Plants for oral biofilms eradication: literature review

Amatul Firdaustia PRATIWI\textsuperscript{1}, Hening Tjaturina PRAMESTI\textsuperscript{2}, Faisal KUSWANDANI\textsuperscript{2}

\textsuperscript{1}. Undergraduate Program, Faculty of Dentistry, Universitas Padjadjaran, Sumedang, Indonesia
\textsuperscript{2}. Department of Oral Biology, Faculty of Dentistry, Universitas Padjadjaran, Sumedang, Indonesia

*Corresponding Author Email: amatul17001@mail.unpad.ac.id

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ABSTRACT Oral Biofilm is a collection of microbial cell colonies related to periodontal diseases and caries. Biofilm bacteria were more resistant to antimicrobial agents than in the planktonic phase. The rapid progression of bacterial resistance to antimicrobial agents such as chlorhexidine has encouraged researchers to find alternative antimicrobial agents from natural plant products with low side effects. The purpose of this review was to summarize plants that contain bioactive compounds for biofilm eradication in terms of preventing caries and periodontal diseases. The method was used Systematic Review without Metha Analysis. Articles to be reviewed were searched from Pubmed, Cochrane, Science Direct, and Google Scholar databases using the PRISMA method and hand searching. The last selected articles were analyzed using narrative analysis. There are 1,610 articles specified in the first stage and only 18 articles left in the final extraction stage. Plants that contain bioactive compounds for oral biofilm eradication include Piper betle (betel), Psidium sp., Mangifera sp., Mentha sp., Caesalpinia sappan (secang), Baccharis dracunculifolia, Laurus nobilis L. (dafnah), Croton nepetapholius, Salvadora persica (miswak), Dryopteris crassirhizoma, Diospyros kaki Thumb. (persimmon), Ginkgo biloba, Azadirachta indica (neem), Camellia sinensis, Lippia alba, Cymbopogon citratus (lemongrass), Citrus aurantifolius, Tamarindus indica (sour), Syzygium cumini (jamblang), Emblica officinalis (malacca), Acacia Arabica (prickly acacia), Terminalia chebula (myrobalan), Terminalia bellerica (bahera), Carica papaya, Ocimum basilicum L. (basil), and Myrmercodia pendants. These plant bioactive compounds are belong to the group of alkaloids, terpenoids, and polyphenols which were tested in the form of single compounds or mixtures, especially against Streptococcus mutans. In conclusion, 26 plant species have reported containing bioactive compounds tested in the form of single or mixed extracts to eradicate oral bacterial biofilm.

KEYWORDS: Plants, eradication, natural products, oral biofilm

INTRODUCTION

The collection of microorganisms colonies attached to biotic and abiotic surfaces and embedded in the extracellular polysaccharide (EPS) matrix will form a biofilm. The biofilm will support these microorganisms to survive in an unfavorable environment.\textsuperscript{1,4} In addition to oral cavities, it can cause several diseases to host.\textsuperscript{3,5} Oral biofilms found on the tongue, buccal mucosa, supragingival or subgingival. Oral biofilm formation begins with a pellicle which facilitates the initial attachment of microbes. There is an interaction between pellicles and adhesins on the surface of microbial cells. Then, it will strengthen the attachment of microbial cells to oral cavity surfaces and give a supporting facility to newcomer microbes. The increasing of microbes in the biofilm results in EPS matrix formation. Biofilms will grow more mature and more complex, which will eventually reach the dispersion stage to form new biofilms on other surfaces.\textsuperscript{2,6}

The EPS matrix produced by biofilm bacteria plays a role in determining the virulence of the biofilm. Bacteria can communicate with each other within the biofilm structure using quorum sensing.\textsuperscript{6} Quorum sensing plays a significant role in regulating the formation of biofilms and EPS matrix and enabling regulation of antimicrobial resistance gene expression.\textsuperscript{7} The metabolism of microorganisms that live in the oral cavity biofilm can change the surrounding environment to form an atmosphere that supports the growth of pathogenic bacteria. The dominance of pathogenic bacteria allows the emergence of oral diseases such as caries and periodontal disease.\textsuperscript{8}

