ANTIMICROBIAL ACTIVITY IN VITRO OF CAMU-CAMU *(Myrciaria dubia)* AGAINST ORAL MICROORGANISMS: A SYSTEMATIC REVIEW

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ABSTRACT

Objectives. To evaluate the antimicrobial activity of *Myrciaria dubia* on oral microorganisms. ***Materials and Methods.*** A systematic review of the literature following PRISMA guidelines was conducted through searches of studies published between 2008 and 2018 in Pubmed, LILACS, SciELO, ProQuest, EBSCO, and Google Scholar. ***Results.*** Eleven (11) in vitro studies were gathered; all the studies showed positive antimicrobial activity on gram-positives, mainly by each of the parts of its fruits. However, such activity compared to chlorhexidine in only two studies, and, in another study, it was better than an antibiotic. A high risk of bias was detected in most studies. Phenolic compounds, including polyphenols and acylphloroglucinols, were identified as responsible for its activity. ***Conclusions.*** There is evidence of antimicrobial activity in *M. dubia*. Its study as an antimicrobial against oral microorganisms is still incipient, but there is great potential thanks to the potent phytochemicals it contains. Also, additional quality studies are required: comparing their activity versus oral antiseptics and on microorganisms associated with dental caries and periodontal disease.

Keywords: Review; Phytotherapy; Myrtaceae; Dental caries; Microbiology; Periodontitis (source: MeSH NLM).

INTRODUCTION

Dental plaque (DP) at supra and subgingival level is linked to gingivitis, dental caries (DC) and periodontal disease (PD), respectively [1]. Its main pathogens are *Streptococcus mutans* (*S. mutans*) and Porphyromonas gingivalis (*P. gingivalis*) [2,3]. To maintain healthy oral tissues, toothbrushes, toothpastes, dental floss, and oral antiseptics [4-6] are required. Chlorhexidine (CHX) gluconate is the first choice [7] because it combines antibiotic/antibacterial effects. However, it is used for a short time because it results in teeth staining and temporary taste disorder [8,9]. Today, phytotherapy has a potentially valuable role as an adjunct in DC and DP management.

Myrciaria dubia (H.B.K) (McVaugh) "camu camu", is a fruiting shrub native to the Amazon region that belongs to the Myrciare family. It accumulates phytochemicals which are related to important properties [10]. For example, fractions of hydro-methanolic and hydro-acetonic extracts, as well as crude extract from *M. dubia* seed [11] and skin showed antioxidant activity due to their C-glucosidic ellagitannins [11,12]. Also, the pulp showed high levels of ascorbic acid (AA) and a large number of phenolic compounds [13]. The aqueous extract of the seed cover of *M. dubia* was also high in phenolic content [14].

In addition, a methanolic extract of *M. dubia* seeds showed anti-inflammatory properties by suppressing edema in mouse legs [15] and a 100% *M. dubia* juice reduced inflammatory markers and IL-6 and IL-8 in smokers with accelerated oxidative stress [16]. Betulinic acid (triterpenoid anti-inflammatory) [15], AA, and unknown phytochemicals [16] are responsible for this property, respectively.

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Probiotic beverages enriched with phenolic compounds of *M. dubia* controlled early stages of type 2 diabetes and the risk of associated hypertension [17], and an extract of seed cover showed antihypertensive activity [14]. In addition, crude extract [18] and pulp [19] from *M. dubia* controlled obesity [18,19] in mice [18] and rats [19], respectively. Also, a dry extract from pulp + shell stopped the growth of tumors and did not develop a greater inflammatory response in rats with colorectal cancer [20]. Finally, an aqueous extract of *M. dubia* pulp showed immunostimulant activity in rats [21].

There is research proving its antimicrobial property, mainly in the areas of Food Science, Chemical Engineering and Microbiology. But studies in dentistry are incipient. To date, there are no systematic reviews studying the antimicrobial activity of *M. dubia* versus oral antiseptics on oral cavity microorganisms. DC and PD are complex chronic diseases induced by pathogenic DP [22]. For this reason, agents that inhibit the growth of oral microorganisms should be studied in order to develop new preventive/therapeutic formulations. Proper mechanical control of the accumulation of DP in teeth has been key for preventing such diseases, but it requires great cooperation and motivation from the patient. Therefore, chemical agents act as useful adjuncts to achieve effective management of dental plaque associated with DC and PD [23]. Consequently, the objective of this study was to evaluate the *in vitro* antimicrobial activity of *M. dubia* against oral microorganisms.

