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Research Article

Phytochemicals - A Novel Therapeutic Approach to Control Oral Biofilm

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ABSTRACT

Humans and micro-organisms have co-evolved having a synergetic relationship with their resident microbiome. The mouth features a diverse microbiota that grows on oral surfaces as functionally and structurally organized biofilms. The oral biofilms are accountable for causing a wide range of chronic diseases and owing to the development of antibiotic-resistant bacteria it has really become tough to treat with efficacy. Operative control of oral biofilm and the resulting infectious diseases epitomizes a significant universal challenge. For this kind of therapeutics, natural herbal products are perfect candidates because of their unique properties.

The current review presents a novel approach to control and eradicate oral biofilm by the phytochemicals. Research on phytochemicals is zealously focused on health promotion, disease prevention, and also on the development of novel therapeutic interventions.

Key words: Dental plaque, Microbial resistance, Medicinal herbs, Oral biofilm, Phytochemicals, Plant extracts, Quorum sensing.

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INTRODUCTION

Biofilm induced oral diseases pose to be a main communal health issue worldwide. Dental caries, gingivitis, periodontitis and peri-implantitis and several other oral infectious diseases are caused by oral biofilm which is clearly recognized as a virulence factor and a has organized community of microorganisms rooted with self-organized matrix of extracellular polysaccharides (EPS).[1,2] Also, there is strong evidence signifying the association of oral microorganisms with the pathogenesis of systemic disease including autoimmune disease cardiovascular disease, chronic obstructive pulmonary disease, preterm delivery, respiratory disorder, and several other conditions.[3]

Biofilms are microbial networks encased in a self-created lattice that adhere to biotic or abiotic surfaces. The perseverance and seriousness of diseases are compounded when microorganisms form biofilms.[4] Biofilm development begins once microbial cells of planktonic origin stick to a surface and initiate secretion of extracellular matrix and includes components like nucleic acids, proteins, lipids, Exopolysaccharides (EPS), lipoteichoic acids and lipopolysaccharides. Standard lifecycle of the biofilm embraces bacterial add-on, biofilm growth, maturation of the biofilm and biofilm dispersal. Potential approach to the control of biofilm includes actions that may disrupt biofilm cycle at any stage and its control incurs large expenditures worldwide.[5]

Presently managing biofilm associated oral infectious diseases might be a challenge worldwide since conventional antibiotic therapy is virtually impossible in case of common infectious diseases due to advent of drug resistant bacteria. Since a number of resistant microorganisms and the extent of resistance in solo organisms are expanding altogether, different microorganisms have different biofilm resistance due to multifactorial effects. The high resistance of biofilms is described through various mechanisms including restricted antibiotic penetration due to the exopolysaccharide matrix, which acts as a diffusion barrier and minimizes the intracellular concentration of antibiotic. Altered chemical environment inside the microorganism is another factor which leads to emergence of resistance. Reduction of oxygen and consequently the nutrient gradient that occur within biofilms alters metabolic activity between the surface and also layers in depth which prompts slow growth[6,7,8] and orientation of cell biofilm–specific phenotypes denoted to as persister cells.[9]

Progress in pre-clinical studies is due to the conventional means of treating infections and a limited of them have thrived in indicating significant clinical results[10] which encompasses the utilization of compounds that stop biofilm formation or the host tissues adherence, constrain quorum sensing (QS), target pathogen virulence, etc [11]. The reasons that weaken biofilm development or interrupt its structure in light of both physical and biological characteristics has to be well distinguished for the hunt for novel medications and alternate treatments. Thus, specializing in the varied phases of biofilm advancement which include attachment, motility, creation of extracellular polymeric substances (EPS) and QS wonders, provoking biofilm deactivation and elimination by approaches of debilitating, scattering or interruption is an expectant procedure.[12-14]

Conventional antibiotic therapy and collective drug resistance has led to the necessity for alternate approaches to handle infections related to oral

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biofilm-. The scientific community have aroused interest in natural compounds to counteract the biofilm resistance issue. One among the innovative strategies proposed is, use of phytochemicals to prevent or eradicate biofilms. With this background, the utilization of plant extracts which exhibit broad biologically activities as an adjuvant have been a great attention over the past few years.[15] The phytochemicals with their multi-target method of activity and structural diversity are of concern and contrasts significant from the normal antibiotics.

Such distinguishing factors can support to beat the resistance problem. To date, there's no proof of bacterial resistance occurrence due to phytochemicals.[16] Plant extracts may, in many cases, signify a superior source of antimicrobial compounds than synthetic Drugs[17] though active constituents may occur in plants in low concentrations. The phytochemicals represent the richest available reservoir of novel therapeutics. Current research on phytochemicals is further focused to specialize in promotion of health, wellbeing, prevention of disease, and therefore the enhancement of therapeutic interventions. This research aims to critically appraise the published literature over the earlier years as relevant to oral biofilm control by the phytochemicals.[18-20] The emphasis of this review is on benefits and importance of current results, looking for the subsequent answers to how the phytochemicals cater to biofilms, its mechanism of action against oral biofilm control and the further researches.

METHODOLOGY

Literature search

Relevant articles were searched in electronic databases like PubMed, EMBASE, Google scholar, and the journals electronic archives. The search terms for papers related to phytochemicals and oral biofilms were considered. Subsequently, the resultant literature reports were from investigated databases.