Microorganisms in the biofilm, especially bacteria, are 10-1000 times more resistant to
antimicrobial agents than bacteria in the planktonic phase.\textsuperscript{9,10} This may be because the biofilm acts as a barrier both physically and chemically, which prevents the penetration of antimicrobial agents and increases the ability of microbes to survive under conditions of unbalanced nutrition.\textsuperscript{10} These problems encourage researchers to find new agents as alternatives to antibacterial and antibiofilm, especially natural plant products. Plants have a way of defending themselves from an unfavorable environment by carrying out secondary metabolism. Bioactive compounds are a product of secondary metabolic processes, and some of these bioactive compounds have been reported to contain antimicrobial properties.\textsuperscript{11,12,13}

Controlling oral biofilm is one way to prevent these diseases. Reducing biofilm can be used mechanically by brushing teeth or chemically by mouthwash containing an antimicrobial compound.\textsuperscript{2,8,10,14} Chlorhexidine 0.2\% is the most effective mouthwash and has been widely used for a long time and has become standard gold mouthwash. Chlorhexidine has strong power and broad-spectrum antibacterial activity. However, it has disadvantages: long-term use can cause staining of the teeth,\textsuperscript{5,10} erosion of the mucosa, and an unpleasant taste in the mouth.\textsuperscript{2,15,16} Extensive use over a long period also causes a problem of bacterial resistance to chlorhexidine.\textsuperscript{17}

The ability of plant bioactive compounds to eradicate oral biofilm and as an antimicrobe has been recorded in several databases. Only a few a summary has reported or a few selected plants that have been studied until the clinical stage to be used widely or for therapeutic purposes as ingredients for making drugs. In this study, we will summarize and review several plants that have oral cavity biofilm eradication activity. And they were published by Pubmed, Science Direct, Cochrane, and Google scholar through the Preferred Reporting Items for Systematic Reviews without Meta-Analyses (PRISMA) method.

**MATERIALS AND METHODS**

**Tools**

This study used Mendeley as a reference manager, Critical Appraisal Skills Program (CASP)\textsuperscript{18} to assess the quality of selected studies in the Randomized Control Trial (RCT) article and the Modified CONSORT checklist\textsuperscript{19} for In Vitro studies. The sample was searched using a laptop.

**Materials**

The material for this study is articles that have been published in Pubmed, Google Scholar, Cochrane, and Science Direct databases.

**Procedures**

This descriptive study used a systematic review method by Preferred Reporting Items for Systematic Reviews without Meta-Analyses (PRISMA)\textsuperscript{20} and manual hand searching. Articles were searched from PubMed, Science Direct, Cochrane, and Google Scholar databases using Boolean operators and keywords ((plant OR medicinal plant OR herb OR natural product OR natural source OR plant extract) AND (anti-plaque OR anti-biofilm OR antibacterial activity)) AND (oral biofilm OR dental plaques). Inclusion criteria were articles published in 2011-2021, available in full text, published in Indonesian and English, were not reviews studies, RCTs, and experimental reports that studied plant bioactive compounds for biofilm eradication and were related to caries bacteria or periodontal disease. Articles that did not report plants’ bioactive compounds and a high risk of bias were excluded from this study. Several articles in the articles reference have been searched for and did not appear in searches using the database but are closely related to the topic, including Indonesian articles, manually hand searched.

The first step PRISMA method is identification. There were 1,610 articles identified from the four databases. Then, ten duplicated articles were removed. The second step will do to screening according to title and abstract. It was 1546 articles excluded, and 55 articles proceeded to the next step. The third step is assessing the eligibility of article content. The Modified CONSORT checklist\textsuperscript{19} was used to determine in vitro studies on dental materials and the Critical Appraisal Skills Program (CASP)\textsuperscript{18} for Randomized Control Trial (RCT) studies. There are 40 articles removed in the eligibility step. The reason for eliminating in was 16 articles did not report the plant bioactive compounds, eight articles did not report the eradication activity of oral biofilm, 1 article was not indexed in Scopus, two articles were not available in full text, and 13 articles were inaccessible and not related to oral pathogens. Finally, only 18 articles entered the final step for qualitative analysis that are 15 articles were obtained of PRISMA method selection and three articles manual hand searched. Then, the 18 selected articles, 17 of them reported on in vitro studies, and only 1 reported on clinical studies in humans using RCT. Lastly, the narrative
approach was used as a qualitative analysis. The research procedure is shown in Figure 1.

