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# Impact of Phytoconstituents on Oral Health Practices: A Post COVID-19 Observation

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**ABSTRACT:** Appropriate oral hygiene significantly reduces the possibility of oral infections. However, dental caries and periodontal diseases are major oral health issues causing chronic diseases due to poor oral health. Recently, herbal compounds have gained interest in maintaining oral health. Extracts of burdock root (*Arctium)*, noni fruit (*Morinda citrifolia)*, and neem leaf (*Azadirachta indica*) are now used as intracanal medicaments in endodontics and periodontics. *Plectranthus amboinicus* species and other plants produces essential oil like β-caryophyllene, p-cymene, and γ-terpinenecan exhibiting antibacterial activity, highlighting phytoconstituents plays a vital role in oral health. The COVID-19 pandemic highlighted the importance of hygiene and sanitization, to curb SARS-CoV-2. Oral cavity is among the gateways for virus entry into saliva. Saliva is a potential reservoir of SARS-CoV-2, and there is an increased risk of infection if there is any fissure in the mouth. This enables entry of virus into the vascular system through gingival or periodontal pocket, possibly reaching lung periphery then to lung vessels by interacting with endothelial surface receptors triggering pulmonary vasoconstriction and lung damage due to endothelial dysfunction. This review aims to draw attention to the possible route of SARS-CoV-2 infection via the oral cavity and the importance of oral hygiene against COVID-19.

**Keywords:** COVID-19; SARS-CoV-2; oral;hygiene; microbiota; Phytochemicals.

## 1. Introduction

### *1.1 Importance of Oral Hygiene*

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Oral well-being is a crucial aspect of overall health. Dental caries (tooth decay), oral cancers, and periodontal disease (gum disease) are the most prevalent chronic oral disorders affecting many of the world'syoung and adult populations. Oral health was recognized as a significant global public health issue at the United Nations summit on preventing non-communicable diseases[1]. Periodontal disease and dental caries are the major chronic diseases, with dental caries ailing people from infancy to old age at any stage. Even though most adults have some gingival inflammation (gingivitis), around 11% of the global adult population has severe progressive periodontal diseases, leading to tooth loss at an early age[2]. According to a recent global burden of disease survey, oral disorders are responsible for 15 million disabilities globally (Figure 1)[2].As perAbbasi-Shavaziand his colleagues, the deciding factors for children's oral health-related quality of life (OHRQoL) involvestrengthening, predisposing, and oral health behaviorand status[3].On the other hand, Zhang and his teammates found that risk predictors responsible for root caries can be categorized based on age, socioeconomic status, and tobacco usage. Moreover, patients with gingival recession, poor oral hygiene, and prior dental caries are more susceptible to developing new root caries[4]. Based on clinical trials, oral diseases are worsened by high-sugar diets, poor oral hygiene, tobacco consumption, lack of fluoride, and excessive alcohol intake. Oral diseases are gradually recognized asbehavioral threats to other major non-communicable diseases[5, 6].

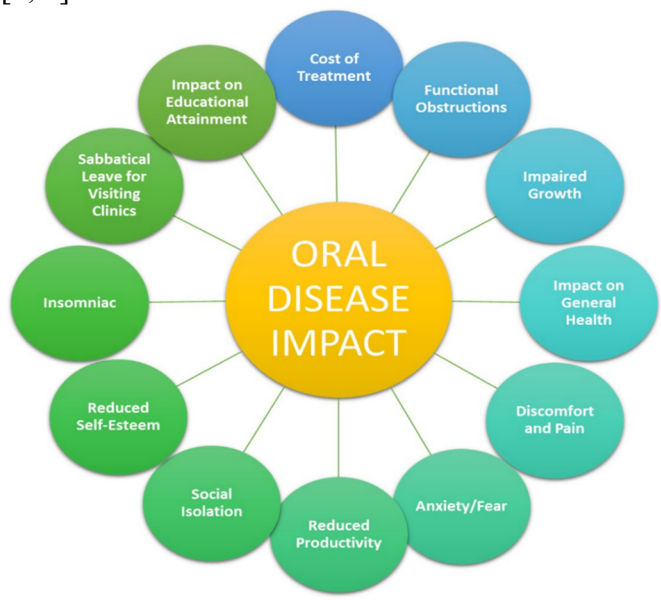



**Figure 1.**The impact of oral diseases[1]

Oral diseases have a socioeconomic impact on human beings; compromised oral health may impact general health and other disorders associated with oral hygiene; it may have psychological effects like anxiety and fear; it may influence an individual's economic growth. This visual representation provides a compact glimpse of different aspects of oral diseases that impact human well-being.

Lately, the diversity and applications of herbal compounds havesignificantly increased through oral care crops and their conjunction with conventional treatment methodsdue to their physical and medicinal value[7].These herbal compounds in dentistry are primarily used to relieve tooth pain, canker sores, and gum irritation[8]. Antiseptics and analgesics are two primaryclasses of compounds derived from plantsextensively used in dentistry for various problems[9]. Burdock root, noni fruit, and neem leaf, are now being extensively used as intracanal medicine in endodontics and periodontics, which have enabled the usage of these herbal

agents in dentistry around the world.For instance, clove oil is primarily used to reduce toothache[10]. Interestingly, clove oil relieves toothache and prevents tooth decay via different bacterial species owing to their antibacterial potential.

*1.2 Oral Health and COVID-19*

Several studies have recently shed light on our understanding of SARS-CoV-2 transmission from the mouth to the lungs and the development of COVID-19(**Figure 2**)[11]. SARS-CoV-2 uses ACE2 receptors, furin, and trans-membrane protease serine 2 (TMPRSS2) to infect host cells. For instance, TMPRSS2 induces endocytosis by binding viral spike proteins to ACE2 receptors on the host 'cell's surface, whereas furin is involved in the release of viral particles to the extracellular compartment[12]. These infection-fighting mediators are commonly found in the oral cavity and nasal airways, including the tongue, gingival tissues, and minor salivary glands[13, 14]. Moreover, although the three mediators of viral entry are not distributed in all oral tissues, the sulcular epithelium cells express ACE2, furin, and TMPRSS2, suggesting that SARS-CoV-2 can spread *via* the gingival sulcus. As a result, the virus can infect many niches in the oral cavity, besides the gingival sulcus[14, 15]. Per a recent analysis of autopsy tissues from deceased COVID-19 patients,oral mucosa and salivary glands were infected with SARS-CoV-2[13]. Five of seven COVID-19 patients reported dead in a post-mortem analysis showed viral RNA in the periodontal tissues[16]. Following these observations, the abundance of SARS-CoV-2 in saliva may lead to the infection of gingival cells, salivary gland tissues, and oral mucosal cells. According to Huang et al., SARS-CoV-2 can survive in saliva or the nasopharynx for over two months. After 0.5-3.5 weeks, viral clearance was observed in asymptomatic individuals[17]. The salivary viral load has been related to mortality, loss of smell and taste, and disease severity. These factors arebetter predictors of poor outcomes than'patients' age or nasopharyngeal viral load[17, 18], and 'patients' age as a potential risk factor isa significant finding[19].

*1.3 Dentistry and COVID-19 management*

COVID-19 have shoot up the risk among the health professionals, since the main hub of this disease initiates from the nasopharynx to mouth and then to the other parts of the body. The plausible guidelines which can be followed by the health professionals which are at higher risk like the dentists and others needs to follow the guidelines which can curb the health risks are: the devices with CAD (Computer Aided Design) and CAM (Computer Aided Manufacturing) technology can be used by the dentists for the production of breathing devices which will reduce the time of the patient and the staff and will transmit a safety message among the patients, this will also reduce the time of invasiveness of the virus [20].

