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 Myrtiace 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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Received: 06/02/2019   Approved: 04/09/2019     Online: 20/11/2019

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.

**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.
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
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 (28,31,34,35) and aqueous (32,36) extracts, whose effects were studied against *S. aureus* (26,28,29,31,32,34,36), *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 (36), 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 that it was 96%) (39), finding that *M. dubia*’s activity was mostly similar (26,30) 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 ("no"). The other guidelines, which include baseline...
### Table 1. Main characteristics and results of the in vitro studies included

<table>
<thead>
<tr>
<th>First author/ year/ country/ Format</th>
<th>Formulation/ fraction (Fr)/part/ Origin of M. dubia</th>
<th>Control group (Co)</th>
<th>Evaluation of the antimicrobial activity</th>
<th>Microorganisms</th>
<th>Main results of M. dubia and controls/ Sample size (n)</th>
<th>Significant difference between M. dubia and control? (p-value)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoda T, et al. 2010/ Japón (Article)</td>
<td>Hydroacetone extract (HAE) from seed (Peru)</td>
<td>Kanamycin</td>
<td>Agar diffusion with disc</td>
<td>S. aureus ATCC 11522</td>
<td>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)</td>
<td>Undetermined 26</td>
<td></td>
</tr>
<tr>
<td>Fujita A, et al. 2013/ Brasil (Artículo)</td>
<td>Hydro-methanol extract (HME) from freeze-dried pulp (Brazil)</td>
<td>Ampicillin</td>
<td>Agar diffusion with well and Microdilution method</td>
<td>S. aureus ATCC 29,213</td>
<td>M. dubia: 25±1 mm and MIC: 0.08 mg/mL (n=3)</td>
<td>Undetermined 31</td>
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</tr>
<tr>
<td>Mori T, et al. 2013/ Perú (Artículo)</td>
<td>Freeze-dried hydroethanolic extract (LHEL) from leaves (Peru)</td>
<td>Ampicillin</td>
<td>Agar diffusion with discs and test on tubes and dilution</td>
<td>S. aureus ATCC 6538P</td>
<td>M. dubia of 900, 700 and 800 mg/mL: showed antimicrobial activity and 15 mm ((higher halo) and MIC on a suspension of 10^5 CFU/mL): 6.38 mg/mL. Co: not mentioned. (n= does not mention)</td>
<td>Undetermined 34</td>
<td></td>
</tr>
<tr>
<td>Castillo-Carranza, CN, et al. 2013/ Perú (Tesis)</td>
<td>Ethanolic extract from and skin (Peru)</td>
<td>Vancomycin and fluconazole</td>
<td>Agar diffusion with disc and tube-dilution method abbreviated</td>
<td>S. aureus ATCC 102311</td>
<td>M. dubia Fr-100%: 23±69 mm and MIC (M. dubia Fr-75%): 0.00 CFU. (n=10)</td>
<td>Undetermined 27</td>
<td></td>
</tr>
<tr>
<td>De-Azevêdo, JCS, et al. 2014/ Brasil (Artículo)</td>
<td>Aqueous extract from skin + seed (EACS), fresh (Brazil)</td>
<td>Ampicillin</td>
<td>Agar diffusion with well and microdilution method</td>
<td>S. aureus ATCC 29213</td>
<td>M. dubia Fr rich in polyphenols (obtained by method 2): 16±1 mm and MIC: 2.5 mg/mL (n=3)</td>
<td>Undetermined 36</td>
<td></td>
</tr>
<tr>
<td>Fujita A, et al. 2015/ Brasil (Artículo)</td>
<td>Three extracts and a component obtained from the skin (Peru)</td>
<td>Kanamycin</td>
<td>Broth microdilution susceptibility test</td>
<td>S. aureus NRIC 1135, S. mutans JCM 5175 and C. albicans JCM 2085</td>
<td>Minimum inhibitory concentration (MIC). Co: 1.56 µg/mL</td>
<td>Undetermined 28</td>
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</tbody>
</table>

(Continued on page 578)
### Table 1. Main characteristics and results of the in vitro studies included (Continued from page 577)