![Figure 1 Flowchart of article search based on the PRISMA method](image)

### RESULTS

A plant containing an anti oral biofilm identified from 18 selected articles in this study are *Piper betle* (betel), *Psidium sp.*,


This study revealed that plant bioactive compounds as anti oral biofilm deposited most in different parts (leaves, cambium, bark, pulp, rind, seeds, or bulbs) in every plant. Plants produce a bioactive compound as secondary metabolites for surviving in hazardous conditions such as thorns, extreme weather. Various plant secondary metabolites chemically grouped into terpenes, steroids, alkaloids, polysaccharides, peptides, and aromatics, most of which have antimicrobial, antiviral, anticancer, anti-parasitic, and anti-allergic properties. Secondary metabolites as anti-biofilm work to inhibit bacterial growth by inhibiting bacterial cells attached to the surface, inhibit the activity of glycolytic enzymes, inhibit biofilm formation, and degrading the existed biofilms.

Alkaloids as anti biofilms have been reported capable of binding to the amyloid matrix protein of the EPS biofilm *Staphylococcus aureus*. Terpenoids from *M. pendans* can also eradicate the biofilm formed as much as 40% within 1 minute. Another ability of terpenoids is to inhibit glucosyltransferase activity in *S. mutans* and...
Streptococcus sobrinus. Low molecular weight terpenoids can affect the integrity of the cell membrane and the release of planktonic cells from the biofilm. Polyphenols from natural ingredients have antibiofilm activity by inhibiting quorum sensing (QS). Inhibition of QS by the active compound will interfere with signal delivery activity for biofilm formation, thereby reducing biofilm virulence.

Aromatic compounds and phenols can disrupt the cytoplasmic membrane, which refers to the death of microbial cells and can inactivate bacterial enzymes. Leaf extract of Psidium sp., Mangifera sp., Mentha sp. and their mixtures are reported to contain phenolic compounds, namely gallic acid, apigenin, quercetin, quercetin-3-O-glucoside, succinic acid, and quinic acid. All types of extracts have been proven effective in reducing the number of bacteria S. mutans and S. sanguinis both in monospecies and multispecies form, biofilm and two types of culture medium, sucrose culture and without sucrose. B. dracunculifolia is reported to contain artemepilin C, baccharin, flavonoids, diterpenes, and triterpenes which have antibacterial, antifungal, and antitumor effects. As an antibiofilm essential oil of B. dracunculifolia was reported to reduce the amount of Colony Forming Unit (CFU) biofilm S. mutans and reached (53.3 ± 21.4)% - (91.1 ± 4.9%). The active compound 4-chromol from leaves is P. betle more sensitive in reducing Gram-negative bacteria because it can penetrate bacterial membranes and can overcome resistance related to changes in membrane proteins and lipopolysaccharides. Casbane diterpene, the active compound from Croton nepetaefolius, has a hydrophobic group that causes these compounds to optimally pass through cell membranes and inhibit cell growth, mainly Gram-negative bacteria.

Plant bioactive compounds were given to bacteria in the form of a single crude extract (Psidium sp., Mangifera sp., Mentha sp.) or a mixture of plant crude extract, ethanol or hexane extract (S. persica), or a single isolate (ginkgolic acid, the active compound of Ginkgo biloba leaves and seed skins, the active compound of n-hexane fraction D. crassii (B. dracunculifolia). Parts of plants that contain active compounds to be used as anti-biofilms also vary, ranging from leaves (P. betle, L. nobilis L., C. sinensis, C. citratus, G. biloba, C. papaya, ), fruit (Psidium sp., Mangifera sp., Mentha sp., T. chebula, T. bellerica, E. officinalis, C. aurantifolia), wood core or cambium (C. sappan), plant stems or stalks (C. nepetaefolius, S. persica), seeds (G. biloba), and tubers (M. pendans). Various extracts concentration and plant parts determine the strength of plant antibiofilm potency. For example, the Minimum Biofilm Eradication Concentration (MBEC) value of ethanol extract P. betle to eradicate 50% biofilm S. mutans is 0.78 ± 0.74 mg/ml. In comparison, the eradication of 90% biofilm is required 6.25 ± 0.58 mg/ml. MBEC of ethanol extract P. betle for eradication of 50% and 90% biofilm A. actinomycetemcomitans was 0.78 ± 0.11 mg/ml and 3.13 ± 0.28 mg/ml.

