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Research Article

Herbal as an Adjunct to Scaling and Root Planning (SRP) in Nonsurgical Periodontitis Treatment in Adult: A Systematic Review of Randomized Controlled Trials

Janaína Escudero[1]*, Mônica Ghislaine Oliveira Alves[2,3], Janete Dias Almeida[1], Nídia Castro dos Santos[4], Huda Gomaa[5,6], Erica A Suzumura[7], Camila Batista da Silva[3], Claudio Pereira Kawakami[1], Eliseu Gabriel Faustino[1], Beatriz Venturoso Simões[1], João Vitor da Silva Rodrigues[1], Luis Eduardo Leite[1], Camilla Tajzler[8], Eliane Chaves Jorge[9], Maria Aparecida Neves Jardini[10], Marianne Spalding[1] and Regina El Dib[1,11]

[1]Department of Biosciences and Oral Diagnosis, Institute of Science and Technology, Universidade Estadual Paulista, São José dos Campos, Brazil

[2]Universidade Anhembi-Morumbi, Campus São José dos Campos, São Paulo, SP, Brazil

[3]School of Dentistry, Universidade Mogi das Cruzes, Mogi das Cruzes, Brazil

[4]Department of Periodontology, Dental Research Division, Guarulhos University, Guarulhos, São Paulo, Brazil

[5]High Institute of Public Health-Alexandria University, Egypt

[6]Drug Information Center, Tanta Chest Hospital, Tanta, Egypt

[7]Departament of Preventive Medicine, Faculdade de Medicina - FMUSP, Universidade de Sao Paulo, Sao Paulo, Brazil

[8]Department of Surgery, McMaster University, St. Joseph's Healthcare, Hamilton, Canada

[9]Department of Ophthalmology, Otorhinolaryngology and Head and Neck Surgery, Botucatu Medical School, UNESP - Universidade Estadual Paulista, Botucatu, Brazil

[10]Department of Diagnosis and Surgery, School of Sciences and Technology, UNESP - Universidade Estadual Paulista, São José dos Campos, Brazil

[11]McMaster Institute of Urology, McMaster University, St. Joseph's Healthcare, Hamilton, Canada

***Corresponding Author:** Janaina Escudero, Department of Biosciences and Oral Diagnosis, Institute of Science and Technology, Universidade Estadual Paulista, São José dos Campos, Brazil.

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Abstract

Background: Periodontitis is an inflammatory disease that affecting people worldwide. The herbal medications might act as adjuvant or to be an alternative therapy in nonsurgical periodontitis treatment in adult.

Objective: To summarize the effects of herbal medications as an adjunct to scaling and root planning (SRP) or chlorhexidine compared to the standard of care (SRP alone) in adult periodontitis treatment.

Methods: Searches of MEDLINE, EMBASE, CENTRAL, LILACS and ISI Web of Science up to March 2019 were performed to identify randomized controlled trials (RCTs). We used the GRADE approach to rate overall certainty of the evidence by outcome.

Results: 30 randomized trials including 1,125 patients proved eligible. Pooled results from five RCTs showed a statistically significant difference in favor of herbal medicine as an adjunct to SRP when compared to SRP alone in reducing probing pocket depth (PPD) (Mean Difference (MD) -0.46, 95% Confidence Interval (CI) -0.67 to -0.26, $p < 0.00001$; $I2 = 38\%$, $p = 0.17$, $n = 166$).

Conclusions: Some possible clinically meaningful differences between herbal medicine as an adjunct to SRP and other comparisons exist, but no definitive conclusions can be drawn from these findings. Low-certainty evidence indicates that combination therapy with herbal medicine plus SRP is more effective than SRP alone to reduce PPD in adult with periodontitis.

Keywords: Herbal Medicine; Periodontitis; Randomized Controlled Trials; Systematic Review; GRADE

Abbreviations

BoP: Bleeding on Probing; CAL: Clinical Attachment Level; GI: Gingival Index; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MD: Mean Difference; PI: Plaque Index; PPD: Probing Pocket Depth; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO: International Prospective Register of Systematic Reviews; RCTs: Randomized Controlled Trials; SoC: Standard of Care; SRP: Scaling and Root Planning

Background

Periodontitis is an inflammatory disease caused by microorganisms that adhere to and grow on the tooth surfaces affecting 56.7% people worldwide [1]. This process culminates with the destruction of periodontal components such as root cementum, periodontal ligament and alveolar bone [2-4]. Severe periodontitis can cause halitosis, occasional pain and discomfort, impaired mastication, and eventually tooth loss [2].

Nonsurgical conventional periodontal treatment involves scaling and root planning (SRP) which is the initial step in periodontal treatment [5,6] and it is provided to be an effective approach for the treatment of infectious periodontal diseases [7]. However, due to the risk of re-colonization also adjunctive chlorhexidine treatment has been proposed [8], but some studies failed to prove the advantage of this association [9-11]. Furthermore, the use of topical chlorhexidine has some adverse effects such as tooth enamel staining, lingual papillae hyperplasia and loss of taste [12].

Antibiotics such as metronidazole and tetracyclines [13-15] may also be prescribed for patients who do not respond to SRP, those with acute periodontal infections associated with systemic manifestations, and as an adjunct to surgical and non-surgical periodontal therapy [16]. However, systemic antibiotic administration in adult periodontitis increase the development of antibiotic resistance and some adverse effects such as nausea, diarrhea, or other gastrointestinal problems [17].

Some herbs such as *Acacia chundra* Willd, *Adhatoda vasica* Nees, *Mimusops elengi* L., *Piper nigrum* L., *Pongamia pinnata* (L.) Pierre, *Quercus infectoria* Oliv, and *Garcinia mangostana* L. are known to have antiinflammatory, antimicrobial and antioxidative effects [18]. They might act as adjuvant or even prove to be an alternative therapy for periodontitis and other biofilm-related diseases [19]. In dentistry, 73% of the new antibacterials approved by the US Food and Drug Administration are herbal medications [20]. Herbs in oral health have received attention lately and plenty of studies have been conducted in this area [21-24].

A recent systematic review (Moro., *et al*. 2018) [25] assessed the effects of herbal medicine as an adjunct to SRP in periodontal disease compared to SRP alone or SRP with placebo. The authors only searched in two out of four main electronic databases (i.e., PubMed and LILACS) in the health field, and included seven randomized controlled trials (RCTs). They found a significant PPD reduction. Another review (Anandakumar &, Malaiappan, 2018) [26] comparing the effects of subgingival irrigation with natural products as an adjunct to scaling and root planning in chronic periodontitis considered only two databases (i.e., PubMed and CENTRAL), and the authors also restricted the years of publication (from 2006 to 2016). Four studies were included and although it was not possible to perform pooling of data; they concluded that there was a significant reduction in microbial count and in clinical parameters. One other review (Freires., *et al*. 2018) [27] summarized the effects of natural products in preventing bone loss when compared to doxycycline. Although the authors only included experimental and animal studies, they concluded that the combined gel of *Myracrodruon urundeuva* extract and *Lippia sidoides* essencial oil, as well as the extracts of *Ginkgo biloba* and propolis might present a strong alveolar bone protective effect.

