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Review article

Functional biomes beyond the bacteriome in the oral ecosystem

A.S. Smiline Girija*, Pitchaipillai Sankar Ganesh

Department of Microbiology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Chennai 600077, Tamilnadu, India

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ABSTRACT

Selective constraint and pressures upon the host tissues often signifies a beneficial microbiome in any species. In the context of oral microbiome this displays a healthy microbial cosmos resisting the colonization and helps in rendering protection. This review highlights the endeavors of the oral microbiome beyond the bacteriome encompassing virome, mycobiome, protozoa and archaeomes in maintaining the oral homeostasis in health and disease. Scientific data based on the peer-reviewed publications on the microbial communities of the oral microbiome were selected and collated from the scientific database collection sites of web of science (WOS), pubmed central, Inspec etc., from 2010 to 2021 using the search key words like oral microbiome, oral microbiota, oral virome, oral bacteriome, oral mycobiome and oral archaeome. Data excluded were from conference proceedings, abstracts and book chapters. The oral homeostasis in both the health and disease conditions, mostly is balanced by the unrevealed virome, mycobiome, oral protozoa and archaeome. The review documents the need to comprehend the diversity that prevails among the kingdoms in order to determine the specific role played by each domain. Oral microbiome is also a novel research arena to develop drug and targeted therapies to treat various oro-dental infections.

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* Corresponding author.
E-mail address: smilinegirija.sdc@saveetha.com (A.S.S. Girija).

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1. Introduction

The human oral cavity encompasses a plethora of microbial community comprising of commensal, symbiotic and a conglomeration of pathogenic bacteria, fungi, archaea and parasites. These microbial cosmos in the oral cavity is referred as oral microbiota, and the term oral microbiome refers to their respective genomes [1]. The oral microbiome often signifies the ecology of the human space shared with the microbes and also is considered as the ignored determinants of systemic health and disease [2]. Oral cavity being the major gateway to the human body, can often spread the ecological and pathogenic flora to the contiguous structures progressing with systemic diseases [3]. Re-focusing on the microbial communities in the oral microbiome had revealed a consortium of organisms rather than a single microbe [4]. Oral microbiota is thus diverse and is influenced by factors like diet, oral hygiene, habitual and other environmental factors in the host. This unique diversity is associated with the number of species that are present and represented in the ecological community attributing species evenness and richness respectively [5].

A synergistic and co-operative mode of action by the microbes in concert with the host immune response renders a dynamic balance and stability for the oral microbiome and determines the progression with a disease [6]. A complete knowledge on the endogenous residents is thus necessary for a comprehensive understanding of any microbiome. This has an intrinsic limitation when the conventional microbiological protocols are considered, where only 50% of the micro-organisms are cultivable with a slew of investigations progressed in this goal [7]. Skyrocketed literatures focusing on the oral microbiome had focused more on bacteriome with lower abundant studies on the other microbiome like mycobiome, virome, archaea and parasites. With the advent of science and next generation sequencing (NGS), identification of the oral microbes had spurred renewed interest, with numerous studies sparking with oral microbiome and on dysbiotic genera [8]. Beyond the bacteriome, the other functional biomes play a pivotal role in maintaining the homeostasis of the ecological niche (Fig. 1). The lack of optimized tools limit the taxonomical identity of the same and thus the microbiome beyond bacteriome is uncharacterized lavishly.

Recently, the dark matter of the oral microbiome has come into limelight through cutting edge scientific technologies with better understanding based on various clinical studies as summarized in Table 1. Most of the oral microbiome being uncultivable, the unique candidate phyla radiation (CPR) had revealed recently, specific "microbial dark matters" such as Saccahribacteria or TM7 in the oral cavity [9,10]. It is efficient in establishing a highly adaptive episymbiotic interactions in complicated niche like oral cavity through their specific arginine deiminise system [11,12]. Additionally, notable members of the potent virome, mycobiome, archaea and parasites are creeping in recent literatures in the context of oral microbiome urging more population based evaluations to underpin their specific roles. It is also an avid scenario that the existence of the microbiome beyond the bacteriome accounts for inter-kingdom networks and also in host-microbe interactions [13,14]. This review thus proposes the commandeered role and keys insights on the oral microbiome on their impact with oral and systemic health.

