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Systematic review

The Therapeutic Potential of Plant Extraction in Oral Health - A Systematic Review

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ABSTRACT

Objectives: *This study aimed to analyze the therapeutic potential of plant extract against oral microorganisms in published literature.* **Material and Method**: *A systematic literature review was performed through electronic databases (Scopus, EBSCO: Dentistry and Oral Science Source) from January 2009 till December 2019 with the search terms ("extract" AND ("ORAL MICROORGANISM" OR "ORAL BACTERIA") AND ("stem" OR "Bark" OR "Leaf")).* **Results**: *Out of 409 articles, 21 articles met our inclusion criteria that were subjected to data extraction and review. The data disclosed antimicrobial and antibiofilm activity of plant extracts against causative microorganisms of caries, periodontitis, endodontic infection, and fungal infection. Ethanol was the most common solvent used for plant extraction. The antimicrobial test was reported in all studies using different methodologies such as minimum inhibitory concentration (MIC), disk diffusion method, agar well method, intracanal irrigation, and Fractional Inhibitory Concentration Index (FICI) . None of the plant extract tested showed significant toxicity in five studies that conducted toxicity assays.* **Conclusion:** *A positive correlation was observed between plant extract and antimicrobial activity against oral microorganisms. In that context, integrating plant extract in oral healthcare products could be an option to enhance effective antimicrobial control. However, further clinical studies are required to provide clinical evidence to support these observations.*

Keywords: *Plant extract, oral microorganisms, antimicrobial, antibiofilm*

INTRODUCTION

Oral diseases such as dental caries, periodontal disease, tooth loss, oral mucosal lesions, and oropharyngeal cancers remain worldwide public health problems . Poor oral health may have a thoughtful effect on general health and several oral diseases related to chronic diseases (Petersen et al., 2005)**.** There is also proof linking poor oral health and systemic diseases, such as cardiovascular diseases, rheumatoid arthritis, and osteoporosis (Rautemaa et al., 2007). In contrast, periodontal diseases will contribute to the risk of pregnancy complications, such as preterm low-birth-weight (Yeo et al., 2005). The experience of pain, problems with eating, chewing, smiling, and communication due to missing, discoloured or damaged teeth have a significant impact on people's daily lives and welfare. Furthermore, oral diseases restrict activities at school, work, and home, causing millions of school and work hours to be lost each year worldwide. In most industrialized countries, dental caries is still a significant health problem as it affects 60–90% of school-aged children and most adults.

The correlation between oral diseases and the activities of microbial species that form part of the microbiota of the oral cavity is well recognized. Interestingly, Over 750 species of bacteria populate the oral cavity (∼50% of which are yet to be cultivated), and many of these are involved in oral diseases (Jenkinson & Lamont 2005). The production of dental caries involves acidogenic and aciduric Gram-positive bacteria, primarily the *mutans streptococci* (*Streptococcus mutans and S. sobrinus*), *lactobacilli* and *actinomycetes*, which metabolize sucrose to organic acids that dissolve the calcium phosphate in teeth, causing decalcification and eventual decay. Thus, it is a supragingival (Loesche 2007). In contrast, periodontal diseases are subgingival conditions correlated to anaerobic Gram-negative bacteria such as *Porphyromonas gingivalis, Actinobacillus sp., Prevotella sp. and Fusobacterium sp.* (Jenkinson & Lamont 2005). The "battle" against oral biofilms is challenging, mainly due to their tendency to persist despite treatment. This tendency has been attributed to numerous factors such as quorum-sensing, horizontal gene transfer, and intrabiofilm metabolic transactions (Kolenbrander et al., 2010)

The standard practices to prevent oral diseases such as dental caries and periodontal diseases are using fluorides in different forms and mechanical plaque control in combination with a professional cleaning by the dentist. Antimicrobial mouthwash such as chlorhexidine gluconate has also been suggested as an alternative to the mechanical plaque control method (Shekar et al., 2015). Consequently, biofilm microorganisms can be up to 1000 times more resistant than planktonic bacteria to conventional antimicrobial therapies with antibacterial agents such as antibiotics or chlorhexidine (Welin-Neilands & Svensäter 2007; Karygianni et al., 2016). Despite several agents being commercially available, these chemicals can disturb the oral microbiota and have undesirable adverse reactions such as vomiting, diarrhoea, and tooth staining. It has been recorded that some bacteria have developed antibiotic resistance to common antibiotics used to treat oral infections, such as penicillin, cephalosporins, erythromycin, tetracycline and derivatives, and metronidazole. Other antibacterial agents used in the prevention and treatment of oral diseases, including cetylpyridinium chloride, have been reported to exhibit toxicity, cause staining of teeth, and are linked to oral cancer in the case of ethanol which is commonly found in mouthwashes (Shekar et al., 2015).