Previous reviews were, however, limited in that they did not include all high-quality studies in this rapidly evolving field, they did not consider all electronic databases in the field as well as years of publication, and (Anandakumar, Malaiappan, 2018) [26] and (Freires., *et al*. 2018) [27] did not use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rating quality of evidence. We therefore conducted an updated systematic review of all RCTs that assessed the impact of herbal medications in adult periodontitis.

Methods

The Cochrane Handbook of Systematic Reviews of Interventions [28] guided our choice of methods. This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [29] and the PRISMA checklist [29] was also used when writing this report. This systematic review was registered in the PROSPERO (International Prospective Register of Systematic Reviews), and the protocol was published under the number CRD42019128926.

Eligibility criteria

The inclusion criteria were:

- Study design: RCTs and/or quasi-RCTs.
- Patients: adults with a clinical diagnosis of periodontitis, however defined by the authors of the included studies. We excluded patients with aggressive periodontitis.
- Interventions: any herbal medications (e.g., aloe vera (*Aloe vera* L.), rosemary *(Rosmarinus officinalis* L.), calendula (*Calendula officinalis* L.) from any of the following plant preparations (i.e., whole, powder, extract, crude drug, standardized mixture, drug extract ratio and solvent) as an adjunct to either SRP or antiseptic treatments (e.g., chlorhexidine). The following routes of administration were considered: oral (e.g., dropping pills) and topical. We excluded RCTs assess-

ing the combination of herbal medication with either an allopathic treatment or mouthwashes such as chlorhexidine and essential oils. We also excluded herbs that were used as toothpaste (i.e., toothpastes).

- Comparisons: we considered at least one of the following control groups:
    - Standard of care (SoC), i.e., SRP alone;
    - SRP in combination with an antiseptic treatment (e.g., chlorhexidine);
    - Systemic antibiotics in combination with SRP or alone;
    - Host response modulation with or without any active drugs;
    - Antimicrobial mouthwashes in combination with SRP or alone;
    - Placebo alone;
    - Placebo associated with SRP;
    - No intervention alone or in combination with SRP; or
    - Another type of alternative therapy (e.g., acupuncture, homeopathy) in combination with SRP or alone.

We also considered comparing different herbal medications as an adjunct to SRP such as green tea versus grape seed extract.

- The patient-important outcomes (primary outcomes) that we were interested in were:
    - Probing pocket depth (PPD) defined as the distance between the gingival margin and the bottom of the groove / pocket, measured with a millimeter probe (mm);
    - Clinical attachment level (CAL) the distance in millimeters (mm) between the enamel cementum junction at the bottom of the groove or pocket, i.e., the point at which resistance is;
    - Bleeding on probing (BoP) and;
    - Tooth loss.
    - Secondary outcomes were:
- Gingival index (GI) measures the gingival inflammatory state. Studies reporting groove bleed index (ISS), papilla bleed index (ISP) and bleed index (IS), we considered as GI. Studies reporting GI as well as ISS, ISO or IS, we extracted data for meta-analysis for GI only;
- Plaque index (PI) measures the presence or absence of bacterial biofilm in the gingival area of dental surfaces obtained by fuchsin solution;
- Adverse events due to periodontal therapy (tooth sensitivity, mouth discomfort);
- Quality of life (Short Form-36 and other validated instruments); and
- Bad breath (i.e., halitosis) measured by organoleptic and / or apparatus identifying volatile sulfur compounds (e.g., methylmercaptan, sulfide, dimethyl sulfide) such as, for example, halimiter and oral chroma.

Data source and searches

No restrictions were placed on language, year of publication or publication status. We searched Cochrane Central Register of Controlled Trials (CENTRAL), US National Library of Medicine (MEDLINE, from 1966 to 2019), Excerpta Medica Database (EMBASE, from 1980 to 2019), ISI Web of Science, and Latin American and Caribbean Health Sciences Literature (LILACS, from, 1982 to 2019). Search terms describing periodontal diseases and herbal medication interventions were combined (Appendix table 1). The last date was 26 March 2019.

Searching other resources

In addition to an electronic database search, we made a manual search in the reference lists of every study deemed eligible in order to identify additional trials that were later included; all potentially eligible studies were screened in duplicate. Furthermore, the coauthors and/or the pharmaceutical companies leading eligible trials were contacted for additional data and information that could be potentially included.

Selection of studies

Pairs of reviewers independently screened all titles and abstracts identified by the search through the Covidence online software. Full-text articles for potentially eligible studies were obtained and screened independently by reviewer pairs using the same eligibility criteria as with title and abstract screening. Consensus for stages of screening, data extraction, and risk of bias assessments were established by discussion and adjudication by a third reviewer, as necessary.

Data extraction and risk of bias assessment

Once a final set of eligible studies were identified, reviewer pairs independently extracted data for the following variables from each study using a pre-standardized data extraction form with: characteristics of the study design; participants; interventions; outcomes event rates (for afore mentioned primary and secondary outcomes) and duration of follow-up.

Reviewers independently assessed risk of bias by using a modified version of the Cochrane Collaboration's tool. The tool includes nine domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding of data collectors, blinding for outcome assessment, blinding of data analysts, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in the previously cited domains [30].

For missing participant outcome data in individual studies reporting dichotomous data, we categorized studies as high risk of bias for missing outcome data when there was more outcome data

missing than total number of events; for instance, 2,000 participants missing versus 1,500 total events [31]. For continuous outcomes, we considered studies at high risk of bias for missing outcome data if missing participant outcome data was 10% or more. Reviewers discussed with a third party adjudication to resolve disagreements.

Confidence in pooled estimates of effect

The reviewers used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the certainty of evidence for each outcome. Quality ratings were assigned as high, moderate, low, or very low [30]. Detailed GRADE guidance was used to assess overall risk of bias [32], imprecision [33], inconsistency [34], indirectness [35] and publication bias [36]. Consensus was established by discussion and adjudication by a third reviewer as necessary, and final results were summarized in an evidence profile.

Data synthesis and statistical analysis

Pooled risk ratios (RRs) were calculated for dichotomous outcomes and mean differences (MDs) for continuous variables with the associated confidential interval (CI) 95% CIs using random-effects models with the Mantel-Haenszel statistical method. We separately assessed the following continuous measures: mean, mean difference (i.e., the delta reported by the included studies), and percentage or distribution of mean. Absolute effects and 95% CI were calculated by multiplying pooled RRs and 95% CI by baseline risk estimates derived from the largest included RCT in the meta-analysis.

Data were extracted with patients as the unit of analysis. Studies reporting data only for sites, not patients, were not included in the meta-analysis. Variability was addressed in results across studies by using I^2 statistic and the p-value obtained from the Cochran Q ($\chi 2$) test. Our primary analyses were based on eligible patients who had reported outcomes for each study (complete case analysis). We therefore assessed the potential influence of patients presenting worse versus better prognosis in the baseline, accordingly for instance to PPD or CAL, through a sensitivity analyses as compared to a primary analysis.

