

COVID-19 in Dental Practice Is Prevented by Eugenol Responsible for the Ambient Odor Specific to Dental Offices: Possibility and Speculation

Hironori Tsuchiya^a Yoshiaki Takai^b

^aAsahi University, School of Dentistry, Mizuho, Japan; ^bGifu University of Health Sciences, School of Rehabilitation, Gifu, Japan

Highlights of the Study

- Despite a high risk of infection with severe acute respiratory syndrome coronavirus 2, the prevalence of coronavirus disease 2019 in dental professionals and patients was not high even during the pandemic.
- Eugenol, which is released from dental materials and aerosolized by dental procedures, has the ability to inhibit viral infectivity, replication, and cellular entry.
- We propose that eugenol prevents coronavirus disease 2019 in dental practice.

Keywords

COVID-19 prevention · Dental odor · Dental practice · Eugenol · SARS-CoV-2

Abstract

Dental professionals routinely work in proximity to patients even when either or both of them have suspected or confirmed COVID-19. The oral cavity also serves as a reservoir for SARS-CoV-2 because the virus is present in and replicates in oral secretions (saliva and gingival crevicular fluid), oral tissues (salivary gland and periodontal tissue), and oral microenvironments (gingival sulcus and periodontal pocket). Despite a high risk of SARS-CoV-2 infection, the prevalence of COVID-19 in dentists, dental hygienists, dental assistants, and their patients was similar to that in the general population even

during the pandemic. We propose that eugenol, which is responsible for the ambient odor specific to dental offices, could contribute to prevention of COVID-19 in dental settings. Eugenol is not only released from dental materials (filling, cement, and sealer) but is also aerosolized by dental procedures (grinding, polishing, and restoration). Such eugenol has been suggested to possess the potential to inhibit the infectivity and replication of SARS-CoV-2, the entry of SARS-CoV-2 into human cells by binding specifically to the viral spike protein, and the protease indispensable for SARS-CoV-2 replication. It has been shown that aerosolized eugenol acts on airborne viruses to reduce their loads. This review highlights a hypothesis that the environment of dental offices impregnated with eugenol suppresses SARS-CoV-2 airborne transmission and SARS-CoV-2 contagion between dental professionals and patients, preventing COVID-19 in dental

practice. Anti-COVID-19 eugenol might give insights into the safe delivery of dental treatment and oral care in the COVID-19 era.

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Introduction

Coronavirus disease 2019 (COVID-19) had rapidly spread all over the world since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), making a significant negative impact on global healthcare systems including dentistry. SARS-CoV-2 is most frequently transmitted through close contact with COVID-19 patients. However, dentists and dental hygienists must routinely work in proximity to patients with face-to-face communication. Such dental settings should increase bidirectional SARS-CoV-2 infection between dental practitioners and patients [1]. In addition to the risk of infection associated with dental treatments, the oral cavity also serves as a reservoir for SARS-CoV-2 [2]. SARS-CoV-2 is present in and replicates in saliva [3], minor and major salivary glands [4], gingival crevicular fluid and gingival sulcus [5], periodontal tissue [6], periodontal pocket [7], dental plaque [8], and dental biofilm [9]. Higher viral loads are found in such oral secretions and tissues even after recovery from COVID-19 [4]. SARS-CoV-2 was also confirmed to persist in the saliva for long periods [10]. Therefore, participants in dental practice are very likely to be exposed to oral secretions contaminated with SARS-CoV-2.

Dental procedures using high-speed rotary handpiece, ultrasonic scaler, air abrasion device, and air-water syringe generate aerosols (particles of $\leq 5 \mu\text{m}$ in diameter), droplets (particles of $>5 \mu\text{m}$ in diameter), and splatters (particles of $>50 \mu\text{m}$ in diameter) [11], all of which can be contaminated with SARS-CoV-2, and mediate the viral transmission via airborne routes and in a ballistic manner [12]. COVID-19 is presumed to spread easily in enclosed environments like dental offices because dental aerosol and droplet contaminated with SARS-CoV-2 travel up to 26 feet and keep the contagiousness up to 3 h [13]. Dental treatment and oral care potentially mediate SARS-CoV-2 infection, facilitating the spread of COVID-19 in dental practice with the consequent increase of COVID-19 prevalence in dentists, dental hygienists, dental assistants, and patients (Fig. 1).