Inclusion criteria

Extracts derived from plant parts such as leaves, seeds, flowers, roots, bulbs, trunks, and fruits against oral biofilms were characterized as Phytochemicals. Various study designs including in vitro, ex vivo and in situ which investigated the impact of the said preparations on multispecies oral biofilms were included in the present review. At least two microorganism species were considered as multispecies. Only microbial oral biofilms of distinctive microbes were reviewed. Studies available in English were considered.

Exclusion criteria

Purified compounds of plant origin and essential oil were excluded. Reports of randomized controlled trials and other kinds of clinical studies were omitted from this review. Studies concerning single species oral biofilm were removed from this review. Besides, studies on plant extracts against planktonic microbes, whether or not they were representative of the oral cavity, were not considered. Studies with combination therapy of routine pharmacologic drugs with herbal interventions were not reviewed.

Selection of studies

According to the established exclusion and inclusion criteria the two independent authors who re-assessed the resulting titles and abstract were responsible for removing the reports dissimilar to the topic, even though the first literature was accomplished by one author. The other studies were downloaded as full-text articles and were later assessed for eligibility after the additional screening. The studies were omitted if full access to the papers was impossible. Lastly, irrelevant articles were filtered during the last screening phase against the above-mentioned criteria and the studies involved for qualitative analysis were achieved.

Data entry

A predesigned proforma was used to organize the data from individual study considered. Precisely, year of publication, study design, comprehensive data about the authors details, varieties of oral microorganisms within the biofilm, methodological details, main conclusions, and limitations were noted.

Data evaluation

The composed data were assessed as per the ideal reporting system for Systematic Reviews (PRISMA; Liberati *et al.*, 2009).[21]

Mechanisms of phytochemicals to control biofilms

Mechanisms of phytochemicals as quorum-sensing inhibitors

An intercellular communication which increases the virulence/ pathogenicity of the bacteria is Quorum sensing (QS). Empowerment and pathogenicity of bacteria against antibacterial compounds to coordinate phenotype, genotype and direct physiological activities is by QS in bacteria. They cover, amongst others, the establishment of structured microbial communities like biofilms[22,23], the production of virulence factors and also secondary metabolites. Certainly, QS systems are synchronized into certain actions essential for biofilm development and differentiation[16]. QS Inhibitors are moreover a potential component to surpass the restraints of antibiotics usage to treat biofilm infections.[24,25] The benefit of not suppressing the cells in their course makes it amicable for disease control and therefore won't apply selective pressure to develop resistance.

The pathways of QS signaling interference can avoid initial biofilm development by modifying its progress by inhibiting the secretion of cellular appendages and adhesins, that affect the development of microcolonies, surface adhesion, bacterial motility, cell auto and coaggregation, and restrict of the EPS production.[16]

QS Inhibition have been found in natural products mainly phytochemicals in the screening tests. Phytochemicals offers enormous biological activity[16, 27] and chemical diversity with structural complexity and have been perceived as a huge and appealing vault of QS Inhibition. In fact, they are similar to what's considered an "ideal" QS Inhibition, which has been profoundly effective, chemically stable, molecules of low molecular weight and being safe to health.[28,29] Hence, in an era where effectiveness of the antibiotics is no longer definite, phytochemicals with QS inhibition activity are often gifted measure to support the treatment of bacterial infections.

Mechanisms of phytochemicals as biofilm metal chelators

Metal Chelators ions like iron, zinc, calcium, copper, magnesium, and manganese are engaged with some natural procedures vital for the development and existence of the microorganisms in their personal atmosphere. All the metals and iron precisely play in pathogenesis and virulence[30], as they function as signaling factors[31] they have also been related to formation of biofilm. The primitive phases of biofilm formation like attachment of the cells and micro colony formation constantly require iron sensing which was evidenced by many investigators, as they are essential for growth, development and adherence of bacterial cell.[32, 33]

Plant-derived compounds such as phenolic acids, polyphenols, and flavonoids, with the 6, 7-dihydroxy iron with chelating properties and are chelation site being exceptionally compelling in flavonoids.[34-36] Despite the extraordinary capability of phytochemicals to take-up metals, the investigation of their efficacy to treat biofilm-based infections remains to be scarce. In the course of screening of quinolines novel compounds having inhibitory and dispersal activity was revealed. Metal-chelating is one among the quinolones testing, as required an