*1.4 Dental implantations and their maintenance*

Airborne transmission of SARS-CoV-2 has regulated the dental health care and implantations, as the procedures followed for it are aerosol generating which aid in risk of producing and with spread of contaminated droplets [21]. It is necessary to have improved ventilation systems in the operating rooms where implants and other regular checkups are being carried to minimize the potential risk through the aerosols. The usage of air purifiers which will reduce the suspended particles present in the room using Highly Efficient

Particulate Air (HEPA) filters. It has been studied in a clinical trial that the use of HEPA filters in the operating rooms reduces the risk of transmission by aerosols to the greater extent[22].

The dental implants have increased tremendously due to less complications and high success rates [23]. In a study functional implant prosthodontics score was calculated over 30 individuals who have undergone soft tissue implants in posterior sites and were followed up for an year indicated great potential of both conical and hexagon connections and their good performances with one year of clinical services [24]. Although implants can also be ruined by poor oral health which subsequently results in periodontal inflammation leading to failure of secondary implant caused due to peri-implantitis. These failures are mainly due to plaque index, bleeding on probing and pocket of depth which leads to implant failure [25]. These implants can be either prosthetic rehabilitation with title, which is an efficient implantation technique for oral cavities such individuals also might get affected if a patient suffers from COVID-19 duration of implant alterations in the ACE2 pathway, inflammatory cytokine storm or due to microvascular dysfunction [26]. The intricacy increases if an individual is diabetic due to large wounds, delay in the healing process, and greater force is applied during the implantation process [27, 28]. Since, Covid-19 patients are more susceptible to plaque, gingivitis and bleeding and poor oral hygiene might have aided in difficulties in maintaining the dental implantation during the pandemic. One of the other major factors is to prevent microeakage from the implant so that infection can be controlled for which the implant-abutment connection should be resistant against bacterial microleakage resulting in stopping infections and success of implantation [29]. If hygiene would have been maintained along with periodic checkups might help reducing the chances of implant failures and other complications caused.

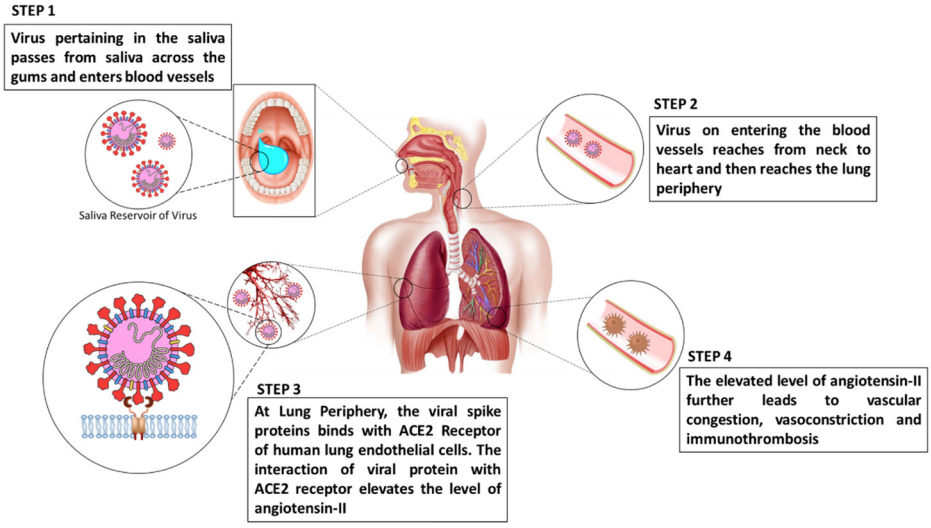



**Figure 2.**COVID-19 pathway: a hypothetical model for the oral-vascular-pulmonary route of infection [Adopted from[11]]

Diagrammatic representation shows the putative oral passage of SARS CoV infection via saliva and its entry into blood vessels leading its way to the lung periphery.The virus may elevate angiotensin-II levels as ACE2 receptors facilitate viral proteins (spike proteins). This elevation may further lead to the progression of congestion, vasoconstriction, and immunothrombosis.

In earlier findings, Epstein-Barr virus (EBV), Zika virus, human immunodeficiency virus (HIV), herpes simplex virus (HSV), cytomegalovirus (CMV), and some other human viruses have been foundin gingival crevicular fluid (GCF), gingival tissues, saliva, and subgingivalplaque[30-34]. Recently, viral RNA has been

found in the GCF of 64% of COVID-19 patients[35]. In the oral cavity, viral particles migrate to the gingival sulcus/periodontal pockets, which are more suitable for survival. In patients with periodontal disease, the periodontal pocket epithelium develops micro-ulcerations that enable microorganisms and viral particles to move through connective tissue and gingival capillary complex, eventually reaching the systemic circulation[15, 16]. In moderate periodontitis, the region of exposed connective tissue and related blood vessels directly contacting the sub-gingival biofilm is 5 $cm^2$, while in severe periodontitis,it is more than 20 $cm^2$[36].Peripheral blood neutrophils in patients with periodontal disease have been shown to have type-1 interferon gene expression signatures, consistent with intravascular exposure to periodontal bacteria, fungi, and viruses[37]. As a result, periodontal pockets can provide favourable conditions for viral replication, infection, and dissemination to gingival capillaries. Studies on bacteriemiaindicated the presence of oral bacteria in the systemic circulation and infective endocarditis of oral origin. These studies suggest that oral bacteria can harm the body, witha higher risk in individuals with poor oral hygiene and periodontal inflammation[38]. Since bacteria can enter the systemic circulation through a mouth lesion, this pathway is used by the SARS-CoV-2 viruses enabled by periodontal disease. In this context, this review highlights the potential route of viral infection, focusing on COVID-19 *via* the oral cavity and the importance of oral hygiene against such infections. The application of simple, inexpensive measures, such as toothpaste and mouthwashes, is underlined. Furthermore, usingvarious phytoconstituentsto oral hygiene products to restrain salivary viral load and mitigate viral infection is also stressed.

## 2. Oral Microbes and Their Effects

### *2.1. Oral Microbiota*

Miller first suggested the "chemical bacteria hypothesis" for dental caries in his book "Microbes in the Human Mouth" in 1890, implying that the dental biofilm is made up of microorganisms[39]. Oral microorganisms, like viruses, bacteria, mycoplasmas, yeasts, archaea, and protozoa, form an ecological environment in the mouth called the oral microbiota[40, 41].The oral cavity offers a warm and healthy habitat for the oral microbiota while controlling bacterial colonization to prevent invasion by pathogenic microbes. Moreover, oral microbiota is essential for maintaining good oral health[42]. On the other hand, invading microorganisms may induce an imbalance in the commensal microbial community of the host, thereby resulting in dental diseases.

### *2.2. Dental Biofilms*

Dental biofilms are a polymicrobial community formed by oral microbiota on the surface of teeth[43]. The extracellular polymeric substances (EPS) matrix providesa pathogenic habitat for dental caries, causing microorganisms. Dental caries ismainly a biofilm-induced disease, not an infectious disease, as it begins with the biofilm surrounding the tooth's surface[44, 45]. Due to a highly active and complex ecosystem with abundant EPS, the biofilm can stimulate caries. Indeed, a biofilm begins to develop when a salivary glycoprotein film, called a dental pellicle, surrounds the tooth surface[46]. Gram-positive bacteria, such as

*Streptococcus mutans* and *Streptococcus mitis* species (known as the biofilm's initial colonizers), produce the EPS, improving the adherence of other microorganisms[47, 48].Acid-producing bacterial species from the genera *Lactobacillus*, *Scardovia*, *Propionibacterium*, and *Veillonella* can trigger cariogenic conditions in the mouth and colonize the dental biofilm[49-52]. However, other acid-producing microorganisms use the EPS to create new binding sites and increase virulence[47].

