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Dissertação

Avaliação do risco de viés de estudos in vitro em Endodontia: Uma revisão guarda-chuva

Rafaella Rodrigues da Gama

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Dissertação apresentada ao Programa de Pós-Graduação em Odontologia da Faculdade de Odontologia da Universidade Federal de Pelotas, como requisito à obtenção do título de Mestre em Clínica Odontológica, com ênfase em Endodontia.

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Banca examinadora:

Prof. Dr. Wellington Luiz de Oliveira da Rosa
Doutor em Odontologia (Área de concentração: Materiais dentários) pela Universidade Federal de Pelotas (UFPel)

Profª. Drª. Anelise Fernandes Montagner
Doutora em Odontologia pela Universidade Federal de Pelotas (UFPel)

Profª. Drª. Carolina Clasen Vieira
Doutora em Clínica Odontológica (Área de Endodontia) pela Universidade Federal de Pelotas (UFPel)

Profª. Drª. Andressa da Silva Barboza (suplente)
Doutora em Biomaterias e Biologia Oral (ênfase em Materiais Odontológicos) pela Universidade Federal de Pelotas (UFPel)

Prof. Dr. Rafael Guerra Lund (suplente)
Doutor em Ciências (Odontologia/Dentística) pela Universidade Federal de Pelotas

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André e Siglia, por todo amor e dedicação
depositados na minha formação.

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“O sucesso é a soma de pequenos esforços dia após dia.”

Robert Collier

Notas Preliminares

A presente tese foi redigida segundo o Manual de Normas para Dissertações, Teses e Trabalhos Científicos da Universidade Federal de Pelotas de 2019, adotando o Nível de Descrição de Artigos do referido manual. <http://sisbi.ufpel.edu.br/?p=documentos&i=7> Acesso em: 01 de março de 2023.

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Resumo

DA GAMA, Rafaella Rodrigues. **Avaliação do risco de viés de revisões in vitro em Endodontia: Uma revisão guarda-chuva.** 2023. 93f. Dissertação (Mestrado em Clínica Odontológica com ênfase em Endodontia) – Programa de Pós-Graduação em Odontologia. Universidade Federal de Pelotas, Pelotas, 2023.

Vários critérios sem padrões estabelecidos foram relatados para avaliar o risco de viés (RoB) em revisões sistemáticas (RSs) de estudos *in vitro* na literatura endodôntica. Essas RSs frequentemente usam critérios adaptados de revisões anteriores, incluindo RSs de estudos clínicos, para ajustar a complexidade dos diferentes fatores que podem ser caracterizados como viés. O objetivo desse estudo foi realizar uma revisão guarda-chuva das ferramentas usadas para avaliar o RoB nas RSs de estudos *in vitro* publicados na área endodôntica, bem como propor uma nova ferramenta para analiar o RoB de estudos *in vitro* em endodontia. Os critérios de inclusão foram RSs de estudos *in vitro* com foco em endodontia e com o RoB avaliado. Cinco bancos de dados foram pesquisados (PubMed, Embase, Web of Science, Scopus e Cochrane Library) e os dados foram extraídos independentemente por dois revisores. Critérios comuns usados para avaliar o RoB foram agrupados e analisados para formular uma nova ferramenta (RoBEndo). Três examinadores utilizaram a ferramenta RoBEndo e a RoBDEMAT para analisar 9 estudos *in vitro* da área de endodontia. A concordância entre eles foi avaliada por meio de estatística Kappa de Cohen no software IBM SPSS Statistics (SPSS Inc., Chicago, IL, USA). A busca eletrônica identificou 6.418 registros potencialmente relevantes e 87 RSs foram incluídas. Todas as RSs avaliaram o RoB com critérios adaptados por outras revisões ou adaptando ferramentas existentes. A *Cochrane Collaboration Tools* foi a ferramenta mais citada para avaliar o RoB (19,5%). Quatorze itens foram selecionados para a elaboração da ferramenta RoBEndo agrupados em 5 domínios principais. *Concordância substancial* e *quase perfeita* foi encontrada entre os examinadores usando o RoBEndo. De maneira geral, a partir do estudo foi encontrado uma grande divergência nos critérios utilizados para avaliar RoB de estudos *in vitro* em endodontia. Com base em todas as revisões, foi possível desenvolver uma nova ferramenta de RoB (RoBEndo) com alta concordância entre os examinadores.

Palavras-chave: endodontia, revisão sistemática, risco de viés, in vitro

Abstract

DA GAMA, Rafaella Rodrigues. **Risk of bias assessment of in vitro systematic reviews in endodontics: an umbrella review. 2023.** 93p. Dissertation project (Masters in Clinical Dentistry with emphasis on Endodontics) – Postgraduation Program in Dentistry. Federal University of Pelotas, Pelotas, 2023.

Several criteria without established standards have been reported to assess the risk of bias (RoB) in systematic reviews (SRs) of in vitro studies in the endodontic literature. These SRs often use criteria adapted from previous reviews, including SRs from clinical trials, to adjust for the complexity of different factors that can be characterized as bias. The aim of this study was to carry out an umbrella review of the RoB tools used in SRs of in vitro studies published in the endodontic area and to synthesize common criteria used, as well as to propose a new RoB tool for in vitro studies in endodontics. Inclusion criteria were SRs from in vitro studies focusing on endodontics with RoB evaluated. Five databases were searched (PubMed, Embase, Web of Science, Scopus and Cochrane Library) and data were extracted independently by two reviewers. Common criteria used to assess RoB were pooled and analyzed to formulate a new tool: RoBEndo. Three examiners used the RoBEndo tool and the RoBDEMAT to analyze 9 in vitro studies in the scope of endodontics. The agreement between them was assessed using Cohen's Kappa statistics in the IBM SPSS Statistics software (SPSS Inc., Chicago, IL, USA). The electronic search identified 6,418 potentially relevant records and 87 SRs were included. All SRs assessed RoB with criteria adapted from other reviews or by adapting existing tools. The Cochrane Collaboration Tools was the most cited tool to assess RoB (19.5%). Fourteen items were selected for the elaboration of the RoBEndo tool, grouped into 5 main domains. Substantial and near-perfect agreement was found between examiners using RoBEndo. A large divergence was found in the criteria used to assess RoB from in vitro endodontic studies. Based on all reviews, it was possible to develop a new RoB tool (RoBEndo) with high inter-rater agreement.

Key-words: endodontics, systematic review, risk of bias, in vitro

Sumário

1 Introdução

As revisões sistemáticas (RS) são uma atualização científica coletiva sobre um determinado tópico ou intervenção com base na síntese de ensaios clínicos randomizados (RCTs), que são classificados no topo da evidência científica (Gopalakrishnan e Ganeshkumar, 2013). Devido à falta de ensaios clínicos sobre algumas questões relevantes, surgiram outros tipos de RS, como os baseados em estudos observacionais ou mesmo baseados em experimentos com animais e estudos *in vitro* (Mickevičienė, Lodienė e Venskutonis, 2020; Moreno-Rabié et al., 2020). Embora a pesquisa *in vitro* não possa reproduzir um ambiente oral dinâmico, experimentos pré-clínicos podem fornecer informações importantes sobre as propriedades e características de um novo material ou técnica (Faggion, 2012). Novos materiais e técnicas introduzidas na rotina da Odontologia requerem uma grande variedade de estudos para avaliar sua eficácia e segurança, e vários estudos *in vitro* têm sido realizados para confirmar os dados fornecidos pelos fabricantes e oferecer maior previsibilidade desses materiais (Da Silva et al., 2023).

A avaliação da qualidade dos estudos incluídos é considerada uma componente essencial de uma RS dos efeitos de uma intervenção (Nagendrababu et al., 2022). As descobertas de estudos de boa qualidade metodológica podem ser mais confiáveis, enquanto um maior grau de incerteza está associado a resultados de estudos com maior risco de viés (Nagendrababu et al., 2020). Dessa forma, a avaliação do risco de viés dos estudos incluídos é uma etapa importante no processo de desenvolvimento de uma revisão sistemática (Faggion et al., 2022).

Viés ou erro sistemático pode ser definido como qualquer viés na coleta, análise, interpretação, publicação ou revisão de dados que leva a conclusões que tendem a se distanciar da verdade (Lorscheitter, Stein e Plentz, 2017). A ferramenta RoB 2 e ROBINS-I (Cochrane Collaboration, Londres, Reino Unido) foram desenvolvidas para avaliar o risco de viés em RCTs e ensaios clínicos não randomizados (NRCTs), respectivamente. Estas ferramentas baseiam-se em domínios específicos e são estruturadas através de questões de sinalização para o julgamento de cada domínio, também direcionadas para a avaliação de resultados individuais (Sterne et al., 2019).

Por outro lado, vários critérios sem padrões foram usados para julgar o risco de viés de RS de estudos *in vitro*, inclusive em muitos estudos publicados na literatura endodôntica (Parolia et al., 2020; Silva et al., 2020; Araújo et al., 2022). Devido à falta de padronização, as RS dos estudos *in vitro* em endodontia não têm uma direção clara sobre quais critérios devem ser adotados para avaliar a qualidade dos estudos incluídos e o risco de viés. Nessa perspectiva, as RSs de estudos *in vitro* têm frequentemente utilizado critérios adaptados de estudos anteriores para se adequar à complexidade dos diferentes fatores que podem ser caracterizados como viés. Normalmente, essas RSs têm adaptado a ferramenta de risco de viés de estudos clínicos para avaliar a literatura *in vitro* (Nagendrababu e Ahmed, 2019; Neelakantan et al., 2019; Ranjan e Ranjan, 2021).

2 Objetivos

O objetivo desta revisão guarda-chuva é avaliar as ferramentas de risco de viés utilizadas nas RSs de estudos in vitro publicados no âmbito endodôntico nos últimos 5 anos, bem como sintetizar critérios comuns utilizados e propor e TESTAR uma ferramenta de risco de viés para avaliar estudos in vitro em endodontia. E ainda, comparar a ferramenta desenvolvida com outra já existente (RoBDEMAT).

3 Projeto

3.1 Introdução

O conhecimento acadêmico está em constante desenvolvimento e evolução. Todos os meses milhares de novos artigos são publicados na literatura científica. Estima-se que o número de artigos acadêmicos publicados ultrapassou 50 milhões em 2009 (JINHA, 2010), com um aumento exponencial na última década devido ao número crescente de periódicos predatórios que publicam grandes volumes de pesquisas de baixa qualidade, muitas vezes em formatos de acesso aberto e sem revisão por pares (DEMIR, 2018). Essa tendência significa que há uma proliferação assistemática do conhecimento científico em diversos veículos acadêmicos.

Na hierarquia das evidências científicas, a revisão sistemática de ensaios clínicos randomizados é listada no topo (GUYATT *et al.*, 1995), e desempenha um papel essencial na pesquisa acadêmica para reunir o conhecimento existente e examinar o estado da arte de um campo específico (KUNISCH *et al.*, 2018). Sendo assim, o principal objetivo das revisões sistemáticas é selecionar e sintetizar todos os estudos que abordam uma determinada questão baseada em critérios previamente estabelecidos, empregando métodos que minimizam o viés por meio de uma metodologia sistemática, rigorosa e replicável (MURAD *et al.*, 2013). Ao contrário disso, nas revisões narrativas assistemáticas são incluídos na análise apenas estudos que sejam considerados adequados pelo pesquisador (Tranfield *et al.*, 2003).

Além disso, a revisão sistemática é uma metodologia útil para identificar, avaliar e integrar estudos sobre um determinado tópico. Quando bem desenhado, conduzido e relatado, é considerado o padrão ouro de evidência para a tomada de decisão clínica e um passo importante para a medicina baseada em evidências (COOK *et al.*, 1997; MANCHIKANTI 2008). Diante do exposto, é possível afirmar que é cada vez mais difícil acompanhar os novos desenvolvimentos científicos devido à grande quantidade de informações publicadas. Sendo assim, é notório que as revisões sistemáticas apresentam uma grande relevância para a aplicabilidade de uma odontologia baseada em evidências. Segundo um estudo recente de Nagendrababu e colaboradores (2018), as revisões sistemáticas em endodontia apresentam variabilidade na

qualidade metodológica e no relato em si, sendo assim a validade e confiabilidade de qualquer conclusão alcançada nestes estudos dependente de como o processo de revisão foi conduzido.

Como acontece com todas as pesquisas, o valor de uma revisão sistemática depende de métodos rigorosos e sistematizados da clareza do relato, e da aplicação de estratégias científicas específicas para esse tipo de estudo para que possíveis erros e vieses sejam limitados (MOHER *et al.,* 2009). A razão primordial de se avaliar qualitativamente as evidências coletadas em uma revisão sistemática justifica-se pela atribuição da devida importância a ser dada para cada desfecho. Quando este requisito básico não é atendido, incorre-se no risco de supervalorizar dados originários de estudos falhos e consequente indução a interpretações errôneas das evidências disponíveis (HIGGINS *et al.,* 2011).

3.1.1 Revisões guarda-chuva

Com o aumento do número de revisões sistemáticas disponíveis, tem sido proposto a realização de revisões das revisões sistemáticas existentes, chamadas de revisões guarda-chuva (no inglês *umbrella review)*, permitindo que os resultados de revisões separadas sejam comparados e contrastados, fornecendo assim aos tomadores de decisão as evidências que precisam. O motivo para a realização de uma revisão guarda-chuva é a necessidade de se resumir os resultados de múltiplas sínteses de pesquisas e também oferecer uma avaliação rápida deuma ampla base de evidências de alta qualidade em um tópico (SMITH *et al,* 2011).

Além disso, uma revisão guarda-chuva permite uma avaliação sobre tópicos de revisão de perguntas semelhantes, e com isso é possível observar resultados similares de forma independente e chegar a conclusões geralmente semelhantes, tendo como objetivo proporcionar uma visão global dos resultados para diferentes questões, e consequentemente fornecer um quadro mais amplo de tratamentos (WORSWICK *et al,* 2013).

Na endodontia existem algumas revisões guarda-chuva publicadas recentemente. Nagendrabadu e colaboradores (2020), realizaram uma revisão guarda-chuva a fim de identificar qual é a solução anestésica local (articaína ou lidocaína) mais adequada para dentes com pulpite irreversível em tratamento de canal radicular. Outra revisão recente de Nagendrabadu e colaboradores (2020), avaliou por

meio de uma revisão guarda-chuva qual a associação da diabetes mellitus com o desfecho do tratamento endodôtico. Ambas revisões tiveram sua qualidade avaliadas pela ferramenta da AMSTAR.

3.1.2 Risco de viés

A avaliação do risco de viés é considerada um componente essencial de uma revisão sistemática sobre os efeitos de uma intervenção. A ferramenta mais comumente usada para ensaios clínicos randomizados é a ferramenta de risco de viés da Cochrane (STERNE *et al.,* 2019). Desta forma, a qualidade metodológica de um estudo está associada a um menor risco de viéses. Resultados procedentes de estudos de boa qualidade metodologica são mais confiáveis, enquanto isso, um maior grau de incerteza estão associados à resultados procedentes de estudos de baixa qualidade. Sendo assim, a análise da qualidade metodológica de estudos é importante no processo de desenvolvimento de uma revisão sistemática. Apesar de ensaios clínicos randomizados serem o padrão ouro para o desenvolvimento de pesquisa em seres humanos, esse tipo de estudo é propenso a viéses, seja pela arbitrariedade dos investigadores na seleção da amostra e aferição das variáveis analisadas, ou seja na dificuldade no controle de outros fatores que podem influenciar no desfecho clínico (PEREIRA, 2008).

Viés ou erro sistemático pode ser definido como qualquer tendenciosidade na coleta, análise dos dados, interpretação, publicação ou revisão dos dados, que induz a conclusões que sistematicamente tendem a se distanciar da verdade (FLETCHER *et al.,* 2006). Para ECR foi desenvolvida a ferramenta RoB 2 (Cochrane Collaboration, London, UK), a fim de avaliar risco de viés em ensaios randomizados. Nesta ferramenta, o viés é avaliado em cinco domínios distintos. Em cada domínio, os usuários do RoB 2 (Cochrane Collaboration) respondem a uma ou mais perguntas de sinalização. Essas respostas levam a julgamentos de "baixo risco de viés", "algumas preocupações" ou "alto risco de viés" e os julgamentos dentro de cada domínio levam a um julgamento geral de risco de viés para o resultado avaliado, o que deve permitir aos pesquisadores estratificar meta-análises de acordo com o risco de viés (STERNE *et al.,* 2019).

Enquanto isso, para ensaios clínicos não randomizados existe a ferramenta ROBINS-I (Cochrane Collaboration, London, UK). Essa ferramenta é similar em estrutura à RoB 2, é baseada em domínios e estruturada através de perguntas

sinalizadoras para o julgamento de cada domínio, também direcionada à avaliação de desfechos individualmente. Para avaliação com a ROBINS-I também é necessário definir o efeito de interesse para o desfecho avaliado, entre efeito de alocação para intervenção (análogo a análise por intenção de tratar) ou efeito de iniciar e aderir a um protocolo. Ainda, a ferramenta avalia sete domínios de viés, classificados por momento de ocorrência: antes da intervenção, durante e após a intervenção (STERNE *et al.,* 2021).

Por outro lado, revisões sistemáticas de estudos *in vitro* não possuem um direcionamento claro quanto a que critérios devem ser adotados pra avaliar a qualidade dos estudos incluídos e o risco de viés. Silva e colaboradores (2021) publicaram recentemente uma revisão sistemática de estudo *in vitro* em que foi avaliado se os cimentos endodônticos à base de resina epóxi apresentam uma solubilidade maior quando comparada aos cimentos à base de silicato de cálcio. Para isso, a avaliação da qualidade foi adaptada de revisões sistemáticas de estudos *in vitro* anteriores (ROSA *et al.,* 2015), onde foram considerados os seguintes parâmetros: tamanho mínimo da amostra de acordo com as diretrizes, amostras com dimensões semelhantes, teste de acordo com as diretrizes, padronização dos procedimentos de solubilidade, análise estatística realizada e risco de parcialidade.

Já em outro estudo publicado por Silva e colaboradores (2018), em que foi comparado se os acessos minimamente invasivos aumentam a resistência à fratura em dentes humanos extraídos quando comparados aos acessos tradicionais, a avaliação da qualidade metodológica também foi adaptada baseado de revisões sistemáticas de estudos in vitro anteriores, e foram considerados os seguintes parâmetros: cálculo do tamanho da amostra, amostras com dimensões semelhantes, presença de um grupo de controle (dentes intactos), execução dos procedimentos de preenchimento, presença de restauração coronária e análise estatística realizada. Ainda, neste mesmo estudo o cegamento do operador não foi considerado, pois os formatos das cavidades de acesso são muito diferentes, permitindo assim ao operador identificar o tratamento realizado. Como demonstrado, tradicionalmente as revisões sistemáticas de estudos *in vitro* tem usado critérios adaptados de outros estudos para adequar à complexidade dos diferentes fatores que podem se caracterizar como viés.