KEY MESSAGES

Research motivation. *M. dubia* possesses a wide variety of phytochemicals responsible for antimicrobial activity against oral microorganisms.

Main findings. We found that extracts from different parts of *M. dubia* inhibited growth and reduced the total count of oral microorganisms. The literature mentions that it is due to phenolic compounds (including polyphenols) and acylphloroglucinols.

Implications. Further *in vitro*, *in vivo*, and subsequently clinical studies should be conducted, in view of their potential antimicrobial activity.

MATERIALS AND METHODS

RESEARCH QUESTION

This systematic review was designed according to PRISMA guidelines (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) [24] to answer the question: does *Myrciaria dubia* (Intervention) exercise true antimicrobial activity (Event/Outcome), compared with positive and/or negative controls (Comparison), on oral microorganisms (Problem) in experimental studies *in vitro* (Study design)?, which was formulated according to the PICO format.

SELECTION CRITERIA

Types of studies. In vitro experimental studies published in the last ten years (January 1, 2008 to December 31, 2018) because they are the most recent, rigorous and contain the most relevant data. Studies researching the antimicrobial activity of *M. dubia* versus controls, against oral microorganisms, without restriction of language and geographical scope.

Types of participants. Oral microorganisms involved in the etiology and progression of DC and PD (*Streptococcus mutans, Streptococcus sanguinis, Streptococcus sobrinus, Candida albicans, Porphyromonas gingivalis, Fusobacterium nucleatum, Aggregatibacter actinomycetemcomitans, Tannarella forsythia, Treponema denticola or Staphylococcus aureus*) using cultures of strains or samples of saliva or dental plaque from humans.

Types of intervention. Extracts (alcoholic, hydroalcoholic and aqueous), extract fractions, isolated phytochemicals, juices and/or antiseptics (solutions) from the fruit or tissues/organs of *M. dubia* versus positive controls (chlorhexidine, chloramphenicol, commercial oral antiseptics, antibiotics and antifungals) and negative controls (placebo solutions).

Types of event measurements. Primary event: antimicrobial activity determined by antimicrobial susceptibility methods, agar diffusion (disc or well), and broth microdilution method. The results were quantified by measuring the microbial growth inhibition zone (mm) and minimum inhibitory concentration (MIC), respectively. Secondary event: Identification of phytochemicals responsible for the antimicrobial activity of *M. dubia.*

EXCLUSION CRITERIA

Types of studies. Literature reviews, case reports, projects/protocols, short communications, personal opinions, letters, posters, conference summaries, and *in vivo* studies.

Types of intervention. Pharmaceuticals (such as tablets, capsules) or extracts containing combinations of *M. dubia* with other pharmaceuticals or other medicinal plants.

SEARCH METHODS FOR THE IDENTIFICATION OF STUDIES

Database information: The search for scientific articles was carried out in electronic databases for each of the predefined interventions between July 11 and September 15, 2018. No language limits were applied, and foreign articles were translated.

Databases and search engines used were PubMed; ProQuest; SciELO (Scientific Electronic Library Online); LILACS (Latin American and Caribbean Health Sciences Literature); EBSCOhost, Google Scholar.

Search strategies. A search model was developed for PubMed, using controlled *MeSH* (Medical Subject Headings) and free terms. For the other databases, this model was adapted, and free terms based on the controlled terms from *MeSH* or *DeCS (Health Sciences Descriptors)* and/or a combination of controlled vocabulary with free terms were used, taking into account differences in controlled vocabulary and syntax rules (Appendix 1).

DATA EXTRACTION AND ANALYSIS

Data extraction. In each article retrieved through the search strategies, two authors (KPA and MPV) applied the selection/exclusion criteria to the abstract, title or both, and reviewed them simultaneously and independently; only studies raising doubt were fully read. All potentially relevant studies were searched in full text. Those which did not meet the selection criteria were registered as articles excluded from the review and the reason for their exclusion was noted. Any discrepancies were resolved through consensus with a third and fourth reviewers (GA and JMUT).