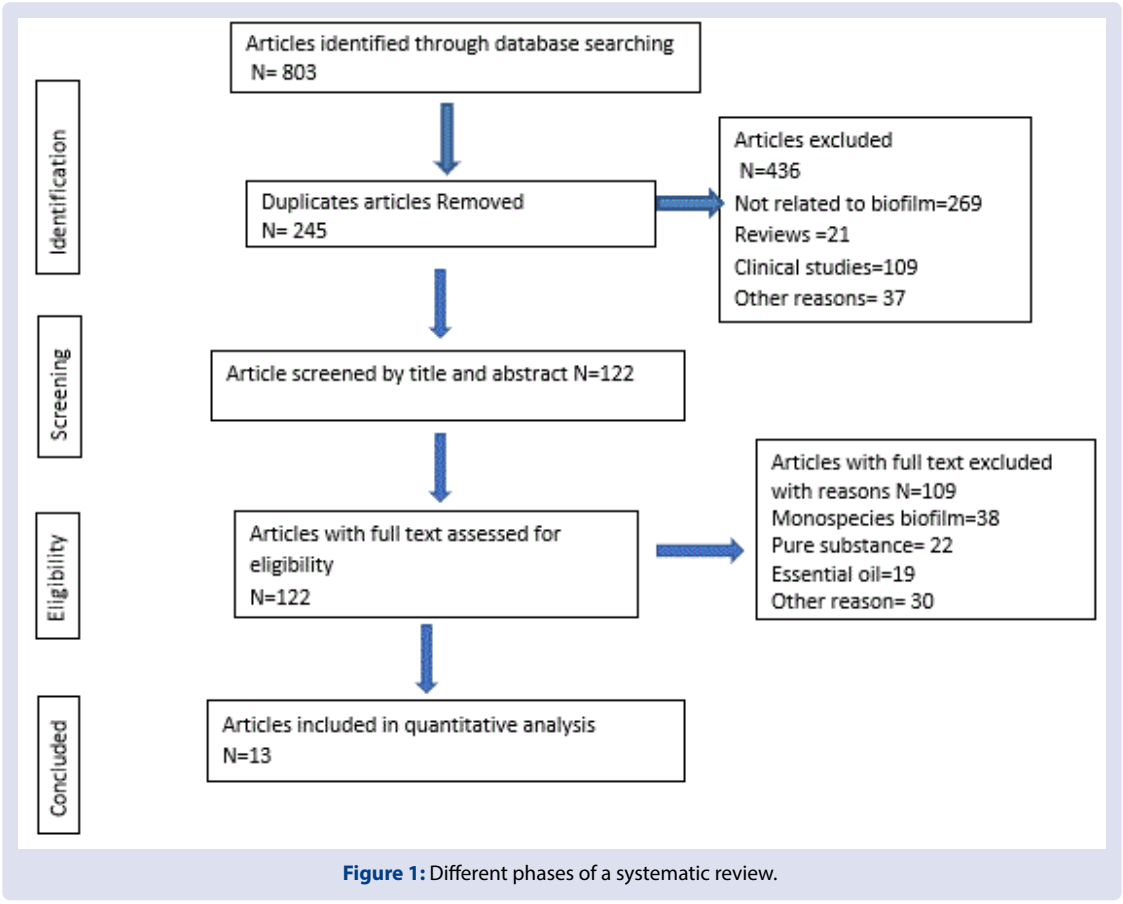


Figure 1: Different phases of a systematic review.

Table 1: Various groups of phytochemicals and their antimicrobial activity.[50,53]

Phytochemicals	General mechanism of action
Phenylpropenoids	Inhibition of energy generation by inhibiting glucose uptake or utilization of glucose and effects on membrane permeability
Flavonoids	Binds to adhesions, complex with cell wall, inactivate enzymes
Benzoic acid derivatives	Enzyme inhibition and non-specific interaction with proteins
Alkaloids	Inhibited biofilm formation
Tannins	Binds to proteins, enzyme inhibition and substrate deprivation
Stilbenes	DNA damage, cell division impairment, oxidative membrane damage, and metabolic enzymes inhibition
Coumarins	Decreased expression of biofilm related genes (adhesion, virulence, motility)
Quninones	Inhibited biofilm formation
Diarylheptanoids	Membrane permeabilization and membrane leakage in bacteria
Monoterpenes	Change in the transmembrane potential and membrane perforation
Sesquiterpenes	Robust inhibitors of biofilm formation and attachment
Triterpenoids	Biofilm formation and attachment inhibitors, repressing flagellar operon, interfere with phosphorylation and DNA binding activities
Sulfur-containing compounds	Reacts with accessible cysteines in proteins and can inactivate essential enzymes, react with glutathione, shifts the cell redox potential to a more oxidized state

equivalent structure to nitroxoline, which is an antibiotic with known antimicrobial and antibiofilm activities, and known to be associated to chelate several metals.[37]

Mechanism of phytochemicals as biofilm efflux pump inhibitors

At present-day, increasing proof has simplified that systems of efflux pumps are not just pumps for the transportation of drugs or additional toxic substances out of the cells but they have been furthermore required for QS regulation[38] and the ensuing articulation of genes liable for virulency and biofilm formation.[39-43] Certainly, during biofilm formation studies showed this linkage, citing the presence of the up regulation of genes encoding efflux pumps (Eps). Application of Eps is often an vital measure to manage biofilm formation, and to diminish biofilm tolerance to antibiotics[44-45] due to their remarkably dynamic nature.

Target areas of phytochemicals

Preventing microbial adhesion

Various factors like Ph, ionic strength, temperature, nutrients, genotype and phenotype of microorganism influence the method of adhesion. The bacterial adhesion mainly depends on the charge, hydrophobicity,

Table 2: Representative Phytochemicals and their mechanisms of action against oral biofilm.

