Adjunctive therapies for the nonsurgical treatment of peri-implant diseases: systemic review and meta-analysis

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Abstract
Background Peri-implant diseases are caused by biofilms around the implant and may lead to implant failure. Non-surgical mechanical debridement (MD) with different adjunctive therapies has been applied in the treatment of peri-implant diseases. This systematic review aimed to deduce the optimal adjunctive therapy.

Methods Two independent authors screened the literature using MEDLINE and Cochrane Library. Only clinical randomized controlled trials (RCTs) about adjunctive therapies for non-surgical treatment of peri-implant diseases were included in this review. Studies selected were published before February 2020. The clinical outcomes were compared in this meta-analysis.

Results: A total of 31 RCTs met the inclusion criteria. The following adjunctive interventions were compared in the included studies: modification of the prosthesis; air abrasive; Er:YAG laser; diode laser; photodynamic therapy; local antibiotics; system antibiotics; probiotics; and enamel matrix derivative. Follow-up ranged from 3 months to 1 year. A statistically significant difference was observed between MD with photodynamic therapy and MD alone at 3 months follow-up (P < 0.01). However, such a difference was not detected between MD with chlorhexidine and MD alone at 3 months follow-up (P = 0.61), between MD with probiotics and MD alone (P = 0.47), and between systemic antibiotics and MD alone (P = 0.96).

Conclusion Currently, the optimal non-surgical intervention is not known. Also, among the interventions with similar efficiency, that with fewer side effects, easy to use, and cost-effective is yet to be identified. Thus, well-designed RCTs with prolonged follow-ups to assess the accurate effectiveness of therapies are imperative.

Background
Peri-implant diseases include peri-implant mucositis and peri-implantitis. Peri-implant diseases are inflammatory responses to tissues adjacent to the implant. The inflammatory response of peri-implant mucositis occurs in the mucosa adjacent to the implant without loss of bone. The inflammatory response of peri-implantitis occurs in the mucosal tissue and bone tissue adjacent to the implant, with the loss of marginal supporting bone. [1, 2]. The incidence of peri-implant diseases is high. According
to a previous review, peri-implant mucositis occurred in approximately 80% of the patients, and the
disease in 28–66% of the patients translated into peri-implantitis [3].
Peri-implant diseases are resulted from oral biofilms around the implant in susceptible individuals,
affecting the inflammation of tissues adjacent to the implant [4]. The decontamination of the implant
surface and elimination of the oral biofilms and endotoxins are the big challenges in the treatment of
peri-implant diseases [5]. Mechanical debridement (MD) is recognized as indispensable, basal
procedure in the non-surgical treatment. It improves the outcomes, such as clinical attachment level
(CAL) gain and pocket probing depth (PPD) reduction [6]. However, some clinical studies showed
recurrence of the peri-implant diseases in a significant percentage of patients several weeks after MD
[7, 8]. The complete resolution of the diseases after MD is still not a frequent event.
To assist MD in treating peri-implant diseases, researchers have applied various adjunctive therapies
to enhance the clinical outcomes. These adjunctive therapies include: 1) air abrasive; 2) Er:YAG laser;
3) diode laser; 4) photodynamic therapy; 4) local drug delivery (for example, chlorhexidine gel,
chloramine, or probiotic); 5) systemic antibiotics; 6) matrix chips; 7) modification of the prosthesis; 8)
combination of some of the above therapies. Previous studies compared these adjunctive therapies
and obtained different results [9–39]. Thus, a consensus regarding the optimal protocol for non-
surgical treatment of peri-implant diseases is yet lacking. A systematic comparison of different
adjunctive therapies for the peri-implant diseases has not yet been undertaken. Therefore, the
present systematic review aimed to deduce whether one adjunctive therapy of non-surgical
decontamination was superior to any other method.
This systematic review was designed and conducted in accordance with the guidelines from the
Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015
statement [40].
Methods
Inclusion criteria
Only clinical randomized controlled trials (RCTs) that reported adjunctive therapies for the non-
surgical treatment of peri-implant diseases published before February 2020 were considered eligible
for inclusion in this review. No language restrictions were applied.