2. Oral virome

In numerous ecosystems, viruses are considered as the significant drivers of the diverse niche in the planet and also on the human tissues. Oral virome is considered as a robust ecosystem present as prominent indigenous members with an ability to infect the host cells as well as other bacterial cells altering the oral health condition (Table 2). Saliva encompasses approximately 10^8 viral particles/ml with bacteriophages as stable community for longer periods [15]. In the oral microbiome, the huge virome size and constraints on the unavailability of the genome data in NCBI databases, limits the identification of the oral virome. However, recent bioinformatics tools such as Metavir, VIROME, ACLAME, Virus seeker, Phage seed etc., it is now possible to render more evaluations on the oral viromes [16]. Analysis on the oral DNA of the virome had revealed a majority of bacteriophages under the family of Siphoviridae and Myoviridae. Oral virome also shows an abundance of phageomes against *Streptococci* together with members of Herpes viridae family under the eukaryotes [17]. The human oral cavity also shows a substantial number of orphan viruses that belongs to the family of Anelloviridae [18]. Thus in the present time, our analytical capabilities have increased enormously due to the availability of multiple annotated databases of the virome sequences.

Oral virome seem to be persisters in the oral cavity and not always a transient flora as evidenced by a study in a cohort population conducted for a 60 days period and its persistence is significantly associated with sex and highly personalized [19]. Also, oral virome shows significant variations in the viral community as analyzed from the plaque sample from periodontitis in comparison with the healthy individuals. These seem to be the major predators of bacteria influencing the oral health status [20].

2.1. Oral phageoms

Interestingly, among the viruses, bacteriophages seem to be predominant in the oral microbiome based on an analysis of the virome reads from the saliva of human subjects [21]. Preponderance of shared homologs and unique differences when compared to gut phages substantiates the role of the host habitat in shaping the viruses and transforming them to be more specific in the oral habitat. These oral phages possess a prominent lysogenic cycle with functional genes and also serve as reservoirs of virulent genes especially drug resistant determinants. Substantial breach in the oral mucosal layers allows the entry of viruses in bloodstream as evidenced by viremia in humans with weakened immune system. In systemic illness like schizophrenia, metagenomic analysis shows huge variations in the oral phageoms when compared to the healthy controls [22]. In addition, oral phageomes are distinct in shaping the bacterial ecosystem of the oral cavity, as well.

A fascinating concept of "intra-body phageome" that emphasizes the role of phages in the classical sterile regions of the body is also proposed recently [23]. Analysis on the viromes and the CRISPR content suggests that, the humans sharing a particular environment or a habitat determine the robust virome community in the oral cavity [24]. In addition, the oral phageomes are also shared frequently among the households and are thus distinct among the individuals in a common household habitat. However, the alpha and beta diversity on the same shows no significant association with the gender of the human population. This suggests that, the alteration in viral ecology may be the significant indicators of disease status, which has to be monitored by the advanced molecular techniques. Albeit, with not much alteration in the viral diversity is observed, these phageoms seem to express an inexorable expansion of putative antibiotic resistant genes [25]. Amidst these genes, oral phageomes are also known to carry several specific genes with complement and antibody degrading functions together with platelet binding properties rendering benefits for their hosts [26].

2.2. Oral viromes in health and diseases

The phageomes in the oral cavity are more involved with the periodontal diseases and significantly alters the bacteriome based on the severity of the disease leading to dysbiosis and further transition promoting the oral disease [27]. Single viral genomes (SVGs) of uncultivable viruses reveal the presence of abundant viruses