Material (Natural products)	Phytochemicals	Mechanism of action	Reference
Propolis (Beeswax)	Trans–trans farnesol	Bacterial membrane interaction with lipophilic moiety	Koo, H. *et al*[54]
Camellia sinensis (Tea)	Catechin, epicatechin, gallocatechin, epigallocatechin, epicatechin gallate (Polyphenols)	Microbial cytoplasmic membrane damage, Reduced Cariogenicity of starch foods because of inactivity of salivary amylase.	Taylor, P *et al*[55]
Allium sativum (Garlic)	Allicin (diallyl-thiosulfinate)	Allicin extracted from garlic inhibits the growth of all strains tested	Bakri, I and Douglas, C[56]
Harungana (Haronga)	D-L, lactide-co-glycolide	Killed all oral bacteria tested	Moulari, *et al*[57]
Psidium guajava (Guava)	Quercetin-3-O-α-l-arabinopyranoside or guaijaverin	Decrease in cell-surface hydrophobicity observed in plaque bacteria	Razak *et al*[58]
Polygonum cuspidatum (Japanese knotweed)	Alkaloids, phenolics and sterol/terpenes	Development of water-insoluble glucan, Delay sucrose dependent adherence, glycolytic acid formation and acid tolerance	J. H. Song *et al*[59]
Piper betel (Betel leaf)	Phenolics	Inhibit the growth, adherence and glucan production Damage the plasma cell membrane and cell wall Thick electron-dense filaments are formed due to coagulated nucleoid material	T. Nalina and Z. H. A. Rahim[60]
Pinus maritima (Pine bark)	Polyphenolic compounds	Inhibited synthesis of glucosyltransferase	Furiga, A *et al*[61]
Apis mellifera (Manuka honey)	Flavonoids, phenolic compounds	Manuka honey presented antiadhesive properties and antibiofilm activity	Badet, C., and Quero, F[62]
Vaccinium subg. Oxycoccus (Cranberry)	Proanthocyanins, flavonol	Prevent bacterial coaggregation by inhibiting biofilm formation, decrease in bacterial hydrophobicity, and cell surface molecules interchange	Feghali *et al*[63]
Armoracia rusticana (Horseradish)	Isothiacyanates	Aerobic and facultative anaerobic oral bacteria were inhibited by isothiocyanates	Park, H.W. *et al*[64]
Vitis vinifera (Grape seed)	Polyphenols	Inhibits glucosyltransferase activity and insoluble glucan synthesis	Furiga, A. *Et al*[65]
Iris pallida (Dalmation Iris)	(iso)flavonoids, phenols	Avoids both adhesion and quorum sensing during biofilm formation.	Lan Hoang *et al*[66]

presence of adhesion components like flagella, fimbriae and pili and therefore the EPS structure of microorganism.[46] The surface property of fabric on which biofilm is made also plays a vital role in its formation.[47]

Control of cellular motility

Bacteria show various styles of movements like swimming, swarming, gliding, etc., and these movements play a vital role in biofilm formations. Varying results were observed by different phytochemicals on cellular motility during different duration of your time. The swarming and swimming motility of P. Aeruginosa, P. Mirabilis and bacteria species were decreased by methanolic extracts of herb Cuminum cyminum.[48] However, cinnamaldehyde and eugenol from laurel decreased the swimming motility of *E. Coli*.[49]

Change in bacterial static properties

The bacterial static property against phytochemicals proves to be helpful in controlling their effects when bacteria were found successful in forming a biofilm. The MIC and MBI values of phytochemicals were needed to be established.[50] The MIC and MBI values for Gram-positive bacteria are usually lesser than for Gram-negative bacteria. [51] The morphology of the *S. Aureus* and *E. Coli* cells in biofilm changed when observed after treatment with phytochemicals (essentials oils). Reduction in cell size, length and diameter was observed and the peptidoglycan structure of cell wall gets disrupted, cell contents leaks out and eventually leads to cell death.[50] Gallic (hydroxybenzoic acid), ferulic acids (hydroxycinnamic acid), were also tested for their antimicrobial activities against *S. Aureus* and *E. Coli*.[52]

CONCLUSION

Additional care is being paid to identify alternate agents to biofilm control because of drug resistance. The meticulousness, efficacy and proficiency of targeting oral biofilm are highlighted. Introduction of phytochemicals into the therapeutic range for dentistry is given due consideration. Medicinal herbs free from side-effect could in this way complement or perhaps substitute for conventional agents in the battle against biofilm related oral diseases. Phytochemicals characterize a possible alternate for effective, inexpensive and safe antimicrobial agents. In future, the active ingredients of more plants should be identified, purified and also their antimicrobial role and the mechanism of action, bioactivity and biocompatibility should be studied.

FUTURE PERSPECTIVES

Though the growth of strategies for control of oral biofilm is uncertain, advances in understanding of the biofilm development and resistance mechanisms are significant. The use of phytochemicals has fascinated significant deliberation, since they are used as a source of newest scaffolds for the event of novel therapeutic compounds with upgraded action. Phytochemicals target bacteria using various mechanisms. Additional captivating aspect of phytochemicals against biofilms is their ability to maintain a non-bactericidal mode of action, influence regulatory mechanisms engaged in biofilm formation and later they do not force selective pressure upon bacteria.