Dessa forma, o objetivo principal desse estudo é realizar uma revisão guarda-chuva à fim de obter um um panorama das revisões sistemáticas in vitro em endodontia nos últimos 5 anos, bem como avaliar as ferramentas de risco de viés

utilizadas e propor uma ferramenta para análise do risco de viés de estudos in vitro em endodontia.

3.2 Justificativa

Uma revisão guarda-chuva em endodontia pode orientar futuros pesquisadores com relação ao estado da arte para que novos estudos foquem em preencher possíveis lacunas no conhecimento. Além disso, os dados bibliométricos podem ser usados para realizar uma análise estruturada de informações, inferir tendências de mudança ao longo do tempo, identificar a área dominante de um campo de pesquisa e detectar os pesqusiadores e instituições mais ativos atualmente.

Enquanto isso, não existe uma ferramenta única para analisar o risco de viés de estudos laboratoriais em endodontia, havendo uma grande variabilidade dos métodos utilizados nos estudos publicados. Dessa forma, a análise geral dos métodos que vem sendo utilizados nos estudos laboratoriais dos últimos 5 anos pode fornecer diretrizes para guiarem a análise de risco de viés em estudos futuros.

3.3 Objetivos

3.3.1 Objetivo geral

Realizar uma revisão guarda-chuva a fim de avaliar as ferramentas de risco de viés utilizadas nas revisões de estudos *in vitro* da área.

3.3.2 Objetivos específicos

- Realizar uma revisão guarda-chuva de revisões *in vitro* em endodontia;
- Analisar os métodos utilizados para avaliar o risco de viés de revisões sistemáticas de estudos laboratoriais;
- Propor ferramenta para análise do risco de viés de estudos *in vitro* em Endodontia

3.4 Metodologia

O protocolo da presente revisão está descrito de acordo com o PRISMA-P (SHAMSEER et al. 2015) e o estudo será posteriormente relatado de acordo com as diretrizes do *Preferred Reported Items for Systematic Reviews and Meta-analysis* (PRISMA 2020) (PAGE *et al.,* 2021). Devido à natureza do desenho de estudo (revisão guarda-chuva), o protocolo será registrado no *Open Science Framework*.

Esse estudo será dividido em duas fases:

Fase I - Análise dos métodos de avaliação do risco de viés em revisões de estudos laboratoriais em endodontia. Para a primeira fase a seguinte questão de pesquisa foi estabelecida: quais os métodos utilizados para avaliar o risco de viés em revisões de estudos laboratoriais em endodontia?

Fase II - Proposta de uma ferramenta para análise do risco de viés de estudos in vitro em Endodontia.

3.4.1 Fase I: Análise dos métodos de avaliação do risco de viés em revisões de estudos laboratoriais em endodontia

3.4.1.1 Critérios de elegibilidade

Serão incluídos no nosso estudo revisões sistemáticas de estudos laboratoriais com enfoque em endodontia, sem restrição de língua, e será aplicado restrição de tempo de publicação para a partir do ano de 2010. Como critério de exclusão serão revisões narrativas, revisões sobre pino intrarradicular e revisões sobre cimentação de pino.

3.4.1.2 Fontes de informações e estratégia de busca

A pesquisa bibliográfica será realizada por dois revisores independentes e as cegas (RRG e LPA) até Outubro de 2021. Serão selecionadas cinco bases de dados: PubMed (MEDLINE), Embase, Web of Science, Scopus, e Cochrane Library. A estratégia de pesquisa foi desenvolvida baseado nos termos MeSH o para PubMed e adaptada de acordo com as outras bases de dados (Apêndice A). Para aumentar a abrangência das buscas, as referências citadas nos artigos incluídos também serão

verificadas manualmente para identificar outros artigos potencialmente relevantes. Após a identificação dos artigos nas bases de dados, eles serão importados para o software Mendeley (Elsevier, Amsterdam, NE) para remoção das duplicatas e após isso o restante dos estudos serão armazenados no aplicativo online Rayyan (Qatar Computing Research Institute, Doha, QA) (OUZZANI et al. 2016) para realizar o processo de seleção dos estudos.

3.4.1.3 Processo de seleção

Inicialmente, dois autores independentes e às cegas (RRG e LPA) avaliarão os títulos e resumos de todos os documentos através da plataforma online Rayyan (Qatar Computing Research Institute). Os artigos que inicialmente preencherem aos critérios de elegibilidade, e os que possuírem dúvidas quanto à inclusão, serão selecionados para leitura integral dos estudos. Será calculada a concordância interobservador através do coeficiente de Kappa de Cohen. Após a leitura integral, os artigos que definitivamente atenderem à todos os critérios de elegibilidade serão incluídos nessa revisão, e os que eventualmente houverem desacordos entre os dois revisores serão esclarecidos através de discussão e formação de consenso com um terceiro revisor mais experiente (WLOR).

3.4.1.4 Processo de coleta

Os dados serão extraídos independentemente por dois revisores utilizando uma planilha padronizada do Microsoft Office Excel (Microsoft Corporation, Redmond, WA, Estados Unidos). Caso haja alguma informação ausente, os autores dos artigos incluídos serão contactados via e-mail.
Os seguintes dados dos estudos incluídos serão tabulados:

- Dados demográficos: autor, ano, país, número de estudos incluídos
- Material analisada: lima endodôntica, cimento endodôntico, técnica de instrumentação, técnica de obturação, terapia pulpar vital, métodos de diagnóstico, exames de imagem, medicações intracanal, controle de dor em endodontia
- Teste avaliado
- Guia de reporte

- Base de dados acessada
- Registro do protocolo e seu local de publicação
- Ferramenta utilizada para avaliar o risco de viés

3.4.1.5 Análise de dados

Os dados tabulados serão analisados qualitativamente e quantitativamente no Microsoft Office Excel (Microsoft Corporation, Redmond, WA, Estados Unidos), considerando os diferentes critérios utilizados para avaliar o risco de viés.

3.4.2 Fase II: Proposta de uma ferramenta para análise do risco de viés de estudos in vitro em Endodontia

Os artigos incluídos na fase I serão analisados e uma lista será feita com todos os critérios utilizados para avaliar o risco de viés nos estudos selecionados. Depois disso, uma seleção de possíveis critérios a serem incluídos na ferramenta será realizada por meio de uma tabela preliminar de critérios com base em guias de ferramentas existentes e revisões sistemáticas de estudos in vitro em endodontia. Por fim, a ferramenta será desenvolvida de acordo com esses possíveis critérios para avaliar a RoB de revisões sistemáticas de estudos in vitro em endodontia, considerando as particularidades da área.

3.5 Resultados

3.5.1 Indicadores de resultados ao final do projeto

- Realizar todas as etapas das metodologias propostas
- Apresentação de um trabalho em congressos científico nacional (SBPqO/SBENDO)

3.5.2 Repercussão e/ou impactos dos resultados

- Apresentar um panorama das revisões sistemáticas publicadas em endodontia na última década
- Obter um panorama dos métodos utilizados para análise do risco de viés de estudos laboratoriais, com a proposta de uma ferramenta que possa ser posteriormente utilizada

3.5.3 Riscos e dificuldades

- Não terem estudos primários suficientes para realizar a revisão
- Não ter acesso as revisões na íntegra que permitam a tabulação de dados

3.6 Cronograma

	2021							2022											
Atividade/mês	**Jun**	**Jul**	**Ago**	**Set**	**Out**	**Nov**	**Dez**	**Jan**	**Fev**	**Mar**	**Abr**	**Mai**	**Jun**	**Jul**	**Ago**	**Set**	**Out**	**Nov**	**Dez**
Revisão de literatura	X	X	X																
Estratégia de busca				X	X														
Análise dos artigos (Mendeley)					X	X	X												
Seleção dos estudos							X	X											
Coleta de dados								X	X	X									
Tabulação dos resultados										X	X	X	X						
Redação do artigo														X	X	X			
Envio para publicação do artigo científico																	X		
Defesa da dissertação do mestrado																			X

3.7 Orçamento

Na Tabela 1 está demonstrado os gastos gerais estimados com o presente projeto. Este projeto não possui financiamento de órgãos de fomento a pesquisa.

Tabela 1 – Orçamento de despesas gerais do projeto

Item	Discriminação	Valor
1	Gastos com correção de inglês para submissão de artigos	R$ 2.000,00
2	Despesas com material e consumíveis de escritório	R$ 500,00
3	Gastos com participação em congresso científico	R$ 5.000,00
	Total	R$ 7.500,00

4 Relatório de Campo

Inicialmente foi realizada a revisão sistemática a fim de analisar quais ferramentas e critérios são utilizados para avaliação do risco de viés de estudos *in vitro* em Endodontia. A seguinte questão de pesquisa foi estabelecida: “Quais os métodos e ferramentas utilizados para avaliar o risco de viés em revisões sistemáticas de estudos laboratoriais em endodontia?”. Com esta revisão guarda-chuva foi possível mapear os analisar os métodos utilizados para avaliar o risco de viés de estudos laboratoriais, bem como analisar a tendência de publicações desse tipo de estudo nos últimos 5 anos.

Após a coleta de dados foi possível criar uma nova ferramenta para avaliar o risco de viés, de acordo com estudos publicados na área nos últimos 5 anos. A fim de melhor demonstrar a aplicação da ferramenta criada, foi acrescentado uma análise por três examinadores independentes que utilizaram a ferramenta em estudos *in vitro* pré-selecionados. A concordância entre os examinadores foi feita utilizando teste Kappa de Cohen por meio do software IBM SPSS Statistics.

Além disso, no decorrer do projeto uma ferramenta para avaliar o risco de viés de estudos laboratoriais em materiais dentários foi publicada, a RoBDEMAT. Inicialmente não estava previsto a análise dos estudos com essa ferramenta. Para melhor justificar a criação de uma ferramenta específica para o âmbito da endodontia, os examinadores também fizeram a análise utilizando a RoBDEMAT. A partir disso, foi redigido um artigo científico que será futuramente submetido a um periódico da área de endodontia, como o *International Endodontic Journal.*

4 Artigo

Risk of bias assessment of *in vitro* studies in endodontics and development of RoBEndo tool: an umbrella review[1]

Rafaella Rodrigues da Gama, DDS; M.Sc. student, Graduate Program in Dentistry, Federal University of Pelotas (UFPel), Pelotas, RS, Brazil.
Lucas Peixoto de Araújo, DDS.; M.Sc.; Ph.D. student, Graduate Program in Dentistry, State University of Campinas (UNICAMP), Piracicaba, SP, Brazil.
Evandro Piva, DDS.; M.Sc.; Ph.D.; Full Professor, Graduate Program in Dentistry, School of Dentistry, Federal University of Pelotas (UFPel), Pelotas, RS, Brazil.
Leandro Perello Duro, Laboratory Technician, Federal University of Pelotas(UFPel), Pelotas, RS, Brazil.
Adriana Fernandes da Silva, DDS.; M.Sc.; Ph.D.; Associate Professor, Graduate Program in Dentistry, School of Dentistry, Federal University of Pelotas (UFPel), Pelotas, RS, Brazil.
Wellington Luiz de Oliveira da Rosa, DDS.; M.Sc.; Ph.D.; Assistant Professor, Graduate Program in Dentistry, School of Dentistry, Federal University of Pelotas (UFPel), Pelotas, RS, Brazil.

Corresponding author:
Prof. Dr. Wellington Luiz de Oliveira da Rosa
Postgraduate Program in Dentistry, School of Dentistry, Federal University of Pelotas, Pelotas, RS, Brazil
457 Gonçalves Chaves street, dean's office, Pelotas, RS, Brazil. 96015-560
Phone: +55 53 99100-6468
darosa.wlo@gmail.com

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ABSTRACT

BACKGROUND: Several criteria without established standards have been reported for assessing the risk of bias (RoB) in systematic reviews (SRs) of *in vitro* studies in the endodontic literature. These SRs have frequently used criteria adapted from previous reviews, including SRs of clinical studies, and recently a tool was developed to assess the RoB in laboratory studies of dental materials, the so-called RoBDEMAT. OBJECTIVE: To conduct an umbrella review the RoB tools used in the SRs of *in vitro* studies published in the endodontic field, and to synthesize common criteria used, as well as propose and evaluate a new RoB tool for *in vitro* studies in endodontics. METHODS: The inclusion criteria were SRs of *in vitro* studies focusing on endodontics with RoB evaluated. Five databases were searched (PubMed, Embase, Web of Science, Scopus, and Cochrane Library) and data were independently extracted by two reviewers. Common criteria used to assess RoB was grouped and analyzed to formulate a new tool: RoBEndo, which was developed in 3 phases: *Analysis of all RoB tools, Criteria grouped to assess RoB in endodontics and Creation of RoBEndo tool*. RoBEndo and RoBDEMAT tools were used to evaluate 9 *in vitro* studies by three endodontic specialists to measure inter-rater reliability with Kappa statistics in IBM SPSS Statistics. RESULTS: The electronic search identified 6418 potentially relevant records and 87 SRs were included. All SR assessed the RoB with criteria adapted for other reviews or by adapting existing tools. The Cochrane Collaboration Tools was the tool most cited to assess RoB (19.5%). Fourteen items were selected for the elaboration RoBEndo tool grouped in 5 main domains. Substantial and nearly perfect agreement were found among examiners using the RoBEndo, and moderate and substantial agreement among examiners in the RoBDEMAT. CONCLUSIONS: A large divergence in the criteria used to assess RoB of *in vitro* studies in endodontics was found. Based on all reviews, it was possible to develop a new RoB tool (RoBEndo) with high agreement between examiners.

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Keywords: risk of bias, in vitro, endodontic, systematic review

1 Introduction

Systematic reviews (SR) typically are a collective scientific update on a particular topic or intervention based on the synthesis of randomized clinical trials (RCTs), which are ranked at the top of the scientific evidence (Gopalakrishnan and Ganeshkumar, 2013). However, due to the limited number of clinical trials on some relevant issues, other types of SRs have emerged, such as that based on observational studies or even based on animal experiments and *in vitro* studies (Mickevičienė, Lodienė and Venskutonis, 2020; Moreno-Rabié *et al.*, 2020). New materials and techniques introduced in Dentistry routines requires a wide variety of studies to evaluate their efficacy and safety, and several in vitro studies have been conducted to confirm the data provided by the manufacturers and offer greater predictability of these materials (Da Silva *et al.*, 2023).

The risk of bias (RoB) assessment of the included studies is considered an essential component of an SR (Faggion *et al.*, 2022; Nagendrababu *et al.*, 2022). Bias or systematic error can be defined as any bias in the collection, analysis, interpretation, publication, or data review which leads to conclusions that tend to distance themselves from the evidence (Lorscheitter, Stein and Plentz, 2017). The findings from studies with good methodological quality are generally considered more reliable, whereas a greater degree of uncertainty is associated with results from studies with a higher RoB (Nagendrababu *et al.*, 2020). Hereof, the RoB 2 and ROBINS-I tool (Cochrane Collaboration, London, UK) were developed to assess the RoB in RCTs and non-randomized clinical trials (NRCTs), respectively. These tools are based on specific

domains and are structured through signaling questions for the judgment of each domain, also directed to the assessment of individual outcomes (Jonathan A C Sterne *et al.*, 2019).

Several criteria without standards have been reported to assess the RoB in SR of *in vitro* studies in the endodontic literature (Parolia *et al.*, 2020; Silva *et al.*, 2020; Araújo *et al.*, 2022). These SRs have frequently used criteria adapted from previous reviews, including SRs of clinical studies, to adjust to the complexity of the different factors that can be characterized as bias (Nagendrababu and Ahmed, 2019; Neelakantan *et al.*, 2019; Ranjan and Ranjan, 2021). There are also SRs (Pereira *et al.*, 2021; Saeed *et al.*, 2021; Silva *et al.*, 2021) that performed the quality assessment by adapting criteria from previously published SRs of in vitro studies (ROSA et al., 2015), in which some of the following parameters were considered: minimum sample size according to guidelines, samples with similar dimensions, adherence to the guidelines, standardization of procedures and proper statistical analysis, among others.

Recently, two RoB tools were developed to assess the risk of bias of *in vitro* studies. One is a tool to evaluate the quality and RoB of in vitro dental studies, called The QUIN (Sheth *et al.*, 2022). In addition, other tool was developed to asssess the RoB in laboratory studies of dental materials, the so-called RoBDEMAT (Delgado *et al.*, 2022). The RoBDEMAT is composed of four different domains: *bias related to planning and allocation*, *bias in sample/specimen preparation, outcome assessment, data treatment and outcome reporting* with nine signaling questions and a guide that can be used for RoB judgement. Although this developed tool covers the area of dental materials, this tool is not optimized for endodontic *in vitro* literature, which has some particularities that can make it difficult to apply. For instance, using teeth with similar

anatomy can lead to more accurate results, as well as the specification whether the test was performed by one or more operators, once different results may also depend on experienced or non-experienced operators (Dablanca-Blanco *et al.*, 2022). Therefore, the aim of this umbrella review is to map criteria used to assess the RoB of *in vitro* studies in the endodontic scope; as well as propose and evaluate a new standardized RoB tool to evaluate *in vitro* studies in endodontic systematic reviews.

2 Methods

2.1 Analysis of quality assessment methods in systematic reviews of *in vitro* studies in endodontics

2.1.1 Protocol registration

This umbrella review followed the recommendations of PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guideline (http://www.prisma-statement.org) (Page *et al.*, 2021), and the protocol was previously registered in Open Science Framework (OSF) Registries (https://osf.io/azd8u/).

2.1.2 Eligibility and exclusion criteria

The following research question was established: “What tools are used to assess the RoB in SRs of laboratory studies in endodontics?”. The eligible studies for inclusion in this review were systematic reviews with or without meta-analysis, scoping reviews and umbrella reviews focused on endodontics that evaluated the RoB. The publication period was restricted to 2018 and onwards to obtain the most recent publications in the field. As exclusion criteria, narrative reviews or systematic reviews

regarding endocrowns, intraradicular posts, or post cementation protocols were excluded.

2.1.3 Sources of information and search strategy

The systematic literature search was conducted by two independent and blinded reviewers (RRG and LPA) on 10th of January, 2023. Five scientific databases were selected: PubMed (MEDLINE), Embase, Web of Science, Scopus, and Cochrane Library. The search strategy was developed based on MeSH terms and adapted according to the other databases, respecting their rules of syntax (Table A1). To increase the pool of studies, references cited in included articles were also manually checked to identify other potentially relevant articles. After identifying the articles in the databases, they were imported into Mendeley software (Elsevier, Amsterdam, NE) to remove duplicates, and then all studies were exported to the Rayyan online application (Qatar Computing Research Institute, Doha, QA) (Ouzzani *et al.*, 2016) to carry out the study selection process by two independent reviewers.