Subgroup and sensitivity analysis

We performed subgroup analyses stratifying by type of control groups (e.g., chlorhexidine plus SRP versus SRP plus placebo) and type of herbs (e.g., chamomile extract versus pomegranate extract). We also planned to conduct subgroup analyses accordingly to route of administration (e.g., oral versus topical); however, we were not able to because there was an insufficient number of studies to allow for this assessment. For, sensitivity analysis we planned to synthesize the evidence separately for bodies of evidence from RCT and quasi-RCT studies by a sensitivity analysis; however, we were also not able to conduct it because there was an insufficient number of included studies.

Publication bias

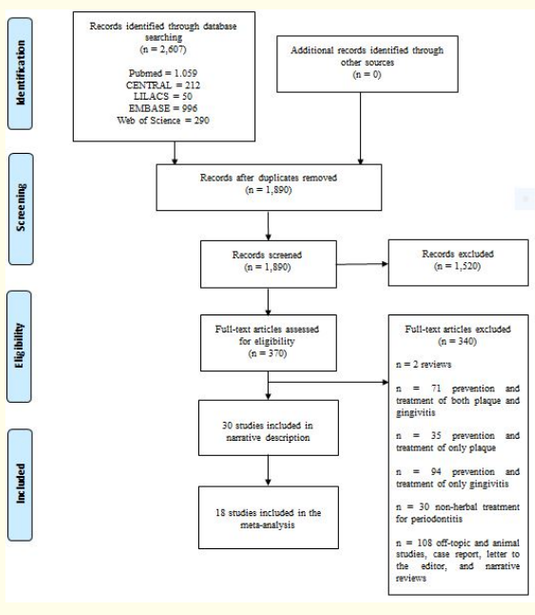
We also planned to perform separate analyses to assess publication bias through visual inspection of funnel plots for outcomes addressed in 10 or more studies; however, we were not able to because there were an insufficient number of studies to allow for this assessment.

We used Review Manager (RevMan) (version 5.3; Nordic Cochrane Centre, Cochrane) for all analyses [37].

Results

Search selection

Our initial searches identified 2,607 citations through database searches. Based on title and abstract screening, we obtained full-paper copies for 370 citations that were potentially eligible for inclusion in the review (Appendix figure 1). We excluded 340 studies for the following reasons reviews (n = 2), studies on prevention and treatment of both plaque and gingivitis (n = 71), prevention and treatment of only plaque (n = 35), prevention and treatment of only gingivitis (n = 94), non-herbal treatment for periodontitis (n = 30), and off-topic and animal studies, case report, letter to the editor, and narrative reviews (n = 108). The remaining 30 RCTs [38-67] involving 1,125 participants met the minimum requirements and were included in this review (Appendix figure 1).



Appendix Figure 1: Study selection.

We contacted the authors of the three included studies [45,49,53] to clarify some methodological and clinical issues, but none supplied us with the requested data.

Study characteristics

Table 1 describes study characteristics related to setting, study design, number of participants, mean age, gender, eligibility criteria, periodontitis definition and criteria used, and follow-up. Twen-

ty-four studies were conducted largely in Asia [38,43-56,58,59-65,67] four [40,42,57,66] in Europe, and two in South America [39,41]: Venezuela [39] and Brazil [41]. Randomized trials sample size ranged from five [56] to 120 [46] patients. Typical participants were splitted between men (57.8%) and women (42.2%) in their 30s, 40s, and 50s. Studies followed participants from two weeks [41] to eight months [42] Table 1.

Table 2 describes study characteristics related to intervention and control groups, population, routes of administration, plant preparations, and assessed outcomes. Twenty nine RCTs [38-56,58-67] evaluated herbal as adjuvant to SRP. Only one RCT [66] evaluated the effects of herbal alone without the standard of care. One RCT evaluated herbal plus chlorhexidine [57].

Related to the control group, 13 RCTs [39,40,42,43,46,47,49,53,55,56,64,66,67] compared the studied interventions with SRP plus placebo, and one trial [66] compared with placebo alone. Chlorhexidine alone was the comparison group in three trials [52,57,66] and in seven studies [38,41,52,53,58,60,66] the control group was the SRP in combination with chlorhexidine (Table 2).

Twelve trials [44,48,50-52,54,59-63,65] were used as control SRP alone and two further trials 45,51 were used as SRP plus allopathic treatment (Table 2).

Risk of bias assessment

Figure 1 and Appendix table 2 describe the risk of bias assessment. Allocation concealment was a significant limitation in 20 trials [38,39,41,43,44,46,48-53,56,58,59,62-66] and it was judged to be at high risk of bias. Blinding of participants was judged to be at high risk of bias in 21 trials [38,41-46,48,50-53,55,58-60,62-65,67] while blinding of outcome assessors were considered at high risk of bias in 19 trials [38,39,41,42,44,45,48,50,52,53,56,58-60,62-65,67] Incomplete outcome data was considered at high risk of bias in 12 trials [38,41,48,50,52,54,56,58,60,61,66,67] due to total loss to follow-up above 10%.

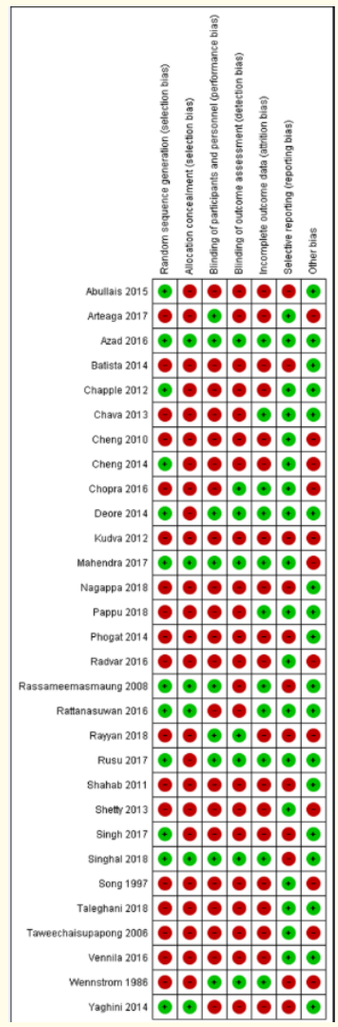


Figure 1: Risk of bias assessment

Outcomes

Probing pocket depth (PPD)

Results from two RCTs [38,58] with a total of 50 patients did not show a statistically significant difference between herbal as an adjunct to SRP versus SRP in combination with chlorhexidine in the reduction of PPD (MD -0.03, 95% CI -0.16 to 0.10, p = 0.65; I^2 = 0%, p = 0.61) (Figure 2, 2.1). The certainty of the evidence was downgraded to low due to risk of bias and indirectness (Table 3).

Also, results from five RCTs [40,47,55,56,64] with a total of 276 patients did not show a statistically significant difference comparing herbal plus SRP versus placebo associated with SRP for PPD (MD -0.11, 95% CI -0.24 to 0.02, p = 0.09; I^2 = 34%, p = 0.20) (Figure 2, 2.2). These data reflects the sensitivity analysis excluding Mahendra., *et al*. (2017) [49] study, because the patients in this study, at the baseline assessment, showed a poor prognosis for PPD confirmed by mean values of 6.65, differently from the initial values of the other included studies in the meta-analysis (average of 3.3[40] and 3.96[47]; 5.43[64] and 5.84) [55]. However, the findings of the primary analysis (MD -0.26, 95% CI -0.37 to -0.14, p < 0.0001; I^2 = 89%, p <0.00001) yielded the same results from the sensitivity analysis. The certainty of the evidence was downgraded to low due to applicability and indirectness (Appendix table 3).