<table>
<thead>
<tr>
<th>First author/ year/ country/ Format</th>
<th>Formulation/ fraction (Fr) part Origin by M. dubia</th>
<th>Control group (Co)</th>
<th>Evaluation of the antimicrobial activity</th>
<th>Microorganisms</th>
<th>Main results of M. dubia and controls/ Sample size (n)</th>
<th>Significant difference between M. dubia and control? (p-value)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camere-Colarossi R., et al./ 2016/ Peru (Article)</td>
<td>Methanolic extract (ME) from freeze-dried seed (Peru)</td>
<td>Chlorhexidine (CHX) 0.12%</td>
<td>Agar diffusion with wells and microdilution method</td>
<td>S. mutans ATCC 25,175</td>
<td>M. dubia: 21.36±6.35 mm and MIC: there was activity even in low concentrations. Co: 23.97±1.75 mm. (n=12)</td>
<td>Undetermined 33</td>
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<td>ME from freeze-dried pulp (Peru)</td>
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<td>S. sanguinis ATCC 10,556</td>
<td>M. dubia: 19.21±5.18 mm and MIC: there was activity even in low concentrations. Co: 22.75±2.52 mm. (n=12)</td>
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<tr>
<td>Moromi-Nakata H, et al./ 2016/ Peru (Articulo)</td>
<td>Hydroalcoholic extract (LHAE) from leaves (Peru), in vitro</td>
<td>CHX 0.2%</td>
<td>Disk diffusion technique</td>
<td>S. mutans ATCC 25,175</td>
<td>M. dubia Fr-100%: 17 mm. Co: 15 mm. (n=1)</td>
<td>Undetermined 35</td>
<td>35</td>
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<td></td>
<td>Mouthwash made of LHAE (Peru), in vitro</td>
<td></td>
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<td>P. gingivalis ATCC 33,277</td>
<td>M. dubia Frs 50% and 100%: 8 mm. respectively. Co: 8 mm. (n=1)</td>
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<td></td>
<td>Mouthwash made of EHH (Peru), in vivo</td>
<td>bacterial flora count X 10^3. Plaque dilution Count of Colony-forming units (CFU)</td>
<td></td>
<td>S. mutans ATCC 25,175</td>
<td>M. dubia Frs 10% and 100%: 8 mm. respectively. Co: 13 mm. (n=1)</td>
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<tr>
<td>Saldarriaga-Mostacero EG, et al./ 2017/ Perú (Tesis)</td>
<td>Ethanolic extract from skin (EEC) (Peru)</td>
<td>Penicillin</td>
<td>Agar diffusion with discs and tube dilution method</td>
<td>S. mutans ATCC 25,175</td>
<td>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: 1.56±0.0 and 0.0 CFU/mL, respectively. (n=13)</td>
<td>p &gt; 0.05 (extract at 100%) and p &lt; 0.05 (other fractions)</td>
<td>30</td>
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<tr>
<td></td>
<td>Three extracts and two components obtained from the skin (Peru)</td>
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<td>S. aureus: 1.56 µg/mL, S. mutans: 3.13 µg/mL y C. albicans: No probado</td>
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<td></td>
<td>Ethanolic extract from skin (EEC) (Peru)</td>
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<td>S. aureus: 6.25 µg/mL, S. mutans: 100 µg/mL y C. albicans: &gt;100 µg/mL</td>
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<td></td>
<td>Three extracts and two components obtained from the seed (Peru)</td>
<td></td>
<td></td>
<td>S. aureus: 6.25 µg/mL, S. mutans: 25.00 µg/mL and C. albicans: Not tested</td>
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<td></td>
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<td>S. aureus: 1.56 µg/mL, S. mutans: 3.13 µg/mL y C. albicans: Not tested</td>
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<tr>
<td>Kaneshima T, et al./ 2017/ Japon (Articulo)</td>
<td>Ethanol extract obtained from the seed (Peru)</td>
<td>Kanamycin</td>
<td>Broth microdilution susceptibility test</td>
<td>S. aureus NRIC 1135, S. mutans JCM 5175 and C. albicans JCM 2065</td>
<td>Co CIM: 1.56 µg/mL</td>
<td>Undetermined 29</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>n-hexane</td>
<td></td>
<td></td>
<td>S. aureus: 1.56 µg/mL, S. mutans: 3.13 µg/mL y C. albicans: &gt;100 µg/mL</td>
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<td></td>
<td>n-hexane</td>
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<td></td>
<td>S. aureus: 6.25 µg/mL, S. mutans: &gt;100 µg/mL and C. albicans: Not tested</td>
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<td></td>
<td>Layer of acetonitrile 90%</td>
<td></td>
<td></td>
<td>S. aureus: 25.00 µg/mL, S. mutans: 25.00 µg/mL and C. albicans: Not tested</td>
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<td>n-hexane</td>
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<td>S. aureus: 6.25 µg/mL, S. mutans: 25.00 µg/mL and C. albicans: Not tested</td>
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<td>n-hexane</td>
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<td>S. aureus: 25.00 µg/mL, S. mutans: 25.00 µg/mL and C. albicans: Not tested</td>
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<tr>
<td></td>
<td>Myrciarone A (Component 1)</td>
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<td></td>
<td>S. aureus: 6.25 µg/mL, S. mutans: 100 µg/mL y C. albicans: &gt;100 µg/mL</td>
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</tbody>
</table>
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 (20). 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 ($r^2 = 0.906 - 0.971$) (22). 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 (26). Finally, two studies isolated four acylphloroglucinols and antimicrobial phytochemicals in the skin (28,29) and seeds (20) 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) (26,28,29,30). 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. In vitro 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. Finally, acylphloroglucinols derived from various medicinal plants exhibited antimicrobial and antifungal activities and possess important structural characteristics that confer antimicrobial activities against resistant strains of S. aureus.

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 and/or superior 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.

**Authors’ Contributions:** KPA participated in the conception and design of the article, data collection, writing and critical review of the article, analysis and interpretation of the results, and approval of the final version. MPV participated in data collection, critical review of the article, and approval of the final version. AG participated in data collection, article writing, critical review of the article, and approval of the final version. JMUT participated in the data collection, critical review of the article, and approval of the final version.

**Funding:** Self-funded

**Conflicts of Interest:** The authors declare that they have no conflicts of interest in relation to the contents of this document.

**Supplementary Material:** Available in the electronic version of the RPMESP.

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