Prevalence of COVID-19 in Dental Practice

Estrich et al. [14] conducted a Web-based survey from June 8 through June 12, 2020, to estimate COVID-19 prevalence among dentists in the USA. They demon-

strated that 90 of 2,195 dentists from every US state had been infected with SARS-CoV-2 with the prevalence of 0.9%. Another survey from June through November 2020 found that the cumulative COVID-19 prevalence among 785 US dentists was 2.6% over a 6-month period and the incidence rates ranged from 0.2% to 1.1% each month [15]. As of October 8, 2020, the prevalence of COVID-19 in 4,776 US dental hygienists was as low as 3.1% among US dentists [16]. A French survey also showed that the prevalence of COVID-19 is 1.9% in 4,172 dentists and 0.8% in 1,868 dental assistants [17]. Similarly, SARS-CoV-2 infection rates among dental practitioners appear to be similar to those of the general population in different countries including France [18], Italy [19], Romania [20], Russia [21], and South Korea [22]. A global questionnaire-based survey was carried out to evaluate morbidity due to COVID-19 among dental professionals from May to August 2020 [23]. This worldwide epidemiological study revealed that the reported rates of COVID-19 for a total of 52,491 dental professionals in 36 countries/areas are not different from those for the general population in each country. Interestingly, the cumulative COVID-19 positive rates among dental professionals were lower than those in the population of many countries such as USA, Singapore, India, Argentina, Egypt, etc.

A study on Romanian dental practitioners found that most of COVID-19 cases of dentists occurred at home (47.9%) or resulted from event attendance (9.7%), suggesting that working in dental offices is not the primary source of SARS-CoV-2 infection [20]. Tanaka et al. [24] performed an online questionnaire survey from February 2020 to January 2021 in dental and oral/maxillofacial surgical departments of 51 Japanese university hospitals to determine confirmed or probable COVID-19 cases among patients and clinicians. While more than 70% of the hospitals had more than 2,000 new patients, SARS-CoV-2 contagion was identified neither between patients with COVID-19 and dental staffs nor between dental staffs with COVID-19 and patients. During and shortly after the height of the pandemic in New York, 2,810 patients were treated in different dental offices over a 6-month period [25]. In a prospective study on COVID-19 incidence in these dental offices, SARS-CoV-2 infection was not found among dentists, dental hygienists, and patients. Moreover, no scientifically confirmed clusters of COVID-19 have occurred in dental settings [26, 27]. Despite a high risk of SARS-CoV-2 infection, dental treatment and oral care are unlikely to mediate SARS-CoV-2 infection and facilitate the spread of COVID-19 in dental practice even during the pandemic.