Results from five RCTs [44,50,51,54,63] with a total of 166 patients showed a statistically significant difference in favor of herbal as an adjunct to SRP compared to SRP alone in the reduction of PPD (MD -0.46, 95% CI -0.67 to -0.26, p < 0.00001; I^2 = 38%, p = 0.17) (Figure 2, 2.3). The herbal medicines responsible for the magnitude of the effect found were:

- Cheng., *et al*. (2010) [44] study: honeysuckle (*Lonicera caprifolium*), forsythia (*Forsythia intermedia*), coptis (*Coptis chinensis*) and scutellar (*Scutellaria barbata*);
- Nagappa., *et al*. (2018) [50] study: Triphala [(*Terminalia chebula, Terminalia bellerica* and *Emblica officialis*)], (*Shuddha sphatika*), cinnamon (*Cinnamomum zeylanicum*), clove (*Syzygium aromaticum*), false black pepper (*Embelia ribes*), neem (*Azadirachta indica*) and apricot (*Mimusops elengi*);

- Pappu., *et al*. (2018) [51] study: flax seed (*Linum usitatissimum*);
- Rassameemasmaung., *et al*. (2008) [54] study: mangosteen (*Garcinia mangostana*) and;
- Taleghani., *et al*. (2018) [63] study: green tea (*Camellia sinensis*).

The certainty of the evidence was downgraded to low due to the risk of bias and indirectness (Table 4).

Results from one study [50] with a total of 20 patients showed a statistically significant difference in favor of gum powder when compared to SRP alone in the reduction of PPD (MD - 0.65, 95% CI -1.19 to -0.11, p = 0.02; I^2 = not applicable) (Figure 2, 2.4).

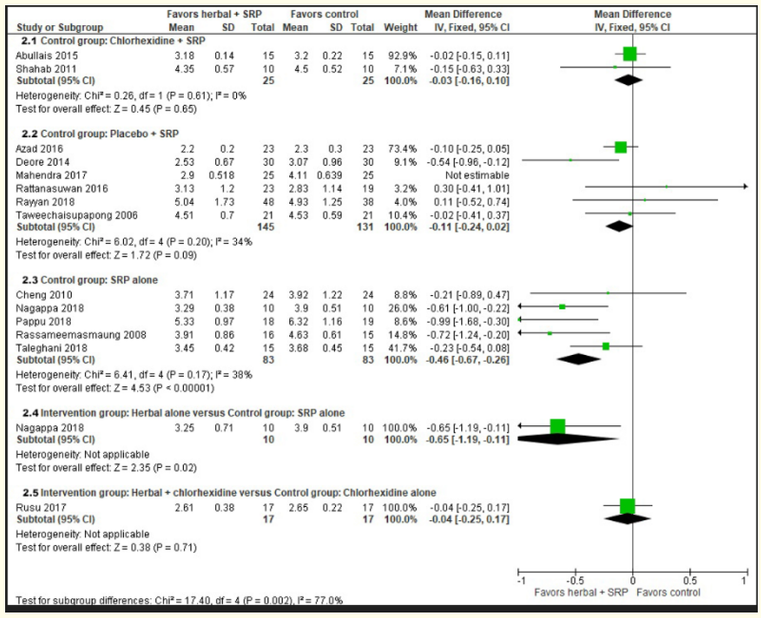


Figure 2: Meta-analysis on probing pocket depth (PPD).

Results from one study [57] with a total of 34 patients did not show a statistically significant difference between hydrophobic chlorhexidine based gingiva-adhering gel containing herbal ingredients rosemary (*Salvia lavandulifolia*), peppermint (*Mentha piperita*), thyme (*Thymus vulgaris*) and comfrey (*Symphytum officinale*) when compared to chlorhexidine alone in the reduction of PPD (MD -0.04, 95% CI -0.25 to 0.17, p = 0.71; I^2 = not applicable) (Figure 2, 2.5).

Clinical attachment level (CAL)

Results from two RCTs [44,62] with a total of 72 patients did not show a statistically significant difference between herbal as an adjunct to SRP and the SRP with chlorhexidine for the improvement of CAL (MD -0.12, 95% CI -0.78 to 0.54, p = 0.73; I^2 = 19%, p = 0.27) (Figure 3, 3.1). The herbal medicines used in Cheng., *et al*. (2010) [44] study were honeysuckle (*Lonicera caprifolium*), forsythia (*Forsythia intermedia*), coptis (*Coptis chinensis*), scutellaria (*Scutellaria barbata*). The herbal medicines used in Song., *et al*. (1997) [62] study were goji (*Lycium chinense*) and gu sui bu (*Drynaria fortunei*). The certainty of the evidence was downgraded to very low due to the risk of bias, applicability and indirectness (Table 3).

Results from four RCTs [40,47,55,67] with a total of 222 patients found no statistically significant difference between herbal medicines as an adjunct to SRP and placebo in association with SRP for the improvement of CAL (MD -0.15, 95% CI -0.37 to 0.08, p = 0.20; I^2 = 32%, p = 0.22) (Figure 3, 3.2). The herbal medicines used were:

- Azad., *et al*. (2016) [40] study: lemongrass (*Cymbopogon flexuosus*), thyme (*Thymus zygis*) and rosemary (*Rosmarinus officinalis*);
- Deore., *et al*. (2014) [47] study: septilin supplementation diet containing: Indian myrrh (*Balsamodendron mukul*), shell calcium (*Shankha bhasma*), gulancha tinospora (*Tinospora cordifolia*), Indian heron (*Rubia cordifolia*), blackcurrant (*Emblica officinalis*), spicy horseradish (*Moringa pterygosperma*) and licorice (*Glycyrrhiza glabra*);
- Rattanasuwan., *et al*. (2016) [55] study: green tea (*Camellia sinensis*) and;
- Yaghini., *et al*. (2014) [67] study: 20% ethanolic extract of oak bark (*Quercus brantii*) and 1% ethanolic extract of coriander (*Coriandrum sativus*).