**Exclusion criteria**

Studies requiring an additional surgical technique, such as flap surgery, guided bone regeneration, or any grafting procedure were excluded. Letters to the editor, reviews, cross-sectional studies, case reports, animal studies, *in vivo* studies and *ex vivo* studies were also excluded.

**Screening process**

Searches were performed without language restrictions in MEDLINE (PubMed) and the Cochrane Library databases until February 1, 2020. For the PubMed library, the key terms used were as follows: ((((oral implant [MeSH Terms]) OR dental implant [MeSH Terms]) AND treatment) OR therapy) AND peri-implantitis). The key terms used for Cochrane Library were as follows: *(Title, Abstract, Keywords):* dental implant AND therapy OR treatment AND peri-implantitis. The electronic search was complemented by manual searches of the reference lists of the selected publications, including *Journal of Clinical Periodontology, Journal of Dental Research, International Journal of Periodontics and Restorative Dentistry,* and the *Journal of Periodontology,* from January 2019 to February 2020.

Two independent reviewers (YX & YQ) screened all the titles/abstracts, and the full texts of the eligible articles were retrieved by the search strategy. Subsequently, the articles that fulfilled the eligibility criteria were included in the present study. The reviewers searched the reference lists of the included articles for additional relevant publications. Any discrepancies between the two reviewers were resolved by discussion with a third reviewer (HY).

**Quality assessment**

The quality of the included studies (RCTs) was assessed according to the Recommendations for Systematic Reviews of Interventions of the Cochrane Collaboration [41]: random sequence generation and allocation concealment (both accounting for selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), or other possible causes of bias.

**Data extraction and statistical analysis**

Two independent reviewers (YX & YQ) extracted the data. The disagreements between the two
reviewers were resolved by discussion with a third reviewer (HY). A standardized data extraction form was used to collect the following parameters: 1) author, year; 2) number of patients; 3) number of implants; 4) mean age of the patients; 5) years of implant in function; 6) gender distribution; 7) smoking history; 8) history of periodontitis; 9) length of follow-up; 10) whether following the CONSORT [42]; 11) adjunctive treatments; 10) clinical outcomes, including method of assessment and time intervals.

Meta-analysis was performed using the Review Manager software (Review Manager version 5.3; The Cochrane Collaboration, Copenhagen, Denmark). The statistical heterogeneity among the RCTs selected for meta-analysis was assessed utilizing the DerSimonian–Laird estimate $\tau^2$ for interstudy variance. Because each clinical outcome was evaluated similarly, preferring smaller values, the meta-analysis could be performed together to investigate a standardized mean difference between the clinical outcomes in the groups of adjunctive therapies and MD. Data for each group were summarized using the standardized mean difference and the standard deviation with a 95% confidence interval (CI).

Results

The initial search retrieved 1621 publications from PubMed and 1460 in the Cochrane Library. Four more publications were identified by manual search. After removing the duplicate studies, 1684 publications of potential interest were left to screen. After excluding the articles based on the titles and abstracts, 35 studies were left for full-text assessment. Following a discussion after full-text analysis, 31 studies were included for systematic review and qualitative synthesis. The process of identification of the included studies from the initial yield is described in Fig. 1. The number of patients, mean age, gender distribution, implant data, and adjunctive treatments are listed in Table 1.

Quality assessment

14/31 RCTs were designed according to CONSORT. The results of the quality assessment of RCTs are listed in Table 2, following the recommendations [41]. The difference between the assessment results was low, and the consensus was reached by discussion.
Meta-analysis

Meta-analysis was carried out, including data reporting the mean values of PPD, bleeding of probing (BOP), CAL, and plaque index (PI), comparing the outcomes of MD combined with photodynamic therapy, chlorhexidine, systemic antibiotics, or probiotics with MD alone. The follow-up time for each study was not identical, and so, only the most comprehensive results reported at 3 months were included. For meta-analysis, only the summary measures of each included study were used, because individual dataset could not be extracted from the studies. Subgroup analyses of these studies concerning different clinical outcomes were performed.

Due to different measurement methods, the standardized mean difference was investigated to compare the clinical outcomes in the groups of adjunctive therapies and MD. The standardized mean difference of clinical outcomes (BOP, CAL, PPD) of 0.60 (CI$_{95\%}$ -1.20–2.40) between the MD group with photodynamic treatment and MD group alone differed significantly from 0 ($P < 0.01$) (Fig. 2).