2.1.4 Selection process

Initially, two reviewers (RRG and LPA) performed a calibration exercise to discuss the eligibility criteria and apply them to a sample of 10% of the retrieved studies to determine the inter-examiner agreement through Cohen's kappa coefficient. After a proper coefficient was achieved ($\kappa = 0.8$), the same two reviewers were blinded and independently screened all titles and abstracts on the online platform Rayyan (Qatar Computing Research Institute). Articles that initially meet the eligibility criteria and those that had doubts about inclusion were selected for full-text reading. In case of disagreement between the two reviewers, a third reviewer (WLOR) acted as a decision-maker.

2.1.5 Data collection process

Data were independently extracted by two reviewers (RRG and LPA) using an Excel spreadsheet (Microsoft Corporation, Redmond, WA, United States) with parameters agreed upon by all reviewers. Another reviewer (WLOR) double-checked the extracted data. If there was any missing information, the correspondent author of the included articles was contacted via e-mail.

The following data from the included studies were tabulated: demographic data such as authors, year of publication, country, journal, number of studies included, study design, category of the study according to the objective, evaluated tests, reported guideline, databases searched, grey literature assessed, protocol register, risk of bias tool with all criteria used to evaluated RoB in *in vitro* studies and statistical software used.

2.1.6 Data analysis

The tabulated data were analyzed in an Excel spreadsheet database (Microsoft Corporation, Redmond, WA, USA), and it was represented through tables and charts considering the different criteria used to assess the RoB. In addition, all studies were categorized according to their main objective and evaluated test.

2.1.7 The RoBEndo tool formulation

All phases used to create the RoBEndo tool are described in Figure 1. Initially, all included articles were analyzed, and a list was made with all the criteria used to assess the RoB in the selected studies (Phase 1). After that, preliminary RoB criteria

list was formulated, considering the sources of bias identified from existing RoB tools found (RoB 2, ROBINS-I, SYRCLE and RoBDEMAT) or from systematic reviews of *in vitro* studies also by reviewing methodological checklists (Phase 2). Then, it was also obtained the percentual of each criteria used by included SRs (Table 1). Finally, in Phase 3 all criteria selected in consensus were evaluated by coauthors to develop a tool to assess the RoB of *in vitro* studies in endodontics (RoBEndo tool) considering the particularities of the area (Table 2). Any eventual disagreements were resolved through discussion.

2.1.8 Reliability analysis

The RobEndo tool developed was evaluated by three endodontic specialists and researchers that previously worked in systematic reviews to serve as independent examiner, allowing measurement of inter-rater reliability (IRR), in line with a previous study (Delgado *et al.*, 2022). A guideline table, a judgment scale, and nine laboratory studies in endodontics from high-impact journals involving physical, mechanical, chemical, and biological tests were provided to be independently evaluated by each examiner. Additionally, the RoBDEMAT (Delgado *et al.*, 2022) tool was also assessed by all examiners using the same in vitro studies. Kappa (κ) statistics were used to assess the IRR for each RoB tool (IBM SPSS Statistics). The agreement scale was judged as poor (0), mild (0.1 - 0.2), regular (0.21 - 0.4), moderate (0.41 - 0.6), substantial (0.61 - 0.8) or nearly perfect (0.81 - 0.99) (Cohen, 1960).

3 Results

3.1 Search strategy

The electronic search identified 6418 potentially relevant records. Figure 2 is a flowchart that summarizes the article selection process according to the PRISMA 2020 Statement. After removing the duplicates, 4592 articles remained to screen by title and abstract, 4471 records were excluded because they did not meet the inclusion criteria, and 128 were held on to full-text analysis. Of these, 34 of them were excluded because they no evaluated RoB, 2 because they were classified as endocrowns and 5 were excluded because were not found the full text available (Table A2). The remaining 87 articles fulfilled all the inclusion criteria and were included.

3.2 Study characteristics

A total of 87 SRs of in vitro studies within the endodontics scope were published in the last 5 years. Of the total, 53 (60.9%) articles only included in vitro studies. However, only 3 (5.8%) of the articles analyzed included three or more types of study design, and Brazil was the country that most published SR in the area totaling 24 (27.6%), followed by Italy with 14 (16.1%). Forty-six (46) periodic were cited, with *"Australian Endodontic Journal"* and *"Materials"* being the most cited, totaling 8 publications each one. Also, 79 (90.8%) studies reported the use of the PRISMA guideline (Table 3), while 8 did not report any guideline. In 76 (87.3%) studies the literature search was carried out in three or more databases, and 31 (35.6%) studies reported searching the grey literature.

Furthermore, in Table 4, it was found that 36 studies did not register the protocol, while 40 registered in PROSPERO, 10 in the Open Science Framework (OSF) and 1 in INPLASY. The most published category in the field of endodontics was "Root canal sealer" (20.6%), followed by "Endodontic file" and "Irrigation technique", both with 16.1%. "Physiomechanical properties" was mainly evaluated, followed by

"Antimicrobial properties", as show in Figure 3. Furthermore, all the studies analyzed assessed the RoB using criteria adapted for other studies or by adapting existing tools. The Cochrane Collaboration Tools was the most cited (19.5%), followed by Joanna Briggs Institute and CONSORT checklist (12.6%). Thirty-six (41.3%) studies performed a statistical meta-analysis, with RevMan (24) being the main software used.

3.4. Risk of Bias criteria used by SRs

A total of 36 items were reported (Table A3) from all 87 SRs. Thus, 14 items were selected for the elaboration of the instrument to assess RoB. Five items most used to assess RoB in the analyzed SRs (Table 5) were: blinding (52.9%), sample size (49.4%), adequate statistical analysis (42.5%), randomization (36.8%) and standardized sample preparation and handling (35.6%). In addition, other selected items are described in Table 5.

3.4 The RoBEndo tool design

The RobEndo tool (Table 2) were developed with five different domains (D): *bias in the intervention preparation and handling (D1), bias arising from the randomization process (D2), bias due to deviations from intended interventions (D3), bias in the outcomes analyzed (D4), and other bias (D5).* The five domains chosen follow a general line, as D1 and D2 can be included in the pre-intervention phase, D3 can be considered as the intervention phase and D4 and D5, the reporting phase. In each of these domains, the most prevalent sources of bias reported by SRs were added.

Fourteen items pertaining to different sources of bias within the domains, along with signaling questions considering the particularities of endodontics were developed, as well as a guide that can be used for RoB judgement (Table 2). The choice of these

five domains and signaling questions was carried out considering the criteria used to assess the RoB in the 87 SRs included.

An Excel spreadsheet (Microsoft Corporation, Redmond, WA, United States) was also developed to automatically generate a figure to analyze the RoB in *in vitro* studies in endodontics (available in: https://osf.io/azd8u/).

3.5 Judgement

Generating a summary RoB score is therefore not recommended as this would require the attribution of weights to different domains which is highly subjective and difficult to justify (Chen *et al.*, 2014; Denison *et al.*, 2019). Therefore, the present study defined that each signaling question should be answered as either “Yes”, “No” and “Insufficiently reported”, with the exception of questions 1.1 and 1.2 which must be answered only with “Yes” or “No”. As recommended in the literature (Delgado *et al.*, 2022), a checklist was developed (Table A4), which brings relevant information about what was performed in the endodontic laboratory studies, what was reported and whether it was done properly, using the scale of response cited above, presented in tabular format, replacing an often subjective final judgment score. Furthermore, "Overall risk of bias for result" has been added according to RoB 2.0 (Jonathan A.C. Sterne *et al.*, 2019) to assess the overall bias, which can be considered as "Low" if "Yes" was answered for all domains for the result. "Some concerns" if it is answered “Insufficiently reported” in at least one domain, and with any "No" reported for any domain. "High" if at least one "No" answered for a domain, or if the study is judged to have "Insufficiently reported" information for multiple domains, as shown in Table 2.

3.6 Reliability analysis

The results for the Cohen's kappa statistics are shown in Table 5. Substantial and nearly perfect agreement were found among examiners using the RoBEndo tool. On the other hand, it was found a moderate and substantial agreement among examiners in the RoBDEMAT tool.

4 Discussion

This umbrella review was able to provide an overview of criteria used to assess RoB in 87 SRs of *in vitro* studies in endodontics, as well as demonstrate which topics have been most published in these studies in the last 5 years. The lack of standardization to assess the RoB was notable, once all used different criteria adapted from other SRs or used tools indicated for other study designs, such those recommended to clinical trials. To address this issue, the RoBEndo tool was developed to provide a systematic approach to evaluate RoB of endodontic *in vitro* literature, considering the particularities of the area and a broad synthesis of common criteria used by SRs evaluated.

The main topics evaluated in the included SRs of Endodontic scope were related to endodontic sealers, endodontic file and irrigation techniques. Also, it was found that some areas have few SRs of *in vitro* studies, such as those related to endoguide, intraorifice barrier and ozone therapy, probably due to the limited data available from primary studies. Furthermore, most of the included studies reported the use of PRISMA guideline, and some recent studies (Ahmad *et al.*, 2022; Shroff *et al.*, 2022) still reported the non-updated guideline, PRISMA 2009 (Moher *et al.*, 2009) and not the 2020 update (Page *et al.*, 2021). Using reporting guidelines is essential in

planning and conducting systematic reviews to ensure that all necessary information is included. In addition, the full reports allow readers to assess the suitability of the methods and therefore the reliability of the SR results (Page *et al.*, 2021).

Regarding the different criteria used for RoB analysis, it was found that CONSORT checklist was considered for this purpose, and in some studies with adaptations (Fonseca *et al.*, 2019; Moreno-Rabié *et al.*, 2020; Sanz *et al.*, 2020, 2021; Ashkar, Sanz and Forner, 2022; Portela *et al.*, 2022; Gómez-Delgado *et al.*, 2023). However, the CONSORT Statement includes a 25-item checklist to guide the report of RCTs and is unrelated to assessing the RoB in *in vitro* studies. These SRs assessed the RoB related to some criteria that cannot be considered bias, such as *summary*, *scientific basis and explanation of justification*, *specific objectives* and/or *hypotheses* and other items used to guide the report. Therefore, bias should be considered an error in the study *design*, that can lead to distortions in its result, threaten the internal validity of the research (such as an incorrect sample calculation or statistical analysis) (Popovic and Huecker, 2023).

Furthermore, “Quality" and "bias" are terms that have been misused to classify the validity of methodological conditions. Some authors have confused "methodological quality" with "risk of bias", such as the use of the MINORS tool to assess RoB (Vendramini *et al.*, 2020; Palczewska-Komsa, Gapiński and Nowicka, 2022; Pimenta *et al.*, 2022). The methodological quality assessment determines how well a primary study was designed and executed to prevent systematic errors or bias (Hartling *et al.*, 2009). On the other hand, a RoB can arise from critical flaws in the methodological design, unreliable or non-reproducible methods, improper or incomplete data analysis, faulty interpretation of the results, or improper or incorrect reporting of the conclusions. When critically appraising a research study, assessors

should prioritize how closely a study's findings may approximate the truth (RoB) over how well the study was conducted given the capabilities of the study investigators (quality) (Buttner, et al 2019). Therefore, while RoB and methodological quality tools may have similar items, they can vary in their outcome applications (Nagendrababu *et al.*, 2022).

The RoBEndo tool was formulated considering that many authors still use inappropriate tools for evaluate the RoB. For this, the present tool includes five domains. In each of these domains, the most prevalent sources of bias were added, with the exception of "description of the type of study in the methodology", which was used only in 3.4% of the studies. However, the criteria were considered, since the design of a study can affect the validity of its results (Ranganathan and Aggarwal, 2018). In addition, some studies did not clearly describe the study design (i.e. *in vitro, in situ* or *ex vivo*).

The description of "sample size" was considered as bias by 43 SRs (49,4%), and was included in D1. Sample calculation is the formula for arriving at the sample size of a survey (Schulz and Grimes, 2005). It is related to precision and not directly to bias, but limitations in sample size may affect the credibility of the results (Delgado et al., 2022). The use of a statistically incorrect sample size may lead to inadequate results in both clinical and laboratory studies as well as resulting in time loss, cost, and ethical problems (Serdar *et al.*, 2021). The elaboration in this criterion reinforces the importance of authors providing a clear rationale and justification for the sample size chosen or featuring an a priori power analysis to determine an appropriate sample size. Another item considered was the description of "interventions" (9.2%), once it is expected that the interventions have sufficient details to allow for replication, including how and when they were administered.

The evaluation of “standardized sample preparation and handling” (35.6%) was also included as RoB to analyze whether the author standardized the sample according to the manufacturers’ instructions with description of lots used in case of commercial materials, and whether they described how standardized samples and materials were employed across groups. In endodontics, for example, the influence of irrigation tip, root canal curvature, and final apical diameter on periapical debris and irrigant extrusion during root canal instrumentation can be affected by the type of needle used for irrigation (Teja *et al.*, 2022). In this case, the description and standardization of the needle type used must be reported clearly. In the same way, “similar dimensions among the samples” (26.4%) may help to standardize the specimens used. For example, in a cyclic fatigue test the files should be evaluated in teeth with a similar anatomy and similar conditions for obtain a reproductible result (Khandagale *et al.*, 2021).

Furthermore, “control group” was an item considered by 20.7% of SRs included. Studies without control group are of limited value as there is no standard or reference to compare (Hickel *et al.*, 2007). Besides, the description of “standard procedures” was considered as a source of bias by 16.1% of SRs included, and it was also included in RoBEndo tool. Studies must report whether identical conditions were provided for all groups. The description of factors that may influence the results must be clearly described by *in vitro* studies, such as temperature, humidity, time and equipment settings. These factors must be identical and controlled, including the presence of a reference standard if applicable (Delgado *et al.*, 2022).

Other criteria evaluated by SRs was the description of a “single operator” (16.1%). Different operators can lead to non-standardization, and considering that results can be biased by this, a “single operator” was included in RoBEndo tool. It was

previously reported that the success rates of endodontic procedures may vary when performed by highly trained and experienced professionals—endodontists or postgraduate students (Chybowski *et al.*, 2018). One study have found that the quality of root-canal obturation performed by endodontists was significantly better in comparison to general dental practitioners general dental practitioners (Habib *et al.*, 2018). Other study found that operators with different competencies and clinical experience were not able to ensure pore-free root-canal fillings when the single cone obturation technique in conjunction with hydraulic calcium silicate-based sealer was used (Drukteinis *et al.*, 2021). The same applies for experimental studies, as laboratory work is usually performed by highly experienced operators too (Kim *et al.*, 2017). Thus, a single operator could provide a lower RoB in the performed technique.

“Allocation concealment, allocation sequence generation and randomization” were criteria that appeared in some SRs. Therefore, these terms were considered as a single item "Randomization" in D2 (36.8%), as all included SRs referred to the same purpose when this was considered. Randomization may eliminates the selection bias, balances the groups with respect to many known and unknown confounding or prognostic variables, and forms the basis for statistical tests (based on an assumption of the equality of treatments) (Suresh, 2011). For this, in this domain it was proposed to assess if the samples were randomized, if their allocation were concealed appropriately and if the author described if the randomization are conduct using computer generated sequences, random number attribution tables, shuffling envelopes, or cards.

The most prevalent source of bias reported by SRs included was “blinding” (52.9%), which was included in D3. This criteria are already used in many other RoB assessment tools such as in Cochrane Collaboration Tools (Higgins *et al.*, 2011). The

"blinding" criteria guides the evaluator to answer whether the blinding was carried out by the personnel involved in the intervention or by the evaluator. The stakeholders are a source of bias in studies because they can consciously or unconsciously influence procedures or outcomes (Park, Voss and Voss, 2023). Also in this domain, “statistical analysis” was the third criteria more assessed by SRs (42.5%). Articles with incomplete or inappropriate statistical report may be of lower quality publications that tend to avoid critique during the peer review process (Nieminen and Uribe, 2021). Also, *in vitro* studies must appropriately report the scale of data (continuous, ordinal, nominal), also its distribution (parametric or non-parametric test), statistical test and software used, and specific study design factors (e.g. factorial design, repeated measures at time points). The elaboration criteria in the present study lay emphasis on the descriptive and analytical statistical approach presented, to evaluate if it is adequate to the yielded data and the aims.

The “account of outcome data” (18.4%) was also considered in SRs included. RoBEndo tool in D4 emphasize that the evaluator must answer "Yes" if the author adequately described and measured the outcomes with testing machine or by independent observers with independent assessment and if outcome measures (e.g fracture strength of endodontic file, antimicrobial evaluation, solubility of endodontic cements) was defined properly to allow interpretation and, if needed, comparison or pooling across studies. In the same way, the “complete reporting of results” was considered by 17.2% of SRs. RoBEndo tool proposed that evaluator answer "Yes" the reviewers reported all outcomes of the study in line with what could be expected or it has been defined as planned outcomes by the researcher before conducting the study. Furthermore, also answer "Yes" if outcomes are reported in sufficient detail for a full appraisal (e.g., measures of central tendency like means or medians; measures of

dispersion like standard deviation or interquartile range if applicable). The substantiation of confidence in the disseminated research findings is normally conditional on the quality of reporting and transparent interpretation of the results (Giannakoulas, Koletsi and Tzanetakis, 2022), which improves the possibility of comparability and reproducibility of studies (Chiriboga *et al.*, 2022).

The “funding” was also considered in some SRs (11.5%) and was included in D5, as well *other sources of bias* - based in RoB 2.0 (Jonathan A.C. Sterne *et al.*, 2019). There is an impasse between scientific and commercial interests, which may reflect in distrust of several research results carried out with the use of commercial materials. The researcher must be impartial to obtain a valid advance in scientific knowledge (Candeiro *et al.*, 2011). On the other hand, conflicts of interest represent circumstances in which professional judgments or actions may be at risk of being unduly influenced by an interest, such as financial gain or career advancement (Romain, 2015). An interest can also be financial or non-financial, and the resulting bias can be conscious or unconscious (Kafaee *et al.*, 2022). So, is it possible that some studies may generate less reliable results in evaluated tests of materials funded and with conflict of interest.

The RoBENDO tool was developed to specifically analyze *in vitro* studies in endodontics with their particularities. The inter-rater reliability obtained by this tool was higher than the reliability reported for RoBDEMAT tool (Delgado *et al.*, 2022) with substantial and nearly perfect agreement. When the risk of bias of the same nine studies used to evaluate RoBEndo was assessed by the RoBDEMAT tool, a moderate and substantial agreement was found. These findings suggest RoBEndo could facilitate RoB assessment of *in vitro* studies in endodontics. One difficult in the application of the tool is related to the lack of standardization of *in vitro* studies reports.