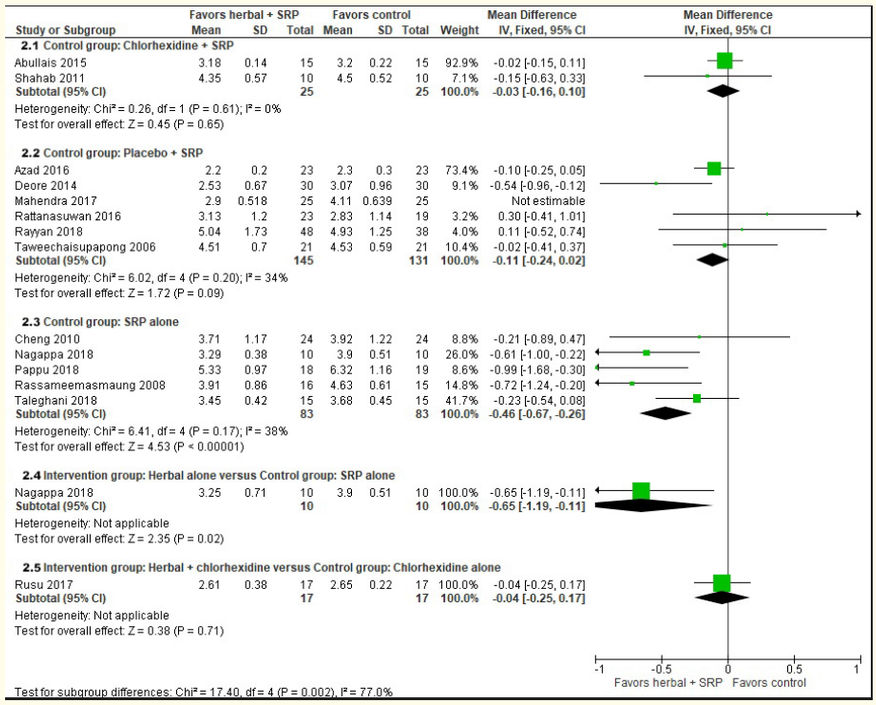


Figure 3: Meta-analysis on clinical attachment level (CAL).

The certainty of the evidence was downgraded to low due to applicability and indirectness (Appendix table 3).

Results from one study [51] with a total of 37 patients demonstrated a statistically significant difference in favor of SRP alone when compared to flax seed gel extract (*Linum usitatissimum*) as adjunct to SRP in the improvement of CAL (whole mouth analysis) (MD -0.99, 95% CI -1.68 to -0.30, p = 0.005; I^2 = not applicable) (Figure 3, 3.3). The certainty of the evidence was downgraded to low due to the risk of bias and indirectness (Table 4).

Results from one study [54] with a total of 31 patients did not show a statistically significant difference in favor of mangosteen gel (*Garcinia mangostana*) as an adjunct to SRP when compared to SRP alone in the improvement of CAL (periodontal pockets analysis) (MD 0.16, 95% CI -0.58 to 0.90, p = 0.67; I^2 = not applicable) (Figure 3, 3.4). The certainty of the evidence was downgraded to very low due to the risk of bias, applicability and indirectness (Table 4).

Results from one study [57] with a total of 34 patients also did not show a statistically significant difference between hydrophobic chlorhexidine based gingiva-adhering gel containing herbal ingredients rosemary (*Salvia lavandulifolia*), peppermint (*Mentha piperita*), thyme (*Thymus vulgaris*) and comfrey (*Symphytum officinale*) versus chlorhexidine alone for the improvement of CAL (MD -0.08, 95% CI -0.47 to 0.31, p = 0.69; I^2 = not applicable) (Figure 3, 3.5). Related to the overall meta-analysis, there was no statistically significant difference regarding the improvement of CAL (MD -0.17, 95% CI -0.36 to 0.03, p = 0.10; I^2 = 34%, p = 0.15) (Figure 3).

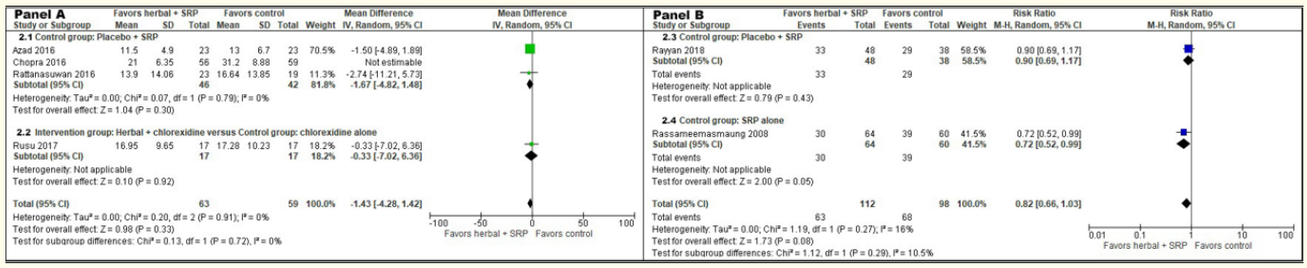
Bleeding on probing (BoP)

Results from two RCTs [40,55] with a total of 88 patients found no statistically significant difference between placebo in association with SRP compared to herbal as an adjunct to SRP for the percentage of BoP (MD -1.67, 95% CI -4.82 to 1.48, p = 0.30; I^2 = 0%, p = 0.79) (Appendix figure 2, panel A, 2.1). These data reflect the sensitivity analysis excluding Chopra., *et al.* (2016) [46] study, because it was the only study that administered herbal via oral while the other studies applied it topically as mouthwash [40] and subgingival [55]. However, the findings of the primary analysis (MD -5,13, 95% CI -11,88 to 1.63, p = 0.14; I^2 = 87%, p = 0.0004) corroborated with the findings of the sensitivity analysis. The herbal medicines used were:

- Azad., *et al.* (2015) [40] study: lemongrass (*Cymbopogon flexuosus*), thyme (*Thymus zygis*) and rosemary (*Rosmarinus officinalis*) and;
- Rattanasuwan., *et al.* (2016) [55] study: green tea (*Camellia sinensis*).

The certainty of the evidence was downgraded to low due to applicability and indirectness (Appendix table 3).

Results from one study [57] with a total of 34 patients did not show a statistically significant difference between hydrophobic chlorhexidine based gingiva-adhering gel containing herbal ingredients rosemary (*Salvia lavandulifolia*), peppermint (*Mentha piperita*), thyme (*Thymus vulgaris*) and comfrey (*Symphytum officinale*) and chlorhexidine alone in the percentage of BoP (MD -0,33, 95% CI -7.02 to 6.36, p = 0.92; I^2 = not applicable) (Appendix figure 2, panel A, 2.2). For the same outcome, in the overall meta-analysis



Appendix Figure 2: Meta-analysis on bleeding on probing.

there was also no statistically significant difference (MD -1.43, 95% CI -4.28 to 1.42, p = 0,33; I^2 = 0%, p = 0.91) (Appendix figure 2, panel A).

