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SYSTEMATIC REVIEW

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Resveratrol as adjuvant of non-surgical periodontitis treatment: a systematic review and meta-analysis

Resveratrol como adjuvante no tratamento não cirúrgico da periodontite: revisão sistemática e meta-análise

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ABSTRACT

Objective: This systematic review aims to raise evidence on the effectiveness of the use of resveratrol supplementation (RV) as an adjuvant therapy for scaling and root planning in the treatment of periodontitis. **Material and Methods:** This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines (PRISMA) and was registered in the International Database of Systematic Reviews (PROSPERO CRD42024507782). PubMed/MEDLINE, Scopus, Embase, and Cochrane Library were searched through October 2024. The PICO question was: "Is the resveratrol supplementation effective as an adjuvant therapy of non-surgical periodontitis disease treatment?". The established inclusion criteria were: 1) randomized controlled clinical trials (RCTs), 2) a minimum of 15 patients with periodontitis disease, and 3) follow-up of at least 4 weeks. The minimum follow-up duration was 4 weeks. **Results:** After searching the identified databases, 166 were screened and 3 were selected for full reading. Therefore, 3 studies were included in the final analysis. The total number of participants included in the control group (placebo) was 82, while in the intervention group (RV) was 160, with a mean age of 38 years. **Conclusion:** Despite the limitations of the number of studies included in this systematic review, resveratrol supplementation as an adjuvant to non-surgical periodontal therapy could contribute to optimizing the treatment of periodontitis.

KEYWORDS

Periodontal diseases; Periodontitis; Phytoestrogens; Resveratrol; Systematic review.

RESUMO

Objetivo: Avaliar as evidências sobre a eficácia do uso da suplementação de resveratrol (RV) como terapia adjuvante para raspagem e alisamento radicular no tratamento da periodontite. **Material e Métodos:** Esta revisão seguiu o Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines (PRISMA) e foi registrada no International Database of Systematic Reviews (PROSPERO CRD42024507782). As bases de dados utilizadas PubMed/MEDLINE, Scopus, Embase e Cochrane Library foram pesquisados até outubro de 2024. A pergunta PICO foi: "A suplementação de resveratrol é eficaz como terapia adjuvante no tratamento não cirúrgico da doença periodontite?". Os critérios de inclusão estabelecidos foram: 1) ensaios clínicos randomizados controlados, 2) mínimo de 15 pacientes com doença periodontal e 3) acompanhamento de pelo menos 4 semanas. A duração mínima do acompanhamento foi de 4 semanas. **Resultados:** Após busca nas bases de dados identificadas, 166

estudos foram triados e 3 foram selecionados para leitura na íntegra. Portanto, 3 estudos foram incluídos na análise final. O número total de participantes incluídos no grupo controle (placebo) foi de 82, enquanto no grupo intervenção (RV) foi de 160, com média de idade de 38 anos. **Conclusão:** Apesar das limitações do número de estudos incluídos nesta revisão sistemática, a suplementação com resveratrol como adjuvante à terapia periodontal não cirúrgica pode contribuir para otimizar o tratamento da periodontite.

PALAVRAS-CHAVE

Doenças periodontais; Fitoestrógenos; Periodontite; Resveratrol; Revisão sistemática.

INTRODUCTION

Periodontitis is a multifactorial chronic inflammatory periodontal disease, the primary cause is inflammation induced by anaerobic bacteria [1,2], including *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis, Tannerella forsythia,* and *Treponema denticola* which cause dysbiosis of the oral microbiota [3,4]. After bacterial invasion, the innate immuno-inflammatory system reacts to these pathogens by producing pro-inflammatory cytokines, such as TNF-α, IL-6, IL-8, and IL-1β [5].

The initial stage of periodontal disease involves the action of TNF-α, which increases the permeability of epithelial cells in the gingival tissue, optimizing the capacity for invasion of the main pathogen *P. gingivalis*, a highly pathogenic bacterium that causes the development and progression of periodontal disease [6,7]. Furthermore, TNF-α regulates the production of innate pro-inflammatory cytokines, such as IL-6 and IL-1β [8].

Periodontitis affects supporting tissues, including the cementum, periodontal ligament, and alveolar bone and, as such, can be detrimental [9].The parameter used to evaluate the extent of support tissue loss, measured as the distance from the cement-enamel junction to the base of the pocket, is the clinical attachment level (CAL), whereas the measured distance from the free gingival margin to the base of the pocket is defined as the probing depth (PD) [10].

According to the classification of periodontal diseases by the American Academy of Periodontology and the European Federation of Periodontology in 2017, patients diagnosed with periodontitis exhibit attachment loss > 3 mm [11]. The primary treatment for periodontitis is mechanical instrumentation aimed at reducing the accumulation of subgingival plaque associated with personal oral hygiene habits [12,13]. In addition, host defense mechanisms must be favorable.