Hence, it is crucial to develop some innovative strategies for the management of oral diseases. One of the strategies is to explore natural resources such as plant extracts or phytochemicals that are abundantly available in the local plant. The wise statement of Hippocrates, "Nature itself is the best physician," has now been updated to include the beneficial influences from the plant kingdom against biofilm-related dental diseases. It is proven that natural herbs used exclusively or in combination are safe and effective in treating many oral health problems such as halitosis, bleeding gums, mouth ulcers, and dental caries. The natural phytochemicals from plants restore health with less harmful effects and maximum efficiency (Shekar et al., 2015). As we know, plants are rich in active compounds such as alkaloids, steroids, tannins, glycosides, volatile oils, fixed oils, resins, phenols, and flavonoids. Wide-ranging phytochemicals are distributed in specific parts of plants such as leaves, flowers, bark, seeds, fruits, root, etc. Many plant extracts and phytochemicals are used as lead compounds in drug development for many diseases (Smith et al., 2005).

According to the World Health Organization (WHO), out of 255 drugs that are considered fundamental and crucial, 11% are obtained from plants, and several synthetic drugs are also derived from natural sources. Phytochemicals exhibit several properties beneficial to humans, such as antioxidant, antibacterial, antifungal, antidiabetic, anti-inflammatory, antiarthritic, and radio-protective activity (Nair et al., 2005). Hence, medicinal plant extracts are considered good alternatives to synthetic chemicals due to their low toxicity (Palombo 2011). This is important for countries with poor financial resources but rich biodiversity (Vieira et al., 2012).

In this context, the present systematic review aimed to qualitatively summarize the therapeutic potential of plant extract in oral health care focusing on activity against oral microorganisms. The hypothesis is that plants' leaves, bark and stem contain substances that are beneficial to human health and could be appropriately used by the population to improve oral health.

MATERIALS AND METHODS

Search Strategy

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) strategy was applied to identify all studies included in this review. A search was carried out from electronic databases (Scopus, EBSCO: Dentistry and Oral Science Source) with the search terms (“Extract” and (“ORAL MICROORGANISM” OR “ORAL BACTERIA”) AND (“Stem” OR “Bark” OR “Leaf”)). All relevant studies published from Jan 2009 until December 2019 were recovered and included in the systematic review. The initial search generated 391 studies for EBSCO Dentistry and Oral Science Source and 18 for Scopus.

Inclusion Criteria

The studies have been selected based on the following inclusion criteria:

English, full text, scholarly (peer-reviewed) journals, and open access, only plant extracts derived from stem, bark, or leaf were chosen and *in vitro* studies reported the antimicrobial effect of plant extract against *in vitro* oral microorganisms.

Exclusion Criteria

The exclusion criteria were as follow: Studies on animals (*in vivo*), anticancer activity, biochemistry, product or formulation, technology, nanoparticle, and immunity were excluded. Reports omitted from this review included clinical study, clinical trial, review article, and case report. Studies not relating to oral microorganisms and oral disease were also filtered out of this review.

Study Selection

The primary literature research was performed independently by two independent reviewers (FAMF and AMM) according to the established inclusion criteria. In case of disagreement a third reviewer (NMZ) decided whether the study met the inclusion and exclusion criteria. The data were screened to prevent any duplication of data. Any article related to the exclusion criteria was excluded. Afterwards, the remaining articles were downloaded and assessed for eligibility. Finally, irrelevant articles against the criteria, as mentioned earlier, were removed, and the studies included for analysis were determined. The studies were downloaded as full-text articles and assessed for eligibility.

Data Organization

A standard document was used to organize the information gained from each study. In particular, comprehensive data about the authors, year of publication, type of study, type of plant, part of plant extract, types of oral microorganisms, antimicrobial test, methodological aspects, significant results, and conclusion were noted. To ensure the credibility of the extracted lists, the selected full texts were controlled twice. Due to the heterogeneity of the selected reports, they were further classified into tested microorganisms, antimicrobial tests, type of extract, and toxicity.