The primary and secondary events were the antimicrobial activity of *M. dubia* and the identification of phytochemicals responsible for this activity, respectively. Additionally, information was extracted on aspects such as the name of the main author, year of publication, country of origin of the study, pharmacological formulation, part/tissue/organ and origin of *M. dubia*, control group, oral microorganisms studied and method to evaluate antimicrobial activity. Figure 1 shows the selection process of the studies according to the PRISMA statement. Information on the antimicrobial activity of *M. dubia* and controls was also extracted.

Risk of bias assessment of the studies included. Two researchers (KPA and AG) independently assessed the risk of bias of the selected studies, following the criteria proposed by the Joanne Briggs Institute *(Joanna Briggs Institute, 2014)* [25]. A third reviewer was involved in case of discrepancy (JMUT). The scale has ten questions, but two were not considered because they did not comply with bias analysis for in vitro studies. Therefore, the following questions were evaluated:

Was allocation to treatment group truly random? Was allocation to treatment groups hidden from the allocator? Were outcome assessors blinded to treatment allocation? Were control and treatment groups comparable at baseline? Were groups treated identically by the interventions mentioned? Was the event measured in the same way for all groups? Was the event measured reliably? Was the statistical analysis used appropriate?

Each question was answered with a "yes" when sufficient information was available, being equivalent to a low risk of bias. In case of non-existent information, the answer "no" was given, which is equivalent to a high risk of bias. The response "unclear" was given when the risk of bias could not be classified as high or low (Figure 2).

Looking for heterogeneity. It was determined according to the intervention (characteristics of the *M. dubia* and types of controls) and the event (methodology) studied in each of the selected articles. Thus, a meta-analysis could not be

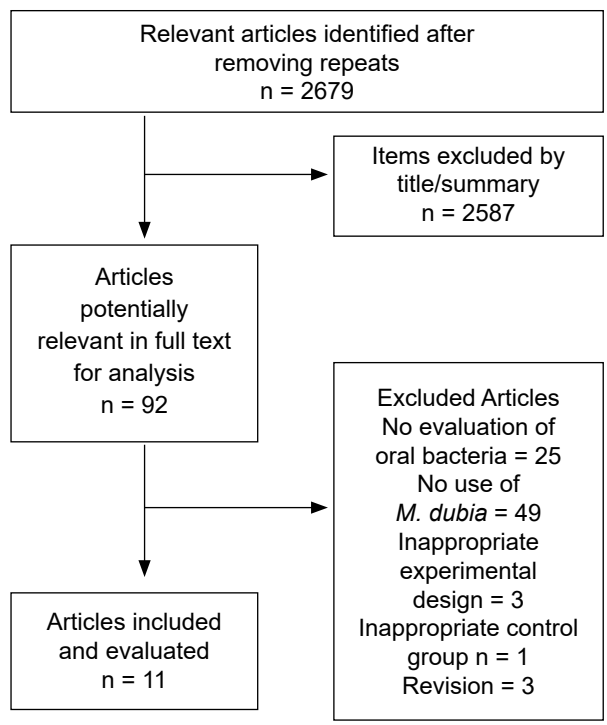

Figure 1. Flow chart of the included studies

performed because the articles showed high heterogeneity, making it impossible to make similar comparisons to assess the main event.

RESULTS

Four thousand nine hundred eight (4908) titles/abstracts were retrieved, of which 2229 were excluded because they were duplicated. Based on the selection criteria, 92 full titles were evaluated and 11 were selected [26-36]. The reasons for exclusion are mentioned in Figure 1.

The main characteristics for which the studies were selected, and their most relevant results are presented in Table 1.