Therefore, future *in vitro* endodontic literature should also better describe the parameters included in RoBEndo tool, which could facilitate RoB assessment and improve the quality of *in vitro* studies in endodontics. Finally, RoBEndo tool requires perpetual reappraisal and, if necessary, modifications. In the future we may further revise the tool considering comments and criticisms that may raise by researchers.

5 Conclusion

This umbrella review mapped the criteria used to assess the risk of bias (RoB) of *in vitro* studies by systematic reviews (SRs) in endodontics. The criteria used to assess RoB were divergent and, in some reviews, inadequate. In this perspective, a new standardized RoB tool was developed, the so called RoBEndo tool, and high agreement between examiners was found. The RoBEndo synthesized common criteria used in recent SRs, and may significantly improve the RoB assessment of *in vitro* endodontic studies.

Conflict of Interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Table 1. Frequency of criteria suggested

Criteria suggested	Criteria used	Frequency	References
Did author identify study design?	Description of study type in the methodology	3,4% (3/87)	Pintor et al (2020); de Araújo, et al (2022); Rahul, et al (2022);
Did the author use adequate sample size?	Sample size calculation	49,4% (43/87)	Del Fabro et al (2018); Fonseca et al (2019); Silva et al (2019); Mickevičienė et al (2020); Gomes et al (2020); Moreno-Rabié et al (2020); Silva et al (2020); Sanz et al (2020); Silva et al (2020); Vendramini et al (2020); Attavar and Hedge (2021); Raghad et al (2020); Saeed et al (2021); Bhandi et al (2021); Dioguardi et al (2021); Bonzanini et al (2021); Sanz et al (2021); Machado et al (2021); Palczewska-Komsa et al (2021); Pereira et al (2021); Eren et al (2021); Silva et al (2021); de Araújo, et al (2022); Alipour, et al (2022); Savitha, et al (2022); Al-Sanabani, et al (2023); Al-Zaka, et al (2022); Reis-Prado, et al (2022); Suresh, et al (2022); Karobari, et al (2022); Puleio, et al (2022); Alkahtany (2023); Dioguardi, et al (2022); Ashkar, et al (2022); Yang, et al (2022); Nisar, et al (2022); Haridoss, et al (2022); Chopra, et al (2022); Milla, et al (2022); Nobar, et al (2022); Bds, et al (2022); Rekha, et al (2023); Gómez-Delgado, et al (2023)
Did the author describe the intervention?	Description of Intervention	9,2% (8/87)	Fonseca et al (2019); Lim et al (2020); Moreno-Rabié et al (2020); Sanz et al (2020); Sanz et al (2021); Puleio, et al (2022); Ashkar, et al (2022); Gómez-Delgado, et al (2023);
Did the author include control group?	Appropriate control group(s)	20,7% (18/87)	Parolia et al (2020); Silva et al (2020); Raghad et al (2020); Saeed et al (2021); Machado et al (2021); Palczewska-Komsa et al (2021); de Araújo, et al (2022); Teja, et al (2022); Reis-Prado, et al (2022); Suresh, et al (2022); Vasudevan, et al (2022); Nisar, et al (2022); Haridoss, et al (2022); Zubair, et al (2022); Nobar, et al (2022); Mehta, et al (2022); Banci, et al (2023); Rekha, et al (2023);
Did the author standardize sample preparation and handling?	Standardized sample preparation and handling	35,6% (31/87)	Neelakantan et al (2018); De Oliveira et al (2018); Silva et al (2019); Schestatsky et al (2019); Mickevičienė et al (2020); Silva et al (2020); Chia et al (2020); Parolia et al (2020); Raghad et al (2020); Attavar and Hedge (2021); Augusto et al (2021); Dioguardi et al (2021); Zubizarreta-Macho et al (2021); Oliveira et al (2021); Bonzanini et al (2021); Dotto et al (2020); Silva et al (2021); de Araújo, et al (2022); Alipour, et al (2022); Savitha, et al (2022); Al-Sanabani, et al (2023); Al-Zaka, et al (2022); Teja, et al (2022); Reis-Prado, et al

			(2022); Teja, et al (2022); Suresh, et al (2022); Alkahtany (2023); Dioguardi, et al (2022); Mazreah, et al (2022); Augusto, et al (2022); Rekha, et al (2023)
Did the author use similar dimensions among the samples?	Similar dimensions among the samples	26,4% (23/87)	Schestatsky et al (2019); Silva et al (2019); Valle et al (2020); Silva et al (2020); Oliveira et al (2021); Raghad et al (2020); Saeed et al (2021); Pereira et al (2021); Silva et al (2021); de Araújo, et al (2022); Savitha, et al (2022); Al-Sanabani, et al (2023); Lin, et al (2022); Al-Zaka, et al (2022); Vasudevan, et al (2022); Alkahtany (2023); Yang, et al (2022); Haridoss, et al (2022); Chopra, et al (2022); Zubair, et al (2022); Nobar, et al (2022); Mehta, et al (2022); Banci, et al (2023);
Did the author describe single operator?	Operator variability (single operator)	16,1% (14/87)	Nagendrababu et al (2019); Silva et al (2020); Raghad et al (2020); Augusto et al (2021); Bhandi et al (2021); Bonzanini et al (2021); Eren et al (2021); Savitha, et al (2022); Al-Sanabani, et al (2023); Al-Zaka, et al (2022); Haridoss, et al (2022); Chopra, et al (2022); Nobar, et al (2022); Rekha, et al (2023);
Did the author use standard procedures?	Standard procedures	16,1% (14/87)	Silva et al (2019); Silva et al (2020); Oliveira et al (2021); Bhandi et al (2021); Machado et al (2021); Eren et al (2021); Silva et al (2021); Alipour, et al (2022); Savitha, et al (2022); Teja, et al (2022); Vasudevan, et al (2022); Chopra, et al (2022); Zubair, et al (2022); Mazreah, et al (2022);
Did the author report randomization?	Allocation concealment/ Allocation sequence generation/ Randomization	36,8% (32/87)	Tavares et al (2019); Razdan et al (2019); Fonseca et al (2019); Harrison (2020); Moreno-Rabié et al (2020); Sanz et al (2020); Dioguardi et al (2021); Sanz et al (2021); Zubizarreta-Macho et al (2021); Pereira et al (2021); Attavar and Hedge (2021); Ranjan and Ranjan (2021); Mathew et al (2021); Sanz et al (2021); de Araújo, et al (2022); Savitha, et al (2022); Lin, et al (2022); Al-Zaka, et al (2022); Reis-Prado, et al (2022); Teja, et al (2022); Suresh, et al (2022); Puleio, et al (2022); Alkahtany (2023); Dioguardi, et al (2022); Ashkar, et al (2022); Yang, et al (2022); Haridoss, et al (2022); Zubair, et al (2022); Nobar, et al (2022); Augusto, et al (2022); Bds, et al (2022); Gómez-Delgado, et al (2023)
Did author perform blinding?	Blinding	52,9% (46/87)	Neelakantan et al (2018); Tavares et al (2019); Razdan et al (2019); Fonseca et al (2019); Schestatsky et al (2019); Mickevičienė et al (2020); Chandak et al (2020); Harrison (2020); Moreno-Rabié et al (2020); Silva et al (2020); Sanz et al (2020); Valle et al (2020); Parolia et al (2020); Attavar and Hedge (2021); Oliveira et al (2021); Raghad et al (2020); Augusto et al (2021); Ranjan and Ranjan (2021); Dioguardi et al (2021); Bonzanini et al (2021); Dotto et al (2020); Mathew et al (2021); Sanz et al (2021); Zubizarreta-Macho et al (2021); Palczewska-Komsa et al (2021); Pereira et al (2021); Eren et al (2021); Alipour, et al (2022); Savitha, et al (2022); Al-Sanabani, et al (2023); Lin, et al (2022); Teja, et al (2022); Reis-Prado, et al (2022); Teja, et al (2022); Suresh, et al (2022); Puleio, et al (2022);

			Alkahtany (2023); Dioguardi, et al (2022); Ashkar, et al (2022); Yang, et al (2022); Chopra, et al (2022); Zubair, et al (2022); Milla, et al (2022); Augusto, et al (2022); Rekha, et al (2023); Gómez-Delgado, et al (2023);
Did author perform a correct statistical analysis?	Appropriate statistical analysis	42,5% (37/87)	De Oliveira et al (2018); Tavares et al (2019); Fonseca et al (2019); Silva et al (2019); Mickevičienė et al (2020); Moreno-Rabié et al (2020); Silva et al (2020); Sanz et al (2020); Parolia et al (2020); Silva et al (2020); Saeed et al (2021); Dioguardi et al (2021); Sanz et al (2021); Zubizarreta-Macho et al (2021); Machado et al (2021); Palczewska-Komsa et al (2021); Silva et al (2021); de Araújo, et al (2022); Savitha, et al (2022); Lin, et al (2022); Reis-Prado, et al (2022); Suresh, et al (2022); Karobari, et al (2022); Puleio, et al (2022); Vasudevan, et al (2022); Dioguardi, et al (2022); Ashkar, et al (2022); Nisar, et al (2022); Haridoss, et al (2022); Chopra, et al (2022); Zubair, et al (2022); Milla, et al (2022); Nobar, et al (2022); Bds, et al (2022); Mehta, et al (2022); Banci, et al (2023); Gómez-Delgado, et al (2023)
Did the author report account of outcome data?	Account of outcome data	18,4% (16/87)	Razdan et al (2019); Fonseca et al (2019); Chandak et al (2020); Gomes et al (2020); Moreno-Rabié et al (2020); Sanz et al (2020); Vendramini et al (2020); Sanz et al (2021); Eren et al (2021); Lin, et al (2022); Teja, et al (2022); Suresh, et al (2022); Vasudevan, et al (2022); Bds, et al (2022); Mehta, et al (2022); Banci, et al (2023);
Did the author report complete reporting of results?	Complete reporting of results	17,2% (15/87)	Razdan et al (2019); Alipour, et al (2022); Lin, et al (2022); Nadalon, et al (2022); Teja, et al (2022); Teja, et al (2022); Suresh, et al (2022); Puleio, et al (2022); Vasudevan, et al (2022); Ashkar, et al (2022); Yang, et al (2022); Augusto, et al (2022); Mehta, et al (2022); Banci, et al (2023); Gómez-Delgado, et al (2023)
Did the author report funding?	Funding	11,5% (10/87)	De Oliveira et al (2018); Fonseca et al (2019); Moreno-Rabié et al (2020); Sanz et al (2020); Sanz et al (2021); Nadalon, et al (2022); Puleio, et al (2022); Ashkar, et al (2022); Bds, et al (2022); Gómez-Delgado, et al (2023)

Table 2. The RoBEndo tool

Domain of bias and signaling question	Elaboration	Response options
D1 - Bias in the intervention preparation and handling		
1.1 Did author identify study design?	• Answer 'Yes' if have a clearly description of study design (in vitro, ex vivo or in situ study). • Answer 'No' with no description of study design.	Y/N
1.2 Did the author provide sample size rationale and reporting?	• Answer 'Yes' if the author provides a rationale and justification for the sample size chosen or feature an a priori power analysis. • Answer 'No' if the author no provides a justification about the sample size chosen in study.	Y/N
1.3 Did the author describe the intervention?	• Answer 'Yes' if the interventions for each group have sufficient details to allow replication, including how and when they were actually administered. • Answer 'No' if no descriptions are reported to the interventions for each group with sufficient details to allow replication. • If these details are incomplete, they should be marked 'Insufficiently reported'.	Y/N/IR
1.4 Did the author include control group?	• Answer 'Yes' if the author includes a control group in study with specifics information, including a reference standard if applicable, with identical and controlled conditions provided for all groups with the reporting of factors such as temperature, humidity, time and equipment settings. • Answer 'No' if there are no inclusion of a control group in the study. • Answer 'Insufficiently reported' in the absence of specific information about the control group.	Y/N/IR
1.5 Did the author standardize sample preparation and handling of materials used according to the manufacturers?	• Answer 'Yes' if there are descriptions regarding the standardization of sample manipulation according to the manufacturers with description of lots used in case of commercial materials and if the author described how standardized samples and materials were employed across groups (e.g., different types of endodontic files being used). • Answer 'No' if there are no descriptions regarding the standardization of sample manipulation according to the manufacturers and if there is no description that the materials were used according to the manufacturers in case of commercial materials. • Answer 'Insufficiently reported' if the author standardized the sample according to the manufacturers, with no description of how it was used (details are incomplete) or of lots used in case of commercial materials.	Y/N/IR
1.6 Did the author use similar dimensions among the samples?	• Answer 'Yes' if the author mentions that used specimens with similar dimensions, with description of dimensions used, and if the sample used was teeth, answer 'Yes' if mentions that used teeth with similar anatomy.	Y/N/IR

	• Answer ‘No’ if the author doesn’t report anything about the dimensions of the samples. • If these details are incomplete, they should be marked ‘Insufficiently reported’.	
1.7 Did the author describe single operator?	• Answer ‘Yes’ if a single operator performed the study design or if the author specificad that more than one operator performed the study design and a previous calibration with the operators was made. • Answer ‘No’ if different operators performed the study design. • Answer ‘Insufficiently reported’ if the author is not clearly about how many operators performed the study design.	Y/N/IR
1.8 Did the author use standard procedures/methods according to normatives or techniques?	• Answer 'Yes' if the author adequately described the chosen evaluation test used (including equipment or instruments) to allow critical appraisal and replication in line with the research question (if applicable); and if the author standardized test procedures according to other studies, or according to normatives (such as ADM guidelines or ISO/ASTM standards) (if applicable). • Answer ‘No’ if there are no use of standard tests or procedures according to the literature or normatives. • If these details are incomplete, they should be marked ‘Insufficiently reported’.	Y/N/IR
D2 - Bias arising from the randomization process		
2.1 Did the author report randomization?	• Answer 'Yes' if the samples were randomized and their allocation was concealed appropriately; and also, if the author describes if the randomization was conducted using computer generated sequences, random number attribution tables, shuffling envelopes, or cards. • Answer ‘No’ if there are no randomization performed. • Studies that only mention “teeth were randomly allocated” but fail to give details of the randomization process should be marked as ‘Insufficiently reported’.	Y/N/IR
D3 - Bias due to deviations from intended interventions		
3.1 Did author perform blinding?	• Answer ‘Yes’ if the blinding was performed by the personal involved in the intervention or by outcome assessor. • Answer ‘No’ if no type of blinding was performed. • Answer ‘Insufficiently reported’ if the only information about blinding is a statement that the study was blinded, with no details about who was blinded.	Y/N/IR
3.2 Did author perform a correct statistical analysis? (**)	• Answer ‘Yes” if the descriptive and analytical statistical approach was adequate to the yielded data and the study aims with description of the scale of data (continuous, ordinal, nominal), data distribution (parametric or non-parametric test), statistical test and software used. Also, answer "Yes" if the study reports the study design factors (e.g. factorial design, repeated measures at time points) if applicable. • Answer ‘No’ if the statistical analysis was inappropriate to the data.	Y/N/IR

	• Answer ‘Insufficiently reported’ if the only information about correct statistical analysis is a statement that the study realized statistical analysis.	
D4 - Bias in the outcomes analyzed		
4.1 Did the author report how outcome data was obtained and the account of outcome data?	• Answer 'Yes' if the author adequately described and measured the outcomes by examiners with independent assessment oy by a testing machine; and if the outcome measured was defined properly (e.g. fracture strength of endodontic file, antimicrobial evaluation, solubility of endodontic cements) to allow interpretation and, if needed, comparison or pooling across studies. • Answer ‘No’ if there are no description of how outcomes was measured. • If these details are incomplete, they should be marked ‘Insufficiently reported’.	Y/N/IR
4.2 Did the author report complete reporting of results?	• Answer ‘Yes' if the study reported all outcomes of the study in line with what could be expected in methods section or by the registered protocol (if available); or it has been defined as planned outcomes by the researcher before conducting the study. Also answer "Yes" if the outcomes are reported in sufficient detail for a full appraisal (e.g., measures of central tendency like means or medians; measures of dispersion like standard deviation or interquartile range if applicable). • Answer ‘No’ if there are some results incompletely reported or in insufficient details.	Y/N/IR
D5 - Other bias		
5.1 Did the author report funding or other source bias?	• Answer ‘Yes’ if the author describes sources of funding that potentially could compromise the study with conflict of interest with support related to the companies of the materials tested; or bias due to problems not covered in other domains in the tool. • Answer 'No' if the funding is not related to the companies of the materials tested or if it is stated that there is no conflict of interest. • Answer ‘Insufficiently reported’ if there are insufficient details to evaluate a possible conflict of interest.	Y/N/IR
OVERALL RISK OF BIAS		
Low, Some concerns or High?	• **Low risk of bias:** The study is judged to be at low risk of bias with "Yes" answered for all domains for this result. • **Some concerns:** The study is judged to raise some concerns if it is insufficiently reported in at least one domain for this result, with any "No" reported for any domain. • **High risk of bias:** The study is judged to be at high risk of bias with at least one "No" answered for a domain, or the study is judged to have insufficiently reported information for multiple domains in a way that substantially lowers confidence in the result	

Table 3. Demographic data of included studies

Author and Year	Country	Periodic	Number of studies included	Study design of studies included	Reporting guideline	Databases searched	Grey Literature
Del Fabbro, et al (2018)	Italy	The Journal of Evidence-Based Dental PracticeThe Journal of Evidence-Based Dental Practice	6	In vivo and in vitro studies	PRISMA 2009	PubMed, Scopus, Embase and CENTRAL	Not reported
Oliveira, et al (2018)	Brazil	European Journal of Dentistry	18	In vitro and in vivo studies	PRISMA 2009	PubMed, Scopus and Web of Science	Not reported
Nagendrababu, et al (2018)	Malaysia	Clinical Oral Investigations	15	In vitro	PRISMA 2009	PubMed, Scopus, Embase, Cochrane Library, Science Direct and EbSCOhost	Not reported
Neelakantan, et al (2019)	Hong Kong	International Endodontic Journal	8	In vitro	PRISMA 2009	PubMed, Scopus and Web of Science	Not reported
Tavares, et al (2019)	Brazil	Acta Odontologica Scandinavica	21	In vitro	PRISMA 2009	Pubmed, Scopus, Web of Science and Virtual Health Library (LILACS)	OpenGrey
Razdan, et al (2019)	Denmark	Acta Odontologica Scandinavica	63	In vitro	PRISMA 2009	PubMed and Embase	Not reported
Dioguardi, et al (2019)	Italy	The Scientifc World Journal	5 (3)	In vitro	PRISMA 2009	PubMed, Google Scholar and EBSCOhost	Not reported
Dioguardi, et al (2019)	Italy	Materials (Basel)	12 (8)	CTs and in vitro studies	PRISMA 2009	PubMed and Scopus	Not reported
Nagendrababu, et al (2019)	Malaysia	Quitessence International	25	In vitro	PRISMA 2009	PubMed and Scopus	Not reported
Fonseca, et al (2019)	Spain	Materials (Basel)	94	In vitro and in vivo studies	PRISMA 2009	PubMed, Web of Science, Embase, Cochrane Library, Science Direct and ClinicalTrials.gov	Not reported
Dioguardi, et al (2019)	Italy	Applied Sciences	26 (11)	In vitro	PRISMA 2009	PubMed and Scopus	Not reported
Schestatsky, et al (2019)	Brazil	Journal of the Mechanical Behavior of Biomedical Materials	3 (2)	In vitro	PRISMA 2009	PubMed and SCOPUS	Not reported
Silva, et al (2019)	Brazil	The Journal of Evidance-Based Dental Practice	20 (17)	In vitro	PRISMA-P 2015	PubMed, Scopus, Web of Science and Science Direct	OpenGrey