Critical appraisal

The Critical Appraisal Skills Programme (CASP) checklist was used to appraise the reliability of the studies that were included in this systematic review. Two researchers appraised all the 21 articles together by assessing the questions in the checklist, whether it was reported or not.

RESULTS

The initial search generated 409 studies out of 21 articles that met our inclusion criteria subjected to data extraction and review. The exclusion of the article can be justified because they investigated different lines of research from the scope of this study (FIGURE 1)**.** There are 30 species of plants included in this review. (TABLE 2).

Risk of bias was conducted in outcome level. Eleven studies received medium risk of bias (score ++), and ten studies represented low risk of bias (score +). Therefore all the 21 articles were included for the analysis.

The studies showed antimicrobial and antibiofilm activity of plant extracts against oral microorganisms that causes oral diseases such as dental caries (10 studies), periodontal disease (9 studies), endodontal infection (4 studies), general oral diseases (3 studies), oral candidiasis (2 studies) and halitosis (1 study).

Different extraction methods were performed to obtain the extract, such as ethanolic extract, methanolic extract and water decoction (Table 3). The concentration of alcohol used also varied from 50%-100%.

The minimum inhibition concentration (MIC) test was the most frequently adopted to determine the antimicrobial activity, followed by disk diffusion assay, well diffusion assay, time-kill assay and checkerboard microdilution activity (Figure 4). Some studies also conducted antibiofilm assay because most of the tested oral microorganisms are causing biofilm-related diseases such as caries, periodontal infection and endodontal infection.

Most of the studies adopted the use of positive control as a comparison. Chlorhexidine was the commonly used positive control agent with concentrations ranging from 0.12%-0.2%. Nystatin was used for the study that involved candida (Sampaio et al., 2017 ; Alves et al., 2013) and sodium hypochlorite was used for bacteria that caused endodontic infection (Sangalli et al., 2018, Sponchiado et al., 2014 and Athiban et al., 2012). Few studies also used commercial antibiotics such as erythromycin, and tetracycline (Xue et al., 2017)

Other tests that included were photochemical constituents assay to determine the phytochemicals in the plant extracts (6 studies) and cytotoxicity of the plant extract (4 studies)

