



Dentistry pathways of coronaviruses transmission: a review

Zahra Setayesh-Mehr¹ · Mahdiye Poorsargol²

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Abstract The nCoV-19 in a short period of time, in lower than two months has been spread as a pandemic in all over the world. This novel type of Coronavirus which shows itself with coughing, sneezing, fatigue and respiratory symptoms which is similar to cold illness has killed more than 100,000 people. However, many protocols have been established to minimize the number of infected people, but without any border and regardless the nationality, this virus has been spread in all countries. In this review, with broad mechanistic and interdisciplinary consideration the dentistry pathways of transmission, physiology, effective and available drugs and their biological inhibiting pathways have been discussed. Among many reasons that have caused higher rate of spreading, the dental services and surgeries involve to professional-patient close contacts could be seen as one of the probable pathways of transmission for this virus. According to the more recently reported literatures, the blueprint of many individual and instrumental reasons in dentistry, could be observed in nCoV-19 infection and spreading which raise the concern of the professionals about the efficiency of conventional antiviral methods. So, results of many studies attributed to the facts that the superhydrophobic antiviral materials and surfaces are potential candidates for designing dentistry instruments with more antiviral properties.

Keywords nCoV-19 · Virus · Infection · Transmission · Dental

Introduction

A simple symptom which known to Severe Acute Respiratory Syndrome (SARS) fomented on one of the most awful pandemic mortality of the human-being in a recent year. The recent complicated global pandemic of Coronavirus (nCoV-19) trapped the modern societies under a disruptive shock, while many allegations in recent years have emphasized the existence of a highly-standard and uniform controlling and therapy systems in modern societies. The first infected case of nCoV-19 has been observed in Wuhan city, China [10], while we after one year are feeling a condition that clearly notify an unfortunate for us which says: the human-being civilization what could be fragile! The results of primary considerations indicated that bat and also anteater possibly been as initial sources for this pandemic. The nCoV-19, RNA-type of virus -six subtypes consist on α , β , γ and δ - in which shows better capability to infect animals than human-being has been categorized in. The degree of ability for mortality are different in these types of viruses, while we now understand that the β are the most dangerous types which show a cold-like respiratory symptom [43]. In a similar condition, we experienced the SARS-CoV in recent decade in which remembered the fact that they had an animal origin for initiation of pandemic and they were probably bats and camels. Dubiously, the first cases for the SARS-CoV pandemic was initiated from the China in 2003. Air is the main pathway of this virus which could be transmitted between people with contacts such as handshaking, or contaminations by coughing in crowding. World health organization (WHO)

✉ Mahdiye Poorsargol
poorsargol.m@uoz.ac.ir
Zahra Setayesh-Mehr
setayeshmehr@uoz.ac.ir

¹ Department of Biology, Faculty of Science, University of Zabol, P.O. Box 35856-98613, Zabol, Iran

² Department of Chemistry, Faculty of Science, University of Zabol, P.O. Box 35856-98613, Zabol, Iran

reports about victims attributed to about ~ 2200,000 people [2]. In accordance to the fact that the nCoV-19 and SARS-CoV have similar transmission pathways [1, 40], the dental transmission can potentially play a role in prevalence of nCoV-19 [51]. Due to serious and fast transition during dental services the New York Times warned that controlling the dentistry services could break the transfection cycle impressively [51], which this could be occurred, if dentists utilize the protective wearing during the surgery and treatment [12]. Its well known that the dental apparatus are in exposure of smearing with saliva, and if the patient have been infected to the coronavirus, the risk of virus transmission by such apparatus could potentially be increased because of dentistry services such as polishing, drilling, making cavity and coating roots the coronavirus can be transfected [39]. For this reason, the continuous disinfecting the dentistry apparatuses is vital for inhibiting viral transfection. On the other hand, because of the close distance between professionals and patients in dentistry process both of them could be act as transmitter and recognizing that which one has been host would be hard and risk of infection in dentistry process is high. Therefore, this review focused on the fundamental and physiological aspects of nCoV-19, the transfection pathways, recently developed virus inhibitors and their mechanism of inhibition [2, 26, 24]. The main aim of this study is representing a better and comprehensive view about nCoV-19 and protective procedures which could be necessary for professional dentists and patients to minimize infection probability.