Interestingly, the standardized mean difference of clinical outcomes (BOP, PPD) of -0.01 (CI$_{95\%}$ -0.24–0.22) between the MD group with chlorhexidine treatment and the MD group alone did not show any significant difference from 0 ($P = 0.61$) (Fig. 3). In addition, the standardized mean difference of clinical outcomes (BOP, PI, PPD) of -0.26 (CI$_{95\%}$ -0.54–0.03) between the MD group with probiotics treatment and the MD group alone did not differ significantly from 0 ($P = 0.96$) (Fig. 4). Also, the standardized mean difference of clinical outcomes (BOP, PPD) of -0.02 (CI$_{95\%}$ -0.32–0.29) between the MD group with systemic antibiotics treatment and the MD group alone showed no significant difference from 0 ($P = 0.47$) (Fig. 5).

Discussion

Photodynamic therapy involves interactions between a light source and a photosensitizer in an aerobic environment. This results in the generation of free oxygen radicals that damage target cells such as bacterial cells [43]. Photodynamic therapy has also been reported to kill pathogenic microbes associated with the etiology of periodontal and peri-implant disease caused *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*), *Prevotella intermedia*, and *Porphyromonas gingivalis* (*P. gingivalis*) [44]. MD with adjunct photodynamic therapy is more effective in reducing
peri-implant PPD than MD alone at 3 months following treatment (Fig. 2). However, the long-term outcomes of MD either with or without photodynamic therapy are comparable [18].

The adjunct use of diode laser did not yield any additional positive influence on the peri-implant healing as compared to MD alone at 3 months or 6 months following treatment [14, 45]. Two included RCTs described the effect of Er:YAG laser (ERL) as an adjunct in the treatment of peri-implant diseases. Studies have indicated that non-surgical periodontal treatment with an ERL significantly improves the clinical outcomes, based on PPD reduction and gain of CAL [46, 47]. The sites treated with ERL demonstrated an alteration in the mean CAL value from 5.8 ± 1 mm at baseline to 5.1 ± 1.1 mm after 6 months. Frank et al. [12] found that ERL reduces BOP significantly at 6 months after the treatment. Thus, further studies are needed to compare the effectiveness of ERL modality to that of other adjunctive therapies.

A total of two included RCTs evaluated the effect of air abrasive as an adjunct in the treatment of peri-implant diseases [10, 11]. Both found that adjunctive air abrasive treatment seemed to have a limited beneficial effect as compared to MD alone. Air abrasive devices have been shown to be a feasible treatment option in periodontal care because of the potential to effectively erase biofilms [48]. Nonetheless, professional MD can also effectively remove the biofilms from the instrument-accessible sites; thus, the adjunctive effect of air abrasive may be limited.

Chlorhexidine is a commonly used topical drug. As shown in Fig. 3, compared to MD alone, MD with chlorhexidine has a limited beneficial effect at 3 months post-treatment. An included article reported the adjunctive effect of chloramine and found that it could not improve the clinical outcomes of peri-implant diseases [31]. The effects of probiotic *Lactobacillus reuteri* in combination with MD were evaluated in implants with peri-implantitis, and no clinical differences between probiotic and placebo treatments were observed over time [35, 36] (Fig. 4). Conversely, minocycline microspheres as an adjunct to MD treatment of incipient peri-implantitis lesions demonstrated improvements in PPD and BI and the improvements were sustained over 6 months [28, 29]. The state, concentrations, and the method of delivery of topical drugs may affect the effectiveness of the drugs. Dental water jet rinse mixed with chlorhexidine gel might supplement the response to non-surgical treatment for peri-
implantitis lesions by reducing the PPD [32]. Some studies demonstrated that repeated application of chlorhexidine chips might resolve the marginal peri-implant inflammation in terms of BOP better than that by chlorhexidine gel, and the PPD was also reduced 0.65 ± 0.40 mm [30, 38]. The efficacy of a single dose is limited, but the repeated application of local drugs can prolong the effectiveness. However, the frequent use of antibiotics causes bacterial resistance in the subgingival biofilm [49]. Currently, there is no consensus on the method of delivery of topical drugs for the treatment of peri-implant diseases, thereby necessitating additional studies.