The exact idea of plant-derived antimicrobial and antibiofilm working mechanisms is extremely important and useful in drug discovery

processes. Computer-based methodologies like molecular docking can be used to predict the ligand-receptor binding and affinity. Besides, the trouble to find new drugs from plants is exposed by the actual fact that this process is slow and difficult, consisting generally of the bioassay-guided isolation of numerous components of the extract and the successive identification of active compounds using several techniques. Screening is additionally applied for antimicrobials/antibiofilm compounds, during this manner accelerating the advancement of recent formulations. Metabolomics and multivariate data analysis are newer perspectives and procedures found to be promising for plant-based drug discovery. Controlled clinical trials study designs with longer observation periods are critical to recognize multiple mechanisms of action, and efficacious and safe doses of the extracts.

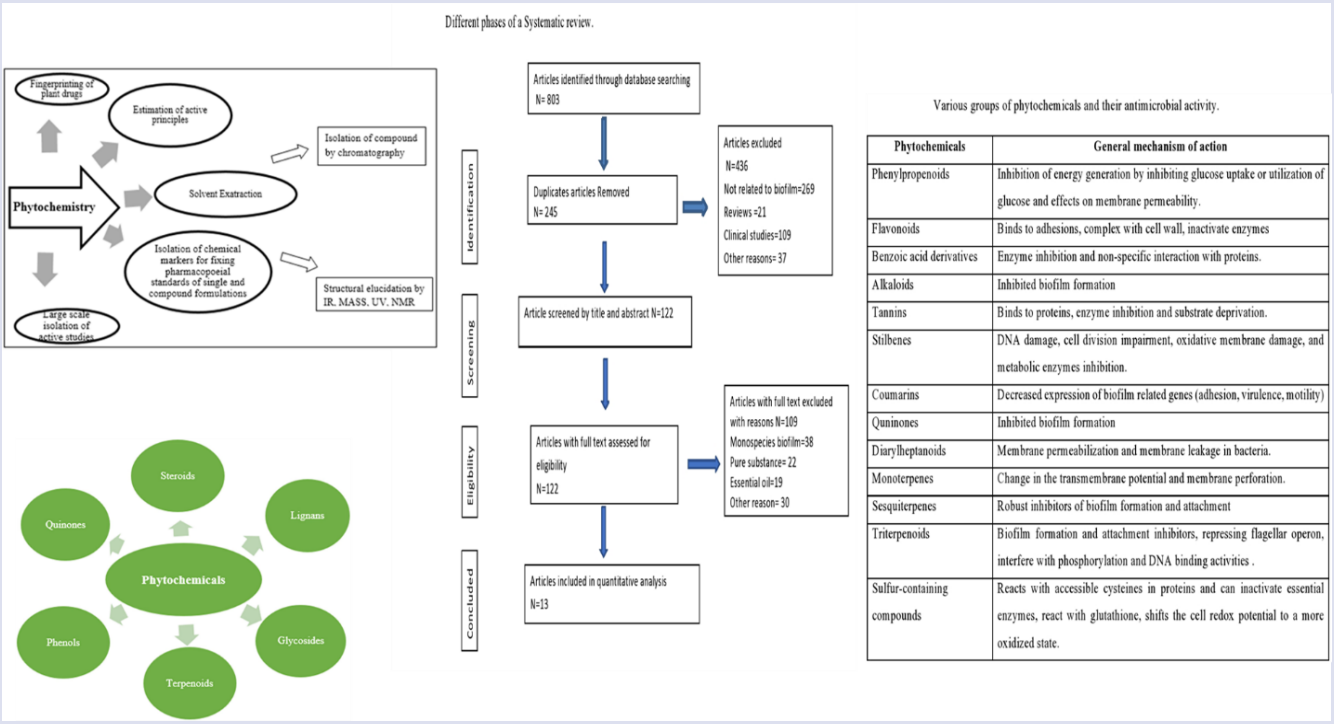
The polymicrobial infectious nature of oral cavity would restrict the clinical translation of the approaches developed based on mono species biofilm since current data available are mostly obtained from *in vitro* or animal studies using mono species biofilm. More studies are needed to additionally evaluate the antimicrobial activities in humans to balance the bioactivity, bioavailability and biocompatibility of the novel agents since the oral cavity is multifaceted environment affected by rapid clearance by saliva, bioavailability and effectiveness of the novel agents *in vivo*.