The microbial composition of cariogenic biofilms has been the subject of intense research. Still, it is now generally acknowledged that the biochemical and structural properties of the EPS play a role in the etiology of dental caries[53]. The EPS matrix protects the biofilm and provides mechanical stability, rendering it resistant to antimicrobials. The microbes are lodged in an EPS substrate and continuously produce acids, which are physically shielded from saliva's rapid buffering[54]. Specifically, research on dental caries has been focused on microbial behavior in biofilm communities employing experimental biofilm models, which can imitate metabolic processes through carbohydrate absorption in the mouth and determine the dose-response sensitivity of anti-caries agents[44]. This approach aids in investigatingthe cariogenicity of dietary sugars and evaluates their anti-caries effects[55].

Biofilm of *S. mutans*is believed to have cariogenic potential based on three main characteristics: (i) acid production, (ii) capability to produce EPS, which has a growth-promoting mechanism that protects cells and allows them to thrive in harsh environments, and (iii) acid resistance, which allows conversion of carbohydrates into organic acids while still thriving in low pH environments[56-58]. Moreover, the matrix-producing glucosyltransferases (GtfBCD) in *S. mutans*are involved in cariogenic biofilm formation[59]. Although much research has covered the treatment and prevention of dental caries, it is apparent that merely limiting sugar consumption and avoiding *S. mutans*cannot overcome dental caries. Polysaccharides, mainly *S. mutans*-derived glucans, and soluble glucans and fructans formed by *Streptococcus gordonii*, *Streptococcus salivarius*, and *Actinomyces* species are vital EPS components in cariogenic biofilms[50, 53].

Recently, molecular studies have detected the presence of pathogenic flora, which include bacteria like *Streptococcus, Actinomyces* and *Scardovia*spp., and fungi, like *Candida albicans,*in dental biofilms[60, 61]. In contrast to *S. mutans*, dental caries-associated colonizers include *Scardovia*, *Lactobacillus*, and *Bifidobacterium*species[50, 51, 62]. Earlier studies have shown that biofilm resistance to anti-adhesion compounds, antibiotics, and preservatives isdirectly linked to microbial diversity[63-65]. Microbial abundance declines during the maturation of cariogenic biofilms due to the competition between cariogenic microorganisms[53]. Hence, the supremacy of cariogenic microorganisms over health-associated commensal species is thought to be the cause of dental caries. Indeed, both the complexity of the biofilm matrix and the proliferation of microorganisms pose challenges in preventing and managingdental caries.

### *2.3. Microbial Ecology and Dental Caries*

The long-term association between fermentable carbohydrates and acid-producing microorganisms isthe key reason for dental caries[40]. The oral microbiome plays a role in developing dental caries and some host

factors like saliva and the physical properties of oral hard tissues. Dental biofilm plays a significant role in the etiology of dental caries. Caries are triggered by the matrix's complexity, the transmission of resistance genes, and the physical security offered by the EPS matrix. Based on the studies, the main associated issues include the lack of a single apparent therapeutic target and poor retention of locally administered therapies. Hence, controlling dental biofilm is best to avoid tooth decay[47, 66].

### *2.4. Microbiota in Periodontal Diseases*

In 1960, research on the relationship between bacterial strains and periodontal diseases began by isolating certain bacterial morphotypes[67].The discovery of *Aggregatibacteractinomycetemcomitans* as a pathogen associated with localizedaggressive periodontitis (LAP) supports the specificity of periodontal microflora[68, 69]. Subsequent cross-sectional and long-term studieslinked bacterial species to health and disease. These studies have established a connection between periodontitis and a small group of periodontal pathogens:*Tannerella forsythia*, *Porphyromonasgingivalis*, and *A. actinomycetemcomitans*. Indeed, they are closely linked to the onset of periodontal disease, progression of periodontal disease, and failure of periodontal therapy. Other bacteria isolated from the subgingivalmicrobiota, like *Prevotellaintermedia, Peptostreptococcus micros*, *Eubacteriumnodatum, Fusobacteriumnucleatum, Campylobacter rectus*, *Treponemadenticola*, and *Prevotellanigrescens,* have also been identified. Still, their etiologic roles are less specific. As a result, periodontal disease may be a polymicrobial infection[67].

## 3. Oral Hygiene Practices

Tooth brushing and interdental cleaning are two of the most popular oral hygiene recommendations[70, 71]. India is a large country with a population of around 1.27 billion. Most people rely on traditional oral hygiene practices, like mango bark or neem tree stick, tobacco leaves-based toothpowder, customized charcoal, or salt recommended in Vedas[72, 73]. Due totheir benefits, numerous healthcare industries have started adding the above constituents to their products and marketing them for their health benefits.The sacred plant, *Ocimum sanctum,* also known as tulsi, is widely known for its medicinal value as it exhibits antimicrobial and antifungal activity against diverse oral pathogens responsible for dental problems. Nowadays, tulsi extracts are incorporated into toothpaste and mouthwash *via* pharmaceutical industries to treat pulpitis and toothache[74]. The essential oil produced by *Salvadorapersica* (*miswak*) has been reported to possess anti-gingivitis, anti-cariogenic, anti-plaque, promotion of gingival wound healing, orthodontic chain preservation and whitening properties[75]. Moreover, the eucalyptus oil synthesized by *Eucalyptus globulus*has been reported to encompass a bioactive compound named eucalyptol, used as a mouthwash and endodontic solvent in dental preparation in dentistry.Studies conducted on *Azadirachtaindica* (Neem) oil and bark have been reported to treat different dental issues *via* different methods to cure cavities, gum disease, and dental plaque[76, 77]. Different mouthwash formulations consist of neem extract to prevent bleeding and soring of gums and treat tooth decay and oral infection[77].Varioustoothpaste and mouthwashes available in the world market and their composition are summarized in table1 and 2.