Physiology

Coronaviruses with extremely small size (50–200 nm) have peplomers in 17–20 nm. These spikes morphologically are cubic, pear and petal-like which their width is about 10 nm and known to hemagglutinin-esterase (HE) protein. Helically symmetric nucleocapsids of the coronavirus attributes to the negative-strand RNA, while surprisingly in all animal case viruses these nucleocapsids are positive-strand RNA. The spikes are contained to three main envelopes. First one is the S glycoprotein (known to E2) which acts as an intermediate for attaching receptor to the host cell surface. The E2, N-exo, C-endo transmembrane protein, which has very enormous molecular structure forms the distinctive surface of spikes. The E2 ectodomain which consists 30 and 50 conserved cysteine residues, has been cleaved by a trypsin protease into polypeptides. Additionally, the E1 glycoproteins which are O- and N- glycosylated structure play role in virus-host interactions. The rate of viral replication has been controlled by interaction between replicase proteins and noncoding 5' and 3'

untranslated region sequences in the genome [71, 46, 52, 61].

Estrogen receptor modulators-based inhibitors

The ER α and ER β estrogen receptors are known as the most important transcripesses that act as regulators of the reproductive system especially in maintaining of cardiovascular and skeletal system. Due to such high biological potentials, they have been targeted for designing drugs for broad types of diseases such as osteoporosis and breast cancer. Their application in desining antiviral drugs recently received much attentions that resulted various types of drugs [13].

Toremifene

Overexpression of estrogen receptor could be targeted as designing inhibitors for these types of viruses because that they play a critical role viral replication process [41]. Using post viral entry step and influencing on fusion process the estrogen receptor expression could be as methods for inhibiting virus [28]. The Toremifene known to non-steroidal inhibitor which shows promising potential in inhibiting MERS-CoV, SARSCoV, and Ebola virus. In comparison what are in the classical ESR1-based pathway for inhibiting viruses, Toremifene works based on preventing the fusion process which occurs between virus and endosomal membrane structure by using destabilizing of the glycoprotein membrane [16, 14]. Principally, this type of drugs could potentially disrupt the proteins action like HNRNPA1, RPL19, EIF3I, NPM1, EIF3E and EIF3F [22, 67].

Equilin

One of the most important and comprehensive studies that considered drugs to reveal their anti-COVID activity, executed in Ohio, USA using analysis of successful combination of different substances. They showed that there are 16 highly-potent materials for this aims that have been obtained by bioinformatics analysis that consider drug-gene interactions with emphasizing on antiviral properties. The Equilin was in their list and they offered that the combining drugs could represent a potentially significant therapeutic influence. Although the antiviral effect of this drug has been proved against Zaire Ebola virus, it could be examined for coronavirus [16, 56].

Blockers of angiotensin receptors

Irbesartan

As blockers of angiotensin receptors, the Irbesartan shows a reliable blocking effect on HCoV-host proteins in interactome. This inhibitor blocks the SLC10A1 and also encodes protein known to sodium/bile acid co-transporters. The SLC10A1 proteins during an interaction with C11orf74 as transcriptional repressor could disrupt the nsp-10 pathway in SARS-CoV. In addition to Irbesartan, Frovatriptan, Eletriptan, and Zolmitriptan are other families of blockers which have similar blocking pathways [50, 59, 23, 69, 38, 27]. The pathway of receptor blocking was depicted in Fig. 1 [58].

Immunosuppressant agents

Sirolimus

Based on the fact that the blueprint of mammalian target of rapamycin complex 1 in replication process of viruses (coronavirus and Andes orthohantavirus) have been proved, suppressing this pathway have been targeted for designing families of drugs. Sirolimus works based on blocking the protein expression process in viruses and could decrease the infection by MERS-CoV more than 60 % [48, 65, 68].