The standardized mean difference of clinical outcomes (BOP, PPD) between the MD with systemic antibiotics treatment and MD alone was not significantly different from 0 (P = 0.47) (Fig. 5). Hitherto, no evidence is available promoting the use of systemic antibiotics in the treatment of peri-implantitis [33, 34].

Tapia et al. [9] found that modifying the contour of the prostheses after MD significantly improved the clinical outcomes of peri-implant mucositis. This conclusion was correlated to the inclusion criteria of the study, which required the included patients to have at least one implant-supported restoration with an inappropriate prosthesis design or contour that made oral hygiene and access to the implant in the neck difficult. The implant-supported prosthesis design is critical to promote accessibility to oral hygiene around the implants [50], suggesting a method for the treatment of peri-implantitis.

Enamel matrix derivatives have been employed successfully in the management of periodontal diseases, especially bone loss associated with periodontitis [51]. Kashefimehr et al. [39] studied the effects of enamel matrix derivative on the non-surgical management of peri-implant mucositis and found that MD in conjunction with enamel matrix derivative, air abrasive, and 0.12% chlorhexidine mouthwash significantly improved BOP and PPD at 3 months after the treatment. In the group with enamel matrix derivative, PPD reduced from 5.40 ± 1.79 mm to 4.66 ± 1.95 mm. However, additional studies are required to prove the efficacy of enamel matrix derivative in long-terms.

After comparing different adjunctive therapies, we found that the use of ERL or repeated minocycline microspheres as an adjunct to MD treatment for peri-implantitis is better than chlorhexidine gel [12, 28]. The adjunct use of photodynamic therapy was as effective as one unit-dosage of minocycline
microspheres or diode laser after 6 months of follow-up [15, 21, 22]. The efficacy of probiotics as an adjunct to the MD treatment was better than that of systemic antibiotics in reducing PPD and mBI (modified bleeding index). Nonetheless, further studies are needed to compare the effectiveness of different adjunctive therapies.

Conclusion
In summary, the current study compared several therapies as adjuncts to the non-surgical MD treatment of peri-implantitis lesions. The results showed that ERL, repeated minocycline microspheres, photodynamic therapy, and modification of prosthesis had significant effects in the short-term (3 months), while air abrasive, chlorhexidine gel, probiotics, and system antibiotics had limited effects. Conversely, ERL and photodynamic therapy did not show any significant long-term effectiveness. These results should be interpreted with caution because only a limited number of studies are included. At present, we do not know which non-surgical intervention is superior, and for the interventions with similar effectiveness, we do not know the one with fewer side effects, ease of use, and cost-efficiency. Thus, it is necessary to conduct well-designed RCTs with longer follow-ups to assess the accuracy and effectiveness of the therapies.

List Of Abbreviations
RCTs: Randomized controlled trials
MD: Mechanical debridement
CAL: Clinical attachment level
PPD: Pocket probing depth
BOP: Bleeding of probing
PI: Plaque index
ERL: Er:YAG laser

Declarations

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable
Availability of data and materials

All data generated during this system review are included in this article. The data supporting our findings can be found in articles included in this systemic review.

Competing interests

The authors declare that they have no competing interests

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Authors’ contributions

YX had made substantial contributions to the design of the system review, the acquisition and interpretation of data, and the revision of the article.

YQ had made substantial contributions to the design of the work, the acquisition of data, and the revision of the article.

HY (corresponding author) had: (i) ensured that original data, figures and materials upon which the submission is based were preserved following best practices in the field so that they are retrievable for reanalysis; (ii) confirmed that data, figures and materials presentation accurately reflects the original; and (iii) foreseen and minimized obstacles to the sharing of data and materials described in the work. The corresponding author should be responsible for managing these requirements across the author group and ensuring that the entire author group is fully aware of and in compliance with best practices in the discipline of publication.

All authors have read and approved the manuscript.