**Table 1** Toothpaste that is available in the world market and their composition[78].

| Brand Name | Manufacturer/ Marketed By | Composition | Oral Hygiene Claim |
|---|---|---|---|
| Colgate Total Whole Mouth Health | Colgate-Palmolive | Sorbitol, CI77891, Water, Sodium hydroxide, CI74160, Hydrated silica, Sodium fluoride, PVM/MA Copolymer, Triclosan, Sodium lauryl sulfate, Flavor, Sodium saccharin, Carrageenan | Anti-gingivitis, Anti-plaque, Anti-cavity |
| Close-Up Anti-cavity Fluoride | Hindustan Unilever Ltd | Hydrated Silica, Water, Sorbitol, PEG-8, Cellulose gum, SD Alcohol 38-B, Sodium lauryl sulfate, Flavor, Red 33, Red 40, Sodium saccharin;Sodium fluoride (0.24%) | Anti-cavity, Fresh breath |
| PepsodentGermi Check | Hindustan Unilever Ltd | Sorbitol, Water, Calcium carbonate, Hydrated silica, Benzyl alcohol, Sodium lauryl sulfate, Cetylpyridinium chloride, Kaolin, Flavor, Limonene, Sodium monofluorophosphate, CI45430, Sodium saccharin, Sodium silicate, Cellulose gum, Potassium nitrate | Remove plaque, Fresh breath |
| Sensodyne Rapid Relief | GlaxoSmithKline plc | Strontium acetate, Sodium fluoride, Purified water, Silica, Sorbitol, Xanthan gum, AC1131 Flavour, Glycerol, Titanium dioxide, Sodium methyl cocoyltaurate, Sodium methyl hydroxybenzoate, Saccharin sodium, Precipitated silica, Propyl hydroxybenzoate | Sensitivity relief |
| Oral-B Pro-Expert | Procter & Gamble | Stannous chloride, Polychelation complex, Sodium fluoride | Anti-cavity, Anti-plaque, Fresh breath |
| Dabur*Meswak* | Dabur India Ltd | Carrageenan, Sorbitol, Water, CI 77891, Silica, Sodium silicate, Sodium lauryl sulfate, Calcium carbonate, Flavour, Meswak extract, Cellulose gum, PVM/MA copolymer, p-Thymol, Zinc gluconate, Sodium saccharin, Benzyl alcohol, Sodium benzoate | Antibacterial, Anti-inflammatory, Astringent |
| *PatanjaliDantKanti* | PatanjaliAyurved Ltd | Haldi (*Curcuma longa*), Akarkara root extract (*Anacyclus pyrethrum*), Laung oil (*Syzygiumaromaticum*), Vidang fruit extract (*Embeliaribes*), Babool (*Acacia arabica*), Tomar seed oil (*Zanthoxylumalatum*), Bakul (*Mimusopselengi*), Pudina (*Menthapiperita*), Majuphal (*Quercusinfectoria*), Neem bark extract (*Azadirachtaindica*), Vajradanti (*Barleriaprionitis*), Pilu (*Salvadorapersica*), Pippalichhoti (*Piper sylvaticum*) | Prevent gingival bleeding and periodontal diseases |
| ViccoVajradantiAyurvedic | Vicco Laboratories | Vajradanti, JeshthamadhAjwain, Babhul, Jambhul, Laung, Manjishtha, Bor, Akhrot, Dalchini, Khair, Patang, Bakul, Harada, Anantmul, Behada, Amla, Maifal, AkkalKadha, Kavab | Anti-plaque, Remedy for pyorrhea |
| Dabur Red | Dabur India Ltd | PudinaSatva, Clove oil, Ginger, TomarBeej (*Zanthoxylumalatum*) | Anti-plaque, Fresh breath |
| Himalaya Complete Care | Himalaya Global Holdings Ltd | Neem, Indian gum Arabic, Triphala, Bishop's Weed, Pomegranate fruit rind, Pepper, False Black | Germ-free mouth |
| Lacalut Extra Sensitive® | TheissNaturwaren, 66424 Homburg, Germany | Sodium fluoride, Aluminium salts, Chlorhexidine, KCl, silicium dioxide, Sodium fluoride Amine | Improvement of nerve cells, Caries prevention |
| Biomed Sensitive® | Splat Oral Care, 121099 Moscow, Russia | L-Arginine, Hydroxyapatite, Natural component (Plantain extract, birch leaf polyphenols and red grape seeds) | Enamel strengthening and eliminating the causes of tooth sensitivity |
| Aslamed for Sensitive Teeth® | Farmec SA, 400616 ClujNapoca, Romania | Sodium fluoride, special clay, potassium nitrate, sodium lauryl sulfate (SLS) free | Remineralization of teeth and strengthens their enamel, astringent effect |

The table is intended to summarize the different kinds of toothpaste available in the global markets and their compositions and claims regarding oral hygiene decreed by the brands.

**Table** 2 Mouthwashformulations in the world market and their composition

| Brand Name | Manufacturer/ Marketed By | Composition | Oral Hygiene Claim |
|---|---|---|---|
| Listerine Cool Mint | Johnson & Johnson Pvt. Ltd | Thymol (0.064%), Menthol (0.042%), Methyl Salicylate (0.060%), Eucalyptol (0.092%); FD&C Green 3 CI 42053, Water, Sodium Benzoate, Alcohol (21.6%), Sorbitol Solution, Sodium Saccharin, Poloxamer 407, Benzoic Acid | Kills 99.9% of germs |
| Colgate Plax | Colgate- Palmolive | Propylene Glycol, Glycerine, Polysorbate 20, Sodium saccharin, Sodium benzoate, Sodium fluoride, Sorbitol | Kills 99% of germs |
| Closeup Red Hot | Aero Pharma/ Hindustan Unilever Ltd | Sodium saccharin, Sorbitol, Water, PEG-40 Hydrogenated, Potassium citrate, glycine, Sodium lauryl sulfate, Benzyl alcohol, Phenoxyethanol, C116035, Zinc sulfate, Eugenol, *Eugenia caryophyllus* leaf oil (Clove), Sodium fluoride, Castor Oil | Kills 100% of germs |
| Dabur Red Pulling Oil | Dabur India Ltd | Sesame oil, Coconut oil, Thyme, Cinnamon, Mint, Tulsi, Clove | Kills 99.9% of germs |
| Amflor | Group Pharmaceutical Ltd | Purified water, Sodium benzoate, Sorbitol, Polyoxyl 40 hydrogenated castor oil, Ponceau 4R, Propylene glycol, Flavours, Amine fluoride, Poloxamer, Sodium saccharin | ND |
| Bioayurveda Basics | ArganshePvt Ltd | Turmeric, Tea tree oil, Basil, Lemon, Mint, Clove, Ginger, Mint | ND |
| Bio Resurge | Bio Resurge Life Coaching Health Services Pvt. Ltd | Aqua, Clove oil Peppermint, Alum, *Rubiacordifolia* (Indian madder), *Glycyrrhizaglabra* (Mulethi), *Terminaliabellirica* (Bahera), *Commiphorawightii* (Guggal) | ND |
| Cur Q Fresh | Onika Organics | Curcumin, Thymol oil, Tea tree oil, Mint, Clove oil, Tulsi, and Eucalyptus oil | ND |
| Organic Aloe Vera | Dr. Organic Ltd | *Aloe vera*, Icelandic moss extract, Peppermint oil, Tea tree leaf oil and Arnica extract, Apple fruit extract, Indian pennywort extract | ND |
| Himalaya HiOra-K | The Himalaya Drug Company | Clove, naturally-derived Potassium nitrate (Suryakshara) | ND |
| Listerine- Vanilla Mint | Pfizer Inc.- Lilitz, Pennsylvania, USA | Thymol, menthol, eucalyptol, methyl salicylate | ND |
| Listerine Tartar Control | Johnson & Johnson Industrial Ltda., São Paulo, Brazil | Thymol, menthol, eucalyptol, methyl salicylate | ND |
| Listerine Fresh Burst | Johnson & Johnson Industrial Ltda., São Paulo, Brazil | Thymol, menthol, eucalyptol, methyl salicylate | ND |

ND: Not Defined, Table is intended to summarize the different mouthwash available in the global markets and their compositions and claims regarding the oral hygiene decreed by the brands.Interestingly, most of the products have phytochemicals in them.

## 4. Bioactive Compounds in Dentistry: Focus on Antibacterial and Antifungal activities

Dental plaque and gingivitis can be managed by brushing with anti-plaque agents containing dentifrice and inter-dental cleaning with dental floss and toothpicks. A proximal brush is usually prescribed to cleaninterdental spaces[71].Competent plaque management by a dental hygienist has been shown to help maintain a safe periodontium[79]. Mouth rinses can also helpprevent plaque formation by reducing the rate at which bacteria reproduce in plaques and by adhering to dental surfaces,thereby enhancing oral health[80].

Various bioactive compounds have been widely exploited in mouthwashes and toothpaste. These bioactive compounds are volatile and abundant in essential oils (EOs). Briefly, EOs are a rich pool of naturally-occurring bioactive agents with antimicrobial effects,and many of them are used to treat various diseases[81, 82]. Most EOsare secondary metabolites produced by plants to protect against pests, microorganisms, and weather adversity[83, 84]. EOs account for over 3,000 of 100,000 recognized secondary metabolites, with around 300 having commercial importance and extensively used in the pharmaceutical, food, and cosmetic industries[81]. Based on their chemical structures, EOs are divided into two groups: terpenes (sesquiterpenes and monoterpenes) and terpenoids (isoprenoids); both have distinct biosynthetic origins, aromatic and aliphatic compounds (phenols and aldehydes), and low molecular weights[83, 85]. Monoterpenes account for most EOs, and their antibacterial activities against dental caries-causing microorganisms have been documented [82, 86]. Yet, only a few studies on EOs explored their wide dental-care applications. Since only a few compounds from these phytochemical groups have been used in anti-plaque and anti-gingivitis mouthwash formulations, further research iswarranted to explore utilizing EOs in anti-caries chemotherapy [87-89].We would also like to highlight, using constant mouth wash may alter the microbiome of the mouth but the evidence-based work on SARS-CoV infected individuals showed reduced viral load[90]. Even though, solid evidence and relationship has still been determined but we speculate using mouth wash during the infection period may vary the micro flora but not in that extent where mouthwash is used as a routine practice.