However, the presence of furcation or retention areas can make subgingival mechanical debridement difficult due to the limited reach of the instruments. Therefore, systemic antimicrobials are used as adjuvants for non-surgical periodontal treatment as therapeutic strategies for periodontal disease [14]. However, the frequent use of antibiotics has led to microbial resistance and systemic side effects [15].

Therefore, researchers are searching for alternatives to immunomodulatory therapeutic approaches associated with nonsurgical periodontal therapy including phytotherapeutics with effective biological properties [16].

Resveratrol (RV), a phytochemical belonging to the polyphenol class, was first isolated in 1939 [17,18]. RV is found in the skin of grapes, berries, and peanuts. Therefore, red wine is also a source of RV; the more intense the grape skin color, the greater the concentration of polyphenols [19]. Furthermore, RV is found in small amounts in cocoa beans; therefore, dark chocolate may also be a source of RV [20].

This biomolecule has garnered significant attention due to its diverse biological properties. Resveratrol (RV) displays antioxidant [19], anti-inflammatory [20,21], and antimicrobial effects [22]. Additionally, in vitro studies have suggested that RV may have osteogenic potential by increasing the expression of RUNX2 genes through the SIRT1/FOXO3A axis [23]. A clinical trial also reported RV's anti-resorptive effect on bone, which may be mediated by the activation of endothelial estrogen receptors [24]. Due to its wide range of effects, RV supplementation or a diet rich in RV has been investigated as an adjunctive treatment for several conditions, including cardiovascular and degenerative diseases, tumors, diabetes, obesity, metabolic

syndrome, and periodontal disease [25-29]. This makes RV a promising candidate for adjuvant therapy in non-surgical periodontitis treatment, where it could help modulate inflammation and support bone metabolism.

Although two systematic reviews analyzed RV and evaluated its association with other phytochemicals (curcumin, quercetin, melatonin, omega 3, and others) [30,31], evidence supporting the benefits of using RV isolated. As such, the present systematic review aims to raise evidence on the effectiveness of RV supplementation as an adjuvant therapy to scaling and root planning in the treatment of periodontitis.

MATERIAL AND METHODS

Protocol registration

This systematic review followed the criteria established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and was recorded in the International Database of Systematic Reviews (PROSPERO CRD42024507782).

Eligibility criteria

The research question was "Is the resveratrol supplementation effective as an adjuvant therapy of non-surgical periodontitis disease treatment?". The PICOS question (population, intervention, comparison, outcome, type of study) was the "Population" included patients with periodontitis. The "Intervention" was RV supplementation, while the "Comparison" was placebo. The "Outcome" evaluated the clinical attachment loss (CAL) as a primary outcome, while the secondary outcomes were probing depth (PD) and inflammatory markers (IL-6, IL-8, IL-1β; TNF-α). Finally, "Type of Study" was a randomized controlled clinical trial, because it is the source of the most reliable evidence on the effectiveness of interventions [32].

The inclusion criteria involve randomized controlled clinical trials; a minimum of 15 patients with periodontitis disease; follow-up of at least 4 weeks; the outcome required in the studies was clinical attachment level (CAL). The exclusion criteria were studies with patients underage; articles involving smokers, and pregnancy; people allergic to resveratrol; patients taking immunosuppressive medications or non-steroidal anti-inflammatory drugs; patients using any antioxidant supplement; people following any specific diets beyond their usual diets during the last six months; in vitro studies, animal studies, reviews, case reports, retrospective studies, non-randomized prospective interventional studies and studies that did not include the analyzed outcomes.

Search strategy

Two investigators (N.D.D. and V.A.A.B) searched independently on the electronic databases of PubMed/MEDLINE, Scopus, Embase, and Cochrane Library, studies published until October of 2024, without language or publication date restriction, according to eligibility criteria. The search terms were used for each database. The selection strategy was based on the following combination of descriptors in association with Boolean Operators (Table I). No filters and database limits were used in the searches. Further, as a complement, a manual search was carried out on high-impact periodontics journals such as the Journal of Periodontology, Journal of Clinical Periodontology, Periodontology 2000, Journal of Periodontal Research, and Journal of Periodontal & Implant Science. Finally, a search was carried out on the Grey Literature Database [33].