REFERENCES

1. W. F. Liljemark and C. Bloomquist, "Human oral microbial ecology and dental caries and periodontal diseases," Critical Reviews in Oral Biology Medicine, 2016; 7(2):180–198.
2. A. Besinis, T. De Peralta, and R. D. Handy, "Inhibition of bioflm formation and antibacterial properties of a silver nano-coating on human dentine," Nanotoxicology, 2014; 8(7): 745–754.
3. Maddi A, Scannapieco FA. Oral biofilms, oral and periodontal infections, and systemic disease. Am J Dent. 2013;26(5):249–54.
4. Karatan E, Watnick P. Signals, regulatory networks, and materials that build and break bacterial biofilms. Microbiol Mol Biol Rev. 2009;73(2):310–47.
5. T. Beikler and T. F. Flemmig, "Oral bioflm-associated diseases: Trends and implications for quality of life, systemic health and expenditures," Periodontology 2000, 2011;55(1):87–103.
6. Donlan, R.M.; Costerton, J.W. Biofilms: Survival mechanisms of clinically relevant microorganisms.Clin. Microbiol. Rev. 2002; 15: 167–193
7. Patel, R. Biofilms and antimicrobial resistance. Clin. Orthop. Relat. Res. 2005;437: 41–47.
8. Dunne, W.M., Jr. Bacterial adhesion: Seen any good biofilms lately? Clin. Microbiol. Rev. 2002; 15:155–166.
9. Stewart, P.S. Mechanisms of antibiotic resistance in bacterial biofilms. Int. J. Med. Microbiol. 2002; 292:107–113.
10. Stewart, P.S.; Costerton, J.W. Antibiotic resistance of bacteria in biofilms. Antibiot. Resist. Bact. Biofilms 2001; 358:135–138.
11. Chatterjee, M.; Anju, C.P.; Biswas, L.; Anil Kumar, V.; Gopi Mohan, C.; Biswas, R. Antibiotic resistance in Pseudomonas aeruginosa and alternative therapeutic options. Int. J. Med. Microbiol. 2016;306:48–58
12. Bjarnsholt, T.; Ciofu, O.; Molin, S.; Givskov, M.; Høiby, N. Applying insights from biofilm biology to drug development - can a new approach be developed? Nat. Rev. Drug Discov. 2013;12: 791–808.
13. Francolini, I.; Donelli, G. Prevention and control of biofilm-based medical-device-related infections. FEMS Immunol. Med. Microbiol. 2010; 59:227–238.
14. Simões, M.; Bennett, R.N.; Rosa, E.A. Understanding antimicrobial activities of phytochemicals against multidrug resistant bacteria and biofilms. Nat. Prod. Rep. 2009; 26:746–757.
15. Al-Jumaili, A.; Kumar, A.; Bazaka, K.; Jacob, M.V. Plant secondary metabolite-derived polymers: a potential approach to develop antimicrobial films. Polymers 2018; 10:515.
16. Borges, A.; Saavedra, M.J.; Simões, M. Insights on antimicrobial resistance, biofilms and the use of phytochemicals as new antimicrobial agents. Curr. Med. Chem. 2015; 22:2590–2614
17. Cox SD, Mann CM, Markham JL, Bell HC, Gustafson JE, Warmingto JR, et al. The mode of antimicrobial action of the essential oil of Melaleuca alternifolia (tea tree oil). J Appl Microbiol. 2000; 88:170-175.
18. Manoharachary, C. and Nagaraju, D. Medicinal plants for human health and welfare. Ann. Phytomed., 2016;5(1):24-34
19. Nooreen, Z.; Rai, V.K. and Yadav N.P. Phytopharmaceuticals: A new class of drug in India. Ann. Phytomed., 2018;7:27-37.
20. Dang, R. Role of antinutrient metabolites of plant on production of secondary metabolites and human health. Ann. Phytomed., 2018;7(1):1-4.
21. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Med 2009; 6(7)
22. Jakobsen, T.H.; van Gennip, M.; Phipps, R.K.; Shanmugham, M.S.; Christensen, L.D.; Alhede, M.; Skindersoe, M.E.; Rasmussen, T.B.; Friedrich, K.; Uthe, F.; et al. Ajoene, a sulfur-rich molecule from garlic, inhibits genes controlled by quorum sensing. Antimicrob. Agents Chemother. 2012; 56:2314–2325.
23. Borges, A.; Serra, S.; Cristina Abreu, A.; Saavedra, M.J.; Salgado, A.; Simões, M. Evaluation of the effects of selected phytochemicals on quorum sensing inhibition and in vitro cytotoxicity. Biofouling 2014; 30:183–195.
24. Qian, P.-Y.; Chen, L.; Xu, Y. Mini-review: Molecular mechanisms of antifouling compounds. Biofouling 2013;29: 381–400.
25. Jakobsen, T.H.; Bragason, S.K.; Phipps, R.K.; Christensen, L.D.; van Gennip, M.; Alhede, M.; Skindersoe, M.;Larsen, T.O.; Høiby, N.; Bjarnsholt, T.; et al. Food as a source for quorum sensing inhibitors: Iberin from horseradish revealed as a quorum sensing inhibitor of Pseudomonas aeruginosa. Appl. Environ. Microbiol. 2012;78: 2410–2421.
26. Castillo-Juárez, I.; Maeda, T.; Mandujano-Tinoco, E.A.; Tomás, M.; Pérez-Eretza, B.; García-Contreras, S.J.; Wood, T.K.; García-Contreras, R. Role of quorum sensing in bacterial infections. World J. Clin. Cases 2015;3: 575.
27. Vattem, D.A.; Mihalik, K.; Crixell, S.H.; McLean, R.J.C. Dietary phytochemicals as quorum sensing inhibitors. Fitoterapia 2007;78: 302–310.
28. Kalia, V.C. Quorum sensing inhibitors: An overview. Biotechnol. Adv. 2013;31: 224–245.
29. Rasmussen, T.B.; Givskov, M. Quorum-sensing inhibitors as anti-pathogenic drugs. Int. J. Med. Microbiol. 2006; 296: 149–161.
30. Porcheron, G.; Garénaux, A.; Proulx, J.; Sabri, M.; Dozois, C.M. Iron, copper, zinc, and manganese transport and regulation in pathogenic Enterobacteria: Correlations between strains, site of infection and the relative importance of the different metal transport systems for virulence. Front. Cell. Infect. Microbiol. 2013; 3:172–194.
31. Banin, E.; Vasil, M.L.; Greenberg, E.P. Iron and Pseudomonas aeruginosa biofilm formation. Proc. Natl. Acad.Sci. USA 2005;102: 11076–11081.
32. O'Toole, G.A.; Kolter, R. Initiation of biofilm formation in Pseudomonas fluorescens WCS365 proceeds via multiple, convergent signalling pathways: A genetic analysis. Mol. Microbiol. 1998; 28: 449–461.
33. Singh, P.K.; Parsek, M.R.; Greenberg, E.P.; Welsh, M.J. A component of innate immunity prevents bacterial biofilm development. Nature 2002;417: 552–555.
34. Mladˇenka, P.; Macáková, K.; Filipský, T.; Zatloukalová, L.; Jahodáˇr, L.; Bovicelli, P.; Silvestri, I.P.; Hrdina, R;Saso, L. In vitro analysis of iron chelating activity of flavonoids. J. Inorg. Biochem. 2011; 105: 693–701.
35. Jayasinghe, S.; Siriwardhana, A.; Karunaratne, V. Natural iron sequestering agents: Their roles in nature andtherapeutic potential. Int. J. Pharm. Pharm. Sci. 2015; 7: 8–12.