Mickevičienė, et al (2020)	Lithuania	Baltic Dental and Maxillofacial Journal	5	In vivo and in vitro studies	PRISMA 2009	Pubmed, Science Direct and Wiley	Not reported
Jamali, et al (2020)	China	Pesquisa Brasileira em Odontopediatria e Clínica Integrada	7	In-vitro studies and randomized controlled trials	Not reported	PubMed, Embase, Cochrane Library, Google Scholar and ISI	Not reported
Chandak, et al (2020)	India	Journal of Clinical and Diagnostic Research	4	Cts and in vitro studies	PRISMA	PubMed, Scopus and Web of Science	Not reported
Lim, et al (2020)	Malaysia	Restorative Dentistry & Endododontics	14	In vitro	PRISMA 2009	PubMed, Scopus and EBSCOhost	Not reported
Gomes, et al (2020)	Brazil	Brazil Oral Reserach	10	In vitro	PRISMA	PubMed, Scopus, Embase, Scielo and Virtual Health Library	OpenGrey
Harrison (2020)	United Kingdom	Endodontic Practice Today	22	In vitro	Not reported	Science Direct, Wiley, PubMed and Google Scholar	Not reported
Moreno-Rabié, et al (2020)	Belgium	International Endodontic Journal	22	In vitro and ex vivo studies	PRISMA 2009	PubMed, Web of Science, Embase and Cochrane Library	Not reported
Pintor, et al (2020)	Brazil	International Endodontic Journal	40	In vitro	PRISMA-P 2015	PubMed, Scopus and Web of Science	OpenGrey
Silva, et al (2020)	Brazil	Restorative Dentistry & Endododontics	5	In vitro	PRISMA-P 2015	PubMed, Scopus, Web of Science, ScienceDirect, Cochrane	OpenGrey
Paterson, et al (2020)	Russia	Imaging Science in Dentistry	9	In vivo and in vitro studies	Not reported	PubMed, Web of Science, Embase, Cochrane Library and Scientific Electronic Library Online	OpenGrey
Dioguardi, et al (2020)	Italy	Jounal of Clinical Medicine	46 (6)	CTs and in vitro studies	PRISMA 2009	PubMed and Scopus	Not reported
Sanz, et al (2020)	Italy	Journal of Clinical Medicine	7	In vitro	PRISMA 2009	PubMed, Scopus, Web of Science, Embase and SciELO	Not reported
Valle, et al (2020)	Brazil	Brazilian Dental Journal	54	In vitro and in situ studies	PRISMA 2009	PubMed and Scopus	Not reported
Pedano, et al (2020)	Belgium	Materials	56 (30)	In vitro and in vivo studies	PRISMA-P 2015	PubMed, Web of Science and Embase	Not reported

Chia, et al (2020)	Malaysia	Restorative Dentistry & Endododontics	13	In vitro	Not reported	PubMed, Scopus and EBSCOhost	Not reported
Parolia, et al (2020)	Malaysia	Giornale Italiano di Endodonzia	16	In vitro	PRISMA 2009	PubMed, Scopus and EBSCOhost	Not reported
Silva, et al (2020)	Brazil	International Endodontic Journal	8	CTs and in vitro studies	PRISMA-P 2015	PubMed, Scopus, Web of Science and Science Direct	OpenGrey
Vendramini, et al (2020)	Brazil	Photodiagnosis and Photodynamic Therapy	27	In vitro	PRISMA 2009	PubMed, Embase, LILACS, SciELO and Google Scholar	Not reported
Attavar and Hedge (2021)	India	Journal of Advanced Oral Research	10	RCTs, clinical studies (in vivo and ex vivo), and in vitro studies	PRISMA	PubMed, Scopus, Web of Science and Cochrane Library	Not reported
Oliveira, et al (2021)	Brazil	Restorative Dentistry & Endododontics	4 (3)	In vitro	PRISMA 2009	PubMed, Scopus, Web of Science and Embase	Not reported
Augusto, et al (2021)	Brazil	Australian Endodontic Journal	12	In vitro	PRISMA 2020	PubMed, Scopus, Web of Science, Embase and LILACS	OpenGrey
Ranjan and Ranjan (2021)	India	International Journal of Dentistry and Oral Science (IJDOS)	2	In vitro	Not reported	PubMed, Scopus and Google Search	Not reported
Sawant, et al (2021)	India	Applied Sciences	13	In vitro	PRISMA-P 2016	PubMed, Scopus, Web of Science and Embase	Not reported
Saeed, et al (2021)	United Arab Emirates	Clinical, Cosmetic and Investigational Dentistry	10	In vitro	PRISMA 2009	PubMed, Scopus, Science Direct, Google Scholar, EBSCOhost, Wiley and ResearchGate	Not reported
Bhandi, et al (2021)	Saudi Arabia	Materials	9	In vitro	PRISMA-P 2015	PubMed, Scopus, Web of Science and Embase	Not reported
Dioguardi, et al (2021)	Italy	Materials	7 (3)	In vitro	PRISMA 2009	PubMed and Scopus	Not reported
Dioguardi, et al (2021)	Italy	Heliyon	9	In vitro and ex vivo studies	PRISMA 2009	PubMed, Scopus and Web of Science	Not reported
Bonzanini, et al (2021)	Brazil	Pesquisa Brasileira em Odontopediatria e Clínica Integrada	10 (8)	In vitro	PRISMA 2009	PubMed, Scopus, Web of Science, Embase, LILACS and Trip	Not reported

Dotto, et al (2020)	Brazil	JOURNAL OF ADHESION SCIENCE AND TECHNOLOGY	39	In vitro	PRISMA 2009	PubMed and Scopus	Not reported
Mathew, et al (2021)	United Arab Emirates	European Endodontic Journal	6	Cs and in vitro studies	PRISMA 2009	Pubmed, Scopus, Embase, EBSCOHost and DOSS	OpenGrey
Fontanele, et al (2021)	Brazil	International Endodontic Journal	8	In vitro	PRISMA 2009	PubMed, Scopus, Web of Science, Embase, Cochrane library and LILACS	Not reported
Aung and Myint (2021)	Myanmar	International Journal of Dentistry	12	Cohort; case-control, and in vitro studies	PRISMA 2009	PubMed, LILACS, Google Scholar, Research Gate and Hinari “Research4Life”	ProQuest and Scopus
Sanz, et al (2021)	Spain	International Endodontic Journal	20	In vitro	PRISMA 2020	PubMed, Scopus, Web of Science, Embase and SciELO	Not reported
Zubizarreta-Macho, et al (2021)	Spain	Journal of Clinical Medicine	7	RCTs, CTs, CS and in vitro RET	PRISMA 2009	PubMed, Scopus, Web of Science and Embase	Not reported
Machado, et al (2021)	Brazil	Australian Endodontic Journal	4 (3)	In vitro	PRISMA 2009	PubMed, Scopus, Web of Science, Embase and BASE	OpenGrey, Google Scholar and ProQuest
Palczewska-Komsa, et al (2021)	Poland	Materials	26	In vitro and in vivo studies	PRISMA 2020	PubMed, Scopus, Web of Science, Scince Direct, EBSCOhost and Wiley	Not reported
Pereira, et al (2021)	Brazil	Iranian Endodontic Journal	31 (10)	In vitro	PRISMA 2009	PubMed, Scopus, Web of Science, Cochrane Library, LLILACS, BBO and IBECS	Not reported
Eren, et al (2021)	Turkey	Restorative Dentistry & Endododontics	17 (7)	In vitro	PRISMA 2009	PubMed, Scopus, Web of Science and Cochrane Library	OpenGrey and Greylist
Sanz, et al (2021)	Spain	Dental Materials	13	In vitro	PRISMA 2009	PubMed, Scopus, Web of Science, Embase and SciELO	Not reported
Silva, et al (2021)	Brazil	Australian Endodontic Journal	22 (19)	In vitro	PRISMA	PubMed, Scopus and Web of Science	OpenGrey
de Araújo, et al (2022)	Brazil	BioMed Research International	30	In vitro	PRISMA 2020	PubMed, Scopus, Embase and Web of Science	Not reported
Alipour, et al (2022)	Iran	Clinical and Experimental Dental Research	13	In vitro	Not reported	PubMed, Scopus and Web of Science	Not reported

Savitha, et al (2022)	India	Journal of Conservative Dentistry	21 (6)	In vitro	PRISMA 2020	PubMed, Scopus and Web of Science	OpenGrey and Google Scholar
Rahul, et al (2022)	India	European Endodontic Journal	4	In vitro	PRISMA 2009	PubMed, Cochrane, Scopus, EMBASE, CINAHL, and Web of Science	OpenGrey and Google Scholar
Al-Sanabani, et al (2023)	Saudi Arabia	Journal of Prosthodontic Research	17	In vitro	PRISMA 2020	PubMed, Scopus, Web of Science, and Google Scholar	Not reported
Lin, et al (2022)	Malaysia	Giornale Italiano di Endodonzia	6	In vitro	PRISMA 2020	PubMed, Scopus, Web of Science, Cochrane Library, Google Scholar and EBSCO	OpenGrey
Nasiri and Wrbas (2022)	Germany	Saudi Dental Journal	15	In vitro and in vivo	Not reported	PubMed, Cochrane Library, ScienceDirect and Google Scholar	Not reported
Nadalon, et al (2022)	Brazil	Clinical Oral Investigations	14	In vitro	PRISMA-P 2015	PubMed, Scopus, Web of Science, Cochrane Library and Lilacs	OpenGrey, Google Scholar and ProQuest
Al-Zaka, et al (2022)	Iraq	Saudi Endodontic Journal	15	In vitro	PRISMA 2009	PubMed, Scopus, ScienceDirect and Google Scholar	Not reported
Teja, et al (2022)	India	International Journal of Environmental Research and Public Health	8	In vitro	PRISMA 2020	PubMed, Scopus and Web of Science	Not reported
Reis-Prado, et al (2022)	Brazil	International Endodontic Journal	36	In vitro and in vivo	PRISMA 2020	PubMed, Scopus, Web of Science, Embase and Cochrane Library	OpenGrey
Teja, et al (2022)	India	Saudi Dental Journal	19	In vitro and ex vivo	PRISMA 2015	PubMed, Scopus, Embase, Google Scholar and CINAHL	Not reported
Suresh, et al (2022)	United Arab Emirates	European Endodontic Jornaul	17	In vitro	PRISMA 2009	PubMed, Scopus, Embase, Cochrane Library, Science Direct, Google Scholar and ProQuest	OpenGrey
Karobari, et al (2022)	Italy	Journal of Clinical Medicine	51	In vitro	PRISMA	PubMed, Scopus, Cocharne Library and Science Direct	Not reported
Puleio, et al (2022)	Italy	Dentistry Journal	20	In vitro	PRISMA 2009	PubMed and Web os science	Not reported
Vasudevan, et al (2022)	India	European Endodontic Journal	14	In vitro and ex vivo	PRISMA 2020	PubMed, Scopus, Web of Science and Embase	OpenGrey

Alkahtany (2023)	Saudi Arabia	Photodiagnosis and Photodynamic Therapy	18	In vitro	PRISMA 2020	PubMed, Scopus and Web of Science	Not reported
Dioguardi, et al (2022)	Italy	Journal of Clinical Medicine	3	CTs and in vitro	PRISMA-ScR	PubMed, Scopus, Web of Science, Cochrane Library, Science Direct and EBSCO	Opengrey and Google Scholar
Ashkar, et al (2022)	Spain	Materials	20	In vitro	PRISMA 2020	PubMed, Scopus, Web of Science, Embase, Scopus and SciELO	Not reported
Yang, et al (2022)	China	European Endoodntic Journal	10	In vitro	PRISMA	PubMed, Embase and Cochrane Library	Not reported
Nisar, et al (2022)	India	European Archives of Paediatric Dentistry	12	In vitro and ex vivo	PRISMA 2020	PubMed, Cochrane Library; Google Scholar and EBSCOhost	OpenGrey
Haridoss, et al (2022)	India	Cureus	12	In vitro	PRISMA 2020	PubMed, Scopus, Cochrane Library, LILACS, Google Scholar, EBSCO,Ovid and Shodhganga	OpenGrey
Chopra, et al (2022)	United Kingdom	Materials	28 (24)	In vitro and ex vivo	PRISMA	PubMed, Web of Science, Cochrane Library and DOAJ	OpenGrey, Google Scholar and Greylist
Ramezanzade, et al (2022)	Denmark	Acta Odontologica Scandinavica	24	In vitro, in vivo and ex vivo	PRISMA 2020	PubMed, Scopus, Cochrane library and Google Scholar	Not reported
Mehta, et al (2022)	India	Journal of Conservative Dentistry	5	In vitro and ex vivo	PRISMA 2020	PubMed, Scopus, Embase, Cochrane Library, Google Scholar and EBSCOhost	Not reported
Zubair, et al (2022)	Saudi Arabia	Australian Endodontic Journal	8	In vitro and ex vivo	PRISMA 2009	PubMed, Web of Science and Embase	OpenGrey and Google Scholar
Milla, et al (2022)	Brazil	Oral Diseases	21	In vitro and in vivo	PRISMA 2020	PubMed, Web of Science and Embase	OpenGrey
Nobar, et al (2022)	United States of America	Australian Endodontic Journal	25 (20)	In vitro and ex vivo	PRISMA 2020	PubMed, Embase, Scopus, Web of Science, Cochrane Library, Google Scholar, and Latin American and Caribbean Health Sciences	OpenGrey, ProQuest, Open Access Theses and Dissertations, and New York

Mazreah, et al (2022)	Iran	Australian Endodontic Journal	17	In vitro and ex vivo	PRISMA 2020	Embase, Scopus, Web of Science, Cochrane Library and Google Scholar	Academy of Medicine Grey Literature Report OpenGrey, LILACS, Open Access and New York
Augusto, et al (2022)	Brazil	Australian Endodontic Journal	12	In vitro	PRISMA 2020	PubMed, Scopus, Web of Science, Embase and LILACS	Academy of Medicine OpenGrey
Bds, et al (2022)	India	Australian Endodontic Journal	17	In vitro	PRISMA 2009	PubMed and Google Scholar	OpenGrey
Banci, et al (2023)	Brazil	Photodiagnosis and Photodynamic Therapy	8 (7)	In vitro	PRISMA 2020	PubMed, Scopus, Web of Science, Embase and Cochrane Library	ProQuest
Gómez-Delgado, et al (2023)	Spain	Odontology	44	RCT and in vitro	PRISMA 2020	PubMed, Scopus and Web of Science	Not reported
Rekha, et al (2023)	India	Journal of Oral Biology and Craniofacial Research	24	In vitro and ex vivo	Not reported	PubMed, Scopus, Google Scholar and EBSCOhost	Not reported

RCT: Randomized Clinical Trial, CT: Clinical trials; CS: Case Series; RET: Randomized Experimental Trial

Table 4. Data regarding protocol, risk of bias evaluation and metanalysis

Author	Protocol Register	Tool used to assess RoB	Metanalysis	Statistical software
Del Fabbro, et al (2018)	Not Registered	Cochrane Collaboration Tools	Yes	RevMan
Oliveira, et al (2018)	PROSPERO: CRD42017056232	Adapted version of the CONSORT checklist	No	Not reported
Nagendrababu, et al (2018)	Not Registered	Checklist for experimental studies by the Joanna Briggs Institute	No	Not reported
Neelakantan, et al (2019)	Not Registered	Based on the Cochrane Collaboration Tools	No	Not reported
Tavares, et al (2019)	PROSPERO: CRD42017077043	Joanna Briggs Institute	No	Not reported
Razdan, et al (2019)	Not Registered	Modified CONSORT checklist	No	Not reported
Dioguardi, et al (2019)	Not Registered	Newcastle-Ottawa Scale	Yes	RevMan
Dioguardi, et al (2019)	Not Registered	Newcastle-Ottawa Scale	Yes	RevMan
Nagendrababu, et al (2019)	Not Registered	Modified of Cochrane Collaboration Tools	No	Not reported
Fonseca, et al (2019)	PROSPERO: ID140445	For in vitro studies: the guidelines for reporting of preclinical studies on dental materials by Faggion Jr. were followed, consisting of several items that were based on the CONSORT guidelines for reporting randomized clinical trials; For in vivo studies: the SYRCLE risk of bias tool was used, which represents an adapted version of the Cochrane's risk of bias tool	No	Not reported
Dioguardi, et al (2019)	Not Registered	The Newcastle–Ottawa scale	Yes	RevMan
Schestatsky, et al (2019)	Not Registered	Based on previous reports (Sarkis-Onofre et al., 2014; Valente et al., 2016)	Yes	RevMan
Silva, et al (2019)	PROSPERO: CRD42016027491	According to the previous published systematic reviews of in vitro studies (da Rosa, et al 2015; Silva, et al 2018)	Yes	RevMan
Mickevičienė, et al (2020)	PROSPERO: CRD42018093710	Checklist for Reporting In-vitro Studies (CRIS)	No	Not reported
Jamali, et al (2020)	Not Registered	Cochrane Collaboration Tools	Yes	Stata
Chandak, et al (2020)	Not Registered	OHAT tool	No	Not reported
Lim, et al (2020)	PROSPERO: CRD42018096763	RoB 2.0 modified for in vitro studies	No	Not reported
Gomes, et al (2020)	PROSPERO: CRD42019123288	Based on a modified version of a previously published risk of bias assessment (Higgins, et al 2011)	No	Not reported
Harrison (2020)	Not Registered	Joanna Briggs Institute	No	Not reported
Moreno-Rabié, et al (2020)	PROSPERO: CRD42018117561	STROBE for observational studies, CARE guideline for case reports and the modified CONSORT checklist (Faggion 2012) for in vitro and ex vivo studies	No	Not reported
Pintor, et al (2020)	Not Registered	ToxRTool and SciRAP	Yes	SPSS® program
Silva, et al (2020)	PROSPERO: CRD42018096428	Based on previous studies (Aurelio, et al 2016)	No	Not reported
Paterson, et al (2020)	PROSPERO	Cochrane Collaboration Tools for RCTs and for basic research studies with the Office of Health Assessment and Translation risk-of-bias questions	Yes	R software
Dioguardi, et al (2020)	Not Registered	Newcastle-Ottawa Scale	Yes	RevMan
Sanz, et al (2020)	(OSF) Registries (DOI: 10.17605/OSF.IO/H35ZE)	Modified CONSORT checklist	No	Not reported
Valle, et al (2020)	Not Registered	Based on previous studies (Onofre, et al 2014; Isolan, et al 2018)	No	Not reported
Pedano, et al (2020)	PROSPERO: CRD42020164374	Cochrane Collaboration Tools for in vivo studies	Yes	RevMan
Chia, et al (2020)	Not Registered	RoB 2.0 modified for in vitro studies	No	Not reported

