2" or "COVID-19" or "Oral " or " Salivary" or "ACE 2" or "Soluble ACE 2" or "Soluble Angiotensin-Converting Enzyme 2" or "Chewing" or "Gum"]. The initial literature databases were further manually screened with the following rules:

- Non-oral or salivary COVID-19-related articles were excluded;
- Articles that did not report an oral or salivary COVID-19 treatment outcome related to (soluble) ACE 2 were not considered, such as commentary articles, or editorial;
- Non-peer reviewed articles were not considered to be of a scholarly trustworthy validity; and
- Duplicated and non-English articles were removed. The in vitro, in vivo, and clinical studied articles were carefully selected to guarantee the literature quality, which is a trade-off for quantity.

With strict literature search and screening processes, it yielded 4 articles from 142 articles of initial literature database. Needed article information was extracted from each article by:

- Direct information including journal, title, authors, abstract, full text documents of candidate studies, publishing year;
- Study period;
- Research method used; and
- The conclusions made about the impact of soluble ACE 2 therapy on COVID-19-related oral and -related organ manifestations.

Results

From initial literature database of 142 articles, there were 4 published articles involving the ACE 2 therapy on COVID-19 as demonstrated in Table 1.

Published Year	Author (s)	Type of Study	Results/Conclusion
2019	Wysocki J, et al. [20]	In Vivo	Two short ACE 2 protein variants were systemically very active in mouse urine. Longer exposure of the 110 kDa native mouse recombinant ACE 2 to proteases from renal apical tubular membrane resulted in high ACE 2 enzymatic activity. Two active short ACE 2 proteins (1-619, 1-605) were around 4-5-fold higher than that of the native mouse recombinant ACE 2 protein. These short ACE 2 proteins were re-absorbable by the renal tubules, thus they could amplify renal ACE 2 protein activity and make attractive to fight against several renal diseases where the renin-angiotensin system (RAS) is over-active, such as acute-kidney- injury-associated COVID-19.
2020	Wrapp D, et al. [21]	In Vivo	SARS-CoV-2 S protein bound ACE 2 protein with higher affinity than did SARS-CoV S protein. SASRS-CoV Receptor-Binding Domain (RBD)-specific monoclonal antibodies did not have adequate binding to SARS-CoV-2, indicating that antibody-cross-reactivity between the two RBDs may be limited.
2020	Lei C, et al. [22]	In Vitro	Both fusion proteins (extracellular domain fusion recombinant human ACE 2 connecting to the Fc portion of the human immunoglobulin (IgG) 1, fusion mutant ACE 2 protein) demonstrated pharmacological properties in mice.
2022	Daniell H, et al. [23]	Case-Control	CTB-ACE 2 activity was completely inhibited by pre-incubation with SARS-CoV-2 RBD, providing the COVID-19 patients' reduction of the saliva ACE 2 activity. SARS-CoV-2-trapping- protein chewing gum demonstrated protecting COVID-19 patients from oral re-infections via debulking or virus transmission minimization.

Table 1: Demonstrating published articles related to ACE 2 therapy on COVID-19.

Discussion

ACE 2 proteins is normally found in the urine [20]. In mice model, small recombimant ACE 2 variants effectively degrade the excess of systemic circulating Angiotensin II (Ang II) and are both filtered and reabsorbed by the proximal renal tubules; therefore they can increase urinary ACE 2 activity and enhance blood pressure recovery [20]. Wrapp, et al. found that ACE 2 protein bound to SARS-CoV-2 (COVID-19) Sect domain with approximately 15 nM affinity that is approximately 10- to 20-fold higher than ACE 2 protein and formed complex of ACE 2 protein binding to SARS-CoV [21]. Increased RAS component activity in the kidney and urines was demonstrated both in rodent models of diabetic kidney disease (DKD) and in patients with DKD and non-diabetic CKD that contributing to both experimental and clinical acute kidney injury (AKI), both hemodynamic and non-hemodynamic mechanisms [20]. Lei et al showed that ACE 2 fusion proteins bund the RBDs of both SARS-CoV-2 (COVID-19) and SARS-CoV with a high affinity contributing to potently neutralized by ACE-Ig and mACE 2-Ig [21]. The IC50 values of ACE 2-Ig for SARS-CoV-2 (COVID-19) and SARS-CoV were 0.1 μg/mL and 0.8 μg/mL, and the IC50 values of mACE 2-Ig for the neutralization of these two viruses were 0.08 μg/mL and 0.9 μg/mL, respectively [22]. Most of the current human antibodies with potent neutralizing activity to the SARS-CoV reveal no cross-reactivity to SARS-CoV-2 [22]. Based on the pseudovirus system, neutralization of SARS-CoV-2 (COVID-19) with ACE 2-Ig can be targeted [22]. Recently, Daniell H, et al. [23] prepared ACE 2 chewing gum tablet containing ground plant powder (expressed CTB-ACE 2 up to 17.2 mg ACE 2/g dry weight (11.7 % leaf protein, having physical characteristics and taste/flavor like conventional gums) by a compression process without protein loss during gum compression) for debulking and bocking of SARS-CoV-2 (COVID-19) entry into human cells and demonstrated that ACE 2 activity was markedly decreased in 10 saliva samples of the COVID-19 patients compared with control group (2,582 +/- 439.82 versus 50,126 +/- 2,101, change in relative fluorescence units : 27.63 +/- 9.52 versus 225 +/- 30.82 mU/mg enzyme activity units) [23]. All 10 COVID-19 saliva specimens revealed a similar and almost undetectable ACE 2 activity, but one specimen demonstrated as an outlier with enzyme

activity (38,504 +/- 9,688 relative fluorescence units; 236.4 +/- 60.28 mU/mg enzyme activity units) similar to healthy saliva [23]. This patient was diagnosed of asymptomatic SARS-CoV-2 (COVID-19)-saliva-positive PCR [23]. By Pre-incubation with SARS-CoV-2 (COVID-19) RBD, CTB-ACE 2 activity was absolutely inhibited, offering a description for decreased saliva ACE 2 activity in COVID-19 patients [23]. Through minimizing or debulking virus transmission, SARS-CoV-2 (COVID-19)-trapping proteins proposes an affordable strategy for protecting people from most oral re-infection, whereas newly evolving strains have higher viral load in saliva and greater transmission [23]. Delta variant viral load in a patient is about 1,260 times higher than those infected with previous strains [23].

Conclusion

ACE 2 fusion proteins or chewing gum can be used as the rapid methods of decreasing SARS-CoV-2 (COVID-19) from saliva and oral cavity of the infected patients for minimizing infection and transmission, diagnosis, inhibitors, vaccine development, and therapy of SARS-CoV-2 (COVID-19) disease.

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