### *4.1 Eugenol*

Eugenol is a versatile natural compound with powerful health-promoting properties. It is found in cinnamon, cardamom, cloves, nutmeg, and variousother plants[91]. It was first isolated from the leaves and buds of clove-like *Eugenia caryophyllata*[91].Moreover, eugenol is synthesized by allylation of guaiacol with allyl chloride, which exhibits the same functional properties as eugenol. The presence of eugenol in the extracts of medicinal herbs has triggered the interest of many researchers and opened the door for further studies to assess its therapeutic potentialagainst many diseases.Eugenolhasanaestheticproperties, neuro-protective properties, antimicrobial activity, hypolipidemicaction, antioxidant activity, anti-carcinogenic effects, anti-diabetic, and anti-inflammatory properties[91].

According to the World Health Organization (WHO), eugenol is non-mutagenic and generally recognized as a safe (GRAS) compound. Clove buds, tulsi leaves, cinnamon bark and berries, pepper, turmeric, ginger, thyme, and oregano are other sources of eugenol[91]. However, several other aromatic herbs, such as nutmeg, marjoram, basil, mace, and bay, have been shown to contain substantial amounts of eugenol. Cinnamon (20-50%) and clove (45-90%) are the most abundant plant sources of eugenol. However, commercial eugenol extraction and higher production costs are the significant issues associated with these sources[91]. On the contrary, bay, pepper, tulsi, and ginger are inexpensive and abundant sources that can be utilized instead of cloves and cinnamon. For example, in Gram-negative and Gram-positive bacteria, eugenol damages cell membranes and cell walls, causing cell lysis and leakage of intracellular fluid and lipid and protein contents[92, 93]. *In vivo* and *in vitro* studies on biofilms have shown that eugenol has a significant eradicative and inhibitory effect against many oral microorganisms (**Table 3**).

*4.2. Thymol*

Thymol, known as 5-methyl-2-isopropylphenol and 2-isopropyl-5-methylphenol, is a crystalline, colourlessmonoterpenoid phenol with a distinct odour. It is also an isomer of carvacrol and is the main active ingredient in thyme oil, obtained from *Thymus vulgaris* species. Thymol has been isolated from a variety of plants, including *Origanum* L., *Trachyspermumammi* (L.), *Ocimumgratissimum* L., genus *Monarda* L., *Satureja* L. (Lamiacaeae), *Oliveriadecumbens* Vent*, Anemopsiscalifornica* (Saururaceae), *Carumcopticum* L. (Apiaceae), species of *Ranunculaceae, Verbenaceae*, and*Scrophulariaceae* [88]. Different communities in many countries use these extracts as medicinal plants. *T. vulgaris* EOs and others containing thymol have been shown to have expectorant, antitussive, digestive, stomachic, antispasmodic, and carminative action against oral diseases like dental caries[94]. These pharmacological applications, modes of action, and pharmacokinetic studies suggest that thymolmay be a potent, natural therapeutic agent with a high medicinal value[95, 96].

Commercial pharmaceuticals are available with Shirazi thyme (*Zatariamultiflora*) EO as the main ingredient widely used in treating respiratory diseases[97]. Listerine is another well-known thymol-containing medication named after Joseph Lister, who identified the medicinal value of thymolin treating oral and throat infections,including gingivitis[95]. Thymol-containing EOs exert antibacterial activity against Gram-negative (*Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa, Salmonella typhimuium* Ty2) and Gram-positive (*Bacillus subtilis*, *Bacillus cereus*, *Streptococcus faecalis*, and *Staphylococcus aureus*) bacteria[98-100]. The antimicrobial action of thymol is mainly due to its ability to incorporate itself within the lipid bilayer of the host cell, increasing its surface curvature (**Table 3**). Briefly, the hydrophilic parts of thymol molecules interact with the polar region of the membrane. At the same time, the aliphatic side chains and hydrophobic benzene rings fall into the biological membrane's inner region. The destabilization of the lipid bilayer increases fluidity and decreases elasticity, leading to significant changes in the membrane structure. This process causes increased permeability to hydrogen and potassium ions and affects internal membrane proteins, including membrane receptors and enzymes. Following incorporation into the cell membrane,

thymol interacts with the embedded proteins through non-specific interactions, causing changes in the conformation and activity of internal and membrane proteins. As a result, the presence of thymol can trigger cell membrane tension and destabilization[101].

*4.3 Terpinen-4-ol*

Terpinen-4-ol [3-cyclohexen-1-ol,4-methyl-1-(1-methylethyl)-,(R)-] is a terpenethat is considered to be the primary component of *Melaleucaalternifolia*EO, also known as tea tree oil (TTO), and can be found in other plants such as *Alpiniazerumbet* and *Eucalyptus* species from HajebLayoun arboreta (Tunisia)[102, 103]. TTO comprises 100 different compounds, including the monoterpenesterpinolene, 1,8-cineole, and terpinen-4-ol, which account for at least 30% of the oil. TTO has anti-inflammatory, antimicrobial, and anticancer properties and was first reported to exert medicinal effects in the 18$^{th}$century[104]. TTO works against Gram-positive,and Gram-negative bacteria,exhibits broad-spectrum activity, avoids antimicrobial resistance, and is effective against multi-resistant microorganisms[105].The antimicrobial properties of terpinen-4-ol are due to itslipophilicity, allowing it to pass through cytoplasmic membranes and cell walls. Internal osmotic pressure causes the cell wall to weaken, rupture the membrane, and lose the cytoplasmic content[106, 107].

In fungi, terpinen-4-ol has hydroxyl groups, making them moderately water-soluble. This helps them pass through water, penetrate cells, and disrupt cell membranes, resulting in osmotic shock[108]. The addition of TTO and terpinen-4-ol in oral care products, such as toothpaste and mouthwashes, has been demonstrated to exert antiseptic effectsdue to their ability to adhere to dental biofilms and inhibit bacterial growth[109-112].

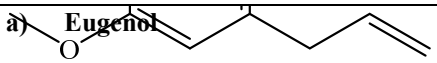
*4.4 Curcumin*

Curcumin (diferuloyl methane) is a polyphenolic compound isolated from the rhizomes of *Curcuma longa* L. It is the natural yellow pigment present in the roots of turmeric (family Zingiberaceae). It accounts for roughly 4% of thedry weight[113],*i.e.,* [1,7-bis (hydroxyl-3-methoxyphenyl)-1,6-heptadiene-3,5-dione]($C_{21}H_{20}O_6$) being one of the essential active ingredients. Turmeric has been a culinary spice in curry for centuries in many Asian countries to give its distinct colour and flavour[114]. Turmeric is a food additive and acolouring agent in yellow mustards, cosmetics, pharmaceuticals, and hair and fur dyes[115].