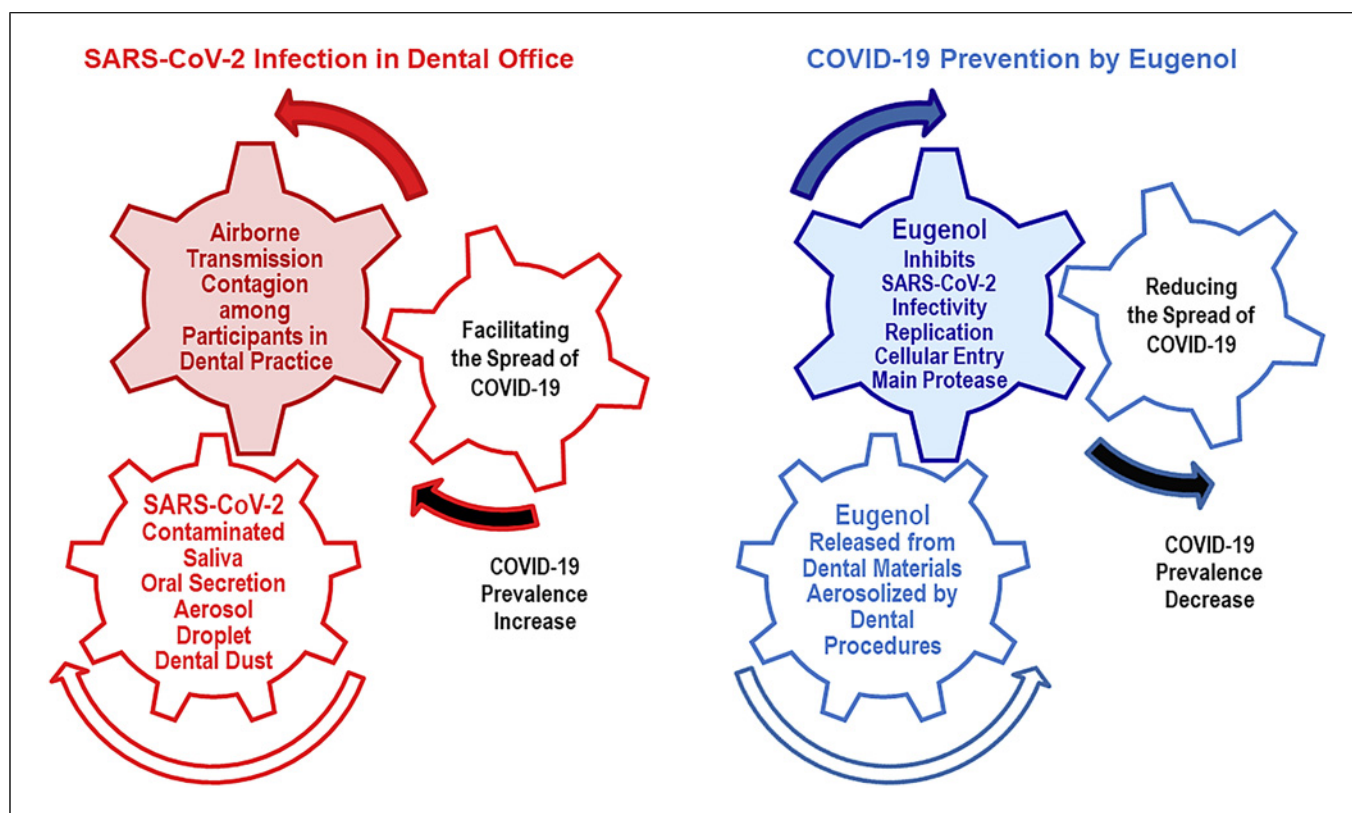


Fig. 1. Eugenol may prevent COVID-19 in dental practice. SARS-CoV-2 airborne transmission and SARS-CoV-2 contagion between dental professionals and patients facilitate the spread of COVID-19, whereas anti-COVID-19 eugenol released from dental materials and aerosolized by dental procedures may reduce the spread of COVID-19.

Prevention of COVID-19 in Dental Practice

The relatively low prevalence of COVID-19 in dental professionals and patients may be attributed to several preventive factors suggested by prospective, experimental, and speculative studies. First, dental visits were drastically decreased during the COVID-19 pandemic except for urgent or non-delayed cases [28]. Second, dental professionals have traditionally maintained high awareness of prevention of viral infections since the emergence of HIV and the epidemic of hepatitis B and C, and have therefore actively adopted preventive measures against viral infection, abided by a protocol for infection control, and used personal protective equipment in routine treatments long before the outbreak of COVID-19 [29]. Third, aerosol-generating dental procedures were confirmed not to induce a significant increase in the risk of transmission of SARS-CoV-2 [30], and fourth dental procedures unexpectedly generated only small amounts of aerosols [31]. Fifth, the microbiota in aerosols were found to originate

from the irrigants used in dental equipment, not from saliva [32]. Finally, evacuation, filtration, and suction systems were confirmed to be effective in decreasing aerosols and droplets contaminated with pathogenic viruses [33] and human saliva contains antiviral substances that potentially inhibit SARS-CoV-2 infection [34]. However, these insights are not applicable to every dental professional and every dental office. Nor do they explain the reason for why the prevalence of COVID-19 in dental practice is lower than expected. It is proposed that eugenol, which is responsible for the ambient odor specific to dental offices, could contribute to prevention of COVID-19 (Fig. 1). To support this hypothesis, we speculate on the possibility that eugenol exhibits the anti-COVID-19 activity to reduce the spread of COVID-19 in dental practice by reviewing the literature.

The dental environment is polluted by volatile or aerosolized chemicals and floating dust (airborne solid particles) that produce the odor to characterize dental offices. Such dental odors are primarily caused by ingredients

in dental materials, aerosols and airborne dust generated by dental procedures, and disinfectants used for infection control. Eugenol in particular has been recognized as the most common odor specific to dental offices because it is widely used in dentistry for many years because of its local anesthetic, dental pulp sedative, anti-inflammatory, and disinfectant effects. Eugenol is a major ingredient in dental materials such as filling, cement, endodontic sealer, periodontal dressing, impression material, dry socket dressing, and disinfectant. Eugenol is combined with zinc oxide to produce an amorphous chelate compound, zinc oxide-eugenol, which is used for dental pulp filling and temporary sealing. These dental materials are known to release eugenol continuously [35]. In addition, dental procedures such as grinding, polishing, and restoration generate dental dusts containing eugenol [36]. In some patients, the odor of eugenol may evoke memories of unpleasant dental experiences and fear of dental treatments [37]. However, if eugenol possesses the significant anti-COVID-19 activity, it could decrease the prevalence of COVID-19 in dental practice. Dental eugenol may be effective in reducing the spread of COVID-19 in dental offices, which is supported by its inhibitory effects on (i) the infectivity and replication of SARS-CoV-2, (ii) the entry of SARS-CoV-2 into human cells, and (iii) the protease indispensable for SARS-CoV-2 replication as discussed below.