Data extraction (selection and coding)

Once the bibliographic research was complete, Rayyan® Software [34] was used to manage the bibliography and remove duplicates. Two independent researchers (N.D.D. and V.A.A.B) carried out the initial selection of studies by reading the title and abstract, then if the studies agreed with this review they were consulted in full, after which the inclusion and

Table I - The search terms used for each database

PUBMED	SCOPUS	EMBASE	COCHRANE
("resveratrol"[MeSH Terms] OR "resveratrol"[All Fields] OR "resveratrols"[All Fields] OR "resveratrols"[All Fields]) AND ("periodontal"[All Fields] OR "periodontally"[All Fields] OR "periodontically"[All Fields] OR "periodontics"[MeSH Terms] OR "periodontics"[All Fields] OR "periodontic"[All Fields] OR "periodontitis"[MeSH Terms] OR "periodontitis"[All Fields] OR "periodontitides"[All Fields])	(TITLE-ABS-KEY (resveratrol) AND TITLE-ABS-KEY (periodontitis))	'resveratrol' AND 'periodontitis'	resveratrol AND periodontitis

exclusion criteria were applied. A third researcher (C.D.D.R.D.R.) checked the information. When there was disagreement, a fourth reviewer (E.P.P.) was consulted. If the articles' full texts were unavailable, the authors were consulted through the corresponding author in up to 3 attempts. For data collection and analysis, two authors (N.D.D. and V.A.A.B.) collected data from the included studies and a third author (C.D.D.R.D.R.) checked the information. When there was disagreement, a fourth reviewer (E.P.P.) was consulted. The qualitative data collected were the author of the study and year, number of patients, age, follow-up in weeks, characterization of control group, RV supplementation concentration, placebo and RV administration protocol, clinical evaluations, biochemical evaluations, outcomes, conclusion, and effect of RV supplementation as an adjuvant therapy of non-surgical periodontitis disease treatment (Table II). The quantitative data collected was the mean and standard deviation (Mean ± SD) of the outcomes: CAL, PD, IL-6, IL-8, IL-1β, and TNF-α (Table III).

Abbreviations: BI: bleeding index; CAL: clinical attachment level; OHI-S: oral hygiene index-simplified; PD: probing depth; PI: plaque index; PPD: probing pocket depth. CRP: C-reactive protein; GMCSF: granulocyte-macrophage colony stimulating factor; IL-10: interleukin-10; IL-12p40: interleukin-12p40; IL-1β: interleukin-1beta; IL-2: interleukin-2; IL-4: interleukin-4; IL-6: interleukin-6; IL-8: interleukin-8; INF-γ: interferon-gamma; MCP-1: monocyte chemoattractant protein-1; MIP-1α: macrophage inflammatory protein-1alpha; TAC: total antioxidant capacity; TNF-α: tumor necrosis factor-alpha.

Abbreviations: CAL: clinical attachment level; PD: probing depth; IL-1β: interleukin-1beta; IL-6: interleukin-6; IL-8: interleukin-8; TNF-α: tumor necrosis factor-alpha; HRV: high dose of RV; LRV: low dose of RV; MRV: middle dose of RV.

Summary measurements

The meta-analysis was based on an inverse variance (IV) method. The primary outcome CAL, in addition to secondary outcomes: PD, IL-6, IL-8, IL-1β; and TNF-α were considered continuous outcomes and were evaluated using the mean difference (MD) evaluated by IV with a 95% confidence interval (CI). The MD values were significant when $p < 0,05$. For statistically significant ($p < 0,10$) heterogeneity, a random-effect model was used to assess the significance of the RV supplementation effect. When no statistically significant heterogeneity was found, an analysis was performed using a fixed-effects model. The software Reviewer Manager 5.4 (Cochrane Group) was used for the meta-analyses [38].

Bibliometric analysis

The quality of the studies was independently analyzed by 2 investigators (V.A.A.B., R.O.) using the ROBINS-I tool that considers the domain according to pre-intervention (bias due to confounding, bias in selection of study participants), intervention (bias in classification of interventions), and post-intervention (bias due to deviations from intended interventions, bias due to missing data, bias in measuring outcomes, and bias in selection of reported outcomes [39].

Risk of bias

Two authors (V.A.A.B. and C.D.D.R.D.R.) performed the quality and risk of bias analysis on the included RCTs using the second version of the Cochrane risk-of-bias tool for randomized trials (RoB 2.0). That tool verifies selection, performance, attrition, reporting, and other biases. RoB 2.0 addresses five specific domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; and (5) bias in the selection of the reported results. After defining the domains, an overall bias will be determined for each study. Each of these domains will be categorized as low, high, or some concerns.

RESULTS

Found 332 studies from the previously selected bases: 104 from PubMed, 109 from Scopus, 102 from Embase, and 17 from Cochrane. After removing 166 duplicates, 166 articles were screened by title and abstract, and 3 were screened by full text. Therefore, 3 studies were included in the final analysis. The details of the search strategy are illustrated in Figure 1. No studies were found in the Journal of Periodontology, Journal of Clinical Periodontology, Periodontology 2000, Journal of Periodontal Research, Journal of Periodontal & Implant Science, and the Grey Literature Database.