Parolia, et al (2020)	Not Registered	RoB 2.0 modified for in vitro studies	No	Not reported
Silva, et al (2020)	PROSPERO: CRD42019134748	Adapted for previous systematic reviews (Sarkis-Onofre et al. 2014, Rosa et al. 2015, Silva et al. 2018) for in vitro studies and for Cochrane Collaboration Tools for RCTs	No	Not reported
Vendramini, et al (2020)	PROSPERO: CRD42017072327	The Methodological Index for Non-Randomized Studies (MINORS) was used to evaluate study quality, as no specific bias analysis protocol was found for in vitro studies	No	Not reported
Attavar and Hedge (2021)	Not Registered	Centre for EvidenceBased Medicine (CEBM) ranking	No	Not reported
Oliveira, et al (2021)	Not Registered	Adapted criteria for systematic reviews of in vitro studies (Lima, et al 2021; Plotino et al, 2020)	Yes	RevMan
Augusto, et al (2021)	PROSPERO: CRD42020150722	Adapted for others studies (Onofre, et al 2014 and Neelakantan, et al 2018)	No	Not reported
Ranjan and Ranjan (2021)	Not Registered	Cochrane Collaboration Tools	No	Not reported
Sawant, et al (2021)	Not Registered	Joanna Briggs Institute	No	Not reported
Saeed, et al (2021)	Not Registered	Was done in accordance with the methods used in previous systematic reviews concerning in vitro studies (Silva, et al 2018/Sarkis-Onofre, et al 2014 and Da Rosa, et al 2015)	No	Not reported
Bhandi, et al (2021)	PROSPERO: 49815	Based on previous studies, but were adapted to include relevant factors that affect the success of root canal treatment (Estrela, et al 2014 and Sarkis-Onofre, et al 2014)	No	Not reported
Dioguardi, et al (2021)	Not Registered	Based on the CRIS (Checklist for Reporting In Vitro Studies) Guidelines	Yes	RevMan
Dioguardi, et al (2021)	Not Registered	The risk of bias within the studies was assessed following the PRISMA guidelines for assessing the quality of studies in meta-analyses	Yes	RevMan
Bonzanini, et al (2021)	PROSPERO: CRD42020152505	Cochrane Collaboration Tools	Yes	RevMan
Dotto, et al (2020)	Not Registered	Based on previous studies (Sarkis-Onofre, et al 2014; Schestatsky, et al 2019)	No	Not reported
Mathew, et al (2021)	PROSPERO: CRD42020176555	The quality of non-randomized studies was appraised using the JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies) and the quality of randomized laboratory studies was appraised using a customized version of Checklist for Randomized Controlled Trials (Tufanaru, et al. 2020), and RoB 2.0 for RCTs	No	Not reported
Fontanele, et al (2021)	PROSPERO: CRD42020145222	QUADAS-2	Yes	RevMan
Aung and Myint (2021)	Not Registered	QUADAS-2	Yes	RevMan
Sanz, et al (2021)	OSF: https://doi.org/10.17605/OSF.IO/SQ9UY	Modified CONSORT checklist (Faggion, 2012)	No	Not reported
Zubizarreta-Macho, et al (2021)	PROSPERO: CRD42020192264	Current Research Information System (CRIS)	Yes	Not reported
Machado, et al (2021)	Not Registered	Based on previous studies (Silva, et al 2020)	Yes	RevMan
Palczewska-Komsa, et al (2021)	Not Registered	The quality of in vitro and in vivo studies was assessed using a modified methodological index for non-randomized studies (MINORS) modified by the authors (Slim et al. 2003)	No	Not reported
Pereira, et al (2021)	Not Registered	Adapted criteria for systematic reviews of in vitro studies (da Rosa, et al 2015)	Yes	RevMan

Eren, et al (2021)	PROSPERO: CRD42018089555	The quality of each study was assessed according to the following parameters: 1. Was the calculation of the required minimum sample size performed before experiments? 2. Were the samples randomly distributed to groups? 3. Was specimen sterilization confirmed after the sterilization procedures? 4. Was specimen contamination confirmed after the procedure of root canal contamination with microorganisms? 5. Were the root canal preparation procedures performed by a single operator? 6. Was the total irrigant volume standard in all groups? 7. Were the analyses performed by evaluators blinded to the groups? 8. Were one or more outcomes of interest reported incompletely?	Yes	MedCalc
Sanz, et al (2021)	OSF (DOI:10.17605/OSF.IO/D2GB8)	Modified CONSORT checklist (Faggion, 2012)	No	Not reported
Silva, et al (2021)	The Open Science Framework (https://osf.io/khgcv/)	According to the previous published systematic reviews of in vitro studies (da Rosa, et al 2015; Silva, et al 2018)	Yes	RevMan
de Araújo, et al (2022)	OSF (osf.io/ qxfhy)	Cochrane risk of bias tool - This tool was carefully modified according to an adaptation made from a previous systematic review of in vitro studies	Yes	RevMan
Alipour, et al (2022)	Not Registred	based on previous modified tools to adapt to the in vitro nature of this systematic review (AlShwaimi et al., 2016; Neelakantan et al., 2018; Shalabi et al., 2019; Samiei et al. 2019)	Yes	Not reported
Savitha, et al (2022)	PROSPERO: CRD42020204286	adapted of a prior systematic review that included *in vitro* investigations (Silva, et al 20220)	Yes	Stata
Rahul, et al (2022)	OSF (https://share.osf.io/registration/461CC-5FB-9CB)	ToxRTool	No	Not reported
Al-Sanabani, et al (2023)	OSF (DOI 10.17605/OSF.IO/63UHK)	based on previously used tool for in vitro studies (Sarkis-Onofre, et al 2021)	Yes	RevMan
Lin, et al (2022)	PROSPERO: CRD42021275860	OHAT Tool	Yes	RevMan
Nasiri and Wrbas (2022)	Not reported	1. This review study selected studies in which the comparison occurred only among generations of EALs. 2. The accuracy of EALs was considered within ±0.5 mm of the WL (except Tselnik et al.). 3. Seven studies were performed in vitro, and 8 studies were conducted in vivo; however, the final evaluation of these 8 studies was also performed in vitro. Thus, all selected studies were performed in the same way. 4. In this study, a comprehensive search was conducted in four databases to select studies on the generation of EALs. For this reason, the probability of an existing article on this topic is not zero but low. 5. Fifteen articles supported the quantitative results of the current study. Although new articles will be published in the future in this regard, they cannot affect the results of the current review study because of the high number of studies included. Hence, the risk of bias in this study is low.	Yes	Comprehensive Meta-Analysis 2.0 (CMA)
Nadalon, et al (2022)	Not reported	Modified CONSORT checklist (Faggion, 2012)	No	Not reported
Al-Zaka, et al (2022)	Not reported	Modified risk of bias assessment was developed similar to a previous study (Isolan, et al 2018)	No	Not reported

Teja, et al (2022)	Not reported	Modified version of the The Joanna Briggs Institute	No	Not reported
Reis-Prado, et al (2022)	PROSPERO: CRD42020205417	Modified version of the Joanna Briggs Institute's (JBI) Critical Evaluation Checklist for Experimental Studies (Dos Reis-Prado et al., 2021; Yaylali et al., 2015)	No	Not reported
Teja, et al (2022)	Not reported	Was carried out by a customized tool by taking previous in vitro based systematic review literature in endodontics into consideration(Cãputã et al., 2019; Neelakantan et al., 2018)	No	Not reported
Suresh, et al (2022)	OSF (osf.io/chg2q/registrations)	Modified version of The Joanna Briggs Institute	No	Not reported
Karobari, et al (2022)	PROSPERO: CRD42021278968	Joanna Briggs Institute	No	Not reported
Puleio, et al (2022)	PROSPERO: CRD42020151451	Checklist for in vitro studies on dental materials (CONSORT)	No	Not reported
Vasudevan, et al (2022)	PROSPERO: CRD42021231643	Modified version of The Joanna Briggs Institute	No	Not reported
Alkahtany (2023)	OSF (https://osf.io/xk5v8)	Adapted from other similar systematic reviews of in vitro reports (Bin-Shuwaish, 2020; Sarkis-Onofre, et al 2014)	No	Not reported
Dioguardi, et al (2022)	INPLASY 202270024	Cochrane Handbook for clinical trials and CRIS guideline for in vitro studies	No	Not reported
Ashkar, et al (2022)	OSF (DOI 10.17605/OSF.IO/6KVEP)	Modified CONSORT checklist of items for reporting in vitro studies of dental materials (Faggion, 2012)	No	Not reported
Yang, et al (2022)	PROSPERO: CRD42020197482	RoB 2.0	Yes	Stata
Nisar, et al (2022)	PROSPERO: CRD42020222327	MINORS	No	Not reported
Haridoss, et al (2022)	PROSPERO: CRD42022315465	Modified risk of bias methodology used in previous systematic reviews for in-vitro studies (Küçükkaya, et al 2021; Silva, et al 2018)	Yes	RevMan
Chopra, et al (2022)	Not reported	Adapted from the previous studies (Silva, et al 2019; Kim, et al 2020)	Yes	RevMan
Ramezanzade, et al (2022)	PROSPERO: CRD42022320332	QUADAS-2	No	Not reported
Mehta, et al (2022)	PROSPERO: CRD42021226225	Joanna Briggs Institute	No	Not reported
Zubair, et al (2022)	PROSPERO: CRD42019151804	Based in previous studies (Caviedes-Bucheli, et al 2016; Faggion, 2012)	Yes	R-Project
Milla, et al (2022)	PROSPERO: CRD42021227711	MINORS for in vitro and in vivo; SYRCLE for animal studies	No	Not reported
Nobar, et al (2022)	PROSPERO: CRD42020147333	Based on modified risk of bias assessment criteria based on the previously published systematic review (Silva, et al 2018)	Yes	Stata
Mazreah, et al (2022)	PROSPERO: CRD42021278537	Based on previous studies (Romualdo, et al 2017; Boutsioukis, et al 2013)	Yes	Stata
Augusto, et al (2022)	PROSPERO: CRD42020150722	Based on previous studies (Sarkis-Onofre, et al 2014; Neelakantan, et al 2018)	No	Not reported
Bds, et al (2022)	PROSPERO: CRD42021259919	Based on Cochrane Handbook	No	Not reported
Banci, et al (2023)	PROSPERO: CRD42022319856	Joanna Briggs Institute	Yes	RevMan
Gómez-Delgado, et al (2023)	PROSPERO: CRD42021267055	PRIRATE checklist for RCTs and modified CONSORT checklist for in vitro studies	No	Not reported
Rekha, et al (2023)	PROSPERO: CRD42021244565	Adapted from a similar systematic review (AlShwaimi, et al 2016)	Yes	RevMan

Table 5. Reliability analysis showing inter-rater reliability test Cohen's k (n=9)

IRR	RoBEndo Cohen's k (SE)	Interpretation	RoBDEMAT Cohen's k (SE)	Interpretation
Examiner 1 and 2	0.74 (0.06)	Substantial	0.54 (0.09)	Moderate
Examiner 1 and 3	0.94 (0.03)	Nearly perfect	0.61 (0.08)	Substantial
Examiner 2 and 3	0.75 (0.06)	Substantial	0.42 (0.10)	Moderate