36. Hatcher, H.C.; Singh, R.N.; Torti, F.M.; Torti, S.V. Synthetic and natural iron chelators: Therapeutic potential and clinical use. Future Med. Chem. 2009;1: 1643–1670.
37. Abouelhassan, Y.; Garrison, A.T.; Burch, G.M.; Wong, W.; Norwood, V.M.; Huigens, R.W. Discovery of quinoline small molecules with potent dispersal activity against methicillin-resistant Staphylococcus aureus and Staphylococcus epidermidis biofilms using a scaffold hopping strategy. Bioorg. Med. Chem. Lett. 2014; 24:5076–5080.
38. Chan, Y.Y.; Chua, K.L. The Burkholderia pseudomallei BpeAB-OprB efflux pump: Expression and impact on quorum sensing and virulence. J. Bacteriol. 2005; 187:4707–4719
39. Sun, J.; Deng, Z.; Yan, A. Bacterial multidrug efflux pumps: Mechanisms, physiology and pharmacological exploitations. Biochem. Biophys. Res. Commun. 2014; 453: 254–267.
40. Soto, S.M. Role of efflux pumps in the antibiotic resistance of bacteria embedded in a biofilm. Virulence 2013;4: 223–229.
41. Van Acker, H.; Coenye, T. The role of efflux and physiological adaptation in biofilm tolerance and resistance.J. Biol. Chem. 2016; 291:12565–12572.
42. Gupta, G.; Wren, M.; Ganguly, K.; Pardington, P. Multi-drug resistance efflux pumps confer additional resistance against host innate immune defense via induction of genes for biofilm formation and virulence (MPF3P. 803). J. Immunol. 2014; 192: 132-3.
43. Yamasaki, S.; Wang, L.-Y.; Hirata, T.; Hayashi-Nishino, M.; Nishino, K. Multidrug efflux pumps contribute to Escherichia coli biofilm maintenance. Int. J. Antimicrob. Agents 2015; 45: 439–441.
44. Kvist, M.; Hancock, V.; Klemm, P. Inactivation of efflux pumps abolishes bacterial biofilm formation. Appl. Environ. Microbiol. 2008; 74: 7376–7382.
45. Baugh, S.; Phillips, C.R.; Ekanayaka, A.S.; Piddock, L.J.V.; Webber, M.A. Inhibition of multidrug efflux as a strategy to prevent biofilm formation. J. Antimicrob. Chemother. 2014;69: 673–681.
46. Donlan, R.M. and Costerton, J.W. Biofilms: Survival mechanisms of clinically relevant microorganisms. Clin. Microbiol. Rev., 2002;15:167-193.
47. Grossner-Schreiber, B.; Teichmann, J.; Hannig, M.; Dorfer, C.; Wenderoth, D.F. and Ott S.J. Modified implant surfaces show different biofilm compositions under in vivo conditions. Clin. Oral Implants Res, 2009;20:817-826.
48. Sybiya, V.P.I.A.; Agilandeswari, P.; Musthafa, K. S.; Karutha, P.S. and Veera, R.A. Antibiofilm and quorum sensing inhibitory potential of Cuminum cyminum and its secondary metabolite methyl eugenol against Gram-negative bacterial pathogens. Food Res. Int., 2012;45:85- 92.
49. Niu, C. and Gilbert, E.S. Colorimetric method for identifying plant essential oil components that affect biofilm formation and structure. Appl. Environ. Microbiol., 2004;70:6951-6956.
50. Chieu Anh Kim Ta and John Thor Arnason,. Mini review of phytochemicals and plant taxa with activity as microbial biofilm and quorum sensing inhibitors. Molecules, 2015;21:1-26.
51. Simões, M.; Rocha, S.; Coimbra, M.A. and Vieira, M.J. Enhancement of Escherichia coli and Staphylococcus aureus antibiotic susceptibility using sesquiterpenoids. Medicinal Chem., 2008;4:616-623.
52. Borges, A.; Ferreira, C.; Saavedra, M.J. and Simões, M. Antibacterial activity and mode of action of ferulic and gallic acids against pathogenic bacteria. Microb. Drug Resistance, 2013;19:256-265
53. Kriti Kanwar, Priyanka Thakur and Wamik Azmi, Use of phytochemicals as emerging strategy for control of biofilm formed by pathogens Annals of Phytomedicine 2018;7(2): 25-37.
54. Koo, H. et al. Inhibition of Streptococcus mutans biofilm accumulation and polysaccharide production by apigenin and tt-farnesol. J. Antimicrob. Chemother. 2003;52: 782–789.
55. Taylor, P. W., Hamilton-Miller, J. M. & Stapleton, P. D. Antimicrobial properties of green tea catechins. Food Sci. Technol. Bull. 2005;2:71–81.
56. Bakri, I., Douglas, C.,. Inhibitory effect of garlic extract on oral bacteria. Arch. Oral Biol 2005;50 (7): 645–651.
57. Moulari, H. Lboutounne, J.-P. Chaumont, Y. Guillaume, J. Millet, and Y. Pellequer, "Potentiation of the bactericidal activity of Harungana madagascariensis Lam. ex Poir. (Hypericaceae) leaf extract against oral bacteria using poly (D, L-lactide-co-glycolide) nanoparticles: in vitro study," Acta Odontologica Scandinavica, 2006; 64(3) 153–158.
58. F. A. Razak, R. Y. Othman, and Z. H. Rahim, "The effect of Piper betle and Psidium guajava extracts on the cell-surface hydrophobicity of selected early settlers of dental plaque," Journal of oral science, 2006;48(2)71–75.
59. J. H. Song, S. K. Kim, K. W. Chang, S. K. Han, H. K. Yi, and J. G. Jeon, "In vitro inhibitory effects of Polygonum cuspidatum on bacterial viability and virulence factors of Streptococcus mutans and Streptococcus sobrinus," Archives of Oral Biology,2006; 51:1131–1140.
60. T. Nalina and Z. H. A. Rahim, "The crude aqueous extract of Piper betel L. and its antibacterial effect towards Streptococcus mutans," American Journal of Biochemistry and Biotechnology, 2007; 3(1):10–15.
61. Furiga, A., Lonvaud-Funel, A., Dorignac, G., and Badet, C. In vitro anti-bacterial and anti-adherence effects of natural polyphenolic compounds on oral bacteria. J. Appl. Microbiol. 2008;105: 1470–1476.
62. Badet, C., and Quero, F. The in vitro effect of manuka honeys on growth and adherence of oral bacteria. Anaerobe 2011;17: 19–22.
63. Feghali, K., Feldman, M., La, V. D., Santos, J. & Grenier, D. Cranberry proanthocyanidins: natural weapons against periodontal diseases. J. Agric. Food Chem. 2012;60: 5728–5735.
64. Park, H.W., Choi, K.D., Shin, I.S. Antimicrobial activity of isothiocyanates (ITCs) extracted from horseradish (Armoracia rusticana) root against oral microorganisms. Biocontrol Sci. 2013;18 (3):163–168
65. Furiga, A., Roques, C., and Badet, C. Preventive effects of an original combination of grape seed polyphenols with amine fluoride on dental biofilm formation and oxidative damage by oral bacteria. J. Appl. Microbiol. 2014; 116:761–771.
66. Lan Hoang et al Phytochemical Composition and In Vitro Biological Activity of Iris spp. (Iridaceae): A New Source of Bioactive Constituents for the Inhibition of Oral Bacterial Biofilms. Antibiotics. 2020; 9: 403.