Mercaptopurine

This drug is known to a powerful antineoplastic agent which able to carries out immunosuppress process

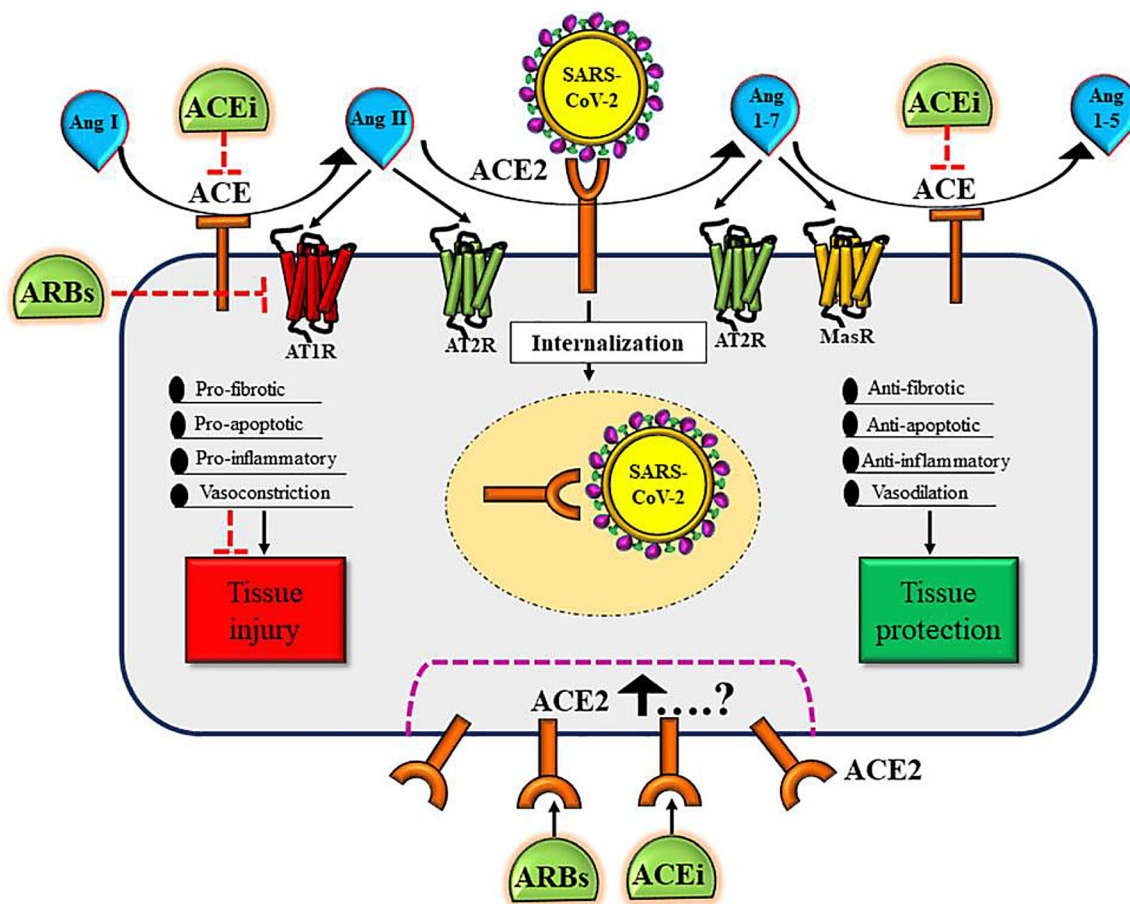


Fig. 1 This schematic image shows that how renin angiotensin system of type 2 alveolar epithelial cells and SARS-CoV-2 interact each other and how a angiotensin receptor blocker works. In this system, the angiotensin II (Ang II) and Ang I have been converted to the Ang 1-7 and Ang 1-9 by angiotensin-converting enzyme 2 (ACE2), respectively. These conversions make the host type 2

alveolar epithelial cells potent for virus internalization process. The internalization could foment on the fibrosis, apoptosis and etc. Angiotensin receptors (ATR) could be blocked by the mentioned blockers and prevent from the virus internalization process. The Figure reproduced with permission from ref [58]. Copyright 2020 Journal of Cardiovascular Pharmacology and Therapeutics

efficiently. This drug which has been utilized for cancer therapy and also controlling the autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and Crohn's-based disease since 1950s. From mechanistic point of the view, this drug could interrupt the host PABPC1, JUN, NPM1, and NCL proteins in HCoV's [29, 5, 8, 4].