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### Tables

| Author, Patient year (n) (M/F) | Gender | Age (mean/SD, years) | Implants (n) | Years of implant in function (mean/SD) | Current smokers | Follow-up Adjunctive treatments (months) | CONSORT |
|-----------------------------|--------|---------------------|-------------|--------------------------------------|-----------------|------------------------------------------|---------|
| Tapia et al. 2019 45        | 23/22  | 60.9/9.12/2.9       | T 73        | T 10.2/5.4                           | C 9.1/4.8       | Y 6 m                                    | T: Modifyi |
| Ji et al. 2019 24           | 10/14  | 46.2                | T 17        | T -                                  | C 0             | 0 3 m                                    | NR      |
| Year | Authors          | Date  | Duration | Power (W) | Beam Diameter (mm) | Waveband (nm) | Surface Adj. | Laser Type | C: Composition                  |
|------|------------------|-------|----------|-----------|--------------------|---------------|--------------|------------|---------------------------------|
| 2012 | Persson et al.   | 12/29 | 68.5/6.4 | 68.9/2.5  | 55                 | 45            | -            | -          | Er:YAG laser C: Air abrasives    |
|      |                  |       |          |           |                    |               | Y           |            |                                 |
|      | Schwaetz et al.  | 12/8  | 48       | 51        | 16                 | 16            | 4.1          | 4.3        | Er:YAG laser C: 0.2% Chlorhexidine digluconate |
|      |                  |       |          |           |                    |               | NR          |            |                                 |
|      | Arsan et al.     | 3/7   | -        | 24        | 24                 | -             | -            | -          | Diode laser C: None              |
|      |                  |       |          |           |                    |               | Y           |            |                                 |
|      | Arsan et al.     | 7/149 | 58.1/1   | 56.8/1    | 110                | 110           | 6.8/3.6/7.4/4.4 | 14         | Diode laser C: None              |
|      | 2018             |       | 0.1      | 0.2       |                    |               | 20          | 4 m       |                                 |
|      | Birang et al.    | 10/10 | -        | 20        | 20                 | -             | -            | -          | Diode laser C: Photodynamic therapy |
|      | 2017             |       |          |           |                    |               | NR          |            |                                 |
|      | Rifaie et al.    | 38    | 38/0     | 33.6/2.8  | 35.4/2.1           | 38            | 27          | 4.06       | Photodynamic therapy C: None     |
|      | 2017             |       |          |           |                    |               | 20          | 18         |                                 |
|      | Karimi et al.    | 2/8   | -        | 15        | 15                 | -             | -            | -          | Photodynamic therapy C: None     |
|      | 2016             |       |          |           |                    |               | 3 m         | NR         |                                 |
|      | Javed et al.     | 120/46| 41.1     | 39.4      | 127                | 122           | 4.1          | 4.9        | Photodynamic therapy C: None     |
|      | 2016             |       |          |           |                    |               | 41          | 43         |                                 |
|      | Javed et al.     | 54    | 54/0     | 50.6/0.8  | 52.2 ± 0.5         | 28            | 26          | -          | Photodynamic therapy C: None     |
|      | 2017             |       |          |           |                    |               | 28          | 26         |                                 |
|      | Wang et al.      | 48/53 | 44.1/9.8 | 42.6 ± 13.0| 66                | 65            | -           | -          | Photodynamic therapy C: None     |
|      | 2019             |       |          |           |                    |               | 13          | 21         |                                 |
|      | Basset et al.    | 20/20 | 59       | 57        | 20                 | 20            | 7.3          | 7.2        | Air abrasives                    |
|      |                  |       |          |           |                    |               | 12 m        | NR         |                                 |
| Study (Year)          | Age | Sex | PI | PI |acial Health | Period | Type | Treatment Details                                                                 |
|----------------------|-----|-----|----|----|--------------|--------|------|----------------------------------------------------------------------------------|
| Schar et al. 2012    | 40  | 20/20 | 59 | 57 | 20 | 20 | 7.3 | 7.2 | 6 m | NR | T: Air abrasiv e & Photodynamic therap y; C: Air abrasiv e & 1 mg Minocycline |
| Heitz et al. 2011    | 29  | -    | 57 | 53 | 14 | 15 | -   | -   | 2   | 2   | 3 m | NR | T: 0.5% Chlorhexidine gel; C: None |