Table II - Detailed data from all studies included. Author and year of the study, number of patients (N), age, follow-up (weeks), control group, RV concentration, placebo and RV administration protocol, clinical evaluations, biochemical evaluations, conclusion, and effect of RV supplementation

Author	Patients (N)	Age	Follow-up (weeks)	Control Group	RV Concentration	Placebo and RV Protocol	Clinical Evaluations	Biochemical Evaluations	Conclusion	RV Effect
Javid et al. 2019 [35]	43	30-60 years	4	Placebo Starch 480 mg (n=22)	240 mg (n=21)	2 pills daily	CAL (mm)	IL-6 (pg/ml) TNF-α (pg/ml) TAC (mmol/L)	The daily RV supplementation in adjunction with non-surgical periodontal treatment may not change CAL and TNF-α	Negative
Zhang et al. 2022 [36]	160	Mean 26.52 (control) 27.57 (RV)	8	Placebo (n=40)	High dose (500 mg) (n=40) Middle dose (250 mg) (n=40) Low dose (125 mg) (n=40)	1 capsule daily	CAL (mm) BI (%) OHI-S PPD (mm)	TNF-α (pg/ml) GMCSF (pg/ml) MIP-1α (pg/ml) Fibrinogen (pg/ml) IL-2 (pg/ml) CRP (pg/ml) INF-γ (pg/ml) IL-1β (pg/ml) IL-8 (pg/ml) IL-10 (pg/ml) IL-12p40 (pg/ml) MCP-1 (pg/ml) IL-4 (pg/ml) IL-6 (pg/ml)	RV treatment has anti-inflammatory capacity and decreases systemic endotoxin in patients with periodontitis.	Positive
Nikniaz et al. 2023 [37]	40	Mean 41.7 (control) 44.5 (RV)	4	Placebo Starch 480 mg (n=20)	480 mg (n=20)	2 capsules daily	PD (mm) CAL (mm) PI (%) BI (%)	IL-8 (pg/ml) IL-1β (pg/ml)	RV supplementation in combination with non-surgical periodontal treatment may be beneficial in improvement the clinical parameters and inflammatory condition in periodontitis patients.	Positive

Abbreviations: BI: bleeding index; CAL: clinical attachment level; OHI-S: oral hygiene index-simplified; PD: probing depth; PI: plaque index; PPD: probing pocket depth. CRP: C-reactive protein; GMCSF: granulocyte-macrophage colony stimulating factor; IL-10: interleukin-10; IL-12p40: interleukin-12p40; IL-1β: interleukin-1beta; IL-2: interleukin-2; IL-4: interleukin-4; IL-6: interleukin-6; IL-8: interleukin-8; INF-γ: interferon-gamma; MCP-1: monocyte chemoattractant protein-1; MIP-1α: macrophage inflammatory protein-1alpha; TAC: total antioxidant capacity; TNF-α: tumor necrosis factor-alpha.

Table III - The quantitative data collected of the outcomes, mean and standard deviation (Mean ± SD)

Parameters	Nikniaz et al. (2023) [37]	Zhang et al. (2022) [36]	Javid et al. (2019) [35]
CAL	**Case group** *Before intervention* *5.17±0.64* *After intervention* 3.37±0.56 **Control group** *Before intervention* 4.97±0.58 *After intervention* 3.74±0.6	**Placebo group** 6.06±0.37 **LRV group** 4.18±0.75 **MRV group** 3.76±0.88 **HRV group** 3.15±0.96	**Control group** *baseline* 2.72 ± 0.5 *4 weeks* 2.2 ± 0.5 **Intervention group** *baseline* 2.35 ± 0.6 *4 weeks* 2 ± 0.4
PD	**Case group** *Before intervention* 4.44±0.63 *After intervention* 2.82±0.58 **Control group** *Before intervention* 4.27±0.58 *After intervention* 3.2±0.66	**Placebo group** 5.74±0.50 **LRV group** 2.82±0.62 **MRV group** 2.15±0.42 **HRV group** 2.00±0.40	
IL-8	**Case group** *Before intervention* 18.67±3.65 *After intervention* 17.36±3.03 **Control group** *Before intervention* 16.83±2.63 *After intervention* 16.97±1.97	**Placebo group** 756±210 - *systemic* 356±116 – *local* **LRV group** 354±142 – *systemic* 142±70 – *local* **MRV group** 350±152 – *systemic* 128±67 – *local* **HRV group** 326±137 – *systemic* 114±43 - *local*	
IL-1β	**Case group** *Before intervention* 7.54±3.74 *After intervention* 4.34±2.27 **Control group** *Before intervention* 6.24±3.16 *After intervention* 4.96±2.67	**Placebo group** 543±150 - *systemic* 408±144 – *local* **LRV group** 220±105 – *systemic* 175±80 – *local* **MRV group** 210±90 – *systemic* 172±76 – *local* **HRV group** 196±68 – *systemic* 163±55 – *local*	

Abbreviations: CAL: clinical attachment level; PD: probing depth; IL-1β: interleukin-1beta; IL-6: interleukin-6; IL-8: interleukin-8; TNF-α: tumor necrosis factor-alpha; HRV: high dose of RV; LRV: low dose of RV; MRV: middle dose of RV.