Anti-inflammatory drugs

Melatonin (N-acetyl-5-methoxytryptamine)

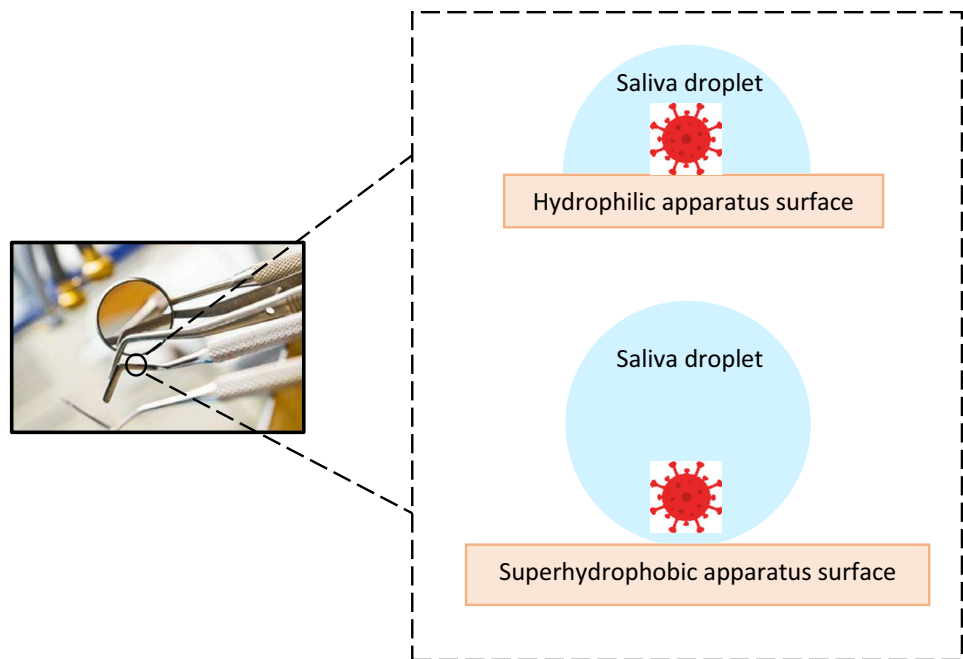
Melatonin represents antioxidant effect which this capability makes it as suitable option for clinical applications. Meanwhile, melatonin does not represent any anti-replicative or transcription effect on coronavirus. Eplerenone is other type of anti-inflammatory drugs which works based on blocking the mast-cell-derived proteinases enzymes and also the suppressing fibrosis and eplerenone could inhibit the encephalomyocarditis-based viruses [60, 64, 66].

Antiviral surfaces

Typically, the chemical solutions, thermal autoclave, ozonizing methods have been used as procedure for cleaning contaminations from the metal, glass and plastic surface of apparatus [72]. Based on the fact that the viral and bacterial adhering mechanism on surfaces could be followed from the similar mechanism, it is expected that the antibacterial surfaces be able to represent antiviral properties. In recent years, the antibiotic infused anti-bacterial surfaces have been developed for many clinical applications which their function in killing Gram-positive and Gram-negative bacteria have been proved so far. However, the bacteria could be adapted against antibiotics using gene mutation process, the superhydrophobic antibacterial surfaces are able to represent the antiviral and antibacterial properties using extreme decreasing in their adhesion. It is well known that the superhydrophobic surface benefit to low adhesion because of low surface free energy and high roughness degree and based on the fact that the adhesion ability is very crucial of bacteria and viruses replication and colonization process, potentially the superhydrophobic surfaces not only are the promising antiviral antibacterial options, but also they could reveal many mechanistic aspects of the bacteria and viruses adhesion. The saliva droplets cannot spread on superhydrophobic apparatuses and causes the low saliva-surface interaction and consequently low virus-surface interactions (Fig. 2). Basically, superhydrophobicity is a property of the