Curcumin has been shown to alter gene expression and prevent bacterial DNA replication (**Table 3**). Moreover, it destroys bacterial cell membranes and decreases the motility of several microorganisms[116]. *In vitro* studies have shown that curcuminpreventsFtsZprotofilament polymerization and GTPase activity disruption in the cytoskeleton of *E. coli*, *S. aureus*, and *B. subtilis*[117, 118]. Moreover, it can affect bacterial cell division and proliferation through this mechanism. According to some studies, curcumin induces an apoptosis-like response in *E. coli*[119]. The downregulation of $\Delta^{5,6}$-desaturase (ERG3) was discovered to be a potential mechanism underlying the antifungal activity of curcumin, resulting in a substantial reduction in ergosterol in fungal cells. Reduced ergosterol levels lead to the accumulation of biosynthetic precursors of

ergosterol, which causes cell death by releasing reactive oxygen species (ROS)[120]. Other potential effectsofthe antifungal activity of curcumin include decreased proteinase secretion and a change in membrane-associated properties of ATPase activity[121].

**Table 3** Antimicrobial activity of EOs against various oral bacteria and fungi

**a) Eugenol** 

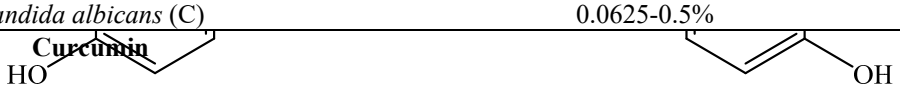
| **Bacteria (Nature)** | **MIC** | **Reference** |
|---|---|---|
| *Porphyromonasgingivalis* ATCC33277 (RS) | 31.25 μM | [122] |
| *Streptococcus salivarius* (C) | >1000 μg/mL | [123] |
| *Streptococcus mutans* (C) | >1000 μg/mL | |
| *Streptococcus sanguinis* (C) | >1000 μg/mL | |
| *Streptococcus sobrinus* ATCC33478 (RS) | 600-800 μg/mL | |
| *Staphylococcus epidemidis* (C) | >1000 μg/mL | |
| *Corynebacteriumpseudodiphtheriticum* (C) | >1000 μg/mL | |
| *Corynebacteriumxerosis* (C) | >1000 μg/mL | |
| *Lactobacillus salivarius* ATCC11741 (RS) | >1000 μg/mL | |
| *Rothiadentocariosa* ATCC17931 (RS) *Neisseria subflava* ATCC49275 (RS) | >1000 μg/mL<br>>1000 μg/mL | |
| *Streptococcus mutans* MTCC497 | 0.625 μg/mL | [124] |
| *Staphylococcus aureus* B234 (C) | 256 μg/mL | [125] |
| *Staphylococcus aureus* B398 (C) | 128 μg/mL | |
| *Staphylococcus aureus* B147 (C) | 512 μg/mL | |
| *Staphylococcus aureus* B193 (C) | 128 μg/mL | |
| *Staphylococcus aureus*, B295 (C) | 32 μg/mL | |
| *Staphylococcus aureus* B285 (C) | 64 μg/mL | |
| *Staphylococcus aureus* B456 (C) | 256 μg/mL | |
| *Streptococcus mutans* B200 (C) | 64 μg/mL | |
| *Streptococcus mutans* B509 (C) | 64 μg/mL | |
| *Streptococcus constellatus* B629 (C) | 64 μg/mL | |
| *Enterococcus faecium* P1 (C) | 256 μg/mL | |
| *Enterococcus feacalis* P2 (C) | 512 μg/mL | |
| **Fungi (Nature)** | **MIC** | **Reference** |
| *Candida dubliniensis* 131 (C) | 750 μg/mL | [126] |
| *Candida dubliniensis* 219 (C) | 375 μg/mL | |
| *Candida dubliniensis* 248 (C) | 375 μg/mL | |
| *Candida tropicalis* 23 (C) | 375 μg/mL | |
| *Candida tropicalis* 150 (C) | 750 μg/mL | |
| *Candida tropicalis* 176 (C) | 375 μg/mL | |
| **b) Thymol** | | |
| **Bacteria (Nature)** | **MIC** | **Reference** |
| *Aggregatibacteractinomycetemcomitans* ATCC33384 (RS) | 100 μg/mL | [127] |
| *Streptococcus mutans* ATCC25175 (RS) | 200 μg/mL | |
| Methicillin-resistant *Staphylococcus aureus*(MRSA) ATCC33591 (RS) | 200 μg/mL | |
| *Escherichiacoli*ATCC10798 (RS) | 200 μg/mL | |
| *Staphylococcus aureus* B234 (C) | 64 μg/mL | [125] |
| *Staphylococcus aureus* B398 (C) | 64 μg/mL | |
| *Staphylococcus aureus* B147 (C) | 256 μg/mL | |
| *Staphylococcus aureus* B193 (C) | 64 μg/mL | |
| *Staphylococcus aureus*, B295 (C) | 32 μg/mL | |
| *Staphylococcus aureus* B285 (C) | 128 μg/mL | |

| | | |
|---|---|---|
| *Staphylococcus aureus* B456 (C) | 256 µg/mL | |
| *Streptococcus mutans* B200 (C) | 32 µg/mL | |
| *Streptococcus mutans* B509 (C) | 32 µg/mL | |
| *Streptococcus constellatus* B629 (C) | 64 µg/mL | |
| *Enterococcus faecium* P1 (C) | 128 µg/mL | |
| *Enterococcus feacalis* P2 (C) | 64 µg/mL | |
| *Streptococcus mitis* (C) | 5 µg/mL | [128] |
| *S. sanguis* (C) | 5 µg/mL | |
| *S. salivarius* (C) | 5 µg/mL | |
| **Fungi (Nature)** | **MIC** | **Reference** |
| *Candida albicans* CBS562 (C) | 39 µg/mL | [129] |
| *Candida tropicalis*(C) | 78 µg/mL | |
| *Candida krusei*(C) | 3 µg/mL | |

**c) Terpinen-4-ol**

| **Bacteria (Nature)** | **MIC** | **Reference** |
|---|---|---|
| *Streptococcus mutans* ATCC25175 (RS) | 0.24% | [130] |
| *Lactobacillus acidophilus* ATCC4356 (RS) | 0.27% | |
| *Streptococcus mutans* ATCC25175 (RS) | 44000 µg/mL | [131] |
| *Streptococcus salivarius* ATCC13419 (RS) | 2750 µg/mL | |
| *Porphyromonasgingivalis* ATCC33277 (RS) | 44000 µg/mL | |
| *Pseudomonas aeruginosa*ATCC 27853 (RS) | 11000 µg/mL | |
| *Staphylococcus aureus*ATCC 25923 (RS) | 44000 µg/mL | |
| *Escherichia coli* ATCC 25922 (RS) | 11000 µg/mL | |
| **Fungi (Nature)** | **MIC** | **Reference** |
| *Candida albicans* ATCC1031 (RS) | 11000 µg/mL | [131] |
| *Candida albicans* (C) | 0.0625-0.5% | [132] |

**d) Curcumin**




| **Bacteria (Nature)** | **MIC** | **Ref** |
|---|---|---|
| *Porphyromonasgingivalis* OMZ314 (C) | 10 µg/mL | [133] |
| *Streptococcus mutans* ATCC35668 (RS) | 333.33 µg/mL | [134] |
| *Actinomyces viscosus*ATCC10048 (RS) | 167.67 µg/mL | |
| *Lactobacillus casei*ATCC334 (RS) | 125 µg/mL | |
| *Porphyromonasgingivalis* ATCC32277 (RS) | 125 µg/mL | |
| *Prevotellaintermedia* ATCC25611 (RS) | 208.33 µg/mL | |
| *Streptococcus mutans* ATCC25175 (RS) | 128 µg/mL | [135] |

RS: Referred Strain; C: Clinical; NA: Not Applicable.