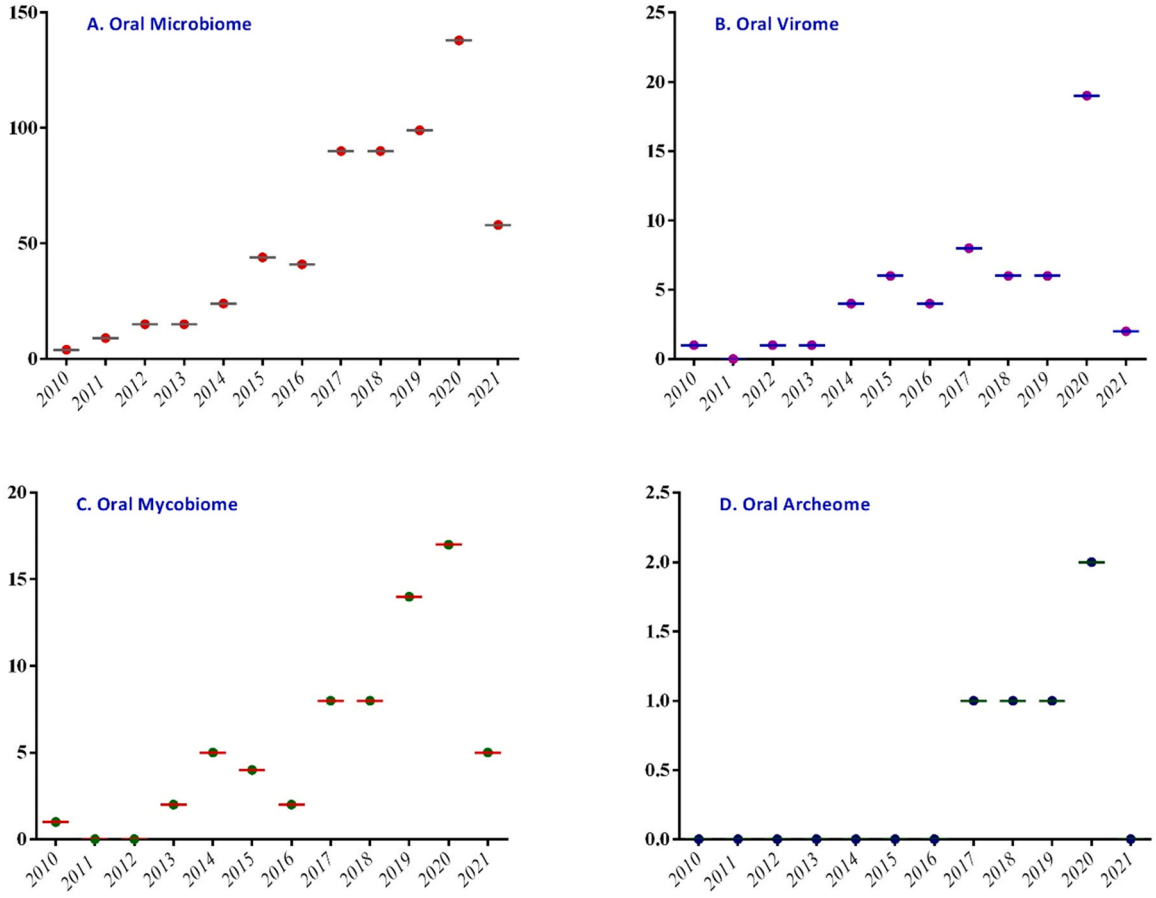

Fig. 1. A schematic representation of the scientific data based on the peer-reviewed publications on the microbial communities of the oral microbiome. All the data were collated from the scientific database collection sites of web of science (WOS), pubmed central, Inspec etc., from 2010 to 2021 using the search key words like oral microbiome, oral microbiota, oral virome, oral bacteriome, oral mycobiome and oral archaeome. Data excluded were from conference proceedings, abstracts and book chapters.

infecting *Streptococcus* followed by *Actinomyces* phage exhibiting their role in oro-dental diseases [28]. In periodontitis, the diversity of oral virome, analyzed via the shot gun sequencing method documents the widening of the PDL space in association with other polymicrobial infections by periodontal pathogens [29]. Genomic analysis together with the clinical findings thus suggests the implications of oral virome in influencing the biomechanical properties involved in the periodontal tissues leading to periodontitis. Investigations on the ecological niche of the patients affected with hand foot and mouth disease showed nine discriminative viral species with elevated levels of *Streptococcus* sp.,. It also correlated with the presence of Enterovirus and Coxsackievirus A5 and A6 together with the altered virome profiles [30]. On the other hand, a healthy human microbiome may be always accustomed with the direct health of the human body. The unexplored dark virome of the oral microbiome may also be a good indicator of health and is often associated with the adverse outcomes of vital diseases as well [31]. Composition, assembly and the dynamics are highly mosaic among the viromes, playing a vital role in the host-virome interactions of the human diseases.

3. Oral mycobiome

The oral cavity also possesses various fungal communities that are commonly referred as mycobiome and are also termed as mycobiota, fungeome or mycome. The basal mycobiome of the oral cavity comprises *Candida* as the frequent community, followed by *Cladosporium*. 50% of the oral mycobiome constitutes of *Aureobasidium* and *Saccharomycetales*. The lowest flora of fungi belongs to *Aspergillus, Fusarium* and *Cryptococcus* [32]. Several reports in recent years have detailed the importance of fungi within the oral cavity in studies involving human and animal (Table 3). Interrogation of the fungal taxa in the oral cavity also had documented nearly 74 fungal species as cultivable and 11 species under non-cultivable genera. A strong taxonomic shift was also documented in the dental mycobiome with a total of 139 fungal species with 32 differentially abundant taxa, an unclassified Microdochium species with 12 taxa that correlates with the health [33]. Analyses on the salivary mycobiome encompass *Candida* mycotype and *Malassezia* mycotypes as two ecologically distinct mycotypes warranting these as significant biomarkers for oral diseases [34].

Fungal component of the oral cavity, being in low proportion, oral mycobiome based studies often rely on internal transcribed spacer (ITS) based amplicon analysis. However, critical appraisal on these ITS based fungal diversity studies detects > 100 fungi signifying *Candida* as the predominant species [35]. Interestingly, over the first month of life in infants, the mycobiome profiles are variable and seem to be more similar in comparison with the vaginal mycobiome and are found to be altered upon age [36]. Similarly it is also varying in community-dwelling elderly population showing significant alterations in candidal species [37].