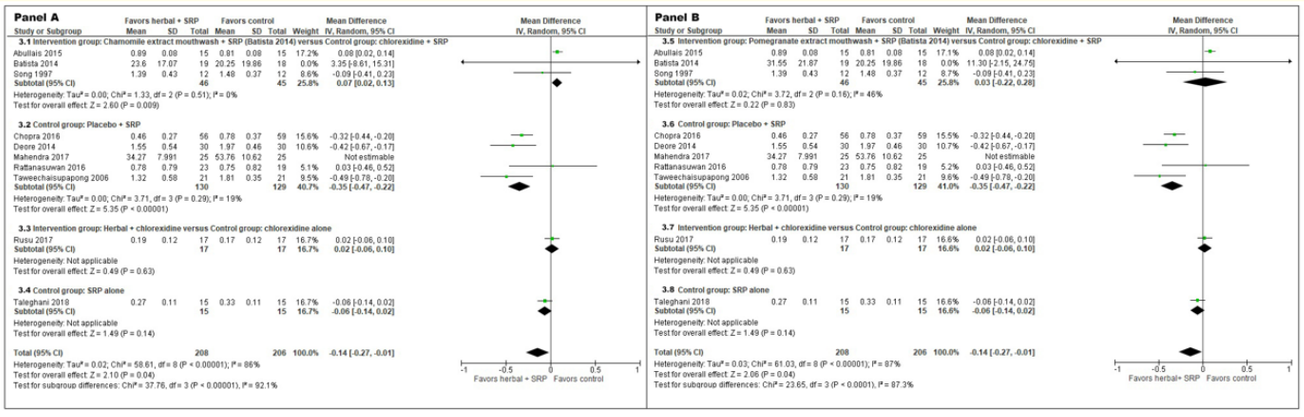
Results from one study [56] with a total of 86 patients did not show a statistically significant difference between grape vine *Vitis vinifera* as an adjunct to SRP and placebo in combination with SRP for BoP (Relative Risk (RR) 0.90, 95% CI 0.69 to 1.17, p = 0.43; I^2 = not applicable) (Appendix figure 2, panel B, 2.3). The certainty of the evidence has been downgraded to very low due to the risk of bias, applicability and indirectness (Appendix table 3).

Yet, results from one study [54] with a total of 124 patients found a statistically significant difference in favor of mangosteen (*Garcinia mangostana*) as an adjunct to SRP compared to SRP alone in the reduction of BoP (RR 0.72, 95% CI 0.52 to 0.99, p = 0.05; I^2 = not applicable) (Appendix figure 2, panel B, 2.4). The certainty of the evidence was downgraded to low due to the risk of bias and indirectness (Table 4).

In the overall meta-analysis, there was no statistically significant difference between grape vine *Vitis vinifera* and mangosteen (*Garcinia mangostana*) as an adjunct to SRP and placebo in combination of SRP and SRP alone for BoP (RR 0.82, 95% CI 0.66 to 1.03, p = 0.08; I^2 = 16%, p = 0.27) (Appendix figure 2, panel B).

Gingival index (GI)

Results from three RCTs [38,41,62] with a total of 91 patients showed a statistically significant difference in favor of SRP in combination with chlorhexidine when compared to chamomile extract as an adjunct to SRP in the improvement of GI (MD 0.07, 95% CI 0.02 to 0.13, p = 0.009; I^2 = 0%, p = 0.51) (Appendix figure 3, panel A, 3.1). The certainty of the evidence was downgraded to low due to the risk of bias and indirectness (Table 3).



Appendix Figure 3: Meta-analysis on gingival index.

However, results from four RCTs [46,47,55,64] with a total of 259 patients found a statistically significant difference favoring the use of herbal as adjunct to SRP compared to placebo in combination of SRP for the improvement of GI (MD -0.35, 95% CI -0.47 to -0.22, p <0.00001; I^2 = 19%, p = 0.29) (Appendix figure 3, panel A, 3.2). These data reflects the sensitivity analysis excluding Mahendra., *et al.* (2017) [49] study, because the patients in this study, at the baseline assessment, showed a poor prognosis for GI confirmed by reasonably high mean values: 91.03 and 92.15 for the intervention and control groups, respectively. The findings from the primary analysis (MD -0.50, 95% CI -1.03 to 0.03, p = 0.06; I^2 = 93%, p <0.00001) did not corroborate with the findings of the sensitivity analysis. The herbal responsible for the magnitude of the effect found were:

- Chopra., *et al.* (2016) [46] study: green tea (*Camellia sinensis*);

- Deore., *et al*. (2014) [47] study: septilin supplementation diet containing: Indian myrrh (*Balsamodendron mukul*), shell calcium (*Shankha bhasma*), gulancha tinospora (*Tinospora cordifolia*), Indian heron (*Rubia cordifolia*), blackcurrant (*Emblica officinalis*), spicy horseradish (*Moringa pterygosperma*), and licorice (*Glycyrrhiza glabra*);
- Rattanasuwan., *et al*. (2016) [55] study: green tea (*Camellia sinensis*) and;
- Taweechaisupapong., *et al*. (2006) [64] study: (*Streblus asper*).

The certainty of the evidence was downgraded to low due to the risk of bias and indirectness (Appendix table 3).

Results from one study [57] with a total of 34 patients did not show a statistically significant difference between hydrophobic chlorhexidine based gingiva-adhering gel containing herbal ingredients rosemary (*Salvia lavandulifolia*), peppermint (*Mentha piperita*), thyme (*Thymus vulgaris*) and comfrey (*Symphytum officinale*) and chlorhexidine alone for the improvement of GI (MD 0.02, 95% CI -0.06 to 0.10, p = 0.63; I^2 = not applicable) (Appendix figure 3, panel A, 3.3).

Results from one study [63] with a total of 30 patients found no statistically significant difference between green tea gel (*Camellia sinensis*) as an adjunct to SRP and SRP alone for the improvement of GI (MD -0.06, 95% CI -0.14 to 0.02, p = 0.14; I^2 = not applicable) (Appendix figure 3, panel A, 3.4). The certainty of the evidence has been downgraded to low due to the risk of bias and indirectness (Table 4).

In the overall meta-analysis, there was a statistically significant difference in favor of herbal as an adjunct to SRP when compared to placebo in combination of SRP, chlorhexidine in combination of SRP, chlorexidine alone and SRP alone for the improvement of GI (MD -0.14, 95% CI -0.27 a - 0.01, p = 0.04; I^2 = 86%, p <0.00001) (Appendix figure 3, panel A).

Results from three RCTs [38,41,62] with a total of 91 patients did not show a statistically significant difference between pomegranate extract as an adjunct to SRP and SRP in combination with chlorhexidine for the improvement of GI (DM 0.03, 95% CI -0.22 to 0.28, p = 0.83; I^2 = 46%, p = 0.16) (Appendix figure 3, panel B, 3.5). The certainty of the evidence was downgraded to low due to the risk of bias and indirectness (Table 3).

Results from four RCTs [46,47,55,64] with a total of 259 patients found a statistically significant difference in favor of herbal as adjunct to SRP compared to placebo with SRP in the improvement of GI (MD -0.35, 95% CI -0.47 to -0.22, p <0.00001; I^2 = 19%, p = 0.29) (Appendix figure 3, panel B, 3.6). These data reflect the sensitivity analysis excluding Mahendra., *et al*. (2017) [49] study, because the patients in this study, at the baseline assessment, showed a poor prognosis for GI confirmed by high mean values of 91.03 and 92.15 for the intervention and control groups, respectively. The findings from the primary analysis (MD -0.50, 95% CI -1.03 to 0.03, p = 0.06; I^2 = 93%, p <0.00001) did not corroborate the findings of the sensitivity analysis (however there was a tendency). The herbal responsible for the magnitude of the effect found were:

- Chopra., *et al*. (2016) [46] study: green tea (*Camellia sinensis*);
- Deore., *et al*. (2014) [47] study: septilin supplementation diet containing: Indian myrrh (*Balsamodendron mukul*), shell calcium (*Shankha bhasma*), gulancha tinospora (*Tinospora cordifolia*), Indian heron (*Rubia cordifolia*), blackcurrant (*Emblica officinalis*), spicy horseradish (*Moringa pterygosperma*) and licorice (*Glycyrrhiza glabra*);
- Rattanasuwan., *et al*. (2016) [55] study: green tea (*Camellia sinensis*) and;
- Taweechaisupapong., *et al*. (2006) [64] study: (*Streblus asper*).
- The certainty of the evidence was downgraded to low due to the risk of bias and indirectness (Appendix table 3).