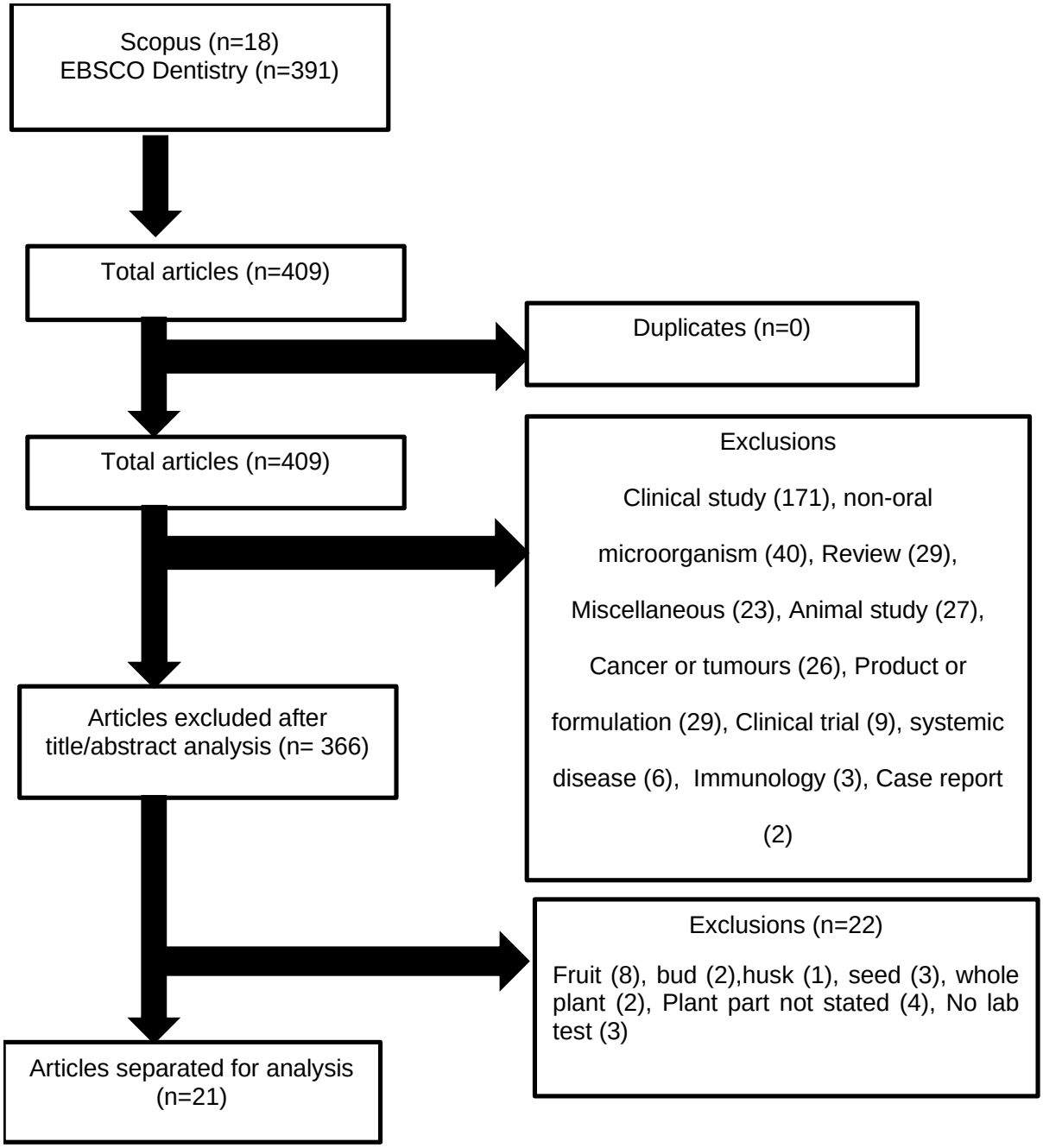

Figure 1 : The flow diagram report of the systematic review literature search results

Table 2 : Overview Of The Representative Plant Extracts Found To Have Antimicrobial Properties Against Oral Microorganism

NO.	PLANT TYPE	PART OF PLANT
1	*Acacianilotica*	Leaves
2	*Murrayakoenigii (L.Sprengel)*	Leaves
3	*Eucalyptus hybrid*	Leaves
4	*Psidium guajava*	Leaves
5	*Houttuynia cordata*	Leaves
6	*Juglans regia*	Bark
7	*Mentha piperita*	Leaves
8	*Heteropyxis natalensis*	Leaves & twigs
9	*Pandanus amaryllifolius (Roxb.)*	Leaves
10	*Clinacanthus nutans*	Leaves
11	*Psidium cattleianum*	Leaves
12	*Anacardium occidentale L.*	Leaves
13	*Azadirachta indica (Neem)*	Leaves
14	*Mimusops elengi (Bakul)*	Leaves
15	*Strawberry guava (Psidium guineense Sw.)*	Leaves
16	*Sambolan (Syzygium cumini (L.) Skeels)*	Leaves
17	*Pothomorphe umbellata*	Leaves
18	*Aloe vera*	Leaves
19	*Black tea (Assam Orthodox variety)*	Leaves
20	*Green tea (Elixir variety)*	Leaves
21	*oolong tea (Enigma variety)*	Leaves
22	*Psidium sp*	Leaves
23	*Mangifera sp.*	Leaves

24	*Mentha sp.*	Leaves
25	*Panax quinquefolius*	Leaves & stem
26	*Cassia bakeriana Craib*	Bark
27	*Fabaceae*	Leaves
28	*Sideroxylon obtusifolium T.D. Penn*	Bark & Leaves
29	*Piper betle Linn*	Leaves
30	*Brazilian pepper tree (Schinus terebinthifolius)*	Stem & Bark

Table 3 : Antimicrobial activity and other test conducted against oral microorganism using selected plant extracts.

No	Plant	Parts used	Solvent for extraction	Microorganism	Antimicrobial assay	Positive control	Other test	References
1.	*Acacia nilotica,* *Murraya koenigii L. Sprengel,* *Eucalyptus hybrid, Psidium guajava*	Leaves	Ethanol	*Fusobacterium nucleatum Porphyromonas gingivalis*	Disk diffusion	0.2% chlorhexidine	Photochemical constituents' assay	Shekar et al., 2018
2.	*Houttuynia cordata*	Leaves	Water decoction	*Methicillin-resistant Staphylococcus aureus MRSA- S. mutans MT8148* *S. mutans UA159,* *S. sobrinus 1310,* *S. gordonii ATCC10558* *S. oralis ATCC10557,* *S. constellatus 4528,* *S. intermedius 40138* *S. mitis JCM 12971,*	MIC	cetylpyridinium chloride (CPC)	Cytotoxicity Assay Biofilm formation assay	Sekita et al., 2017