Anti-COVID-19 Activity of Eugenol

Given the global outbreak of COVID-19 and the lack of effective drugs, medicinal plants have been actively studied to identify their bioactive components, phytochemicals, with antiviral and anti-inflammatory activity [38]. One of the promising phytochemicals is eugenol originating from clove (*Syzygium aromaticum* L.). If eugenol derived from dental materials and dental procedures inhibits the infectivity and replication of SARS-CoV-2, it should affect SARS-CoV-2 airborne transmission and SARS-CoV-2 contagion between dental professionals and patients with the consequent reduction of the spread of COVID-19, resulting in prevention of COVID-19 in dental practice (Fig. 1).

Tragoolpua and Jatisatienr [39] investigated ethanol extracts from clove flower buds and the isolated eugenol for herpes simplex virus (HSV)-inhibitory effects on standard HSV-1(F), standard HSV-2(G), and ten HSV isolates. Plaque reduction assay showed that eugenol is able to inhibit these viruses more potently than the crude extracts. In in vitro experiments, eugenol inhibited viral replication with IC_{50} of 25.6 $\mu\text{g/mL}$ for HSV-1 and IC_{50} of

16.2 $\mu\text{g/mL}$ for HSV-2, and topical application of eugenol delayed the development of herpesvirus-induced keratitis in the mouse model [40]. Eugenol was also found to inhibit influenza A virus replication [41]. Eugenol has antiviral activity against different types of viruses [42], supporting the possibility that eugenol inhibits SARS-CoV-2 infectivity and replication.

When SARS-CoV-2 enters human cells, its spike protein plays a critical role by binding to angiotensin-converting enzyme 2 (ACE2) on host cells [43]. The SARS-CoV-2 spike protein is composed of two subunits S1 and S2; S1 contains a receptor-binding domain, which recognizes and binds to ACE2 [44]. Molecular docking analysis indicated that eugenol interacts with the SARS-CoV-2 spike protein as a possible ligand [45]. Torres Neto et al. [46] determined the antiviral activity and cytotoxicity of essential oils (the secondary metabolic products of plants) by the cell-based pseudoviral entry assay with SARS-CoV-2 delta pseudovirus and the XTT assay with human ACE2-expressing HeLa cells, respectively. They found that essential oils, which are rich in eugenol, inhibit the cellular entry of SARS-CoV-2 delta variant but exhibit relatively low cytotoxicity. Paidi et al. [47] screened eugenol, ursolic acid, oleanolic acid, and β -caryophyllene to identify a substance capable of binding to SARS-CoV-2 spike protein S1 by using an ACE2: SARS-CoV-2 spike inhibitor screening assay kit. Among tested phytochemicals, eugenol inhibited the interaction between spike S1 and ACE2 and suppressed the entry of pseudotyped SARS-CoV-2 into human ACE2-expressing human embryonic kidney 293 cells. Their analysis of ligand-to-receptor binding by a thermal shift assay indicated that eugenol binds to SARS-CoV-2 spike S1 but not to ACE2. ACE2 is a functional receptor that plays a pivotal role in the renin-angiotensin-aldosterone system as ACE2 cleaves angiotensin II to angiotensin (1-7) with vasodilating, anti-inflammatory, and anti-fibrotic effects, counterbalancing the activity of ACE to convert angiotensin I to angiotensin II that induces vasoconstriction, inflammation, and renal sodium reabsorption. Thus, eugenol is expected to inhibit the cellular entry of SARS-CoV-2 without adversely affecting the physiological functions of ACE2. Paidi et al. [47] revealed that eugenol reduces not only the SARS-CoV-2 spike S1-induced activation of NF- κ B (nuclear factor kappa-light-chain enhancer of activated B cells) that regulates early innate immunity, chronic inflammatory states, and viral infection but also the expression of proinflammatory cytokine interleukin-6, interleukin-1 β , and tumor necrosis factor- α in human A549 lung cells. In their experiment using mice intoxicated with recombinant

SARS-CoV-2 spike S1, oral administration of eugenol suppressed lung inflammation, decreased fever, improved heart function, and increased locomotor activity.