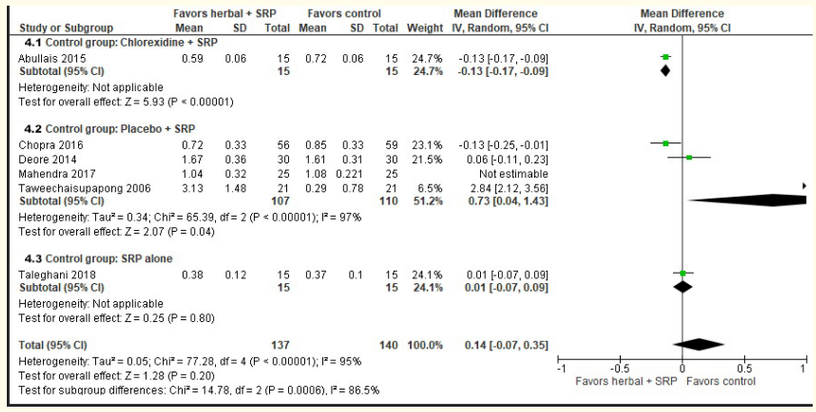
Results from one study [57] with a total of 34 patients did not show a statistically significant difference between hydrophobic chlorhexidine based gingiva-adhering gel containing herbal ingredients rosemary (*Salvia lavandulifolia*), peppermint (*Mentha piperita*), thyme (*Thymus vulgaris*) and comfrey (*Symphytum officinale*) and chlorhexidine alone for the improvement of GI (MD 0.02, 95% CI -0.06 to 0.10, p = 0.63; I^2 = not applicable) (Appendix figure 3, panel B, 3.7).

Results from one study [63] with a total of 30 patients found no statistically significant difference between the green tea gel (*Camellia sinensis*) as an adjunct to SRP and standard treatment (SRP alone) in the improvement of GI (MD -0.06, 95% CI -0.14 to 0.02, p = 0.14; I^2 = not applicable) (Appendix figure 3, panel B, 3.8). The certainty of the evidence has been downgraded to low due to the risk of bias and indirectness (Table 4).

In the overall meta-analysis, there was a statistically significant difference in favor of herbal as an adjunct to SRP for the improvement of GI (MD -0.14, 95% CI -0.27 a -0.01, p = 0.04; I^2 = 87%, p <0.00001) (Appendix figure 3, panel B).

Plaque index (PI)

Results from one study [38] with a total of 30 patients found a statistically significant difference in favor of pomegranate fruit rind *(Punica granatum)*, black pepper (*Piper nigrum)* and detoxified copper sulfate as an adjunct to SRP compared to SRP with chlorhexidine for the improvement of PI (MD -0.13, 95% CI -0.17 to -0.09, p <0.00001; I^2 = not applicable) (Appendix figure 4, 4.1). The certainty of the evidence was downgraded to low due to the risk of bias and indirectness (Table 3).



Appendix Figure 4: Meta-analysis on plaque index.

Results from three RCT s [46,47,64] with a total of 217 patients found a statistically significant difference in favor of the placebo associated with SRP compared to placebo with SRP for the improvement of PI (MD 0.73, 95% CI 0.04 to 1.43, p = 0.04; I^2 = 97%, p < 0.00001) (Appendix figure 4, 4.2). These data reflect the sensitivity analysis excluding Mahendra., *et al*. (2017) [49] study, because the patients in this study, at baseline assessment, showed a poor prognosis for PI confirmed by mean values of 1.99 and 2.00 for the intervention and control groups, respectively. The findings from the primary analysis (MD 0.43, 95% CI -0.01 to 0.86, p = 0.05; I^2 = 95%, p <0.00001) did not yield same results from the sensitivity analysis. The herbal medicines responsible for the magnitude of the effect found were:

- Chopra., *et al*. (2016) [46] study: green tea (*Camellia sinensis*);
- Deore., *et al*. (2014) [47] study: septilin supplementation diet containing: Indian myrrh (*Balsamodendron mukul*), shell calcium (*Shankha bhasma*), gulancha tinospora (*Tinospora cordifolia*), Indian heron (*Rubia cordifolia*), blackcurrant (*Emblica officinalis*), spicy horseradish (*Moringa pterygosperma*) and licorice (*Glycyrrhiza glabra*) and;
- Taweechaisupapong., *et al*. (2006) [64] study: (*Streblus asper*).

The certainty of the evidence was downgraded to very low due to the risk of bias, inconsistency, applicability and indirectness (Appendix table 3).

Results from one study [63] with a total of 30 patients did not find a statistically significant difference between green tea gel (*Camellia sinensis*) as an adjunct to SRP and SRP alone for the improvement of PI (MD 0.01, 95% CI -0.07 to 0.09, p = 0.80; I^2 = not applicable) (Appendix figure 4, 4.3). The certainty of the evidence was downgraded to low due to the risk of bias and indirectness (Table 4). For the same outcome, in the overall meta-analysis, there was no statistically significant difference (MD 0.14, 95% CI -0.07 to 0.35, p = 0.20; I^2 = 95%, p <0.00001) (Appendix figure 4).

Discussion

Main findings

The results of this review showed that the use of herbal as an adjunct therapy for SRP is superior than SRP alone in the reduction of PPD. Among the studies analyzed, five [44,50,51,54,63] compared herbal as an adjunct to SRP, which three [50,51,54] of them showed a significant difference in the reduction of PPD. Although there is no gold standard in the literature for choosing the primary outcome to evaluate the efficacy of treatments for periodontitis [68] PPD is often used as the main clinical outcome in controlled trials due to its relationship to both inflammation and the presence of periodontal pockets.

Furthermore, a statistically significant difference was found in favor of the use of herbal as an adjunct to SRP in the reduction of BoP also compared to the standard treatment (SRP alone), specifically using mangosteen (*Garcinia mangostana*) that is rich in xanthones [69].

Thus, we can notice a tendency towards the use of herbal medicines as adjunct to SRP and their benefits to patients with periodontitis. However, the clinical variability regarding the different types of herbal used and the different degrees of periodontitis not reported by the included studies as well as the high risk of bias presented in the clinical trials make the classification of evidence from low to very low certainty.

Due to the reducing effect of chlorhexidine digluconate biofilm accumulation on acquired enamel film, SRP with chlorhexidine was used as a positive control in two studies [38,55] analyzed. Even herbal medicines as adjunct to SRP were not inferior than SRP with chlorhexidine for PPD, CAL, and GI, suggesting therefore a possible alternative to chlorhexidine treatment.