3.1. Alterations in the oral mycobiome

The mycobiome of the oral cavity is specifically altered by various factors, such as administration of certain drugs. An effective antifungal drug nystatin is known to affect the colonization by *Candida* thereby influencing the risk of biofilm formation by other potent

Table 1
Summary of the few significant studies on the oral microbiota comprising the bacterial, viral and fungal biota.

Type of microbiota	Samples	Type of Analysis	Reads/contigs/Sequences	Reference
Bacteria	4154	SGB (kSGBs and uSGBs analysis)	Assembled: 56,213, average 14,094 contigs/sample, taxonomically assigned: Saccharimonadaceae (17.99%), Campylobacteraceae (9.51%) *Streptococcus* (12.88%) and *Campylobacter* (7.65%),	[98]
	25	RDP, LCA, MySQL, ITS, LCA and phymmBL	Assembly reads 1103 contigs	[99]
	41	QIIME, OUT	17,129 reads per sample; 702,304 sequences	[100]
	747	HOMD, TORQUE	35,000 clone sequences	[101]
	44	PCoA, SOAPaligner 2.1, SOAPdenovo	27.8% ± 16.7% sequences/reads; 49.8% ± 3.8% of the reads/sample	[102]
	88 (31 confirmed patients with COVID-19, 29 flu patients with influenza B, and 28 healthy controls)	Kraken2 v2.0.9, QIIME 2, MEGAHIT	Assembled contigs 3356–842,961 bp/sample *Veillonella* sp. (22.7%), *Streptococcus* sp. (20.3%), *Prevotella* sp. (7.1%), *Acinetobacter* sp. (5%), *Megasphaera* sp. (4.21%), *Actinomyces* sp. (4.19%), *Atopobium* sp. (3.65%), *Klebsiella* sp. (3.25%), and *Solobacterium* sp. (2.07%)	[103]
Viral	88	FGenesV/ BLASTX homology/ Qiime	Contig (16% ± 4.2% - 60 days) - 69.9% ± 5.5% versus 30.1% ± 5.5% - 7th day)	[104]
	04	VirSorter/ vConTACT v.2.0	Novel phages (0–7(0–44%) – 3–26 (12–46%) Novel prophages (25–54 (42–59%)– 73–323 (56–77%)	[105]
	05	FGenesV	27429 nucleotides, 1421 reads,	[21]
	15	vSAGs (Illumina Tech), ProDeGe	MiSeq sequencer (2 × 250, pair-end); Reads ≥ 70% identity, ≥ 70%, viruses with ≥ 40% coverage	[28]
Fungi	20	Internal transcribed spacer (ITS),ITS1 & 2, AFTOL, WASABI, aligned (KALIGN)	39,226 sequence; 1702 sequences per sample/ average length of 248 bases	[32]
	30	Internal transcribed spacer (ITS), ITS1-F/ITS2, QIIME	QIIME/UNITE: 8607,862 reads; OTU- α-diversity (13,000 sequence reads/sample) (Total: 8943 OTUs sequence/read)	[106]
	18	ITS	Merged sequences 712 295 MiSeq: 1 580 028 reads	[107]
	17	ITS (ITS2 & 4)	MiSeq – 250 bp length; R/phyloseq:10,000 sequences per sample; 37,119 sequences	[108]

bacterial pathogens [38]. Disease conditions may alter the oral mycobiome profiles as documented from various studies. Mycobiome profiles in children with and without caries showed an extremely low profile of fungal loads and extremely a higher prevalence of *C. albicans* respectively. *Malassezia globosa* was significant in caries free subjects primarily suggesting the role of mycobiome profiles in disease and disease-free conditions [39]. Alterations in the oral mycobiome is also evidenced in conditions with atopic dermatitis, leukemia and in immuno-compromised patients like HIV, with *C. albicans* in abundance in all the cases and PCR seem to be the best method to analyze the mycobiomes in comparison with the conventional methods [40]. Mycobial diversity was also evidenced in the sub-gingival plaque specimens in patients under ART therapy, with high levels of Candidal species and significantly low levels of *Exseohilum* sp., *Guehomyces* sp., *Debaryomyces* sp., together with three unidentified fungi [41]. A global snapshot on the alterations in the oral mycobiome in relation to the bacteriome is also documented in genetic associated disorder like Down's syndrome [42].