## 5. Possible use of eugenol, thymol, terpinen-4-ol, and curcumin against SARS-CoV-2

Eugenolcan inhibit viral infection and replication in herpes simplex viruses in a specific way (**Table 4**). Eugenol prevents the replication and autophagy of the influenza A virus by inhibiting the initiation of IKK/NF-κB, p38MAPK, and ERK signalling pathways[136]. For example, Silva and colleagues used molecular docking techniques to test the potential anti-SARS-CoV-2 efficacy of eugenolagainst various SARC-CoV-2 targets. According to docking ratings, eugenol has a binding affinity for main protease ($M^{pro}$), SARC-CoV-2 spike (S) protein, human ACE-2 protein, and RNA-dependent RNA polymerase[137]. SARS-CoV-2 pulse glycoprotein crystal structure was also determined in detail[138]. The S protein is made up of two sections, S1 and S2. S1 is a receptor-binding domain (RBD), which binds to the peptidase domain of angiotensin-converting enzyme 2 (ACE2) and allows the virus to adhere to the host cell's surface.On the other

hand, S2 is responsible for virus-host membrane fusion[139]. S1 subunit is crucial according to clinical aspects as inhibiting RBD can trigger S protein conformational changes, which is the first step in preventing viral infections.

Based on recent studies, thymol has a good affinity for hydrophobic residues surrounding the ligands in the binding pocket, contributing to the stability of the protein-ligand complex[138, 140].Thymol binds to the SARS-CoV-2 spike receptor-binding domain (PDB ID: 2AJF) and SARS-CoV-2 spike ectodomain structure (PDB ID: 6VYB), preventingthe virus from binding to the host receptor ACE2[141]. Terpinen-4-ol binds to the 3CL protease enzyme (**Table 5**)[142].

Curcumin is a potent antiviral compound withvarious antiviral activities against multiple viruses. Because of its rate-limiting involvement in the *de novo* synthesis of guanine nucleotides, the inosine monophosphate dehydrogenase (IMPDH) enzyme has been proposed as a therapeutic target for antiviral and anticancer compounds[143].Curcumin has been shown to exert inhibitory activity against IMPDH function, either in a competitive or a non-competitive manner[144].

Long terminal repeat (LTR) of type 1 human immunodeficiency virus (HIV-1) provirus plays a vital role in transcription. Antiviral drug candidates may block HIV-1 replication by inhibiting LTR activity[145, 146]. Curcumin was an effective inhibitor of HIV-1 LTR-directed gene expression with no significant side effects on cell viability[147]. Curcumin and its derivatives, such as allyl-curcumin, tocopheryl-curcumin, and reduced curcumin, inhibited Tat protein transactivation of HIV-1 LTR by 70-85%, as measured by $\beta$-galactosidase activity in HeLa cells[148]. Moreover, curcumin displays anti-influenza efficacy against influenza viruses H1N1, H6N1, and PR8[149]. Results showed that using 30 μM of curcumin reduced virus yield by more than 90% in cell culture. The inhibition of hemagglutinin interaction in H1N1 and H6N1 subtypes illustrated the direct effect of curcumin on viral particle infectivity, as shown by an opioid abuse experiment[149].In addition, in cell culture assays, curcumin significantly reduced HSV-1 immediate-early (IE) gene expression and infectivity[150]. Compared to other natural products(gallic acid, luteolin, naringenin, quercetin, resveratrol, and zingiberene) and controls, docking analysis revealed that curcumin has the most potent interaction with spike glycoprotein and ACE2 receptor[151]. In contrast to the two anti-malarial drugs (Chloroquine and Hydrochloroquine), Gonzalez-Paz and colleagues reported that curcumin strongly binds to 3CL-protease of SARS-CoV-2 and promotes significant structural changes and folding ofthe viral protease[142].

**Table 4**. Anti-viral activity of eugenol, thymol, terpinen-4-ol, and curcumin

| Compound | Target Viruses* | Mechanism Type | $IC_{50}$ | Reference |
|---|---|---|---|---|
| Eugenol | HSV-1 | Intercellular | 35μg/mL | [152] |
| Eugenol | IFV-A (H1N1) | ND | <3.1 μg/mL | [153] |
| Thymol | HSV-1 | Intercellular | 0.002% | [150] |
| Thymol | HSV-1 | Intercellular | 7μM | [154] |
| Thymol | BVDV | Intercellular | 248.56μg/mL | [155] |
| Terpinen-4-ol | Influenza | Intercellular | 0.0025% | [156] |
| Terpinen-4-ol | HSV-1 | Intercellular | 0.05% | [156] |

| | | | | |
|---|---|---|---|---|
| Terpinen-4-ol | HSV-2 | Intercellular | 0.05% | [156] |
| Terpinen-4-ol | ECHO 9 | Intercellular | 0.05% | [156] |
| Terpinen-4-ol | Cox B1 | Intercellular | 0.05% | [156] |
| Terpinen-4-ol | Polio 1 | Intercellular | 0.05% | [156] |
| Terpinen-4-ol | Adeno 2 | Intercellular | 0.05% | [156] |
| Curcumin | IFV (H1N1), (H6N1) | Intercellular | 0.47μM | [149] |
| Curcumin | ZIKV | Intercellular | 1.90μM | [157] |
| Curcumin | CHIKV | Intercellular | 3.89μM | [157] |

*HSV, human herpes viruses; IFV, influenza virus; BVDV, bovine viral diarrhoea virus; ECHO, enteric cytopathic human orphan virus; Cox, coxsackievirus; ZIKV,zika virus; CHIKV, chikungunya virus; ND, not determined

**Table 5**. Molecular docking analysis of the anti-SARS-CoV-2 activity of eugenol, thymol, terpinen-4-ol, and curcumin

| Compound | Target Component | Interacting Amino Acid Residues | Ref |
|---|---|---|---|
| Eugenol | Spike glycoprotein of SARS-CoV-2 (6VXX) | Gln314, Thr315, Asn317, Asn764, Arg765 | [151] |
| Eugenol | Angiotensin-converting enzyme 2 (1R42) | His401, Glu402, Arg514 | [151] |
| Thymol | Spike receptor binding domain (2AJF) | HIS 401, HIS 378, ASP 382, ALA348, ASP 350, TRP 349, PHE 40 | [141] |
| Thymol | Spike ectodomain structure (6VYB) | LEU 865, PRO863, PHE 782, ILE 870, ALA1056, GLY 1059 | [141] |
| Terpinen-4-ol | 3C-like protease ($3CL^{pro}$) | Lys102, Asp153 | [142] |
| Curcumin | Spike glycoprotein of SARS-CoV-2 (6VXX) | Thr302, Lys304, Gln314, Thr315, Asn317, Asn764, Arg765, Thr768 | [151] |
| Curcumin | Angiotensin-converting enzyme 2 (1R42) | Ala348, His378, Asn394, Tyr385, His401, Glu402 | [151] |
| Curcumin | 3C-like protease ($3CL^{pro}$) | Lys5, Val125, Asp289, Lys137 | [142] |

*6. Unprecedented Challenges associated with COVID-19*

With the surge of the SARS-Cov-2 virus rapidly in different parts of the world, it has become essential to look at its architecting and structural identity to decipher the reasons for the 'virus's evolution to form a new variant with mutations in its morphic structure.The development of these variations hasled to the prevalence of new variants. Notably, the arisen variants include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Mu (B.1621), Eta (B.1.525), Iota (B.1.526), Kappa (B.1.617.1) and currently Omicron (B.1.1.529)[158, 159]. Thus, to understand the mutations of Coronavirus, there is a need to understand the genomic structure of the virus. The SARS-Cov-2 consist of four protein-encoding genes, which are:

1.S Protein-This is a transmembrane protein, also called S-Glycoprotein or the Spike, that is present on the outskirts of the virus; its role is to establish the pathogenicity and range of the host organism.It acts as a medium of entry for the virus by arbitrating the attachment of the virus to the host 'cell's plasma membrane, thereby interacting with the receptor known as Angiotensin-converting enzyme 2 (ACE2) and in some conditions uses CD209L as an alternate receptor[160].

2.M Protein- A membrane protein that dictates the shape of the virus; it also functions as a small transmembrane protein that binds to various proteins[160].