Table III - Continued...

Parameters	Nikniaz et al. (2023) [37]	Zhang et al. (2022) [36]	Javid et al. (2019) [35]
TNF-α		**Placebo group**	**Control group**
		625±210 - *systemic*	*baseline*
		415±101 – *local*	10.56 ± 0.61
		LRV group	*4 weeks*
		112±102 – *systemic*	10.57 ± 0.68
		174±96 – *local*	
		MRV group	**Intervention group**
		108±118 – *systemic*	*baseline*
		124±118 – *local*	10.49 ± 0.47
		HRV group	*4 weeks*
		104±98– *systemic*	10.33 ± 0.66
		104±98 – *local*	
IL-6		**Placebo group**	**Control group**
		285±100 - *systemic*	*baseline*
		342±105 – *local*	2.08 ± 0.82
		LRV group	*4 weeks*
		456±142 – *systemic*	1.85 ± 0.59
		610±179 – *local*	
		MRV group	**Intervention group**
		486±162 – *systemic*	*baseline*
		635±198 – *local*	2.19 ± 1.09
		HRV group	*4 weeks*
		493±172 – *systemic*	1.58 ± 1.06
		550±202 – *local*	

Abbreviations: CAL: clinical attachment level; PD: probing depth; IL-1β: interleukin-1beta; IL-6: interleukin-6; IL-8: interleukin-8; TNF-α: tumor necrosis factor-alpha; HRV: high dose of RV; LRV: low dose of RV; MRV: middle dose of RV.

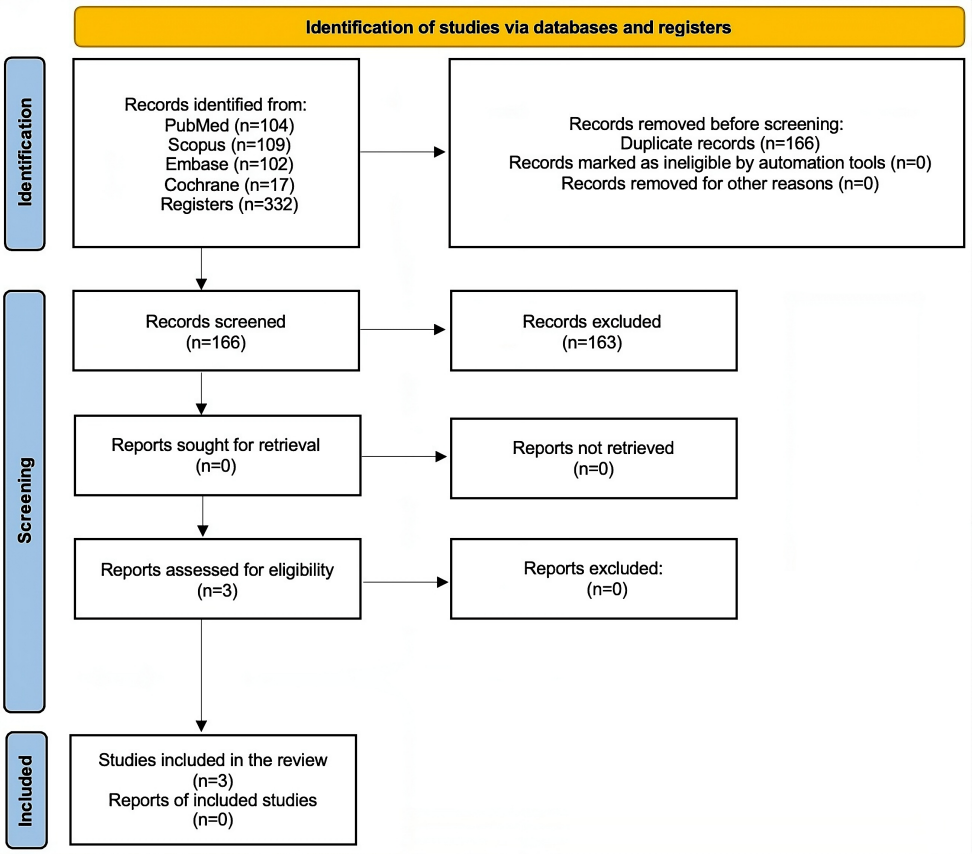

Figure 1 - Search strategy.

Detailed data from all studies included are listed in Table II and Table III. The total number of participants included in the control group (placebo) was 82, while in the intervention group (RV) was 160, with a mean age of 38 years. The important difference to consider between the patients included in the papers is that in the study by Javid et al. [35], the patients have type 2 diabetes, while in the other two studies Zhang et al. [36] and Nikniaz et al. [37] the patients were not diabetic. The follow-up period it was ranged from 4 to 8 weeks. In the study by Zhang et al. [36] three concentrations of RV were tested, high-dose (500 mg/d), middle-dose (250 mg/d), and low-dose (125 mg/d), while in the other studies only one dose of RV was tested, 240 mg - 2 pills/d Javid et al. [35] and 480 mg - 2 pills/d Nikniaz et al. [37].