Different parts of *M. dubia* were used (in correlative order, skin [26-30], pulp [31-33], seed [26,29,33], leaves [34,35], bark [34], a skin + seed combination) [36] and four phytochemicals [28,29] were isolated. All studies were *in vitro* [26-36] and one of them included an in vivo [35]. The two methods applied to evaluate antimicrobial activity against oral microorganisms (primary event) were broth microdilution [27-34,36] and agar diffusion (disc [26,27,30,34,35] or well [31-33,36]), whose results quantified the minimum inhibitory concentration (MIC) [27-34,36] and the microbial growth inhibition zone [26,27,30-36], respectively. The least used method was the colony forming unit (CFU) [30]. Phenolic and lipophilic compounds, polyphenols and acylphloroglucinols were identified as the phytochemicals responsible for the antimicrobial activity of *M. dubia* (secondary event).

M. dubia came mainly from Peru [26-30,33-35] and Brazil [31,32,36], whereas its most used phytopharmacological formulations were alcoholic (ethanol [27,30], hexane [28,29], and methanol [33]), hydroalcoholic [26,31,34,35] and aqueous [32,36] extracts, whose effects were studied against *S. aureus* [26-29,31,32,34,36], *S. mutans* [28-30,33,35], C. albicans [27-29], *P. gingivalis* [35] and *S. sanguinis* [33]. It also shows that the application of a *M. dubia* mouthwash on volunteer subjects reduced the microbial flora count up to ten minutes. In addition, it is important to mention that the studies carried out showed positive results with respect to the safety of *M. dubia*, since no visible adverse reactions were mentioned in the use of a leaf mouthwash in humans [35], and methanolic extracts from seeds and pulp were not cytotoxic in high concentrations [33].

Nine studies used, predominantly, an antibiotic as a positive control (ampicillin [31,32,34,36], kanamycin [26,28,29], vancomycin [27] and penicillin [30]); one of them included fluconazole [27] and another one, an alcohol (only indicated

	P1	P2	P3	P4	P5	P6	P7	P8
Myoda T, 2010	?	?	?	+	+	+	+	
Fujita A, 2013	?	?	?	+	+	+	+	?
Mori T, 2013	?	?	?	+	+	+	+	-
Castillo-Carranza CN, 2013	?	?	?	+	+	+	+	?
Silva de Azevedo JC, 2014	?	?	?	+	+	+	+	?
Moromi-Nakata H, 2014	?	?	?	+	+	+	+	
Fujita A, 2015	?	?	?	+	+	+	+	?
Kaneshima T, 2015	?	?	?	+	+	+	+	
Camere-Colarossi RV, 2016	?	?	?	+	+	+	+	?
Saldarriaga Mostacero, 2017	?	?	?	+	+	+	+	+
Kaneshima T, 2017	?	?	?	+	+	+	+	

Q1: Was allocation to the treatment group truly random?

Q2: Was allocation to treatment groups hidden from the allocator?

Q3: Were outcome assessors blinded to treatment allocation?

Q4: Were control and treatment groups comparable at baseline?

Q5: Were the groups treated identically by the interventions mentioned?

Q6: Was the event measured in the same way for all groups?

Q7: Was the event measured reliably?

Q8: Was the statistical analysis used appropriate?

+ Yes»	There was enough information	Low risk of bias
- «No»	There's a lot of information	High risk of bias
? «Not clear»	Risk of bias could not be classified as high or low.	
	No statistical analysis was carried out	

Figure 2. Risk of bias of the studies included

that it was 96°) [35], finding that *M. dubia.'s* activity was mostly similar [29,30] or superior [28,29,31,33,36] to such antibiotics. Two studies used chlorhexidine (CHX) (in solution) as a positive control [33,35], and one study used a negative control. Finally, the statistical analysis of such study found no significant difference between the activity of four fractions of an extract from M. dubia skin versus penicillin [30].

Study bias was assessed using the criteria described by the *Joana Briggs Institute* [25], used in systematic reviews of in vitro studies [37-39]. Figure 2 shows the risk of bias found in the studies included in this review. Analysis showed that all studies had an 'unclear' risk of bias for randomization, concealment of the randomization list, and blinding of assessors. Regarding an appropriate statistical analysis, it was only conducted in one of the eleven selected studies ("yes") [30]. Four studies did not require statistical analysis because they generated results through point estimation [26,28,29,35]. In addition, in five studies, statistical analysis was 'unclear' [27,31-33,36] and one did not use appropriate statistical analysis [34] ('no'). The other guidelines, which include baseline