				A. actinomycetemcomitans Y4 *F. nucleatum JCM8532, P. gingivalis ATCC33277 P. aeruginosa PAO1* *C. albicans CAD1"*				
3.	*Houttuynia cordata*	Leaves	water solution ethanol extract	*"Methicillin-resistant Staphylococcus aureus MRSA* *S. mutans MT8148* *S. mutans UA159,* *S. sobrinus 1310,* *S. gordonii ATCC10558* *S. oralis ATCC10557,* *S. constellatus 4528,* *S. intermedius 40138* *S. mitis JCM 12971,* *A. actinomycetemcomitans Y4* *F. nucleatum JCM8532, P. gingivalis ATCC33277 P. aeruginosa PAO1* *C. albicans CAD1"*	MIC	0.1% Triton X-100	Cytotoxicity Assay Biofilm formation assay	Sekita et al.,2016
4.	Juglans regia	bark	Ethanol	*Streptococcus mutans, Streptococcus salivarius, Streptococcus sanguis, Staphylococcus aureus*	Disk diffusion and MIC	Tetracycline 30 μg and Erythromycin 15 μg		Zakavi et al.,2013
5.	Mentha piperita	leaves	Cold water method	*Streptococcus mutans,* *A. actinomycetemcomitans* *Candida albicans*	Disk Diffusion, MIC	Chlorhexidine 0.2%		Raghavan et al.,2018
6.	Heteropyxis natalensis	Leaves and twig	ethanol	A. *israelii (ATCC 10049), P. intermedia (ATCC 25611), S. mutans (ATCC 25175), L. paracasei (oral clinical strain A54), C.*	MIC , MBC, MFC	Chlorhexidine 0.12%, Metronidazole	Cytotoxicity on human monocyte cell.	Henley-Smith et al., 2018

				albicans (ATCC 10231), and a strain of Candida albicans resistant to the drugs; imidazole and polyene (1051604).				
7.	*Pandanus amaryllifolius (Roxb.)*	Leaves	Ethanol (70%)	*Porphyromonas gingivalis (ATCC33277), Streptococcus mutans (ATCC 35668), Streptococcus sanguinis and Streptococcus salivarius (ATCC 9222)*	MIC	Chlorhexidine 0.12%, Metronidazole	Cytotoxicity activity	Suwannakul et al.,2018
8.	Clinacanthus nutans (belalai gajah)	leaves	Ethanol (100%, 50% and 10%) and chloroform	*P. gingivalis and A. actinomycetemcomitans*	Disk diffusion, MIC, MBC	Chlorhexidine 0.2%		Hanafiah et al.,2019
9.	*Psidium cattleianum*	leaves	Ethanol	*E. faecalis ATCC 29212* *C. albicans ATCC 10231*	Intracanal dressing (dentin block) using bovine teeth	CaOH2		Sangalli et al.,2018
10.	Anacardium occidentale L. (cashew leaves)	leaves	Methanol and aqueous extract	*C.albicans(ATCC 24433)* *E.faecalis(ATCC 24212)*	Disk diffusion	-	-	Ballal et al.,2013
11.	strawberry guava (Psidium guineense Sw.) and of the jambolan (Syzygium cumini (L.) Skeels)	leaves	70% ethanol	*Streptococcus* *mutans (ATCC 25175), Streptococcus oralis (ATCC 10557), Streptococcus parasanguis (ATCC 903), Streptococcus salivarius (ATCC 7073),* *Streptococcus sp (ATCC 15300), and Lactobacillus casei (ATCC 9595).*	MIC MIC of adherence	0.12% chlorhexidine digluconate	-	Vieira et al.,2012
12.	Pothomorphe umbellata	Leaves	80% ethanol	*Enterococcus faecalis*	Agar diffusion ,intracanal medication	calcium hydroxide	-	Sponchiado et al., 2014
13.	Aloe vera	Leaves	Aloe vera gel + DMSO	*S.mutans, Aggregatibacter actinomycetemcomitans,*	Disk diffusion, MIC	-	-	Fani et al.,2012