It is also fascinating to note that there could be a significant alteration in the mycobiome based on the postnatal acquisition either from maternal source or from an environmental source. However, a systematic review documents that during the early life period, vaginal delivery may promote oral yeast colonization with maternal breastfeeding not showing a significant influence on the oral mycobiome [43]. Poly-microbial interactions in association with the environmental fungi may also lead to antagonistic or synergistic effect in the oral mycobiome exhibiting similarities between the host and the environment [44]. A gargantuan diverse mycobiome was functionally deciphered through next generation sequencing platforms and shows significant variations in both health and disease [45]. In this line, a pronounced mycobiome shift and fungal dysbiosis is demonstrated in patients with recurrent aphthous stomatitis with negative correlation with the occurrence of bacteriome [46]. Demonstration on the significant changes in the core oral mycobiome in HIV infected cases was observed and is independent with that of the age and sex variables leaving an impact of fungal community among the same [47]. The role of mycobiome is highly specified to be associated with colorectal cancers portraying the importance of its presence and dysbiosis in the oral cavity in relation to the gut microbiome as well [48].

4. Oral archaeome

The microbiome of the oral cavity comprises of archaeome as a third domain of cellular life and exhibits less diversity and is highly plausible as secondary colonizers. Elucidation of its importance in the oral cavity is a herculean task, as it is difficult to cultivate. It is thus evident to document its presence through PCR by detecting the specific functional genes coding for the methyl co-enzymes as most of the archaeomes fall under the category of methanogenic organisms [49]. However, the detection of archaeome, in most of the cases depends on the composition of the primer pairs and often the universal primers fail to evaluate the diversity of the archaeal signatures from the oral and also from holobiotic samples [50]. The full spectrum of archaeome is not yet elucidated due to the impediment of the bacteria targeting protocols being inapplicable for this process. Search on oral archaeome evidenced a moderate category where 4 domains of archaea correlated in inducing periodontitis with the cultivable archaea as *Methanobrevibacter oralis* [51] and *M.oralis* HOT 815 as uncultivable species under the phylum Euryarchaeota

Table 2
Summary of the few significant oral virome in healthy and infectious conditions.

Model	Sample	Type of infection	Study type	Findings	References
Children	Saliva	Food and Mouth Diseases, Mouth ulcer	Young children (n = 55)	Bacteriophages (*n* = 27, 67.5%) vertebrate viruses (*n* = 11, 27.5%) and plant viruses (*n* = 2, 5%)	[30]
Human	Saliva, Sub gingival & Supragingival plaque, Control (healthy adults)	Periodontal diseases and healthy mouth	n = 16 (Chronic severe generalized periodontitis (n = 7) and good periodontal health n = 9).	Siphoviridae Myoviruses Podoviridae	[100]
Young adults	Oral rinse	Healthy individuals	Young adults (n = 72)	Bacteriophages (*Siphoviridae* and *Myoviridae*, and *Streptococcus* phages) Viral (*Herpes viridae)* Caudovirales, Siphoviridae (71 samples) and Myoviridae (68 samples), *Streptococcus* phages (up to 69 samples), Eukaryotic viruses (Herpes viridae family (65 samples), Human herpes virus 7 (from 61 samples out of the 72 samples)	[17]
Volunteer's	Salivary sample	good overall periodontal health individuals	n = 15	Prophage (*Streptococcus* phages), *Caudovirales*	[28]
Oral cavity Patients	Oral rinse	Patients admitted in the hospital with oral cavity diseases	n = 124 patients (Male: n = 48 Female: n = 76)	Human papilloma virus (HPV)16 – Male: N-38 and Female: N-56	[109]
Infants	Oral swab	HIV infected women and Non HIV infected women	n = 32	Identified: Cytomegalovirus	[110]

Table 3
Significant role of oral mycobiome in causing infections in human, immune-compromised patients and animals.

Model	Sample	Study type	Findings	References
Participants from Kips Bay Endoscopy Center in New York City	Oral wash	n = 30 (Age between 18 years or older (29–86))	> 86.5% phyla were identified as Ascomycota and < 3.1% were identified as Basidiomycota, Glomeromycota and Chytridiomycota. Identified: *Candida* and *Aspergillus* sp. (100%), *Penicillium* sp. (97%), *Schizophyllum* sp. (93%), *Rhodotorula* sp. (90%), and *Gibberella* sp. (83%)	[108]
Healthy Individuals	Oral rinse	n = 20 (Age: > 18, non-smoking, no symptoms of oral mucosal diseases and no recent use of antifungal agents)	*Cladosporium* (65%), *Aureobasidium* (50%), *Saccharomycetales* (50%), *Aspergillus* (35%), *Fusarium* (30%), and *Cryptococcus* (20%).	[32]
HIV Infected and Uninfected participants	Oral rinse	n = 24 (HIV infected – 12 and Uninfected individuals – 12, Age: > 18 years)	*Candida albicans* (58% in uninfected and 83% in HIV-infected participants).	[111]
Australian children	Dental plaque	n = 17 (age: 7–10 year)	Phyla were identified: Ascomycota, Basidiomycota, Zygomycota, Ascomycota, Basidomycota Taxa identified: *C. albicans* (12%), *Naganishia diffluens* (8%), *R. mucilaginosa* (8%) and *M. globosa* (6%)	[108]
ANIMAL BASED STUDIES				
Dog	Swab	n = 51 (with and without Periodontal diseases).	Most predominant fungal species were identified: *Cladosporium* sp (n = 46), *Malassezia restricta* (N = 44), and *M. Arunalokei* (N = 36).	[112]
Cat	Swab	n = 14 (Healthy cat), FCGS affected cat (n = 14)	Taxa were identified: *Malassezia restricta, Cladosporium penidielloides, M. arunalokei and Aspergillaceae sp.* New species identified: *Bergeyella zoohelcum*	[113]