Table 1. Main characteristics and results of the *in vitro* studies included

First author/ year/ country/ Format	Formulation/ fraction (Fr)/part/ Origin of *M. dubia*	Control group (Co)	Evaluation of the antimicrobial activity	Microorganisms	Main results of *M. dubia* and controls/ Sample size (n)	Significant difference between *M. dubia* and control? (p-value)	Reference
Myoda T, *et al*/ 2010/ Japón (Article)	Hydroacetone extract (HAE) from seed (Peru) HAE from skin (Peru)	Kanamycin	Agar diffusion with disc	*S. aureus* ATCC 11522	*M. dubia* 5.0 mg/mL: 2.7 mm; *M. dubia* Fr-100% of 5.0 and 1.0 mg/mL: 4.7 and 3 mm, respectively. (n=3) *M. dubia* 5.0 mg/mL: 3.1 mm; *M. dubia* Fr-100% at 5.0 and 1.0 mg/mL: 3.8 and 2.0 mm, respectively. Control (Co): 3.3 mm. (n=3)	Undetermined	26
Fujita A, *et al*/ 2013/ Brasil (Artículo)	Hydro-methanol extract (HME) from freeze-dried pulp (Brazil) HME from spout-fluid bed-dried pulp (Brazil)	Ampicillin	Agar diffusion with well and Microdilution method	*S. aureus* ATCC 29,213	*M. dubia*: 25±1 mm and MIC: 0.08 mg/mL (n=3) *M. dubia* 60 C° and 0% maltodextrin: 19±1 mm and MIC: 0.08 mg/mL. MIC of the Co: 0.26 mg/mL (n=3)	Undetermined	31
Mori T, *et al*./ 2013/ Perú (Artículo)	Freeze-dried hydroethanolic extract (LHEL) from leaves (Peru) LHEL from bark (Peru)	Ampicillin	Agar diffusion with discs and test on tubes and dilution	*S. aureus* ATCC 6538P	*M. dubia* of 500, 700 and 800 mg/mL: showed antimicrobial activity and 15 mm ((higher halo) and MIC (on a suspension of 10^6 CFU/mL): 6.38 mg/mL. Co: not mentioned. (n= does not mention)	Undetermined	34
Castillo-Carranza CN, *et al*./ 2013/ Perú (Tesis)	Ethanolic extract from and skin (Peru)	Vancomycin and fluconazole	Agar diffusion with disc and tube-dilution method, abbreviated	*S. aureus* ATCC 10231 *C. albicans* ATCC 25923	*M. dubia* Fr-100%: 23±69 mm and MIC *(M. dubia* Fr-75%): 0.00 CFU. (n=10) *M. dubia* Fr-100%: 21±91 mm and MIC (*M. dubia* Fr-100%): 0.00 CFU. Co: none mentioned. (n=10)	Undetermined	27
De Azevêdo JCS, *et al.*/ 2014/ Brasil (Artículo)	Aqueous extract from skin + seed (EACS), fresh (Brazil) Freeze-dried EACS (Brazil)	Ampicillin	Agar diffusion with well and microdilution method	*S. aureus* ATCC 29213	*M. dubia Fr rich in polyphenols* (obtained by method 2): 16±1 mm and MIC: 2.5 mg/mL (n=3) *M. dubia* Fr rich in polyphenols (method 2): 15±1 mm and MIC: 2.5 mg/mL, respectively. MIC of the Co: 0.25 mg/mL. (n=3)	Undetermined	36
Fujita A, *et al.*/ 2015/ Brasil (Artículo)	Aqueous extract from freeze-dried pulp (EAPL) from the Amazon EAPL from Sao Paulo Aqueous extract from pulp dried by aspersion (EAPA) from the Amazon EAPL from Sao Paulo	Ampicillin	Agar diffusion with well and microdilution method	*S. aureus* ATCC 29213	*M. dubia:* 25±3 mm and MIC: 0.08 mg/mL (n=3) *M. dubia:* 29±0 mm and MIC: 0.08 mg/mL (n=3) *M. dubia* with 6% maltodextrin at 150 °C: 19±0 mm and MIC: 0.31 mg/mL. (n=3) *M. dubia* with 6% Arabic gum at 120°C and 150 °C: 19±1 mm and MIC: 0.16 mg/mL, respectively. Co: 0.26 mg/kg mL. (n=3)	Undetermined	32
Kaneshima T, *et al.*/ 2015/ Japón (Artículo)	Three extracts and a component obtained from the skin (Peru) n-hexane n-hexane layer 90% acetonitrile layer *Rhodomyrtone* (Component 1)	Kanamycin	Broth microdilution susceptibility test	*S. aureus* NRIC 1135, *S. mutans* JCM 5175 and *C. albicans* JCM 2085	Minimum inhibitory concentration (MIC). Co: 1.56 µg/mL *S. aureus:* 12.50 µg/mL, *S. mutans:* 25.00 µg/mL and *C. albicans:* >100 µg/mL *S. aureus:* 12.50 µg/mL, *S. mutans:* Not tested and *C. albicans:* >100 µg/mL *S. aureus:* 0.78 µg/mL, *S. mutans:* 1.56 µg/mL and *C. albicans:* >100 µg/mL	Undetermined	28