				Porphyromonas gingivalis and Bacteroides fragilis.- clinical isolate				
14.	Black tea (Assam Orthodox variety), green tea (Elixir variety), and oolong tea (Enigma variety)	Leaves	Ethanol (100%), methanol (100%) and aqueous extract	*S.mutans*	Well diffusion agar	0.2% chlorhexidine	Phytochemicals analysis	Subramaniam et al.,2012
15.	Psidium sp., Mangifera sp., Mentha sp.	Leaves	Water decoction	*S. sanguinis ATCC BAA-1455 (strain SK36) and S. mutans ATCC 25175*	MIC, MBC, Fractional inhibitory concentration index (FICI)	0.12% CHX	Anti-adherence effect and SEM	Shafiei et al.,2016
16.	Panax quinquefolius	Leaves	Water decoction	*F. nucleatum, C. perfringens, and P. gingivalis.*	MIC, MBC, Cell membrane integrity, membrane potential	Erythromycin, tetracycline, and chlorhexi-dine	Phytochemicals analysis	Xue et al.,2017
17.	Cassia bakeriana Craib., Fabaceae,	Bark and leaves	ethanol 96%	*S. mutans (ATCC 25175), S. mitis (ATCC 49456), S. sanguinis (ATCC 10556), S. sobrinus (ATCC 33478), E. faecalis (ATCC 4082) and A. actinomycetemcomitans (ATCC 43717) and anaerobic F. nucleatum (ATCC 25586), B. fragilis (ATCC 25285), A. naeslundii,(ATCC 19039), P. nigrescens (ATCC 33563) and P. gingivalis (ATCC 48417).*	MIC	Chlorhexidine dihydrochloride	Phytochemicals analysis	Cunha et al.,2017
18.	Sideroxylon obtusifolium T.D. Penn	Bark and leaves	Ethanol 70%	*Streptococcus mutans, Streptococcus oralis, Streptococcus salivarius, Streptococcus parasanguinis, and Candida albicans*	MIC, MBC MFC	chlorhexidine 0.12% for bacteria, and nystatin 100,000 IU/mL for yeast, and solvent control	Phytochemicals analysis	Sampaio et al.,2017

19.	Piper betle	Leaves	water, ethanol 50%, 95% ethanol, and hexane.	*Aggregatibacter actinomycetemcomitans (Aa)*	Disc Diffusion	chlorhexidine	Phytochemicals analysis	Yanti et al., 2018
20.	Brazilian pepper tree (Schinus terebinthifolius)	Bark	60% hydroalcoholic	*Candida albicans (ATCC 289065)*	MIC, MFC, Effect on growth kinetic, effect on fungal cell wall	Nystatin	-	Alves et al., 2013
21.	Aloe vera	Leaves	Ethanol extract	*Eschericia coli, Enterococcus faecalis Staphylococcus aureus*	Agar well diffusion technique, Gutta percha decontamination	5.25% of sodium hypochlorite	-	Athiban et al.,2012

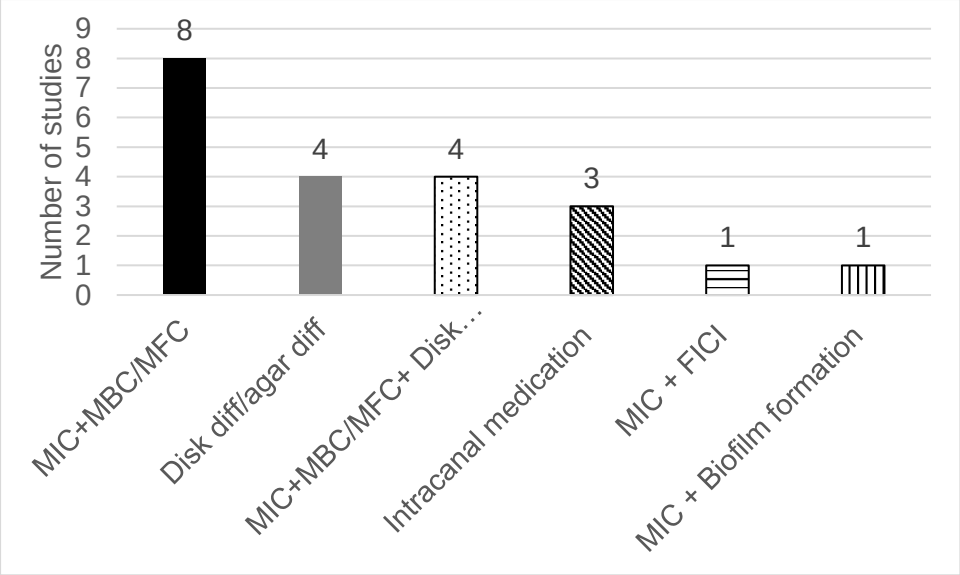

Figure 4: Distribution of antimicrobial assays in the twenty one studies analyzed. A major portion of them (n = 12, constituting the 57%) employed either MIC, or MBC, or their combination also with disk diffusion agar, while 19% were based only on a disk diffusion agar test. Three studies conducted intracanal medication application and only one study conducted the MIC in combination with Fractional Inhibitory Concentration Index (FICI) and biofilm formation.