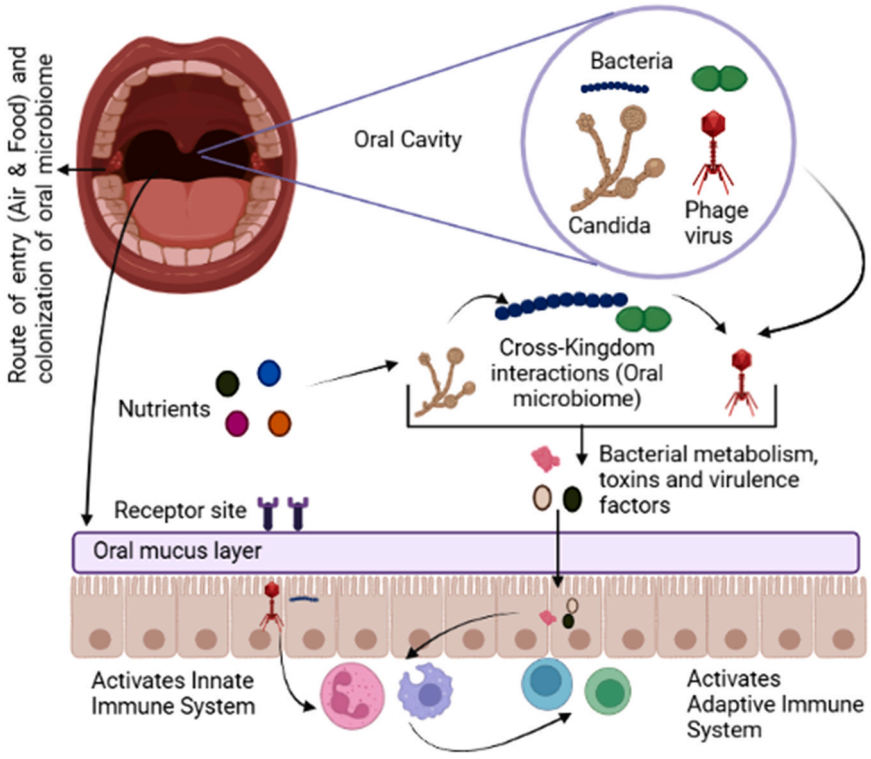

Fig. 2. Cross-kingdom interactions between the various members of different kingdoms. Specific attachment of the different microbial community on to the specific receptor sites on the oral mucosa interact with each other for their survival, nutrients, metabolism, energy production, modulating the immune system and in maintaining the oral homeostasis both in oral health and disease.

(Bringuier). *M. oralis* is also reported as the frequent archaeome in relation to periodontal infections [52].

Among the oral microbiome, nearly 5% of the subgingival metagenome mass revealed the presence of archaeome together with viruses and fungi analyzed through metagenomic shot gun sequencing [53]. In comparison with the healthy mucosa, Archaea were observed in patients with dental caries and also in the various oral niches from the individuals from different geographical locations implicating their role in oro-dental diseases. A better comprehension in evaluating the human oral archaeome is hampered due to methodological limitations. Contrasting results were observed in studies among healthy population, where few studies showing its absence and few other studies showing its presence in healthy population respectively [54–56]. In patients with peri-implantitis, *Methanobrevibacter* and *Methanobacterium* were reported from the study subjects from Brazil [57], but however, no significant variations from the French populations.[58] Ethnicity and dietary factors thus seem to influence the archeal signatures and often they are considered as ordinary members of sub-gingival biofilms [59]. Archaea were also associated with patients with pericoronitis erupting molars and detected exclusively in a study [60].

In the endodontic sites, *M. oralis* and *M. smithii* were more prevalent inside the root canals [61] and a positive correlation is observed between the methanogens and the Synergistes spp.,.[62]. A recent document explores the presence of the phylum *Thaumarcheota* in both caries and caries free healthy subjects [63]. Presence of archaeomes and “Archaea effect” is been documented from various archaeological samples/sites [64] and includes 4 specific archaeal classes such as *Halobacteria*, methanogenic archaeomes and *Thaumarchaeota* [65]. Among the methanogens, *Methanobrevibacter massiliense*, *Methanoculleus bourgensis* and *Methanomassiliicoccus* phylotypes were observed in dental calculus archeological samples during 15th century showing much diversity as well [66].