| Menezes et al. 2016  | 37  | 6/31 | 57.4/9.1 | 57.4/1.3 | 61 | 58 | -   | -   | -   | -   | 6 m | NR | T: 0.12% Chlorhexidine Glucon ate; C: None |
| Pulcini et al. 2019  | 46  | 21/25 | 61.3/8.9 | 61.0/1.2 | 22 | 24 | -   | -   | 2   | 4   | 12 m | Y | T: Air abrasiv e & 0.03% Chlorhexidine rinse; C: Air abrasiv e & 0.05% Chlorhexidine rinse |
| Porras et al. 2002   | 16  | -    | -  | -  | 16 | 12 | -   | -   | -   | -   | 3 m | NR | T: 0.12% Chlorhexidine rinsing & 0.12% Chlorhexidine gel; C: None |
| Pena et al. 2019     | 50  | 21/29 | 56.0/1.08 | 61.2/1.06 | 25 | 25 | -   | -   | 0   | 1   | 4.5 m | Y | T: 0.12% Chlorhexidine rinse & Lactob acillus reuteri probiot ic |
| Study                  | Month/Year | Patient | Follow-up | T: | C: | Notes                                      |
|------------------------|------------|---------|-----------|----|----|--------------------------------------------|
| Renvert et al. 2008    | 10/22      | 57      | 2          | 2  | 5  | 12 m NR                                    |
|                        |            |         |            |    |    | 1 mg Minocycline                           |
|                        |            |         |            |    |    | C: 1% Chlorhexidine                         |
|                        |            |         |            |    |    | rinse                                      |
| Renvert et al. 2006    | 12/18      | 16      | 2          | 2  | 3  | 12 m NR                                    |
|                        |            |         |            |    |    | 1 mg Minocycline                           |
|                        |            |         |            |    |    | C: 1% Chlorhexidine                         |
|                        |            |         |            |    |    | gel                                        |
| Sahrmann et al. 2019   | 16/16      | 17      | 2          | 2  | 3  | 6 m NR                                    |
|                        |            |         |            |    |    | Chlorhexidine chip                         |
|                        |            |         |            |    |    | C: Chlorhexidine gel                       |
| Roos et al. 2017       | 3/16/6     | 16      | 2          | 2  | 3  | 3 m Y                                     |
|                        |            |         |            |    |    | Threonine                                 |
|                        |            |         |            |    |    | C: None                                   |
| Levin et al. 2015      | 19/20      | 18      | 2          | 2  | 3  | 3 m NR                                    |
|                        |            |         |            |    |    | Dental water jet rinse mixed with chlorhexidine gel |
|                        |            |         |            |    |    | C: None                                   |
| Shibli et al. 2019     | 11/29      | 20      | 2          | 2  | 3  | 12 m NR                                    |
|                        |            |         |            |    |    | Systemic antibiotics                      |
|                        |            |         |            |    |    | C: None                                   |
| Hallstrom et al. 2012  | 23/21      | 22      | 2          | 2  | 3  | 6 m Y                                     |
|                        |            |         |            |    |    | Systemic antibiotics                      |
|                        |            |         |            |    |    | C: None                                   |
| Galofre et al. 2018    | 9/10       | 9       | 2          | 2  | 0  | 6 m Y                                     |
|                        |            |         |            |    |    | Lactobacillus reuteri probiotic            |
|                        |            |         |            |    |    | C: None                                   |
| Lalemian et al. 2020   | 64/11      | 9       | 2          | 2  | 0  | 6 m Y                                     |
|                        |            |         |            |    |    | Lactobacillus reuteri probiotic            |
|                        |            |         |            |    |    | C: None                                   |
| Author, Year | Random Sequence Generation (Selection Bias) | Allocation Concealment (Selection Bias) | Blinding of Participants and Personnel (Performance Bias) | Blinding of Outcome Assessment (Detection Bias) | Incomplete Outcome Data (Attrition Bias) | Selective Reporting (Reporting Bias) |
|-------------|---------------------------------------------|-----------------------------------------|----------------------------------------------------------|---------------------------------------------|------------------------------------------|----------------------------------|
| Tapia et al. 2019 | Low | High | Low | Low | Low | Low |
| Ji et al. 2012 | Low | Low | Unclear | High | Low | Low |
| Persson et al. 2011 | Low | Low | Unclear | Low | Low | Low |
| Study                          | Methodology | Blinding | Randomization | Allocation | Reporting | Internal validity | External validity | Overall quality |