Although our goal was to verify the effectiveness of herbal as an adjunct to SRP when compared to any control groups in the non-surgical treatment of periodontitis, according to the findings

of this review, the efficacy of the standard treatment is somewhat questionable, because although SRP alone was more effective in the improvement of CAL when compared to the herbal as an adjunct to SRP, we may perhaps attribute this effect due to the lack of effectiveness of the specific herbal used – in this case, the flaxseed gel extract.

Regarding the CAL outcome, no additional benefits were observed in the use of herbal as an adjunct to SRP compared to other control groups. CAL is an important periodontal parameter because of its relationship to long-term tooth maintenance. Therapies that promote greater insertion gain such as the adjunctive use of antibiotics [70,71] and immunomodulators [72,73] represent major benefits in the treatment of periodontitis, because its ultimate goal is the maintenance of the dental element.

Regarding BoP, the use of herbal as an adjunct to SRP was possibly similar to placebo associated with SRP; however we cannot rule out the possibility of bias in this result due to the lack of statistical power (type II error) nor the type of herbal that was used. Furthermore, BoP was also evaluated in a study that compared the use of herbal as an adjunct to chlorhexidine versus chlorhexidine alone without mechanical interventions, and no statistically significant difference was observed between both groups.

Strengths and limitations

Strengths of our review include a comprehensive search; assessment of eligibility, risk of bias and data abstraction independently and in duplicate; assessment of a sensitivity analysis, and use of the GRADE approach in rating the certainty of evidence for each outcome. Furthermore, based on the protocol registered in this review (PROSPERO - CRD42019128926), a priori established subgroup analyzes were performed [74].

Although we included a reasonable number of studies (n = 30) in which 25 of them reporting data on PPD, 21 on CAL, 19 on BoP, 20 on GI, and 25 on PI, the primary limitation of our review was the very low- to low-certainty evidence. Though we used a random-effects model, we found a high level of heterogeneity $I^2 > 89\%$ in the PPD, PI and GI outcomes, and therefore we performed sensitivity analysis excluding studies with extremely poor prognostic values, which demonstrated the vulnerability of borderline values in two of the five sensitivity analysis.

Furthermore, there were not enough studies to perform sensitivity analyzes with respect to randomized versus quasi-randomized clinical trials. Besides that, no included studies reported on tooth and bone losses as well as adverse effects and quality of life, so there is no information available on the safety profile of the herbal medicines.

Relation to prior work

Only two systematic reviews Freires., *et al*. (2018) [27] and Moro., *et al*. (2018) [25] have been published, Freires., *et al*. (2018) [27] involving 15 rat studies and the other Moro., *et al*. (2018)25] seven clinical trials with a total of 164 patients with periodontitis, respectively. Freires., *et al*. (2018) [27] published a review presenting as primary outcome the reduction of bone loss assessed by radiography, photography, and other methods in animal models. The review was restricted to only articles written in English, Spanish or Portuguese. The systematic review by Moro., *et al*. (2018) [25] considered primary outcomes PPD and CAL – likewise our review, and as secondary outcomes BoP, GI, PI, and occurrence of adverse effects.

Regarding the exclusion criteria, Freires., *et al*. (2018) [27] review did not provide any information about it. However, Moro., *et al*. (2018) [25] review excluded clinical trials that included patients with systemic disease (e.g., diabetes), studies using systemic herbal medicine, and daily supplementation with herbal medicines or other natural products not extracted from plants (e.g., propolis).

Regarding the results obtained, the mentioned reviews suggested a trend in favor of the use of herbal medicines. The combined gel of *Myracrodruon urundeuva* extract and *Lippia sidoides* essential oil as well as *Ginkgo biloba* extracts and propolis showed strong efficacy in modulating bone loss in rat induced periodontitis, and the authors suggested that additional translational research should bridge the gap between study results in rats and the clinical efficacy and long-term toxicity of these formulations in humans (Freires., *et al*. 2018) [27].

However, Moro., *et al*. (2018) [25] review found a statistically significant reduction in PPD from six clinical trials with a total of 206 patients in favor of herbal medicine as adjunct to SRP when compared to SRP (MD 0.65 mm, 95% CI 0.47 to 0.83, $p < 0.00001$; $I^2 = 41\%$, $p = 0.13$). Furthermore, this systematic review Moro., *et al*. (2018) [25] observed a statistically significant in outcomes from five RCTs with a total of 176 patients demonstrating that there is a statistically significant difference in favor of herbal medicine as adjunct to SRP in the improvement of CAL when compared to SRP (MD 0.79 mm, 95% CI 0.19 to 1.38, $p = 0.01$; $I^2 = 92\%$, $p < 0.00001$). However, the authors conclude that the results should be interpreted with caution due to the small sample size, high risk of bias, and heterogeneity of the included studies.

Implications for clinical practice and for research

Although we found improvement in some clinical outcomes with the use of herbal as adjunct to SRP in patients with periodontitis, there is a huge range of effect magnitudes found in this review. This justifies the need for further RCTs with adequate sample size to rule out any residual biases related to type II error and to confirm the statistically significant findings here in this review. In addition, studies should report the degrees of periodontitis to facilitate the development of specific recommendations for different patient scenarios, considering the range of treatments available to dentists. Furthermore, evaluating the safety profile of herbal and chlorhexi-

dine, both as adjunct to SRP, and their long-term effects, as well as improving the internal validity of these studies, is essential.

Conclusions

Some possibly clinically meaningful differences between herbal medicine as adjunct to SRP and other comparisons exist, but no definitive conclusions can be drawn from these findings. Low-certainty evidence indicates that combination therapy with herbal medicine plus SRP is more effective than SRP alone to reduce PPD in adult with periodontitis; however we found no statistically significant difference between herbal as adjunct to SRP and SRP in combination with chlorhexidine for the same outcome. In addition, SRP alone seems better compared to herbal plus SRP in CAL, but there was no difference between herbal plus SRP versus SRP plus chlorhexidine for the same outcome. No evidence was found for the following outcomes: tooth loss, adverse events due to periodontal therapy, quality of life, and bad breath. Even if some differences were identified, the findings from this review are better if these conclusions could be reassured in future trials.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

RED, JE and MGOA conceived and designed the original idea/out-line. JE, MGOA, JDA, NCS, HG, EAS, CBS, CPK, EGF, BVS, JVSR, LEL and RED conducted the literature search. JE, MGOA, JDA, NCS, HG, EAS, CBS, CPK, EGF, BVS, JVSR, LEL and RED extracted the Titles and Abstracts of the relevant papers. JE, MGOA, JDA, NCS, HG, EAS, CBS, CPK, EGF, BVS, JVSR, LEL and RED evaluated the full text. MGOA, JDA, NCSM and RED performed quality assessment of the eligible papers. JE, MGOA, JDA, NCS, HG, EAS, CBS, CPK, EGF, BVS, JVSR, LEL and RED extracted the data from original reports. RED, MGOA and JE performed the meta-analysis. JE and RED wrote the first draft of the manuscript. JE and RED wrote, review and editing manuscript. JE, MGOA, JDA, NCS, HG, EAS, CBS, CPK, EGF, BVS, JVSR, LEL, CT, ECJ, MANJ, MS and RED review and editing manuscript. All authors read and approved the final manuscript.

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