highly hydrophobic surfaces which obtains this ability from low surface free energy ($> 10 \text{ mN/m}^2$) and high roughness degree which depends on the surface morphological aspects (shape, size and symmetry). Nanomaterials as one of the most important options with vast applications in biological [17, 20, 6, 21, 18] and non-biological [7, 31, 34, 36] sciences have played significant roles for obtaining mentioned properties. The water contact angle on these surfaces that mainly can influence by surface morphology typically greater than 150° which such high contact angle could be interpreted by the collaboration between surface free energy and roughness degree and recently received various applications [37, 32]. The mechanistic aspects of this phenomenon have recently reviewed and their suitable capabilities in representing antibacterial and antiviral features have comprehensively been highlighted [35]. Fundamentally, hydrodynamic layer of the surfaces plays critical role in mechanistic aspects of viral and bacterial adhesion where a micron layer of absorbed water could be found in that zone. The physicochemical properties of this layer which predominant the adhesion of viruses and bacteria has recently evaluated by Ali Najji and co-workers. Based on their findings, the upstream swimming in hydrodynamic layer makes the viruses and bacteria to swim in this layer in opposite side of flow during shear-induced force that tries to remove them from the surface. Height-dependent torques are the main reason for upstream swimming. Therefore, in contrast to believes, sterilizing with a simple wet napkin could not be enough [54]. There are many reports for this application. For example, the $\text{La}_2\text{Mo}_2\text{O}_9$ ceramics-based hydrophobic surfaces (contact angle = 105.7°) show the dual antiviral and antibacterial properties against *Escherichia coli* and *Staphylococcus aureus* and bacteriophage $Q\beta$ and bacteriophage $\Phi 6$ [47]. Another strategy could be using photocatalytic antibacterial and antiviral materials and surfaces. There are many types of self-cleaning photocatalytic-based surfaces that significantly utilize photodegradation process during UV-Vis light absorption for destructing bacteria, viruses and organic molecules on the surfaces [33]. They are fast enough due to the photochemical-based reactions of the photodegradation process [45]. Not only they could be used as cleaning agent and self-cleaning antiviral surfaces, but also their application in designing medical and dental implants have been proved and well documented so far. Additionally, they provide a great capability for designing biosensors for detecting viruses with low limit of detection. Also, they could provide a biosensor approach for detection of broad range of viruses [19].

Fig. 2 Schematic illustration of the dentistry apparatus surfaces in (up) hydrophilic and (down) superhydrophobic condition. As shown, saliva droplets could not spread on the superhydrophobic surface and minimizes the virus-surface interactions



Prevalence pathways

Up to April 14, 2020, the number of infected and dead victims by coronavirus in the world were about $\sim 1,930,000$ and $\sim 119,000$ respectively [55]. Now, all of the world are struggling with pandemic and in accordance to breaking news USA and some European countries unfortunately have the rank of highest infected and mortality by the nCoV-19 [25]. Depends on many cultural, geographical and many other factors related to the social communications, this virus has various statistics of pandemic. It seems that social collaboration, safety and health welfare, local weather condition and many other factors be impressive in spreading rate of nCoV-19. However, in cold and warm regions activity of the virus has been restricted in an unknown mechanism [1, 63], but in middle zones the rate of infection is high [55]. It is a hard to recognize the complex pathways of infection and there are many proved pathways which relate to the respiratory system. The social contacts are the first reason for fast infection while the blueprint infection during dentistry and saliva could not be ignored. The oral fluids with spreading during eternal sneezing and also dry coughing could explain that how much is the risk of infection, if a person be under this condition [42]. Dental apparatus, inappropriate wearing could be as potential origin of virus. Physiologically, even though the mechanism of nCoV-19 adhesion on various surfaces is unknown issue, some reports clearly showed that open reading frame (ORF8) proteins and also the interfacial glycoproteins give a great ability for the virus to adhere many surfaces. This mechanism of adhesion is

significant enough to help virus for establishing an effective interaction with host cells [43, 44]. Another report by Andrew et al. revealed the probable of interaction between renin-angiotensin system (RAS) and virus. The results indicated the pathogenic role of RAS which could play in interactions. This process relates to hypertension and transmission in patients which foments on more RAS inhabitation in comparison to what occurs for SARS-CoV [62]. Based on the fact that the majority of dentistry apparatus are metal and nCoV-19 adhesion on such materials is strong and stable, the scenario of virus pandemic could raise these speculations that how much the cleaning process of the apparatus and surfaces significant is? [42, 53]. In order to reach to an apt response to this questions, deep understanding about the stability, mechanism of adhering and more importantly the property of hydrodynamic layer of the substrate which fundamentally the majority of viruses are adhered in that region would be as promising clues to find the best cleaning instructions. Still, in reported documents the lack of considering such parameters have been felt and there are a few studies that fundamentally have evaluated them so far. The coronavirus is able to endures a period of time about nine days on surfaces [72]. So, the long-time persistence could be as a key factor that could raise the risk of transmission [9]. Elderly, the probable transmission of Hepatitis B and C and HIV in dentistry process has been proved and well documented so far and similar to these viruses, coronavirus possibly could be transmitted in this pathway. These pathways consist on the contaminated apparatus which routinely have direct contact with blood veins or saliva in