GRAPHICAL ABSTRACT



Various groups of phytochemicals and their antimicrobial activity.

Phytochemicals	General mechanism of action
Phenylpropenoids	Inhibition of energy generation by inhibiting glucose uptake or utilization of glucose and effects on membrane permeability.
Flavonoids	Binds to adhesions, complex with cell wall, inactivate enzymes
Benzoic acid derivatives	Enzyme inhibition and non-specific interaction with proteins.
Alkaloids	Inhibited biofilm formation
Tannins	Binds to proteins, enzyme inhibition and substrate deprivation.
Stilbenes	DNA damage, cell division impairment, oxidative membrane damage, and metabolic enzymes inhibition.
Coumarins	Decreased expression of biofilm related genes (adhesion, virulence, motility)
Quninones	Inhibited biofilm formation
Diarylheptanoids	Membrane permeabilization and membrane leakage in bacteria.
Monoterpenes	Change in the transmembrane potential and membrane perforation.
Sesquiterpenes	Robust inhibitors of biofilm formation and attachment
Triterpenoids	Biofilm formation and attachment inhibitors, repressing flagellar operon, interfere with phosphorylation and DNA binding activities .
Sulfur-containing compounds	Reacts with accessible cysteines in proteins and can inactivate essential enzymes, react with glutathione, shifts the cell redox potential to a more oxidized state.

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