The scaling and root planning protocol was performed for all participants using ultrasonic Gracey curettes and scalers during the study by Javid et al. [35] and a piezoelectric ultrasonic by Nikniaz et al. [37]. The non-surgical periodontal therapy protocol was not specified in the study by Zhang et al. [36]. To measure the pocket depth (CAL and PD), Nikniaz et al. [37] used a Williams probe, and Javid et al. [35] used a University of North Carolina nº 15 probe. In the Zhang et al. [36], it was not specified which instrument was used to measure the pocket depth.

The inflammatory markers were analyzed using a salivary sample collected between 9 AM and 12 PM and were measured by ELISA method using a laboratory kit [37]. In the other two studies, was collected 5 ml of blood in the morning hours [35,36]. The levels of inflammatory markers were determined using fluorescence detection kits [36], while in the study carried out by Javid et al. [35] was performed ELISA method. All patients received non-surgical periodontal treatment and oral hygiene instructions during the studies.

Meta-analysis

The meta-analysis included three studies that contained quantitative data related to the outcomes. The three studies were included for the first outcome on clinical attachment loss [35-37]. The Zhang et al. [36] study was divided into HRV (high-dose), MRV (middle-dose), and LRV (low-dose). The results showed that associating RV supplementation with non-surgical periodontal therapy gains the clinical attachment level (CAL): ($P<0.00001$; MD 1.53 [CI 0.51 to 2.56]; $I^2=98\%$; $P=0.003$) (Figure 2). About the secondary outcomes, Zhang et al. [36] and Nikniaz et al. [37] reduced periodontal pocket depths (PD): ($P<0.00001$; MD 2.68 [CI 1.55 to 3.80]; $I^2=99\%$; $P<0.0001$) (Figure 2). Inflammatory markers analysis in Zhang et al. [36] investigation showed IL-8: ($P<0.00001$); MD 313.24 [CI 243.27 to 383.21]; $I^2=90\%$; $P<0.00001$). IL1-β: ($P<0.00001$); MD 285.35 [CI 242.40 to 328.30]; $I^2=76\%$; $P=0.0009$). TNF-α: ($P<0.00001$); MD 395.61 [CI 297.62 to 493.60]; $I^2=95\%$; $P<0.00001$). IL-6: ($P<0.00001$); MD -222.22 [CI -258.82 to -185.62]; $I^2=51\%$; $P=0.07$) (Figure 3). Therefore, the study showed the anti-inflammatory effect of RV, through the reduction of inflammatory markers, except for IL-6.

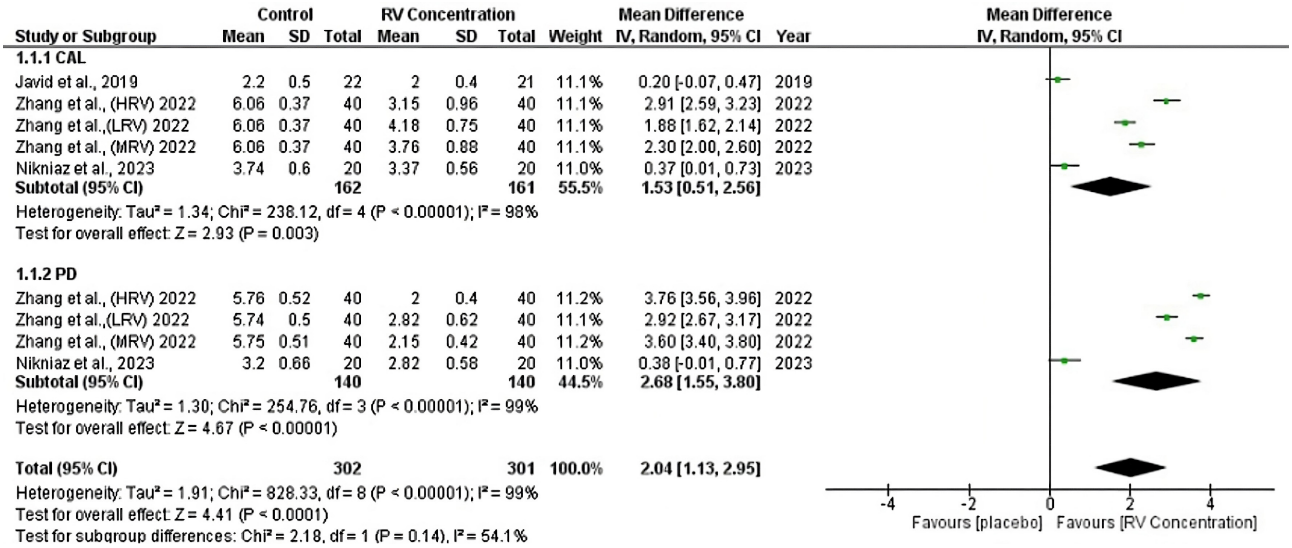

Figure 2 - Forest plot evaluating clinical attachment level (CAL) and probing pocket depth (PD) - a statistically significant difference ($p < 0.05$) favorable to RV supplementation.