Several plant bioactive compounds have been shown antibacterial activity in the planktonic phase, including T. indica (tamarind), S. cumini (jamblang), and E. officinalis (malacca). On the other hand, single isolates linoleic acid from the n-hexane fraction of D. crassirhizoma as much as 200 g/ml was reported to reduce 50% of biofilms. The study concluded that linoleic acid could reduce the weight of the biofilm without reducing the number of cells by interfering with the formation of the biofilm matrix but without killing bacteria. So, Linoleic acid is more effective on the biofilm than on planktonic bacteria.

Most of the selected articles in this study conducted antibiofilm experiments using S. mutans as an object treatment. Several plant bioactive compounds inhibit glucosyltransferase activity resulting in decreasing sucrose synthesis and suppressing the initiation and elongation of glycan chains (biofilm component). S. mutans are pioneers that initiate bacterial attachment in the tooth surfaces. Glucosyltransferases (Gts) secreted by S. mutans will bind to the bacterial cell and saliva-coated teeth. They also attract other bacteria or microorganisms that will make thickened biofilm. Tooth demineralization or the initial occurrence of caries caused by acid as a by-product of glucosyltransferase activity. Inhibiting Gtfs activity, in addition to controlling biofilm formation, control biofilm virulence as well.

Plant antibiofilm that have been reported are still in the experimental stage. Only a few plants have been applied directly as mouthwash (S. persica or siwak, 0.5% tea, 2% Neem, 0.2% v/v O. basilicum L.). Tea (0.5%) and 2% Neem also reported reducing dental plaque in respondents and producing other positive effects such as increasing salivary pH and improving oral health, with the highest levels of effectiveness being 0.5% Tea, 2% Neem, respectively. However, Developing plant bioactive compounds as oral antibiofilm in preventing dental caries and periodontal disease still needs more study. The most important study is clinical to overcome the resistance of oral bacteria to the antibacterial agent.
Table 1 Summary of literature review on the plant for oral biofilm eradication