(Continued on page 578)

Table 1. Main characteristics and results of the *in vitro* studies included *(Continued from page 577)*

First author/ year/ country/ Format	Formulation/ fraction (Fr)/ part/ Origin by *M. dubia*	Control group (Co)	Evaluation of the antimicrobial activity	Microorganisms	Main results of *M. dubia* and controls/ Sample size (n)	Significant difference between M. dubia and control? (p-value)	Reference
Camere-Colarossi R., *et al.*/ 2016/ Peru (Article)	Methanolic extract (ME) from freeze-dried seed (Peru)	Chlorhexidine (CHX) 0.12%	Agar diffusion with wells and microdilution method	*S. mutans* ATCC 25,175	*M. dubia:* 21.36±6.35 mm and MIC: there was activity even in low concentrations. Co: 23.97±1.75 mm. (n=12)	Undetermined	33
				S. sanguinis ATCC 10,556	*M. dubia*: 19.21±5.18 mm and MIC: there was activity even in low concentrations. Co: 22.75±2.52 mm. (n=12)		
	ME from freeze-dried pulp (Peru)			*S. mutans* ATCC 25,175	*M. dubia*: 16.20±2.08 mm and MIC: 62.5 mg/mL. Co: 23.97±1.75 mm. (n=12)		
				S. sanguinis ATCC 10,556	*M. dubia*: 19.34±2.90 mm and MIC: 62.5 mg/mL. Co: 22.75±2.52 mm. (n=12)		
Moromi-Nakata H, *et al.*/ 2016/ Perú (Artículo)	Hydroalcoholic extract (LHAE) from leaves (Peru), *in vitro*	CHX 0.2%	Disk diffusion technique	*S. mutans* ATCC 25,175	*M. dubia* Fr-100%: 17 mm. Co: 15 mm. (n=1)	Undetermined	35
				P. gingivalis ATCC 33,277	*M. dubia* Frs 50% and 100%: 8 mm. respectively. Co: 8 mm. (n=1)		
	Mouthwash made of LHAE (Peru), *in vitro*			*S. mutans* ATCC 25,175	*M. dubia* Frs 10% and 100%: 8 mm. Co: 15 mm. (n=1)		
				P. gingivalis ATCC 33,277	*M. dubia* Frs 20%, 50%, and 100%: 6 mm. respectively. Co: 13 mm. (n=1)		
	Mouthwash made of EHH (Peru), *in vivo*	inexistent	bacterial flora count X 10^2. Plaque dilution Count of Colony-forming units (CFU)	Total bacterial count	Reduction of 55% and 85% of bacteria and *S. mutans*, respectively, in saliva up to 10 minutes after application. (n=10 subjects)		
				S. mutans count			
Saldarriaga-Mostacero EG, *et al.*/ 2017/ Perú (Tesis)	Ethanolic extract from skin (EEC) (Peru)	Penicillin	Agar diffusion with discs and tube dilution method	*S. mutans* ATCC 25,175	*M. dubia* Fr-100%: 16.38±2.22 mm. Co negative and positive: 6.00±0.0 (did not antimicrobial activity) and 17.3±2.4 mm,respectively. MIC of *M. dubia* Fr-25%: 4.15±1.92 CFU/mL. Co negative and positive: 108±0.00 and 0.0 CFU/mL, respectively. (n=13)	p > 0.05 (extract at 100%) and p < 0.05 (other fractions)	30
Kaneshima T, *et al.*/ 2017/ Japón (Artículo)	Three extracts and two components obtained from the skin (Peru)	Kanamycin	Broth microdilution susceptibility test	*S. aureus* NRIC 1135, *S. mutans* JCM 5175 and *C. albicans* JCM 2085	Minimum inhibitory concentration (MIC). Co: 1.56 µg/mL	Undetermined	29
	n-hexane, n-hexane layer, layer of acetonitrile 90% and *Rhodomyrtone* (Component 2)				Results of the three extracts, component 2 (obtained from the skin) and control (Co) are the same as 2015		
	Myrciarone A (Component 1)				*S. aureus*: 1.56 µg/mL, *S. mutans*: 3.13 µg/mL y *C. albicans*: No probado		
	Three extracts and two components obtained from the seed (Peru)				Co CIM: 1.56 µg/mL		
	n-hexane				*S. aureus*: 6.25 µg/mL, *S. mutans*: 100 µg/mL y *C. albicans*: >100 µg/mL		
	Layer of acetonitrile 90%				*S. aureus*: 6.25 µg/mL, *S. mutans*: 25.00 µg/mL and *C. albicans*: Not tested		
					S. aureus: 6.25 µg/mL, *S. mutans*: 100 µg/mL and *C. albicans*: Not tested		
	Isomyrtucommulone B (Component 3)				*S. aureus*: 1.56 µg/mL, *S. mutans*: 3.13 µg/mL and *C. albicans*: Not tested		
	Myrciarone B (Component 4)				*S. aureus*: 1.56 µg/mL, *S. mutans*: 1.56 µg/mL and *C. albicans*: Not tested		