DISCUSSION

Dental caries is the most prevalent oral disease that is disseminated all around the world. The exploration in combating cariogenic bacteria focuses on eliminating or reducing the bacteria and interfering with virulence factors such as the production of acid. Thus many studies were conducted to search for plant extract that has antimicrobial activity against cariogenic bacteria such as *S. mutans* and *S. sobrinus*. In our review, ten studies were conducted against *S.mutans,* and they found significant antimicrobial and antibiofilm activities in the tested plants against *S.mutans*. Fani and Kohanted (2012) reported the antimicrobial activity of aloe vera gel against *S. mutans* with the widest zone of inhibition **.** Vieira et al. (2012) stated that *S.mutans* adhering to *Psidium sp.* treated experimental pellicle was highly reduced compared to the non-treated pellicle. Therefore the leaves of *Strawberry guava (Psidium guineense Sw.)* and *jambolan (Syzygium cumini (L.) Skeels)* were recommended for further studies to confirm the effectiveness in the control of dental caries. Shafie et al. (2016) also conducted treatment of experimental pellicles with plant extract, and they found that the numbers of *S. sanguinis* and *S.mutans* adhering to *Psidium sp*. treated experimental pellicles was highly reduced. This can be good preventive action in reducing biofilm formation, which can lead to dental caries.

Tea is consumed as a daily routine in many parts of the world. The chemical composition of tea is complex, which contains alkaloids, tannins, saponins, steroids, flavonoids, and cardiac glycosides in all three types of tea. In *oolong tea, green tea* and *black tea,* terpenoids were present only in *green* and *black tea,* and phlobatannins were absent in all three types of tea. Amongst different types of tea, oolong tea showed the highest amount of phytochemicals quantitatively. Depending on the manufacturing process, tea can be 'non-fermented' green tea, 'semifermented' *oolong tea*, or 'fermented' *black tea***.** According to Subramaniam et al. (2012) , oolong tea and green tea methanol extract showed significantly greater inhibition zones against *S.mutans* than black tea extract. Ethanol extract of oolong tea showed more significant inhibition than the extract of green and black tea. The differences in the efficacy of the tea could be contributed by the different solvents used for the extraction. Solvents used to extract biomolecules from plants are chosen based on the polarity of the solute of interest. Ethanol, methanol and hexane are examples of commonly used solvents to isolate and purify the active compounds that are responsible for the bioactivity in the plant (Altemimi et al., 2017)

Bacterial adherence has a central role in the pathogenesis of oral diseases such as periodontal diseases, which are also known as plaque-related diseases. Endogenous oral bacterial species such as *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Streptococcus mutans, Streptococcus sobrinus, Bacteroides sp., Prevotella sp., Fusobacterium sp.* and their metabolites play major roles in the initiation and progression of these infections (Tanzer et al., 2001). Based on studies by Shekar et al. (2018), *M. koenigii L. Sprengel* leaves extract exhibited antimicrobial activity against *P. gingivalis*. *M. koenigii L. Sprengel* leaves decoction in the form of mouthwash was reported to reduce plaque formation in clinical studies conducted by Varghese et al. (2018)

Some microorganisms are resistant to antimicrobial treatment in endodontic infection and can survive in the root canal after biomechanical preparation. *E. faecalis* and *C. albicans* have been reported as common species recovered from root canals undergoing retreatment in cases of failed endodontic therapy and canals with persistent infections (Narayanan et al., 2010). In this review, the effectiveness of plant extract in eliminating *E. faecalis* and *C. albicans* was conducted using the intracanal dressing method. The intracanal medication containing *P. umbellata* was effective against *E. faecalis* after 7, 14, and 28 days of treatment without statistically significant difference compared to calcium hydroxide treatment, making this phytotherapy a viable option for endodontic treatment (Sponchiado et al, 2014). Interestingly, in three out of four studies (Sangalli et al., 2018, Sponchiado et al., 2014, Athiban et al., 2012) the plant extracts were reported to have significant antimicrobial activities against *E.faecalis*, almost equivalent to the activity of positive control the sodium hypochlorite.