<table>
<thead>
<tr>
<th>No</th>
<th>Source</th>
<th>Type of research</th>
<th>Research method</th>
<th>Active compound</th>
<th>Test object</th>
<th>Result</th>
<th>Biased</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>In Vitro</td>
<td>MBEC assay and MTT assay</td>
<td>4-chromanol (Piper betle)</td>
<td>S. mutans ATCC 25175 and A. actinomycetemcomitans ATCC 33384</td>
<td>MBEC&lt;sub&gt;90&lt;/sub&gt; ethanol extract of P. betle - S. mutans = 0,78 ± 0,74 mg/ml and MBEC&lt;sub&gt;90&lt;/sub&gt; ethanol extract of P. betle-S. mutans = 6,25 ± 0,58 mg/ml; and MBEC&lt;sub&gt;90&lt;/sub&gt; ethanol extract of P. betle-A. actinomycetemcomitans = 0,78 ± 0,11 mg/ml and MBEC&lt;sub&gt;90&lt;/sub&gt; ethanol extract of P. betle-A. actinomycetemcomitans = 3,13 ± 0,28 mg/ml</td>
<td>No limits and potential for bias</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>In Vitro</td>
<td>Calculati on of CFU</td>
<td>Phenol compounds: gallic acid, apigenin, quercetin, quercetin-3-O-glucoside, succinic acid, quinic acid (Psidium sp., Mangifera sp. Mentha sp. and their mixed forms)</td>
<td>S. mutans ATCC 25175 and S. sanguinis ATCC BAA-1455</td>
<td>On medium without sucrose: PEM- S. mutans, CFU 1,02 ± 0,14%; Mangifera sp.-S. mutans, CFU 0,59 ± 0,12%; Psidium sp.- S. mutans, CFU 18,9 ± 5,17% and Mentha sp. - S. mutans, CFU 13,83 ± 3,70%. In medium with sucrose: Psidium sp.- S. mutans + S. sanguinis, CFU 9,85 ± 4,65%; Mentha sp.-S.mutans CFU 2,39 ± 0,98%; Mangifera sp. -S. sanguinis CFU 5,71±1,58% Mangifera sp-S.mutans CFU and 3,85±1,58%. Mixture: Psidium sp. and Mangifera sp. - S. mutans were able to reduce ±50% of the population. Mentha sp. and PEM leaves ±12-15% of the bacterial population. On SEM observation, only a few bacteria were seen in the biofilm after PEM administration. extract C. sappan with MBC value 125 g/mL reduced 95-98% and brazillin reduced 90-98% of cells S. mutans</td>
<td>No limits and potential for bias</td>
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<tr>
<td>3</td>
<td>8</td>
<td>In Vitro</td>
<td>Cristal violet staining assay</td>
<td>Brazilin (Cambium C. sappan)</td>
<td>S. mutans DMST956 7, S. mutans DMST187 77, and S. mutans DMST412 83</td>
<td>It did not reveal limits and potential for bias</td>
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<tr>
<td>4</td>
<td>10</td>
<td>In Vitro</td>
<td>Viable CFU counting</td>
<td>Artepilin C, baccharin, flavonoids, diterpenes, and triterpenes (leaf extract Baccharis dracunculifolia)</td>
<td>S. mutans ATCC® 35688</td>
<td>essential oil B. dracunculifolia 6% reduced 53,3 ± 21,4% to 91,1 ± 4,9% biofilm of clinical isolates of oral mixed bacteria, and 39,3 ± 17,5% of S. mutans</td>
<td>No limits and potential bias</td>
</tr>
<tr>
<td>No.</td>
<td>Design</td>
<td>Methodology</td>
<td>Species</td>
<td>Concentration</td>
<td>Results/Findings</td>
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<td>5</td>
<td>In Vitro</td>
<td>CFU (Crystal Violet staining) and MTT assays</td>
<td>S. aureus ATCC 6538</td>
<td>1.8-Cineole, methyl eugenol and -terpinyl Acetate (Leaves of <em>L. nobilis</em> L.)</td>
<td>The active compound in the essential oil of <em>L. nobilis</em> L. reduced biofilms <em>S. aureus</em> 27.2 ± 8.5% up to 78.4 ± 1.57%. On the MTT assay, the reduction rate was 79.6 ± 2.27 to 95.2 ± 0.56.</td>
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<tr>
<td>6</td>
<td>In Vitro</td>
<td>Staining with Crystal violet and CFU calculations</td>
<td><em>S. mutans</em></td>
<td>Cineole, methyl eugenol and -terpinyl Acetate (Leaves of <em>L. nobilis</em> L.)</td>
<td>Casbaine diterpene 250 μg/ml reduced the bacterial biofilm cells of <em>S. mutans</em> to 94.28%</td>
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<tr>
<td>7</td>
<td>In Vitro</td>
<td>Calculations of CFU and MTS assay</td>
<td><em>S. mutans</em> ATCC 25175</td>
<td>Ethanol Extract and plant stems Hexana <em>S. persica</em></td>
<td>Hexane extract stem <em>S. persica</em> 5 mg/ml was more effective in eradicating <em>S. mutans</em> biofilm than its ethanol extract. Chlorhexidine CFU (0.18 x 10^2 ± 0.13 x 10^2), hexane extract CFU (8.7 x 10^3 ± 6.1 x 10^2) and ethanol extract CFU (2.9 x 10^4 ± 7.5 x 10^3), saline +2 % DMSO CFU (3.6 x 10^7 ± 5.5 x 10^6)</td>
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<td>8</td>
<td>In Vitro</td>
<td>Calculations of CFU, BCRC and BDRC</td>
<td><em>S. mutans</em> UA159</td>
<td>n-hexane fraction (HF) and linoleic acid (Root of <em>D. crassirhizoma</em>)</td>
<td>HF and linoleic acid reduced bacterial biofilm depending on the concentration, with values: 50% BCRC HF=100 g/ml and linoleic acid 200 g/ml, 30% BDRC HF= 50 g/ml Linoleic acid= 100 g/ml</td>
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<tr>
<td>9</td>
<td>In Vitro</td>
<td>Calculations of CFU and SEM</td>
<td><em>S. mutans</em></td>
<td>Tannin (Persimmon)</td>
<td>Saliva influenced to form oral cavity biofilms with no clarity on the bacterial biofilm samples used.</td>
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<td>10</td>
<td>In Vitro</td>
<td>MBRC and SEM</td>
<td><em>S. mutans</em> ATCC 25175</td>
<td>Ginkgoneolic acid (Ginkgo biloba extract)</td>
<td>Value MBRC Ginkgoneolic acid against <em>S. mutans</em> = 32 mg / ml, the dose of 8 and 16 g/mL resulted in biofilm disintegration in SEM observations. Ginkgoneolic acid 16 g/mL in <em>S. mutans</em>, few and scattered, cells seen with short chains.</td>
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<tr>
<td>11</td>
<td>RCT</td>
<td>30 subjects were randomly divided into 3 groups</td>
<td>Oral biofilm</td>
<td>Neem: trimethylamine, chlorides, nimbidin, azadarachitin, lectin,</td>
<td>Three effective mouthwash against plaque, gingivitis, maintain oral health and salivary pH, in the order of 0.5% tea, 2% Neem, then 0.2% chlorhexidine.</td>
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</table>
into chlorhexidine, neem, and tea groups. Before the intervention, the assessment was carried out on DMFT, plaque score, salivary pH, OHIS, and gingival score. Subsequent assessments are carried out every week for three weeks. Side effects were evaluated with a questionnaire.