comparison between experimental groups, identical treatments, and event measurements were conducted reliably and comparably, showing a "yes" for low risk of bias in all studies.

In one of the studies, it was observed that despite the loss of phytochemicals in the pulp of *M. dubia* after it was subjected to dehydration processes, the pulp dust still maintained high levels of phenolics, ascorbic acid, proanthocyanidins, and antimicrobial activity [31]. An article also concluded that seed and skin extracts inhibited *S. aureus*, owing to the action of lipophilic constituents [26]. Two other publications demonstrated the antimicrobial activity of phenolic compounds of *M. dubia*; in the first, they identified these compounds in freeze-dried pulp and found that they had a high correlation coefficient with the inhibition of S. aureus (r^2 = 0.906 – 0.971) [32]. And in the second, Powder from *M. dubia* seed + shell presented phenolic compounds and polyphenols obtained by freeze-drying and hot air, respectively, indicating that they could play a role in inhibiting *S. aureus* [36]. Finally, two studies isolated four acylphloroglucinols and antimicrobial phytochemicals in the skin [28,29] and seeds [29] of *M. dubia*, respectively, which showed strong antimicrobial activities against five gram-positive bacteria, including *S. mutans* and *S. aureus* [28,29].

DISCUSSION

This systematic review showed, for the most part, that *M. dubia* has antimicrobial activity against microorganisms, gram-positives (G+) [26-36], only one gram-negative (G-) [35], and one fungus [27] from the oral cavity. Also, against G- microorganisms that do not belong to the oral cavity [28,29,40], which suggests that *M. dubia* could inhibit G- pathogens relevant to the development of PD. Therefore, it is necessary to carry out more in vitro studies on other G+ and G- bacteria linked to DC and PD, respectively, applying other methodologies/techniques and with chlorhexidine as the control group. Then, studies should be conducted in an *in vivo* environment, such as the mouth. In particular, its substantivity could be studied, which is the property that allows its therapeutic action to persist for as long as possible in the oral cavity. Therefore, further *in vitro, in vivo*, and later clinical studies should be conducted in view of its potential antimicrobial activity.