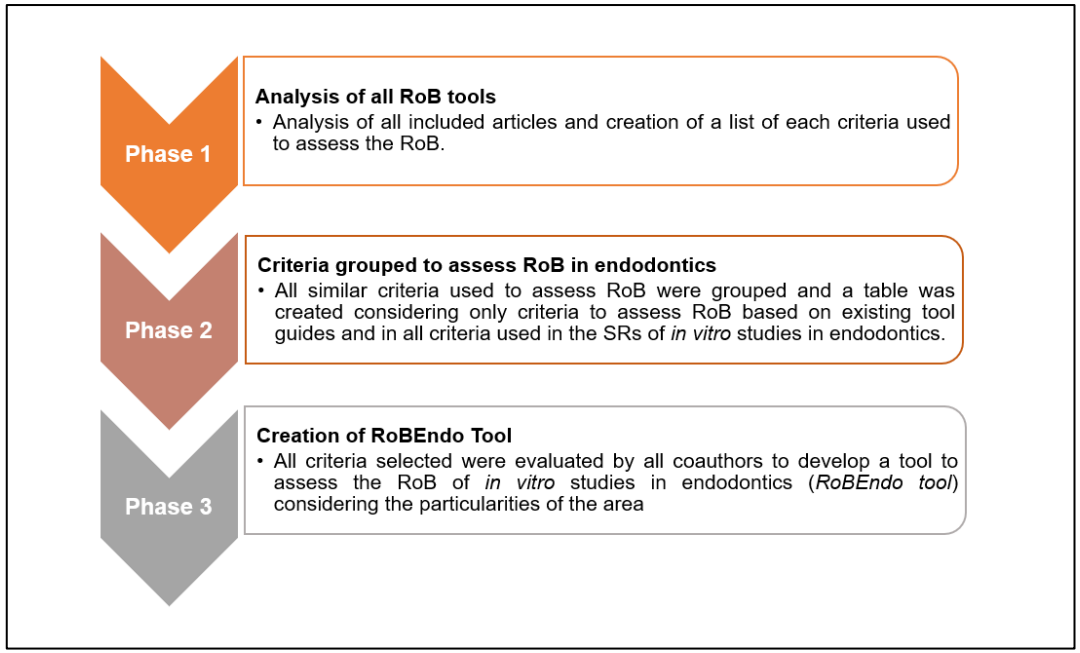

Figure 1. Stages involved in the development of the RoBEndo tool

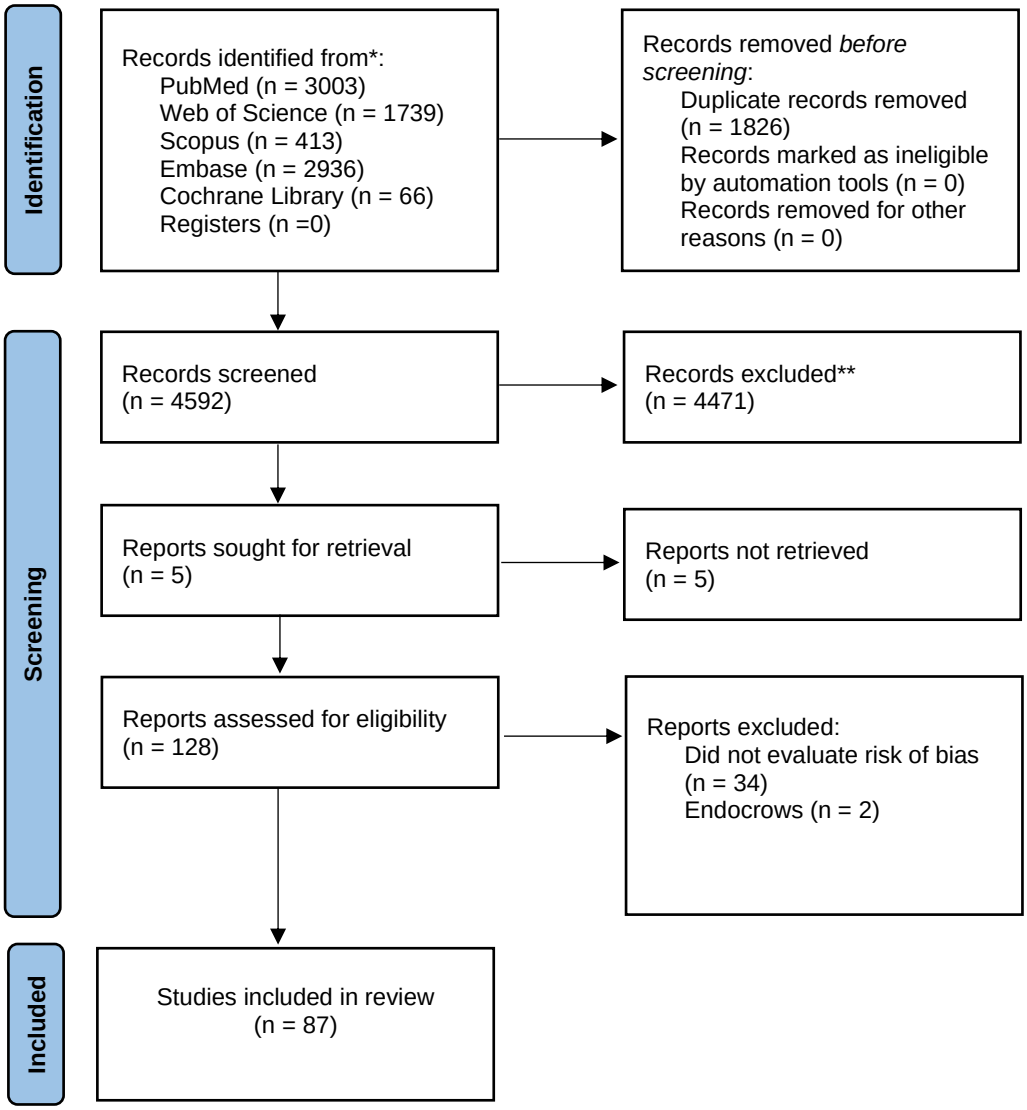

Figure 2. The PRISMA 2020 flow diagram

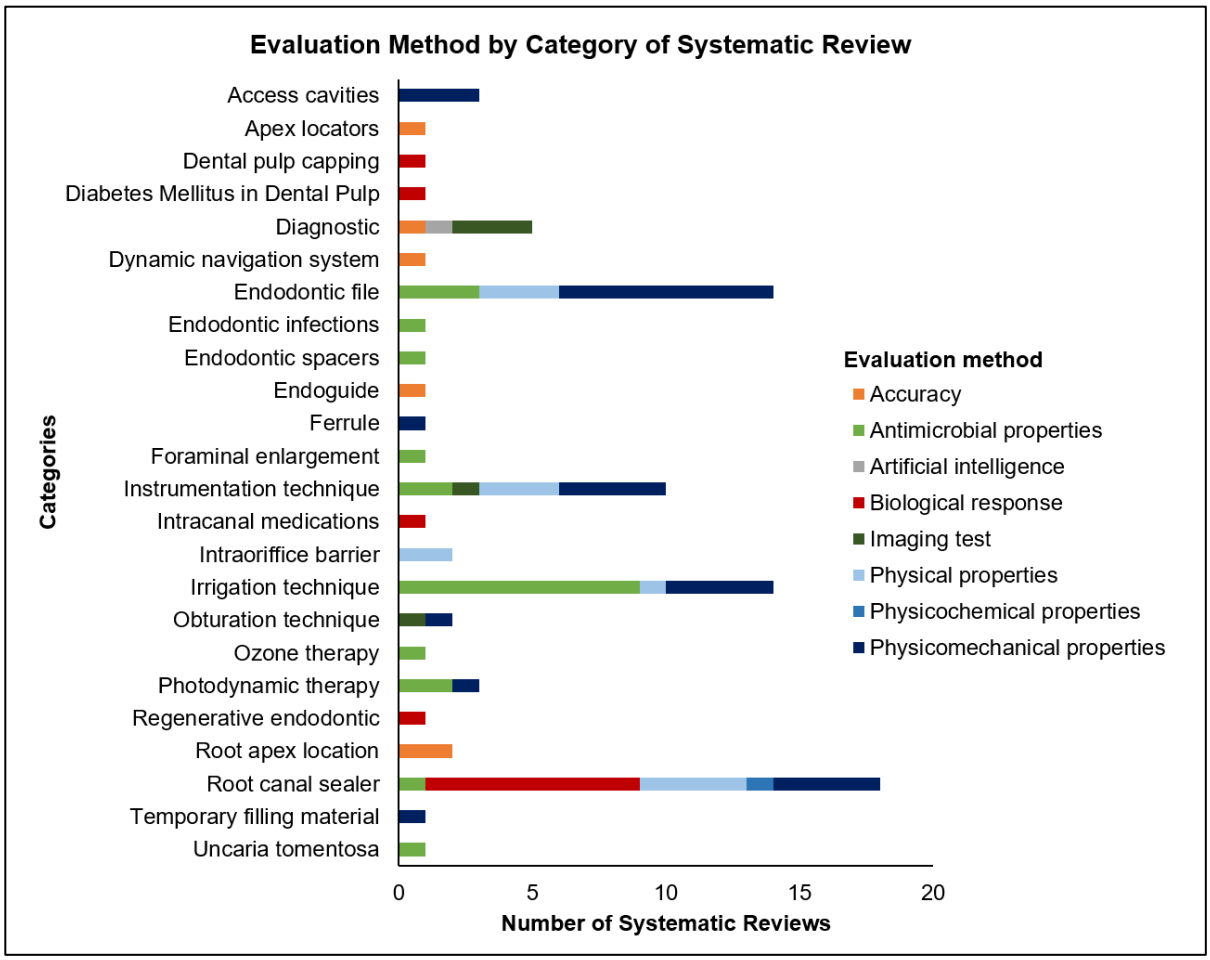

Figure 3. Evaluation Method by Category of Systematic Review

Table A1. Strategy used for the systematic search in the five databases

	Search Terms
Pubmed	
#3	Search #1 AND #2
#2	(Systematic Review) OR (Meta-Analysis) OR (Network Meta-Analysis) OR (Review, Systematic) OR (Scoping Review) OR (Umbrella Review) OR (((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt]
#1	(Tooth, Nonvital) OR (Tooth, nonvital) OR (Nonvital Tooth) OR (Tooth, Devitalized) OR (Devitalized Tooth) OR (Tooth, Pulpless) OR (Pulpless Tooth) OR (Teeth, Pulpless) OR (Pulpless Teeth) OR (Teeth, Devitalized) OR (Devitalized Teeth) OR (Teeth, Nonvital) OR (Nonvital Teeth) OR (Teeth, Endodontically-Treated) OR (Endodontically-Treated Teeth) OR (Teeth, Endodontically Treated) OR (Tooth, Endodontically-Treated) OR (Endodontically-Treated Tooth) OR (Tooth, Endodontically Treated) OR (Root Canal Therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontics) OR (Endodontics) OR (Endodontology) OR (Sodium Hypochlorite) OR (Chlorhexidine) OR (Chlorhexidine Gluconate) OR (Endodontic, Regenerative) OR (Endodontics, Regenerative) OR (Regenerative Endodontic) OR (Dental Pulps) OR (Pulp, Dental) OR (Pulps, Dental) OR (Dental Pulp Capping) OR (Pulp Capping, Dental) OR (Pulp Capping) OR (Capping, Pulp) OR (Cappings, Pulp) OR (Pulp Cappings) OR (Capping, Dental Pulp) OR (Cappings, Dental Pulp) OR (Dental Pulp Cappings) OR (Pulp Cappings, Dental) OR (Apicoectomy) OR (Canal Preparation, Root) OR (Canal Preparations, Root) OR (Preparation, Root Canal) OR (Preparations, Root Canal) OR (Root Canal Preparations) OR (Reciprocating) OR (Rotary) OR (Epoxy Resin-based Root Canal Sealer) OR (Root Canal Sealer) OR (Calcium Silicate-based Root Canal Sealer)
Embase	
#3	Search #1 AND #2
#2	“Systematic Review” OR “Meta-Analysis” OR “Network Meta-Analysis” OR “Review, Systematic” OR “Scoping Review” OR “Umbrella Review”
#1	“Tooth, Nonvital” OR “Tooth, nonvital” OR “Nonvital Tooth” OR “Tooth, Devitalized” OR “Devitalized Tooth” OR “Tooth, Pulpless” OR “Pulpless Tooth” OR “Teeth, Pulpless” OR “Pulpless Teeth” OR “Teeth, Devitalized” OR “Devitalized Teeth” OR “Teeth, Nonvital” OR “Nonvital Teeth” OR “Teeth, Endodontically-Treated” OR “Endodontically-Treated Teeth” OR “Teeth, Endodontically Treated” OR “Tooth, Endodontically-Treated” OR “Endodontically-Treated Tooth” OR “Tooth, Endodontically Treated” OR “Root Canal Therapy” OR “Canal Therapies, Root” OR “Canal Therapy, Root” OR “Root Canal Therapies” OR “Therapies, Root Canal” OR “Therapy, Root Canal” OR “Endodontics” OR “Endodontics” OR “Endodontology” OR “Sodium Hypochlorite” OR “Chlorhexidine” OR “Chlorhexidine Gluconate” OR “Endodontic, Regenerative” OR “Endodontics, Regenerative” OR “Regenerative Endodontic” OR “Dental Pulps” OR “Pulp, Dental” OR “Pulps, Dental” OR “Dental Pulp Capping” OR “Pulp Capping, Dental” OR “Pulp Capping” OR “Capping, Pulp” OR “Cappings, Pulp” OR “Pulp Cappings” OR “Capping, Dental Pulp” OR “Cappings, Dental Pulp” OR “Dental Pulp Cappings” OR “Pulp Cappings, Dental” OR “Apicoectomy” OR “Canal Preparation, Root” OR “Canal Preparations,

	Root" OR "Preparation, Root Canal" OR "Preparations, Root Canal" OR "Root Canal Preparations" OR "Reciprocating" OR "Rotary" OR "Epoxy Resin-based Root Canal Sealer" OR "Root Canal Sealer" OR "Calcium Silicate-based Root Canal Sealer"
Web of Science	
#3	Search #1 AND #2
#2	TS=((Systematic Review) OR (Meta-Analysis) OR (Network Meta-Analysis) OR (Review, Systematic) OR (Scoping Review) OR (Umbrella Review))
#1	TS-((Tooth, Nonvital) OR (Tooth, nonvital) OR (Nonvital Tooth) OR (Tooth, Devitalized) OR (Devitalized Tooth) OR (Tooth, Pulpless) OR (Pulpless Tooth) OR (Teeth, Pulpless) OR (Pulpless Teeth) OR (Teeth, Devitalized) OR (Devitalized Teeth) OR (Teeth, Nonvital) OR (Nonvital Teeth) OR (Teeth, Endodontically-Treated) OR (Endodontically-Treated Teeth) OR (Teeth, Endodontically Treated) OR (Tooth, Endodontically-Treated) OR (Endodontically-Treated Tooth) OR (Tooth, Endodontically Treated) OR (Root Canal Therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontics) OR (Endodontics) OR (Endodontology) OR (Sodium Hypochlorite) OR (Chlorhexidine) OR (Chlorhexidine Gluconate) OR (Endodontic, Regenerative) OR (Endodontics, Regenerative) OR (Regenerative Endodontic) OR (Dental Pulps) OR (Pulp, Dental) OR (Pulps, Dental) OR (Dental Pulp Capping) OR (Pulp Capping, Dental) OR (Pulp Capping) OR (Capping, Pulp) OR (Cappings, Pulp) OR (Pulp Cappings) OR (Capping, Dental Pulp) OR (Cappings, Dental Pulp) OR (Dental Pulp Cappings) OR (Pulp Cappings, Dental) OR (Apicoectomy) OR (Canal Preparation, Root) OR (Canal Preparations, Root) OR (Preparation, Root Canal) OR (Preparations, Root Canal) OR (Root Canal Preparations) OR (Reciprocating) OR (Rotary) OR (Epoxy Resin-based Root Canal Sealer) OR (Root Canal Sealer) OR (Calcium Silicate-based Root Canal Sealer))
SciVerse Scopus	
#3	Search #1 AND #2
#2	TITLE-ABS-KEY (Systematic Review) OR (Meta-Analysis) OR (Network Meta-Analysis) OR (Review, Systematic) OR (Scoping Review) OR (Umbrella Review)
#1	TITLE-ABS-KEY (Tooth, Nonvital) OR (Tooth, nonvital) OR (Nonvital Tooth) OR (Tooth, Devitalized) OR (Devitalized Tooth) OR (Tooth, Pulpless) OR (Pulpless Tooth) OR (Teeth, Pulpless) OR (Pulpless Teeth) OR (Teeth, Devitalized) OR (Devitalized Teeth) OR (Teeth, Nonvital) OR (Nonvital Teeth) OR (Teeth, Endodontically-Treated) OR (Endodontically-Treated Teeth) OR (Teeth, Endodontically Treated) OR (Tooth, Endodontically-Treated) OR (Endodontically-Treated Tooth) OR (Tooth, Endodontically Treated) OR (Root Canal Therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontics) OR (Endodontics) OR (Endodontology) OR (Sodium Hypochlorite) OR (Chlorhexidine) OR (Chlorhexidine Gluconate) OR (Endodontic, Regenerative) OR (Endodontics, Regenerative) OR (Regenerative Endodontic) OR (Dental Pulps) OR (Pulp, Dental) OR (Pulps, Dental) OR (Dental Pulp Capping) OR (Pulp Capping, Dental) OR (Pulp Capping) OR (Capping, Pulp) OR (Cappings, Pulp) OR (Pulp Cappings) OR (Capping, Dental Pulp) OR (Cappings, Dental Pulp) OR (Dental Pulp Cappings) OR (Pulp Cappings, Dental) OR (Apicoectomy) OR (Canal Preparation, Root) OR (Canal Preparations, Root) OR (Preparation, Root Canal) OR (Preparations, Root Canal) OR (Root Canal Preparations) OR (Reciprocating) OR (Rotary) OR (Epoxy Resin-based Root Canal Sealer) OR (Root Canal Sealer) OR (Calcium Silicate-based Root Canal Sealer)
Cochrane Library	

#1	(Tooth, Nonvital) OR (Tooth, nonvital) OR (Nonvital Tooth) OR (Tooth, Devitalized) OR (Devitalized Tooth) OR (Tooth, Pulpless) OR (Pulpless Tooth) OR (Teeth, Pulpless) OR (Pulpless Teeth) OR (Teeth, Devitalized) OR (Devitalized Teeth) OR (Teeth, Nonvital) OR (Nonvital Teeth) OR (Teeth, Endodontically-Treated) OR (Endodontically-Treated Teeth) OR (Teeth, Endodontically Treated) OR (Tooth, Endodontically-Treated) OR (Endodontically-Treated Tooth) OR (Tooth, Endodontically Treated) OR (Root Canal Therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontics) OR (Endodontics) OR (Endodontology) OR (Sodium Hypochlorite) OR (Chlorhexidine) OR (Chlorhexidine Gluconate) OR (Endodontic, Regenerative) OR (Endodontics, Regenerative) OR (Regenerative Endodontic) OR (Dental Pulps) OR (Pulp, Dental) OR (Pulps, Dental) OR (Dental Pulp Capping) OR (Pulp Capping, Dental) OR (Pulp Capping) OR (Capping, Pulp) OR (Cappings, Pulp) OR (Pulp Cappings) OR (Capping, Dental Pulp) OR (Cappings, Dental Pulp) OR (Dental Pulp Cappings) OR (Pulp Cappings, Dental) OR (Apicoectomy) OR (Canal Preparation, Root) OR (Canal Preparations, Root) OR (Preparation, Root Canal) OR (Preparations, Root Canal) OR (Root Canal Preparations) OR (Reciprocating) OR (Rotary) OR (Epoxy Resin-based Root Canal Sealer) OR (Root Canal Sealer) OR (Calcium Silicate-based Root Canal Sealer)

Table A2. Excluded studies and reasons for exclusion

Studies that not evaluated risk of bias **(n = 34)**
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Table A3. Risk of Bias criteria used by SRs

List of items used to assess RoB in SRs **(n = 36)**
1. Presence of a structured abstract
2. Clearly describing the rationale
3. Introduction containing a scientific context
4. Objectives, and hypothesis tested
5. Scientific background and rationale
6. Allocation concealment
7. Allocation sequence generation
8. Blinding
9. Intervention
10. Description of study type in the methodology
11. Independent assessment
12. If materials were used according to the manufacturers
13. Operator variability (single operator)
14. Protocol (if available)
15. Randomization
16. Reference standard
17. Reporting reasons of exclusion or withdrawals
18. Standardized sample preparation and handling
19. Sample size calculation
20. Similar dimensions among the samples
21. Standard procedures
22. Appropriate statistical analysis
23. Appropriate control group(s)
24. Repetition of experiment/Consistent measurements for repeated experiments
25. Account of outcome data
26. Complete reporting of results
27. Evaluation time between groups studied
28. Main results from each experiment being described
29. Incomplete outcome data
30. Selection of the reported result
31. Observer(s) reliability assessment
32. Appropriate statistical analysis
33. If in the discussion section the results and their clinical implications were interpreted
34. Limitations
35. Whether these results could be translated into other species or systems
36. Funding

6 Considerações finais

Esta revisão guarda-chuva mapeou os critérios usados para avaliar o risco de viés de estudos *in vitro* por revisões sistemáticas em endodontia. Os critérios usados para avaliar o risco de viés foram divergentes e, em algumas revisões, inadequados. Nessa perspectiva, uma nova ferramenta padronizada foi desenvolvida (RoBEndo), e encontrou-se alta concordância entre os examinadores. O RoBEndo sintetizou critérios comuns usados em RSs recentes e pode melhorar significativamente a avaliação risco de viés de estudos endodônticos *in vitro*.

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APÊNDICES

APÊNDICE A – Estratégia de busca

Estratégias de busca por base de dados

	Search Terms
Pubmed	
#3	Search #1 AND #2
#2	(Systematic Review) OR (Meta-Analysis) OR (Network Meta-Analysis) OR (Review, Systematic) OR (Scoping Review) OR (Umbrella Review) OR (((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt]
#1	(Tooth, Nonvital) OR (Tooth, nonvital) OR (Nonvital Tooth) OR (Tooth, Devitalized) OR (Devitalized Tooth) OR (Tooth, Pulpless) OR (Pulpless Tooth) OR (Teeth, Pulpless) OR (Pulpless Teeth) OR (Teeth, Devitalized) OR (Devitalized Teeth) OR (Teeth, Nonvital) OR (Nonvital Teeth) OR (Teeth, Endodontically-Treated) OR (Endodontically-Treated Teeth) OR (Teeth, Endodontically Treated) OR (Tooth, Endodontically-Treated) OR (Endodontically-Treated Tooth) OR (Tooth, Endodontically Treated) OR (Root Canal Therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontics) OR (Endodontics) OR (Endodontology) OR (Sodium Hypochlorite) OR (Chlorhexidine) OR (Chlorhexidine Gluconate) OR (Endodontic, Regenerative) OR (Endodontics, Regenerative) OR (Regenerative Endodontic) OR (Dental Pulps) OR (Pulp, Dental) OR (Pulps, Dental) OR (Dental Pulp Capping) OR (Pulp Capping, Dental) OR (Pulp Capping) OR (Capping, Pulp) OR (Cappings, Pulp) OR (Pulp Cappings) OR (Capping, Dental Pulp) OR (Cappings, Dental Pulp) OR (Dental Pulp Cappings) OR (Pulp Cappings, Dental) OR (Apicoectomy) OR (Canal Preparation, Root) OR (Canal Preparations, Root) OR (Preparation, Root Canal) OR (Preparations, Root Canal) OR (Root Canal Preparations) OR (Reciprocating) OR (Rotary) OR (Epoxy Resin-based Root Canal Sealer) OR (Root Canal Sealer) OR (Calcium Silicate-based Root Canal Sealer)
Embase	
#3	Search #1 AND #2
#2	“Systematic Review” OR “Meta-Analysis” OR “Network Meta-Analysis” OR “Review, Systematic” OR “Scoping Review” OR “Umbrella Review”
#1	“Tooth, Nonvital” OR “Tooth, nonvital” OR “Nonvital Tooth” OR “Tooth, Devitalized” OR “Devitalized Tooth” OR “Tooth, Pulpless” OR “Pulpless Tooth” OR “Teeth, Pulpless” OR “Pulpless Teeth” OR “Teeth, Devitalized” OR “Devitalized Teeth” OR “Teeth, Nonvital” OR “Nonvital Teeth” OR “Teeth, Endodontically-Treated” OR “Endodontically-Treated Teeth” OR “Teeth, Endodontically Treated” OR “Tooth, Endodontically-Treated” OR “Endodontically-Treated Tooth” OR “Tooth, Endodontically Treated” OR “Root Canal Therapy” OR “Canal Therapies, Root” OR “Canal Therapy, Root” OR “Root Canal Therapies” OR “Therapies, Root Canal” OR “Therapy, Root Canal” OR “Endodontics” OR “Endodontics” OR “Endodontology” OR “Sodium Hypochlorite” OR “Chlorhexidine” OR “Chlorhexidine Gluconate” OR “Endodontic, Regenerative” OR “Endodontics, Regenerative” OR “Regenerative Endodontic” OR “Dental Pulps” OR “Pulp, Dental” OR “Pulps, Dental” OR “Dental Pulp Capping” OR “Pulp Capping, Dental” OR “Pulp Capping” OR “Capping, Pulp” OR “Cappings, Pulp” OR “Pulp Cappings” OR “Capping, Dental Pulp” OR “Cappings, Dental Pulp” OR “Dental Pulp Cappings” OR “Pulp Cappings, Dental” OR “Apicoectomy” OR “Canal Preparation, Root” OR “Canal Preparations, Root” OR “Preparation, Root Canal” OR “Preparations, Root Canal” OR “Root Canal