oral cavity. So, based on the results the nCoV-19 should be added to the list of viruses that have dental transfection pathway [11]. Unfortunately, scenario transfection in nCoV-19 with dental pathways could be very complicated due to the fact that many factors could intervene which mainly consist direct and close dentist-patient, patient-apparatus and dentist apparatus contacts. These contacts concentrate on the unsafe using of splutter system and aerosols unwanted spreading. As mentioned earlier, there is not exact understanding about the mechanism of transmission and many factors could intervene in this cycle. But the dental aerosol microdroplets spreading could be considered as a potential virus carrier and could have many origins such as splutter system and dental polishing [11]. Therefore, understanding about the suitable interfacial cleaning methods would be promising and urgent.

Professional-patient contacts

The professionals and patients could be as host or guest and be infected or infect others during a close human-human contact. The non-invasive salivary-based symptoms such as sneezing or coughing and other treatment procedures which could spread saliva, such as handpiece or instruments or bleeding during dental surgery could enhance the risk of infection. Therefore, appropriate protective wearing would be promising for minimizing the contacts. By the mean that, because of the close distance between professionals and patients the probability of virus containing saliva and also the dental fluids could be increase, if the mentioned procedures have not been observed [57, 49].

Dental aerosols

Polishing process in dentistry produces the virus containing saliva smeared dental microparticles. The extreme exploding and spreading oral cavity environment potentially increase the risk of virus spread and transmission especially under the condition that the particles with smaller sized than the pore size of the masks are more dangerous because of that the controlling these particles would be harder than bigger ones. One method for significant gathering is using from superhydrophobic cotton fabrics which represents antibacterial and antiviral properties for producing masks and other wearing. Additionally, the dental implants with superhydrophobic antibacterial and antiviral properties could be as potential candidates for prevention from contaminated aerosols [35, 70, 30].

What are the solutions?

Masks with pore sizes lower than about 50 micrometers is urgent for applying in dentistry, because that the polishing process produces aerosols with diameters about 50–100 micrometers [57, 73, 15]. These particles are able to transmit in to eyes and cause to infections. Therefore, suitable glasses would be necessary to prevent from the direct exposure of eyes and these particles and subsequently weaken the infections risk. Because of that typically the aerosols' surface has charges, provides an opportunity to be gathered electrostatically from the air. Based on the fact that there is not any commercial vaccine available and drugs have shown inhibiting impact with side-effects [3] the persecution procedures could be promising. Due to the close distance between patients and professionals, their hands are in contact with aerosols novel antiviral materials and surfaces not only are necessary, but also could be promising.

Conclusion and outlook

This review with an interdisciplinary consideration discussed that what is the biology of the coronavirus and what are the pathway transmission? Using an interdisciplinary approach, we tried to evaluate the coronaviruses physiology and explain the dental transmission pathways of coronaviruses. In this study, using surface chemistry and dentistry science, the mechanistic aspects of the transfection and elimination of the pandemic of these types of viruses have been considered and the factors that could play role have been comprehensively highlighted. To the best of our knowledge, the aerosol spreading during dentistry, close professional-human contact and non-efficient sterilizing procedures could be accounted as the pathway of the coronavirus pandemic by dentistry transmission pathway. The drugs that could restrain these types of viruses involve to the estrogen receptor modulators-based inhibitors, blockers of angiotensin receptors, immunosuppressant agents and anti-inflammatory families of drugs which their pathway of function have been explained in detail. The interfacial insight about this issue revealed that due to the stable adhesion of these virus on various types of the surfaces, the conventional methods do not provide significant methods for eliminating viruses. Mechanistically, this problem which fundamentally relates to the upstream swimming capabilities of viruses in hydrodynamic layer on the surface of dentistry instruments. The superhydrophobic and photocatalytic self-cleaning antiviral surfaces have been discussed as potent candidates for designing highly applicable dentistry apparatus. These

types of materials with low surface free energy and high roughness degree which benefit them to superhydrophobic properties (contact angle $> 150^\circ$ and surface free energy $< 5\text{mN/cm}^2$) open new horizon in antiviral dentistry implants and instruments. They could be used in many general and advance dentistry apparatus and potentially inhibit the viral replication and adhesion process.

Declarations

Conflict of interest The authors declare no conflict of interest.

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