M. dubia has traditionally been used by indigenous communities in Loreto (Peru) to treat gingivitis [41] and because it keeps gums healthy [42]. Nowadays, it is considered a super fruit because it has several phytochemicals and improves people's quality of life. In recent years, extracts of the whole fruit and its parts have been studied, demonstrating their effects against different pathologies, including their antimicrobial action against oral pathogens [43]. Studies on oral microorganisms suggest the antimicrobial activity of *M. dubia* [26-36].

Strict anaerobic bacteria were studied, as they are considered the main etiological agents of PD [44], but also G+ bacteria—for being causal agents of the CD [45]—and other microbial components of PD. In particular, it was decided to evaluate the antimicrobial activity because it is specific to microorganisms of the oral cavity. For example, the polymicrobial community's representative of DC and periodontitis show a sophisticated structural and functional integration, conferring an almost organic state to these microorganisms [46]. Other properties, such as anti-inflammatory activity, were not studied because it is not specific to the oral cavity and can be evaluated by other experimental models frequently applied to the whole organism.

In relation to the bias analysis of the studies included, there is a perception of bias in most of them because the guidelines for randomization, concealment of the randomization list, and blinding of assessors were not met. However, these guidelines are not normally followed in *in vitro* microbiological research. With respect to the other guidelines, they were applied, except for statistical analysis, which was not complied with in all the studies as they did not compare experimental groups versus positive controls [26-29,31-36]. In others, it was not required because the method used to measure the main event generated results through point estimation (presented a single value) [26,28,29,35]. However, the results would show us the potential to generate evidence.

The mechanism of action of *M. dubia's* phytochemicals identified in this review and usually studied as new antimicrobial constituents [28,29,47], is still unknown. However, it has been shown that G+, like S. aureus, showed microbial sensitivity to phenolic compounds from fruits, which act through various mechanisms, including cell membrane destabilization and inhibition of key enzymes [47].

A number of phenolic compounds were the best choice as a supplement during antibiotic therapy because they accelerated antimicrobial activity and inhibited the overproduction of reactive oxygen species by antimicrobial agents [48]. In addition, animal studies indicated that many of them improved or prevented the development of PD in terms of inflammation and periodontal destruction [49]. Lipophilic compounds would be relevant for the potential of two extracts to prevent dental erosion [50]. The term polyphenols are often used as a synonym for phenolic compounds, but it only refers to molecules bearing at

least two phenolic rings [51]. *In vitro* [52] cell biology studies in animals and humans have shown that selected dietary polyphenols have important antimicrobial, antioxidant, and anti-inflammatory properties that improve the clinical markers of periodontitis [53]. Finally, acylphloroglucinols derived from various medicinal plants exhibited antimicrobial and antifungal activities [54] and possess important structural characteristics that confer antimicrobial activities against resistant strains of *S. aureus* [55].

Certain limitations were encountered in the present review due to heterogeneity in the intervention and outcomes. In the first, it refers to differences in the *M. dubia* with respect to the place of origin, type of extract, parts of the fruit used, and different positive controls; in the second, to differences in the methodology for quantifying antimicrobial activity and in its units of measure. In addition, as the results were based on experimental *in vitro* studies, they do not lead to direct clinical application, but do constitute a necessary prior step. Despite of the limitations in intervention and results, the antimicrobial activity of *M. dubia* was generally similar [29,30] and/or superior [28,29,31,32,36] to antibiotics, suggesting its antimicrobial potential in the oral cavity, although in the only two studies where it was compared with CHX [33,35] it showed no superiority. This indicates the need for further study in the dental field and thus be able to measure its antimicrobial activity versus conventional oral antiseptics. It is worth mentioning that there are reviews of *M. dubia* [56,23,57], but this is the first systematic review that evaluates its antimicrobial activity against microorganisms in the oral cavity.

It can be concluded that *M. dubia* has antimicrobial potential to control dental caries and periodontal disease in the oral cavity, in addition to reducing the total count of microorganisms. In order to corroborate its antimicrobial effect, it should be studied in other formulations such as antiseptics (solutions), toothpastes, chewing gum, etc. The poor methodological design of the studies included in this systematic review does not allow its direct use as an antimicrobial in the oral cavity. We recommend conducting more studies with better design and low risk of bias.

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