The oral fungal included in this review was *C. albicans*. Alves et al. (2013) reported that S. terebinthifolius bark extract could significantly reduce the number of candida up to 60 min compared to growth control. No toxicity study was conducted in that study; however, another study by Silva et

al. (2010) reported no significant toxicity was observed in the animal studies using *S. terebinthifolius* bark extract in dosages smaller than 225 mg/Kg.

In this systematic review, chlorhexidine was widely used as a positive control. Chlorhexidine has been regarded as a "gold" standard in chemical plaque control for over 45 years in dentistry for the prevention of plaque and gingivitis due to its extended broad-spectrum activity toward microorganisms and plaque-inhibitory potential similar to Balagopal and Arjunkumar (2013) and Mathur et al. (2011). Chlorhexidine consist of varying strength 0.2%, 0.12%, 0.1% up to 5%. The lower strength has been used as mouth rinses (0.12%, 0.2%, 0.1%) while (2%, 5%) has been used as an endodontic irrigant and surface disinfection. It has been observed that while efficacy is directly proportional to the concentration, it increases side effects. A systematic review conducted by Samanth et al.(2017) yielded no significant difference between 0.2% and 0.12% in terms of Plaque Index, Taste or Periodontal pathogens. In this review , three studies used chlorhexidine 0.2% as positive control (Hanafiah et al., 2019, Raghavan et al., 2018, Shekar et al., 2018) while two other studies using 0.12% concentration (Shafiei et al., 2016 ,Vieira et al., 2012)

There are many techniques to recover antimicrobial compound from plants, but extraction yield and antimicrobial depend on the extraction method and the solvent used for extraction. The polarity of the solvent used will determine the kind of compounds that can be extracted.The most suitable solvents are aqueous mixtures containing ethanol, methanol, acetone, and ethyl acetate. In this review about 57% of the study used ethanol extracts. Ethanol has been known as a suitable solvent for polyphenol extraction. It is safe for human consumption, while methanol has been generally found to be more efficient in extracting lower molecular weight polyphenols (Turkmen et al., 2006)**.** Zakavi et al. (2013) stated that ethanolic extract of *Juglans Regia* bark had significant antibacterial effect as it inhibits the growth of oral bacteria such as *S. mutans, S. salivarius*, *S. sanguis*, and *S. aureus***.** The ethanol leaves extract of *Pandanus amaryllifolius (Roxb.)* also demonstrated the highest level of total phenol contents (TPC) and free radical scavenging activities compared to water or methanol extracts (Suwannakul et al., 2018)**.** However, Subramaniam et al. (2012) reported that for green tea extracts, the number of phytochemicals obtained after boiling with distilled water might have been more than that obtained by using methanol and ethanol as solvents. Therefore, for the primary study of plant extracts, it is recommended to screen the antimicrobial activity of different types of extract such as water decoction, ethanol, methanol, hexane, and chloroform. Further studies can be focused on the use of extracts that have the best efficacy.

An important task of the clinical laboratory is the antimicrobial susceptibility testing (AST) . In this review MIC was the highest adopted method followed by disk diffusion method with few studies also combined the antimicrobial methods. Each method has its strength and limitation. The method such as MIC and E-test provide quatitative results for the antimicrobial activity (effective concentration of plant extract) while disk diffusion/well diffusion provides qualitative assesment according to the categories (susceptible, intermediate or resistant). Each method is best suited to different needs and none can be regarded as the universal "best" method.(Bubonja-Šonje et al., 2020)

Minimal to no toxicity is essential for the successful development of pharmaceutical or cosmetic preparation, and in this regard, cellular toxicity studies play a crucial role (McGaw et al., 2014). In this review, four studies were identified to conduct cytotoxicity studies using the cell culture method. (Henley-Smith et al., 2018, Suwannakul et al., 2018, Sekita et al., 2017, Sekita et al., 2016). However, none of these four studies used oral-related cells for the cytotoxicity assay.

CONCLUSION

The present systematic review revealed the beneficial antimicrobial and antibiofilm properties of the selected plant extracts. Overall, there is a positive correlation between the therapeutic potential of plant extract and the antimicrobial and antibiofilm properties of various oral microorganisms.

CONFLICT OF INTEREST

The authors would like to declare that there is no conflict of interest

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