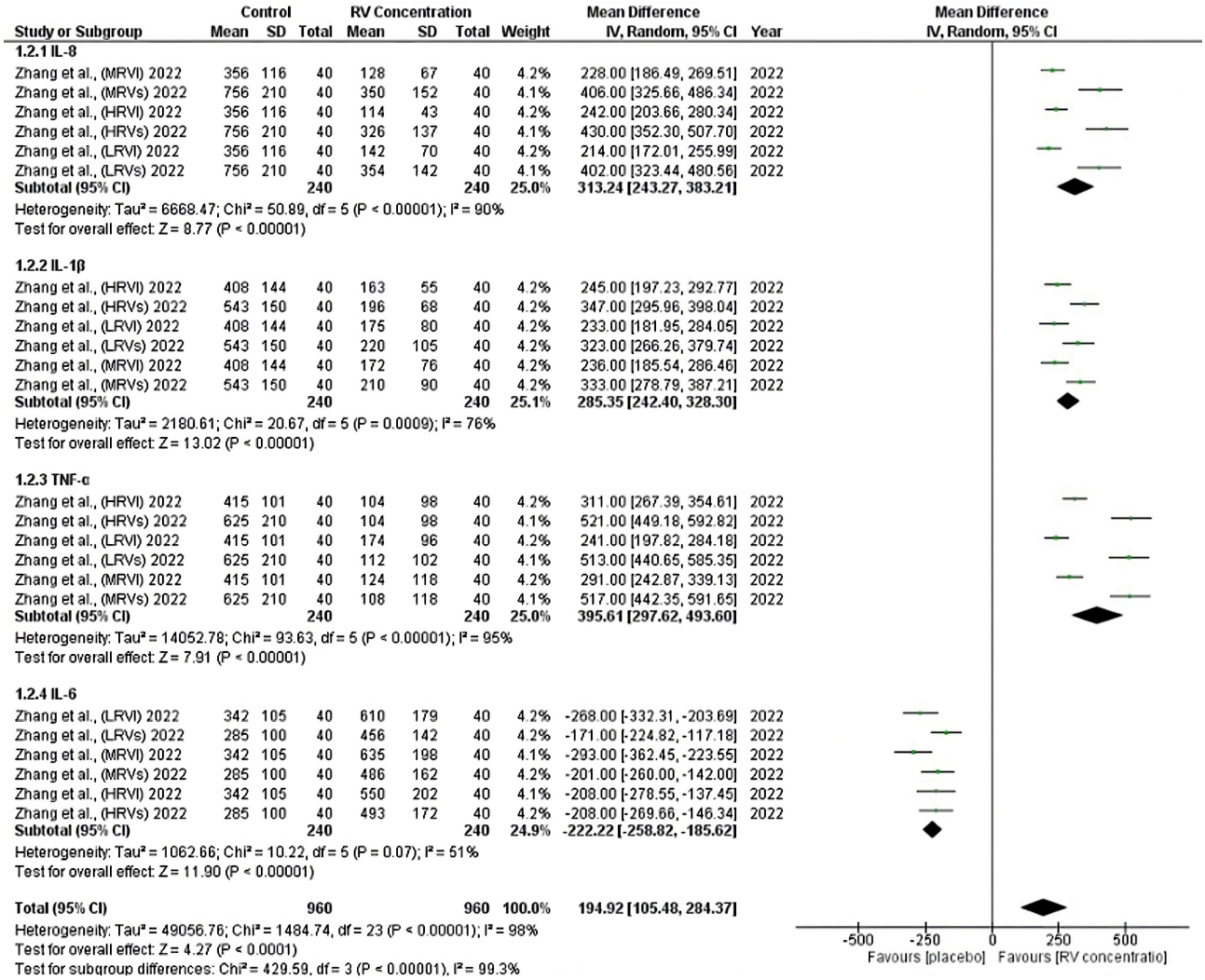

Figure 3 - Forest plot evaluating inflammatory markers - a statistically significant difference (p < 0.05) favorable to RV supplementation.

Risk of bias

The evaluation of results for the quality of the methodology using the RoB 2.0 tool for randomized interventional studies indicated a moderate risk of bias in studies Zhang et al. [36] and Nikniaz et al. [37], identifying deficiencies, mainly in the domain D4 and D5, while the study of Javid et al. [35] indicated a serious risk of bias, identifying deficiencies in domain D3, D4, and D5 (Figure 4).

DISCUSSION

In this study, the hypothesis that supplementation with RV, as an adjuvant to nonsurgical periodontal therapy, could improve the treatment of periodontitis was confirmed, and a significant difference between groups treated with RV versus placebo was observed.