5. Oral parasites

The polymicrobial consortium of the oral microbiome also encompasses the protozoans as typical members in the dental plaques and in the periodontal pockets. Little has been revealed on the presence of the oral protozoa and about its commensalism in the oral microbiome. NGS based exploration of oral protozoa was a failure, however, their role is been identified only through the microscopic methods [67]. Electron microscopic studies reveal the presence of *Entamoeba gingivalis* (*E. gingivalis*) and *Trichomonas tenax* (*T. tenax*) and free living amoebae in many cases with and without diseases. Its presence is influenced by the host factors showing a mixed composition together with its prominent role along with bacteria and fungi [68]. In patients with genetic diseases, a highest prevalence of *E. gingivalis* and *T. tenax* is observed among the age group of 41–50 years portraying its role in the oral microbiome and in inducing diseases upon the alteration of the homeostasis [69].

Studies from 19th century also do document the presence of these two organisms in abundance and in highest frequency and increased endemia in a direct proportion of OHIS index. In periodontal deep pockets, a 3-fold increase in *T.tenax* was observed and *E.gingivalis* at an increased rate in case of gingivitis [70]. These organisms had been proven to be potent pathogens among the oral microbiome, capable of lysing the mucosal epithelial barriers and ingesting the RBC's and the nuclear components of the lymphocytes as well [71]. Though the potential correlations were much discussed, the synergistic and the commensalism roles of the oral protozoa is yet an unexplored arena which might aid in future therapeutic arguments.

6. Inter-kingdom interactions among the oral microbiome

Dense colonization of the oral microbiome in the intense niche compels each microbial kingdom to be more competitive for their

survival in the oral cavity, in search for space and nutrients. Advancements in the omics approach render a better understanding between the inter-kingdom interactions. Like the environmental ecosystems, the oral microbiome is highly dynamic and mosaic and are known to interact by the cross-kingdom relations (Fig. 2). This intricate interactions between the microbe and the host, influences the host response in maintaining a proper balance and homeostasis. It is also evident that an interdependent balance is essential in the maintenance of oral health and any imbalance between the kingdoms may give rise to oro-dental infections [72].

Oral bacteria, bacteriophages and the mammalian immune system are highly inter-linked in exhibiting an efficient immune response upon the oral infections. Many models have been predicted to evaluate the role of the complex and dynamic interactions between the phageomes and bacteria in the oral cavity. It is hypothesized that a mutual benefit exists between the bacteria and the phages through the interaction of the phages via the mucosal surface leading to bacterial adhesions. A commensalism may thus prevail between them through additional binding sites for the bacteria elevating the frequency of colonization [73]. The cross-relations between archaea and aerobic bacteria promote a protective effect against the aerobic methanogens allowing them to thrive in aerobic niches of the oral cavity [74]. Aerobic bacteria also provide a micro-aerophillic environment for the *Methanobrevibacter* species to thrive [75]. Presence of sulphur reducing bacteria permits the growth of methanogenic archaeome to grow around the periodontal tissues with reduced co-occurrence in later stages of the disease [76]. This shows the role of the cross-relations between the kingdoms in the oral cavity in the establishment of oral health and disease. Similar positive correlations between archaeome and the anaerobic bacteria *Tannerella forsythia*, *Porphyromonas* sp., and *Prevotella* sp., also occur in conditions of chronic periodontitis with 10-fold increase in the numbers of *M. oralis* [77].

The cross-relations between bacteria and fungi is accomplished by a direct fungal-bacterial cellular interactions and the survival is assisted by the products of bacteria through metabolic interactions or alternatively by varying the host immune response. Contrastingly, an unperturbed resident bacterial commensals, limits the colonization of *C. albicans* in oral mucosa [78]. On the other hand, the virulence of *C. albicans* can be enhanced through the activation of the proteolytic pathways which is assisted by bacteria like *Streptococci* sp., contributing to the breach of the oro-mucosal barriers [79]. It is documented that *C. albicans* competitively and co-operatively survive together with 300 or more bacterial species and through these associations, adhesion and colonization is promoted onto the host tissues [80]. A four category principle is thus finally documented to explain the fungal-bacterial cross-kingdom interactions, where, as an initial step a synergistic role is played by each kingdom assisting them to colonize or infect. It is followed by the predisposition of the first microbe by the second microbe interacting with the host for its own colonization, and as a third step, the second microbe dominates exhibiting antagonism, finally leading to disease through the addition property [81].