<table>
<thead>
<tr>
<th>Plant Type</th>
<th>Assay Type</th>
<th>MBEC</th>
<th>S. mutans</th>
<th>Monoterpenoids</th>
<th>Ethanol, methanol and acetone of seeds</th>
<th>Does not disclose statistical methods used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lippia alba</td>
<td>In Vitro MBEC</td>
<td>Geraniol and Neral (Citral) (C. citratus essential oil; L. alba essential oil)</td>
<td>S. mutans ATCC 35668</td>
<td>Monoterpenoids (C. aurantiifolia shell)</td>
<td>S. mutans UA 159</td>
<td>-</td>
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<tr>
<td>Cymbopogin citratus</td>
<td>In Vitro MBEC</td>
<td>Cymbopogin citratus</td>
<td>S. mutans</td>
<td>Monoterpenoids from C. aurantiifolia bark can reduce 34.75% S. mutans biofilm with a concentration of 3% within 30 minutes</td>
<td>Ethanol, methanol and acetone of seeds were T. indica and S. cumini extractable to kill 80% of cells S. mutans in biofilm at a concentration of 500-1000 g/mL and 95% of cells at a concentration of 600-2000 g/mL</td>
<td>-</td>
</tr>
<tr>
<td><em>Eucalyptus</em> officinalis, T. indica, S. cumini, and P. sylvestris, and M.</td>
<td>In Vitro MBEC</td>
<td>Ethanol, Methanol, acetone (E. officinalis, T. indica, S. cumini, and P. sylvestris, and M.</td>
<td>S. mutans</td>
<td>Ethanol, methanol and acetone of seeds were T. indica and S. cumini extractable to kill 80% of cells S. mutans in biofilm at a concentration of 500-1000 g/mL and 95% of cells at a concentration of 600-2000 g/mL</td>
<td>-</td>
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</table>
Literature Review

JDS. 2021; 6(2): 122-132

CONCLUSION

From 18 articles selected, it has been reviewing 26 plants only as plants containing bioactive compounds for eradicating oral cavity biofilms, namely Psidium sp., Mangifera sp., Mentha sp., Caesalpinia sappan (secang), Baccharis dracunculifolia, Laurus nobilis L. (dafnah), Croton nepetaefolius, Salvadora persica (miswak), Dryopteris crassirhizoma, Diospyros kaki Thunb. (persimmon), Ginkgo biloba, Azadirachta indica (neem, neem), Camellia sinensis, Lippia alba, Cymbopogon citratus (lemongrass), Citrus aurantifolia, Tamarindus indica (tamarind), Syzygium cumini (jamblang), E. officinalis (malacca), Acacia Arabica (thorny acacia), Terminalia chebula (myrobalan), T. bellerica (bahera), Carica papaya, Ocimum basilicum L. (basil), and Myrmercodia pendans (ant nest).
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