Although non-surgical periodontal treatment (scaling and root planning) is considered to be the "gold standard" method for treating patients diagnosed with periodontitis, the search for adjuvant alternatives to enhance periodontal tissue repair is ongoing.

Recently, phytotherapy has become a hot topic in Dentistry due to its accessibility, cost-effectiveness, and absence of side effects compared with synthetic drugs [40]. Systemic treatment with RV is currently used in Periodontology. However, clinical studies are limited, which explains the existence of only four published randomized clinical trials (RCTs). Currently, most studies available in the literature investigating RV treatment associated with nonsurgical periodontal therapy are in vitro and in vivo.

Results of the present systematic review are consistent with many preclinical studies in

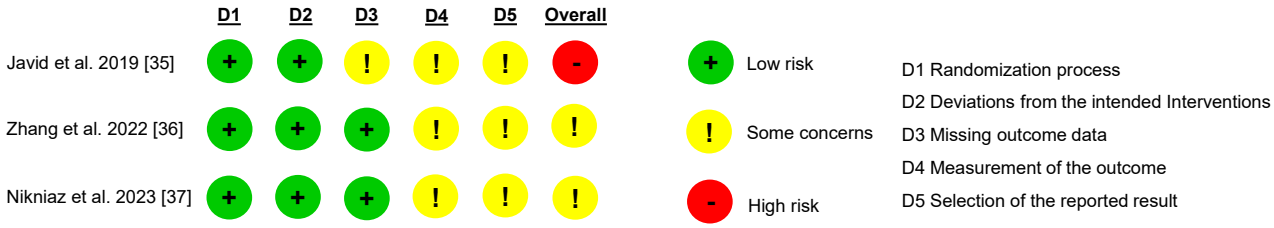

Figure 4 - Results of risk of bias in studies based on RoB 2.0 tool.

rats demonstrating that nonsurgical periodontal treatment associated with RV supplementation has beneficial effects against the progression of experimental periodontitis [16,41]. In addition, the anti-inflammatory properties of RV protect against further damage to the periodontal tissues [42,43]. A previous systematic review evaluated the effect of RV on the progression of periodontitis in rats and reported positive results [44]. The studies by Zhang et al. [36] and Nikniaz et al. [37] consider that RV supplementation associated with non-surgical periodontal treatment has anti-inflammatory capacity and can be beneficial in improving clinical parameters in patients with periodontitis.

In contrast, the study by Javid et al. [35] included diabetic patients with periodontitis, in which there was no benefit from RV supplementation in the adjuvant treatment of non-surgical periodontal therapy. Considering systemic factors that can modify the host's susceptibility to periodontal disease progression and response to non-surgical periodontal therapy [45,46]. The mechanism involved in the pathogenesis of diabetes mellitus-associated periodontitis is by AGE-RAGE axis, which intensifies inflammation and compromises periodontal tissue repair after scaling and root planning [45]. Therefore, clinicians must consider this issue to ensure appropriate patient management and successful treatment of periodontitis.

One aspect in common between the three included studies [35-37] is that patients taking immunosuppressants, anti-inflammatory drugs, or antioxidant supplements were excluded to avoid interference with the results and to ensure the validity of the data. Immunosuppressive and anti-inflammatory can affect the host's inflammatory and immune responses, potentially interfering with the effects of resveratrol, which has anti-inflammatory properties [20,21]. Additionally, these medications could compromise the reliability of immunological markers analysis. Similarly, antioxidant supplementation, like vitamin C [47], selenium [48], and others, may affect RV effects, making it difficult to evaluate the isolated action of RV.

As a limitation, this systematic review and meta-analysis considered only one RCT involving patients with type 2 diabetes, as this topic is still scarce in the literature. Therefore, in this study, two investigations involving patients with periodontitis without systemic diseases and one involving patients with diabetes were included. Furthermore, other limitations included variations in the RV dose, different frequencies of RV consumption across the studies, and the number of available RCTs.

Therefore, new RCTs with dose standardization and different evaluation methods should be conducted to confirm the results of this review. Regarding the heterogeneity in the meta-analysis of outcomes, the I^2 value demonstrated that study variability was high.

The development of new RCTs to test RV supplementation associated with nonsurgical periodontal therapy in patients with periodontitis without systemic diseases and those with diabetes is fundamental to filling current knowledge gaps in the literature and contributing to the evidence supporting the benefits of RV for the treatment of periodontitis and improving the success of the therapy.

CONCLUSION

Despite the limitations of the number of studies included in this systematic review, resveratrol supplementation as an adjuvant to non-surgical periodontal therapy could contribute to optimizing the treatment of periodontitis.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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Regulatory Statement

This systematic review was conducted through a search strategy in electronic databases. The approval for ethics committee for the reviewed studies were obtained in their original work.

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