SARS-CoV-2 main protease (M^{Pro}) or 3-chymotrypsin-like protease (3CL^{Pro}) has an indispensable role in viral replication and cleavage of nonstructural polypeptides to functional proteins [48]. Therefore, this enzyme is referred to as a possible target for COVID-19 prevention and treatment. For targeting the M^{Pro}, Chandra Manivannan et al. [49] investigated a total of 53 clove components by molecular docking, molecular dynamics simulation, and pharmacokinetic profiling. Among tested phytochemicals, eugenol showed a possible antagonistic property against SARS-CoV-2 M^{Pro}. In an in vitro inhibition study of Rizzuti et al. [50], eugenol inhibited the activity of SARS-CoV-2 3CL^{Pro} with Ki of 0.81 μ M. Eugenol was also suggested to act on the active site of SARS-CoV-2 papain-like protease that is responsible for regulation of the viral spread [51].

Taken together, these observations suggest that eugenol has the potential to prevent COVID-19 by reducing the infectivity and replication of SARS-CoV-2, binding to the spike protein of SARS-CoV-2 but not to its receptor ACE2, suppressing the cellular entry of SARS-CoV-2, and inhibiting the SARS-CoV-2 replication-relevant protease. Eugenol is also considered to be a preventive agent against the pathopoiesis of COVID-19 [52].

SARS-CoV-2 was confirmed to remain viable in aerosols for 3 h and on inanimate material surfaces for up to 3 days after application [53]. SARS-CoV-2 can survive at room temperature for 3 days and can persist even longer in environments with higher humidity [54]. Bacterial viruses (bacteriophages or phages) have been used as surrogates for viruses in aerosol studies because they display physical characteristics similar to those of pathogenic viruses. Turgeon et al. [55] aerosolized several chemicals, including eugenol, together with four distinct phages: MS2 (single-stranded RNA), Φ 6 (double-stranded RNA), Φ X174 (single-stranded DNA), and PR772 (double-stranded DNA) and then maintained the resulting aerosols in suspension in the environmental chamber at 19°C with different humidity. Consequently, eugenol reduced viral loads in the air by exposure for 10 min to 2 h, especially with greater effects on airborne RNA phages, suggesting the strategy of inhibiting SARS-CoV-2 infection by eugenol aerosols. In their airborne phase model, viral load reduction by eugenol was more significant with increasing humidity. Such a humidity-depending effect of aerosolized eugenol is advantageous for reducing the infectivity of SARS-CoV-2 because this virus has a preference for humid conditions to survive in the air [54, 56].

Another monoterpenoid thymol originating from thyme (*Thymus vulgaris* L.) is used in dentistry for root canal filling, dental resin, and mouthwash. This phytochemical provides dental offices with additional odor. Thymol has antiviral activity against SARS-CoV-2 [57] and inhibits SARS-CoV-2 spike protein binding to ACE2 receptor [58]. Dental thymol may contribute to prevention of COVID-19 along with eugenol.

Possibility of Prevention of COVID-19 by Dental Eugenol

To the best of our knowledge, the concentration of eugenol in the air of dental offices has not been determined in the literature. Most patients can smell eugenol in dental practice, and this odor may be negatively associated with dental treatments in some patients with dental phobia [59]. Wise et al. [60] measured the olfactory detection threshold of eugenol by using a 2-alternative force-choice-modified staircase method. Consequently, the obtained threshold ranged from 5.23 ppm to 376 ppm for humans. It is speculated that dental offices are possibly impregnated with eugenol in these concentrations because most patients can recognize eugenol as the typical odor of a dental office or “dentist odor.” In an aerosolization experiment, eugenol significantly reduced the viral loads of airborne RNA phages at a concentration of 16 ppm [55], which is not only perceptible as the dental odor but effective in preventing COVID-19 in dental practice.

Conclusions

While there are no clinical data to support our hypothesis, eugenol has the potential to suppress SARS-CoV-2 infection among dental professionals and patients because of its multimodal anti-COVID-19 effects on the infectivity and replication of SARS-CoV-2, the cellular entry of SARS-CoV-2, and the main protease of SARS-CoV-2 indispensable for viral replication. Aerosolized eugenol is able to act on airborne viruses and reduce their loads. As eugenol may help prevent COVID-19 in dental practice, further studies on eugenol responsible for dental odor will yield insights into the safe delivery of dental treatment and oral care in the COVID-19 era.

Statement of Ethics

Not applicable because the present study includes neither human nor animal experiments.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

Hironori Tsuchiya designed the study and the figure. Hironori Tsuchiya and Yoshiaki Takai wrote and reviewed the manuscript.

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Data Availability Statement

All data generated by the present study are included in this article. Further inquiries can be directed to the corresponding author.

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