|-------------------------------|-------------|----------|---------------|------------|-----------|-------------------|-------------------|-----------------|
| Schwarz et al. 2003           | Low         | Low      | Low           | Unclear    | Low       | Low               | Low               | Low             |
| Ansan et al. 2015             | Low         | Unclear  | Low           | Low        | High      | Low               | Low               | Low             |
| Aimetti et al. 2018           | Low         | Unclear  | Unclear       | Unclear    | Low       | Low               | Low               | Low             |
| Birang et al. 2017            | Low         | Unclear  | Unclear       | Low        | High      | Low               | Low               | Low             |
| Rifaiy et al. 2017            | Low         | Low      | Unclear       | Low        | Unclear   | Low               | Low               | Low             |
| Karimi et al. 2016            | Low         | Low      | Low           | Unclear    | Low       | Low               | Low               | Low             |
| Javed et al. 2016             | Low         | Low      | Unclear       | Unclear    | High      | Unclear           | Low               | Low             |
| Javed et al. 2017             | Low         | Low      | Unclear       | Unclear    | Low       | Low               | Low               | Low             |
| Wang et al. 2019              | Low         | Low      | Unclear       | Low        | Low       | Low               | Low               | Low             |
| Bassetti et al. 2014          | Low         | Unclear  | Low           | Unclear    | Low       | Low               | Low               | Low             |
| Schar et al. 2012             | Low         | Low      | Low           | Low        | Low       | Low               | Low               | Low             |
| Heitz et al. 2011             | Low         | Low      | Low           | Low        | Low       | Low               | Low               | Low             |
| Menezes et al. 2016           | Low         | High     | Unclear       | Unclear    | Low       | Low               | Low               | Low             |
| Pulcini et al. 2019           | Low         | Low      | Low           | Low        | Low       | Low               | Low               | Low             |
| Porras et al. 2002            | High        | High     | High          | Unclear    | Low       | Low               | Low               | Low             |
| Pena et al. 2019              | Low         | Low      | Low           | Low        | Low       | Low               | Low               | Low             |
| Renvert et al. 2008           | Low         | High     | Low           | Unclear    | Low       | Low               | Low               | Low             |
| Renvert et al. 2006           | Unclear     | Unclear  | Low           | Low        | Low       | Low               | Low               | Low             |
| Sahrmann et al. 2019          | Low         | Low      | Low           | Unclear    | Low       | Low               | Low               | Low             |
| Roos et al. 2017              | Low         | Low      | Unclear       | Low        | High      | Low               | Low               | Low             |
| Levin et al. 2015             | Low         | Low      | Unclear       | Low        | High      | Low               | Low               | Low             |
| Shibli et al. 2019            | Low         | Low      | Low           | Unclear    | High      | Low               | Low               | Low             |
| Hallstrom et al. 2012         | Low         | Low      | Unclear       | Low        | Low       | Low               | Low               | Low             |
| Galofre et al. 2018           | Low         | Unclear  | Unclear       | Low        | Low       | Low               | Low               | Low             |
| Laleman et al. 2020           | Low         | Unclear  | Low           | Low        | Low       | Low               | Low               | Low             |
| Tada et al. 2018              | Low         | Low      | Unclear       | Low        | Low       | Low               | Low               | Low             |
| Machtet et al. 2012           | Low         | Low      | Unclear       | Low        | Low       | Low               | Low               | Low             |
| Kashefimehr et al. 2016       | Low         | Low      | Unclear       | Low        | Low       | Low               | Low               | Low             |

Table 2
Results of the quality assessment of RCTs.

Figures
Figure 1

Flow chart of manuscripts screened throughout the review process.
Figure 2

Meta-analysis compares the clinical outcomes of MD with photodynamic treatment versus MD alone after 3 months follow-up.
Figure 3

Meta-analysis compares the clinical outcomes of MD with chlorhexidine versus MD alone after 3 months follow-up.

Figure 4

Meta-analysis compares the clinical outcomes of MD with probiotics versus MD alone after 3 months follow-up.
Meta-analysis compares the clinical outcomes of MD with systemic antibiotics versus MD alone after 3 months follow-up.

Supplementary Files
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