3.N protein-Nucleocapsid is the structural component of the Corona Virus and is bound/attached to the RNA of SARS-CoV-2. It regulates signalling, replication cycle, and immune response toward SARS-CoV-2 infection[160].

4.E protein- Envelope protein interacts with the cell membrane of the host organism to regulate itself in the production and maturation of the virus[160].

By looking into the COVID-19 vaccines genomes, we can ascertain that almost all vaccines except the SARS-CoV-2 viral vaccine are produced based on the genetic makeup of the Spike (S) gene of the SARS-CoV-2 virus and the S gene is concentrated by researchers and pharma companies as the S gene along with its receptor-binding domain (RBD) encodes 1,273 amino acids; therefore the availability of Spike protein is the key element for the pathogenesis of Coronavirus[161]. It also regulates T-cell response, immunity, neutralizing antibody (NAb), and mediating the binding of the 'host's ACE2 receptors with its RBD,which is crucial for infection into the host organism.This is why the vaccines are targeted in this region to neutralize the antibody to safeguard an organism from SARS-CoV-2 infection. The presence of mutations in this site paves the way for the development of variants[162].

The SARS-CoV-2 virus is an RNA virus, and they have an evolutionary change of 10-4 nucleotides per site/year. They mutate over time due to either factor such as genetic drift, natural selection, or environmental influence, therefore playing a pivotal role in strengthening transmissibility, the severity of the virus, its infectivity rate, pathogenicity, transmission, evasion of the immune system and resisting vaccine.The SARS-CoV-2 virus, the mutation in the S protein area includes its RBD region. The ACE2 receptor is the main focus due to its high mutability rate,which is very severe and impacts the vaccination effects[163-165]. Due to the changes in Spike protein, changes in the genome occur, leading to the production of a new kind of virus with changes in its genome known as variants where changes to spike protein exist[166]. The changes to the S protein and RBD region differ among every arisen variant, such as the SARS-CoV-2-α variant exhibits its primary mutations in RBD sites of E484K, S494P, and N501Y;the β variant shows deletions similar to the α variant. Still, the mutation in K417N is unique to this variant. The δ variant of this virus makes the mutationsidentical to all other lineages. Still, they illustrate three distinct mutations of E156del, R158G and T478K unique to the δ variant, making it possible to be one of the deadliest variants[167-169].

The arisen variants have produced a unique challenge for oral health maintenance.Keeping hygienic oral health is become a necessity, as it is known that the SARS-Cov-2 virus is present in the nasal and oral cavity.This allows variants with specific mutations to worsen it.The periodontal tissue is an area that niches the SARS-CoV-2 virus due to an unconditionally favourable environment, with changes to the spike protein.The emergence of variants has raised concerns regarding their biological interactions and implicationsfor oral health[170]. The hypothesis is that variants with better invasive capabilities and changes to their genome can overexpress themselves in the oral region, thereby migrating to the bloodstream and organs and may cause a higher rate of infection to cells such as T-lymphocytes, B-lymphocytes, macrophages, etc. as new variants possess the ability to evade the immune system[38]. The potential arrival of new

SARS-CoV-2 variants raises many questions regarding their pattern of infection and severity.With only the available previous data, we can only contemplate the actions of the variants prepared for them; the need to investigate each strain in-depth and their association with various receptors, body organs, and functional pathways is required.

*7. Phytochemicals against Coronaviruses*

After the outbreak of SARS-CoV-2, many researchers primarily focused on using natural entities to treat the complication associated with COVID-19[171]. Thus, the primary *in-vitro* and *in-vivo* studies were targeted to screen different phytochemicals effective against coronaviruses (especially SARS-CoV-2). Bio-informaticians were performing computer docking using other models to predict the anti-CoVs of the various phytochemicals against the members of the coronavirus family like MERS-CoV, SARS-CoV and SARS-CoV-2[172, 173]. This investigation unveiled that natural polyphenol compounds like apigenin,kaempferol, myricetin, quercetin and resveratrol have significant activities against different coronaviruses[171].Cho and his teammates isolated geranylated flavonoids (tomentin A-E) from *Paulownia tomentosa* (Thunb.) Steud. (Paulowniaceae), which inhibit the activity of papain-like protease involved in SARS-CoV propagation[174]. Another study reported three flavonoids,*i.e.,* apigenin-7-O-rhamnoglucoside, pectolinarin and herbacetin, which at the concentration of 20 μM ceases the activity of 3C-like protease, a crucial enzyme involved in SARS-CoVreplication[175]. Additionally, the ten polyphenols isolated from *Broussonetiapapyrifera* (L.) L'Hér.ex Vent. (Moraceae), also reported the inhibition of 3C-like protease, exclusively with papyriflavonol A at 3.7 μM[176].On the other hand, the molecular docking assessment was done on the theaflavin, a flavonoid compound isolated from black tea, *Camellia sinensis* (L.) Kuntze (Theaceae) (Traditional Chinese Medicinal Plant) inhibits the normal functioning of SARS-CoV-2 RNA-dependent RNA polymerase and exhibitsthe antiviral potential of these compounds, especially SARS-CoV-2[177]. Furthermore, the compound hesperidin, predominantly found in citrus fruits, has also been proposed to show an inhibitory effect on ACE2; owing to this, it has been proposed as a good candidate against SARS-CoV-2 for clinical trials[178].Interestingly, Alam and his colleagues reviewed the use of an oral spray ArtemiC (containing a mixture of artemisinin, *Boswelliaserrata,* curcumin and vitamin C) in 50 covid patients. The oral administration of ArtemiC twice a day for two consecutive days during treatment showed negative COVID-19 PCR after 14 days[179].

*8. Conclusion and Future Prospects*

The importance of oralhygiene in the current COVID-19 pandemic is very evident. It is assumed that virus transmission can occur through the oral cavity to the lungs, but it elucidates the disease's clinical variability and radiological aspects. Viral transmission can also occur through the oral mucosa and nasal route in healthy individuals, whereby those with poor oral health impose themselves infected by SARS-CoV-2. On the other side, individuals with a weakened immune system are more likely to develop severe symptomsrequiring intensive care with mechanical ventilation, whichmight lead to death in many cases.

Moreover, new variants of COVID-19 are imposing health challenges and risks. Thus, considering the risk, following proper oral hygiene and other measures for controlling plaque needs to be prioritized. These precautions will improve oral health and well-being and reduce the risk of developing COVID-19. The pandemic has acted as an opportunity for the oral health plan to be renewed. The health care policymakers should promote oral health by giving training programs to the health workers and educating the local communities about oral health care. Through this practice,the health workers and locals can be prepared for the causalities like the pandemic of COVID-19 beforehand.

Considering the Indian scenario, where most of the population resides in the villages, the concept of oral health is almost negligible. As a result, toothpaste and mouthwashes are not readily available or, in some places, unaffordable. Insuch cases, awareness of simple measures, such as gargling with saltwater and rinsingwith boiled water,helps reduce gingival inflammation. Following these simple measures will aid in reducing the viral load in saliva. Thus, healthcare industries need to take the initiative to spread awareness and incorporate effective phyto compounds in their products, making them affordable for people worldwide. This step will substantially help curb the progression of lung diseases and mitigate the chances of severe COVID-19, ultimately reducing the mortality rate. The health care workers should be trained; in their training programs, interdepartmental professionals should be involved like the dentists, clinicians, and researchers, where the ground information about oral health care can be discussed, and effects parameters can be designed which can work in Indian picture at the ground level in villages and towns. By following this cumulative approach, a bridge between the departments can be made, which will benefit swaying the oral health statistics in India.

## Declaration of competing interest

The authors declared that there was no conflict of interest.Consent for publication

## Competing interests

The authors declare that they have no competing interests.

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