A cross-kingdom mutualism is also observed between *S. gordonii* and *C. albicans* where the former aids in the persistence of the later and the later provides a reduced oxygen tension for the *S. gordonii* to grow. The nutrient by-products of the bacterium helps in enhancing the formation of the hyphal filaments of *C. albicans* with a huge number of interactive signals and additional grow factors or catabolites playing behind the cellular interactions in promoting synergy in this inter-kingdom partnership [82].

7. Immunity and genetics behind the modulations in the oral microbiome

Interleukins and other cytokines play a vital role in shaping the oral microbiome barrier interacting between the microbes and the host immunity. Among various cytokines, IL-17 is considered as the sentinel breaching the mucosal barrier through multiple mechanisms. It also contains the microbial pathogens at the barrier sites and are strategically positioned at various barrier sites preventing infections [83]. In mucosal associated immunity, IL-17 is known to enhance the production of reactive oxygen species and helps in the development of neutrophils in concert with the increase of GM-CSF modulating lymphocyte differentiations too [84]. Cytokines also do immune-surveillance and induces antimicrobial chemotactic factors in co-ordination with other cytokines like IL-22 and are known to induce substances like β-defensins, cathelicidins, lactoferrin etc., [85]. Cytokines are known to interact both under normal and critical physiological and pathological conditions in balancing the normal flora rendering mucosal homeostasis [86].

Examination on the saliva and supra-gingival plaque using the genome wide association studies had documented the host genetics playing a significant role showing similarity in the oral microbiomes of genetically related cases. Heritability also plays a vital role in influencing the bacterial adhesions, with mucins acting as energy sources, and specific immune molecules regulating the bacterial compositions to maintain colonization. Heritability is also associated with the taste receptors determining the dietary preference that can indirectly alter the oral microbiome and the salivary flow rate assisting the same [87]. Many species seem to be heritable, with *Aggregatibacter* and *Leptotrichia* sp., to be more heritable and mostly the oral taxa that are heritable tend to lie on the periphery rather than co-occurring with each other [88]. A higher abundance of *Prevotella pallens* was evident in patients without dental caries and most of the heritable taxa are highly influenced by host genetic factors involving various genes and associated mutations as well [89].

8. Oral microbiome and disease

Amidst the symbiosis and commensalism exhibited by the oral biomes in health, perturbation of an inflammatory response occurs in disease conditions, leading to formation of the pathobionts. Periodontitis and caries are two such disease conditions of the oral cavity that is often established by the increased numbers of these pathobionts dominating the oral commensals [90]. Apart from the inflammatory conditions, there are spurring documents evidencing the association of the oral microbiome with the non-communicable diseases like diabetes, obesity and cancers [91]. Various metagenomic, sequencing and other advanced molecular studies have characterized the variations of the microbiome of the plaque samples from periodontitis cases from healthy controls displaying unique biomes [92]. In the same line, the microbiome of the tongue, palatine, and mucosa of HIV patients, have revealed the enriched symbionts and pathobionts and their unique interactions in both disease and healthy conditions [93]. The vital niches of different study population show majority of bacteriomes with less significance of mycobiomes [94]. These literatures substantiates, that considerable redundancy prevails among the oral microbiome with specific phylogenetic diversity in health and disease conditions.

9. Unraveling the oralomes towards a paradigm shift in therapeutics

A vivid understanding of the oral microbiome, its dysbiosis in disease condition and its interactions with the host, would explore various specific novel therapeutic targets. In this context, many antimicrobial peptides of the oral microbiome have been documented to act against the potential pathogens associated with cancers [95]. Prebiotic and probiotic approach is also a novel research arena that can efficiently modulate the oral microbiome both in health and disease conditions [96]. Genome wide studies revealing the genetic

and epigenetic modulations in the oral microbiome is yet another milestone towards targeted therapy of oro-mucosal diseases. “Epi-drugs” garner the significant research area ameliorating the effect of disease associated epigenetic proteins such as the bromodomain motif proteins in potential periodontal pathogen *P.gingivalis* [97]. The association of the oral microbiome with the life-style disorders also have transformed them as potential targets, in improving the physical health of humans. The dynamics of the integrated microbiological and clinical studies will thus comprehensively may explore many regulatory pathways, revealing potential diagnostic and therapeutic targets.

10. Conclusion and perspectives

The cosmos of the oral microbiome is maintained by the significant role played by various microbial kingdoms and cross-reacting species. The most unrevealed virome, mycobiome, oral protozoa and archaeome seem to be the vital part of the oral microbiome, prominently balancing the oral homeostasis in both oral health and oro-dental diseases. The potential involvement of the different microbiome is yet to be explored due to the limitations in the availability of numerous methodological approaches. A better comprehension is thus needed to report on the diversified presence of each kingdom in determining the specific domain of the oral microbiome in different niches of the oral cavity under different conditions.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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