	Preparations” OR “Reciprocating” OR “Rotary” OR “Epoxy Resin-based Root Canal Sealer” OR “Root Canal Sealer” OR “Calcium Silicate-based Root Canal Sealer”
Web of Science	
#3	Search #1 AND #2
#2	TS=((Systematic Review) OR (Meta-Analysis) OR (Network Meta-Analysis) OR (Review, Systematic) OR (Scoping Review) OR (Umbrella Review))
#1	TS-((Tooth, Nonvital) OR (Tooth, nonvital) OR (Nonvital Tooth) OR (Tooth, Devitalized) OR (Devitalized Tooth) OR (Tooth, Pulpless) OR (Pulpless Tooth) OR (Teeth, Pulpless) OR (Pulpless Teeth) OR (Teeth, Devitalized) OR (Devitalized Teeth) OR (Teeth, Nonvital) OR (Nonvital Teeth) OR (Teeth, Endodontically-Treated) OR (Endodontically-Treated Teeth) OR (Teeth, Endodontically Treated) OR (Tooth, Endodontically-Treated) OR (Endodontically-Treated Tooth) OR (Tooth, Endodontically Treated) OR (Root Canal Therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontics) OR (Endodontics) OR (Endodontology) OR (Sodium Hypochlorite) OR (Chlorhexidine) OR (Chlorhexidine Gluconate) OR (Endodontic, Regenerative) OR (Endodontics, Regenerative) OR (Regenerative Endodontic) OR (Dental Pulps) OR (Pulp, Dental) OR (Pulps, Dental) OR (Dental Pulp Capping) OR (Pulp Capping, Dental) OR (Pulp Capping) OR (Capping, Pulp) OR (Cappings, Pulp) OR (Pulp Cappings) OR (Capping, Dental Pulp) OR (Cappings, Dental Pulp) OR (Dental Pulp Cappings) OR (Pulp Cappings, Dental) OR (Apicoectomy) OR (Canal Preparation, Root) OR (Canal Preparations, Root) OR (Preparation, Root Canal) OR (Preparations, Root Canal) OR (Root Canal Preparations) OR (Reciprocating) OR (Rotary) OR (Epoxy Resin-based Root Canal Sealer) OR (Root Canal Sealer) OR (Calcium Silicate-based Root Canal Sealer))
SciVerse Scopus	
#3	Search #1 AND #2
#2	TITLE-ABS-KEY (Systematic Review) OR (Meta-Analysis) OR (Network Meta-Analysis) OR (Review, Systematic) OR (Scoping Review) OR (Umbrella Review)
#1	TITLE-ABS-KEY (Tooth, Nonvital) OR (Tooth, nonvital) OR (Nonvital Tooth) OR (Tooth, Devitalized) OR (Devitalized Tooth) OR (Tooth, Pulpless) OR (Pulpless Tooth) OR (Teeth, Pulpless) OR (Pulpless Teeth) OR (Teeth, Devitalized) OR (Devitalized Teeth) OR (Teeth, Nonvital) OR (Nonvital Teeth) OR (Teeth, Endodontically-Treated) OR (Endodontically-Treated Teeth) OR (Teeth, Endodontically Treated) OR (Tooth, Endodontically-Treated) OR (Endodontically-Treated Tooth) OR (Tooth, Endodontically Treated) OR (Root Canal Therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontics) OR (Endodontics) OR (Endodontology) OR (Sodium Hypochlorite) OR (Chlorhexidine) OR (Chlorhexidine Gluconate) OR (Endodontic, Regenerative) OR (Endodontics, Regenerative) OR (Regenerative Endodontic) OR (Dental Pulps) OR (Pulp, Dental) OR (Pulps, Dental) OR (Dental Pulp Capping) OR (Pulp Capping, Dental) OR (Pulp Capping) OR (Capping, Pulp) OR (Cappings, Pulp) OR (Pulp Cappings) OR (Capping, Dental Pulp) OR (Cappings, Dental Pulp) OR (Dental Pulp Cappings) OR (Pulp Cappings, Dental) OR (Apicoectomy) OR (Canal Preparation, Root) OR (Canal Preparations, Root) OR (Preparation, Root Canal) OR (Preparations, Root Canal) OR (Root Canal Preparations) OR (Reciprocating) OR (Rotary) OR (Epoxy Resin-based Root Canal Sealer) OR (Root Canal Sealer) OR (Calcium Silicate-based Root Canal Sealer)
Cochrane Library	
#1	(Tooth, Nonvital) OR (Tooth, nonvital) OR (Nonvital Tooth) OR (Tooth, Devitalized) OR (Devitalized Tooth) OR (Tooth, Pulpless) OR (Pulpless Tooth) OR (Teeth, Pulpless) OR (Pulpless Teeth) OR (Teeth, Devitalized) OR (Devitalized Teeth) OR (Teeth, Nonvital) OR (Nonvital Teeth) OR (Teeth, Endodontically-Treated) OR (Endodontically-Treated Teeth) OR (Teeth, Endodontically Treated) OR (Tooth, Endodontically-Treated) OR (Endodontically-Treated Tooth) OR (Tooth, Endodontically Treated) OR (Root Canal Therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root

	Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontics) OR (Endodontics) OR (Endodontology) OR (Sodium Hypochlorite) OR (Chlorhexidine) OR (Chlorhexidine Gluconate) OR (Endodontic, Regenerative) OR (Endodontics, Regenerative) OR (Regenerative Endodontic) OR (Dental Pulps) OR (Pulp, Dental) OR (Pulps, Dental) OR (Dental Pulp Capping) OR (Pulp Capping, Dental) OR (Pulp Capping) OR (Capping, Pulp) OR (Cappings, Pulp) OR (Pulp Cappings) OR (Capping, Dental Pulp) OR (Cappings, Dental Pulp) OR (Dental Pulp Cappings) OR (Pulp Cappings, Dental) OR (Apicoectomy) OR (Canal Preparation, Root) OR (Canal Preparations, Root) OR (Preparation, Root Canal) OR (Preparations, Root Canal) OR (Root Canal Preparations) OR (Reciprocating) OR (Rotary) OR (Epoxy Resin-based Root Canal Sealer) OR (Root Canal Sealer) OR (Calcium Silicate-based Root Canal Sealer)

Apêndice B – Nota da Dissertação

Avaliação do risco de viés de estudos in vitro em Endodontia: Uma revisão guarda-chuva.

A presente dissertação de mestrado visou analisar por meio de uma revisão guarda-chuva da literatura, as ferramentas de risco de viés utilizadas nas RSs de estudos in vitro publicados no âmbito endodôntico nos últimos 5 anos, bem como sintetizar critérios comuns utilizados. A partir da análise de estudos da área, foi possível propor uma ferramenta de risco de viés para avaliar estudos in vitro em Endodontia. Devido a maior parte dos estudos disponíveis basearem-se em ferramentas inadequadas, foi possível a criação da ferramenta RoBEndo, que sintetiza critérios comuns utilizados nas revisões sistemáticas existentes. Com a implementação dessa nova ferramenta espera-se padronizar a análise de risco de viés de estudos *in vitro* em Endodontia.

Campo da pesquisa: Clínica Odontológica, Endodontia.

Candidato: Rafaella Rodrigues da Gama, Cirurgião-dentista pela Universidade Federal de Pelotas (2019) e Especialista em Endodontia pelo Instituto Educacional Odontológico do Mercosul (2021)

Data da defesa e horário: 05/04/2023 às 8:30h.

Local: Auditório do Programa de Pós-graduação em Odontologia da Universidade Federal de Pelotas. 5º andar da Faculdade de Odontologia de Pelotas. Rua Gonçalves Chaves, 457.

Membros da banca: Profª. Drª. Anelise Fernandes Montagner, Profª. Drª. Carolina Clasen Vieira, Dr. Rafael Guerra Lund (suplente), Profª. Drª. Andressa da Silva Barboza (suplente)

Orientador: Prof. Dr. Wellington Luiz de Oliveira da Rosa

Informação de contato: Rafaella Rodrigues da Gama, rafaelladagama@gmail.com, Rua Antonio Cury, 306, Centro, Pelotas, RS, Brasil.

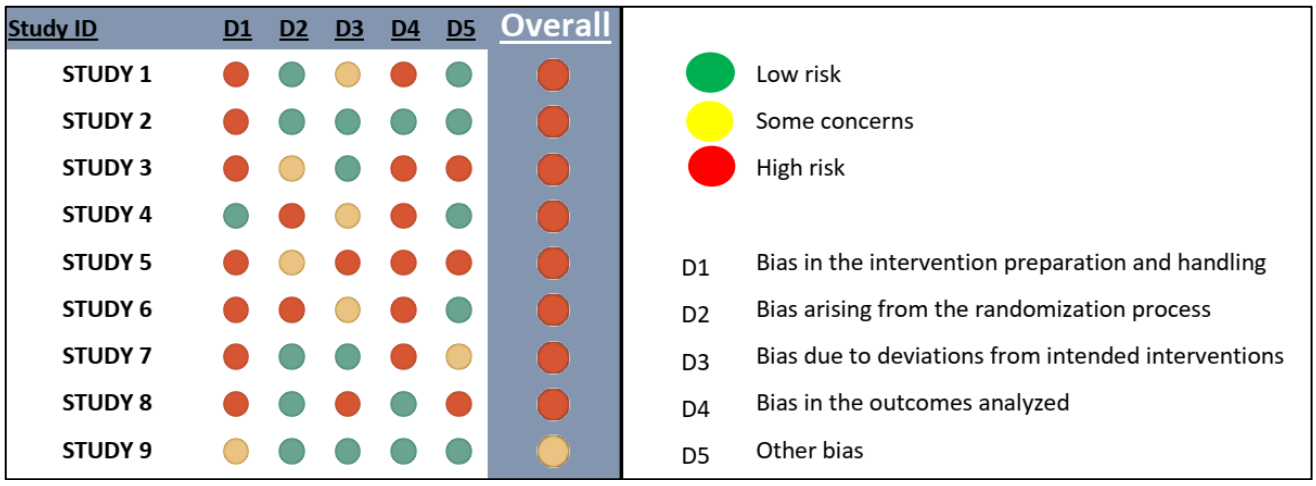
Apêndice C – Súmula do currículo do candidato

Súmula do currículo

Rafaella Rodrigues da Gama nasceu em 24 de janeiro de 1996, em Pelotas, Rio Grande do Sul, Brasil. Ingressou na Faculdade de Odontologia da Universidade Federal de Pelotas (FO-UFPel) em 2013, tendo sido graduada cirugiã-dentista em 2019. Em 2021 ingressou no Mestrado do Programa de Pós-graduação em Odontologia da Universidade Federal de Pelotas (UFPel), área de concentração Endodontia, sob orientação do Prof. Dr. Wellington Luiz de Oliveira da Rosa. É especialista em Endodontia pelo Instituto Educacional Odontológico do Mercosul sob orientação da Profª Drª Fernanda Graziela Côrrea Signoretti. Atualmente, é professora visitante do curso de especialização em Endodontia do Instituto Orofacial das Américas de Pelotas e foi aprovado na seleção para o doutorado em Clínica Odontológica, área de concentração em endodontia, na Universidade Federal de Pelotas.

APÊNDICE D – Exemplo da Ferramenta RoBENDO em planilha automatizada do Excel

Domain of bias	Signaling question	Elaboration	Responses STUDY 1	STUDY 2	STUDY 3	STUDY 4	STUDY 5	STUDY 6	STUDY 7	STUDY 8	STUDY 9
D1 - Bias in the intervention preparation and handling	1.1 Did author identify study design?	• Answer 'Yes' if have a clearly description of study design (in vitro, ex vivo or in situ study). • Answer 'No' with no description of study design.	Y	Y	N	Y	N	N	N	N	Y
	1.2 Did the author provide sample size rationale and reporting?	• Answer 'Yes' if the author provide a rationale and justification for the sample size chosen or feature an a priori power analysis. • Answer 'No' if the author no provide a justification about the sample size chosen in study.	N	N	Y	Y	Y	Y	Y	Y	Y
	1.3 Did the author describe the intervention?	• Answer 'Yes' if the interventions for each group have sufficient details to allow replication, including how and when they were actually administered. • Answer 'No' if no descriptions are reported to the interventions for each group with sufficient details to allow replication.	N	Y	N	Y	Y	Y	Y	Y	Y
	1.4 Did the author describe a control group?	• Answer 'Yes' if the author includes a control group in study with specifics informations, including a reference standard if applicable, with identical and controlled conditions provided for all groups with the repeats of factors such as temperature, humidity, time and equipment settings. • Answer 'No' if there are no inclusion of a control group in the study. • Answer 'Insufficiently reported' in the absence of specific information about the control group.	Y	Y	Y	Y	N	N	N	N	Y
	1.5 Did the author standardize sample preparation and handling of materials (according to the manufacturers if commercial materials were used)?	• Answer 'Yes' if there are descriptions regarding the standardization of sample manipulation according to the manufacturers with description of lots used in case of commercial materials and if the author described how standardized samples and materials were employed across groups (e.g., different types of endodontic files being used). • Answer 'No' if there are no descriptions regarding the standardization of sample manipulation according to the manufacturers and if there is no description that the materials were used according to the manufacturers in case of commercial materials. • Answer 'Insufficiently reported' if the author standardized the sample according to the manufacturers, with no description of how it was used (details are incomplete) or of lots used in case of commercial materials.	IR	Y	N	Y	Y	Y	Y	Y	IR
	1.6 Did the author describe similar sample dimensions?	• Answer 'Yes' if the author mentions that used specimens with similar dimensions, with description of dimensions used, and if the sample used was teeth, answer 'Yes' if mentions that used teeth with similar anatomy. • Answer 'No' if the author doesn't report anything about the dimensions of the samples. • If these details are incomplete, they should be marked 'Insufficiently reported'.	Y	Y	Y	Y	Y	Y	Y	Y	Y
	1.7 Did the author describe single operator?	• Answer 'Yes' if a single operator performed the study design. • Answer 'No' if different operators performed the study design. • Answer 'Insufficiently reported' if the author is not clearly about how many operators performed the study design.	IR	Y	Y	Y	Y	Y	Y	Y	Y
	1.8 Did the author use standard procedures/methods according to literature or normatives?	• Answer 'Yes' if the author adequately described the chosen evaluation test used (including equipment or instruments) to allow critical appraisal and replication in line with the research question (if applicable), and if the author standadized test procedures according to other studies, or according to normatives (such as ADM guidelines or ISO/ASTM standards) (if applicable). • Answer 'No' if there are no use of standard tests or procedures according to the literature or normatives. • If these details are incomplete, they should be marked 'Insufficiently reported'.	N	Y	N	Y	N	N	IR	N	Y
D2 - Bias arising from the randomization process	2.1 Did the author report randomization?	• Answer 'Yes' if the samples were randomized and their allocation was concealed appropriately; and also if the author describes if the randomization was conducted using computer generated sequences, random number attribution tables, shuffling envelopes, or cards. • Answer 'No' if there are no randomization performed. • Studies that only mention "teeth were randomly allocated" but fail to give details of the randomization process should be marked as 'Insufficiently reported'.	Y	Y	IR	N	IR	N	Y	Y	Y
D3 - Bias due to deviations from intended interventions	3.1 Did author perform blinding?	• Answer 'Yes' if the blinding was performed by the personal involved in the intervention or by outcome assessor. • Answer 'No' if no type of blinding was performed. • Answer 'Insufficiently reported' if the only information about blinding is a statement that the study was blinded, with no details about who was blinded.	Y	Y	Y	Y	Y	Y	Y	Y	Y
	3.2 Did author perform a correct statistical analysis?	• Answer 'Yes' if the descriptive and analytical statistical approach was adequate to the yielded data and the study aims with description of the scale of data (continuous, ordinal, nominal), data distribution (parametric or non-parametric test), statistical test and software used. Also, answer "Yes" if the study reports the study design factors (e.g. factorial design, repeated measures at time points) if applicable. • Answer 'No' if the statistical analysis was inappropriate to the data. • Answer 'Insufficiently reported' if the only information about correct statistical analysis is a statement that the study applied statistical analysis.	IR	Y	Y	IR	N	IR	Y	N	Y
D4 - Bias in the outcomes analyzed	4.1 Did the author report how outcome data was obtained and the measurement of outcome data?	• Answer 'Yes' if the author adequately described and measured the outcomes by examiners with independent assessment oy by a testing machine; and if the outcome measured was defined properly (e.g. fracture strength of endodontic file, antimicrobial evaluation, solubility of endodontic cements) to allow interpretation and, if needed, comparison or pooling across studies. • Answer 'No' if there are no description of how outcomes was measured. • If these details are incomplete, they should be marked 'Insufficiently reported'.	N	Y	N	N	N	N	N	Y	Y
	4.2 Did the author completely reported results?	• Answer 'Yes' if the study reported all outcomes of the study in line with what could be expected in methods section or by the registered protocol (if available); or it has been defined as planned outcomes by the researcher before conducting the study. Also answer "Yes" if the outcomes are reported in sufficient detail for a full appraisal (e.g., measures of central tendency like means or medians; measures of dispersion like standard deviation or interquartile range if applicable). • Answer 'No' if there are some results incompletely reported or in insufficient details.	Y	Y	Y	Y	Y	Y	Y	Y	Y
D5 - Other Bias	5.1 Are there a conflict of interest or other source of bias?	• Answer 'Yes' if the author describes sources of funding that potentially could compromise the study with conflict of interest with support related to the companies of the materials tested; or bias due to problems not covered in other domains in the tool. • Answer 'No' if the funding is not related to the companies of the materials tested or if it is stated that there is no conflict of interest. • Answer 'Insufficiently reported' if there are insufficient details to evaluate a possible conflict of interest.	Y	Y	N	Y	N	Y	IR	N	Y
Overall Risk of Bias to the result	Low, Some concerns or High?	• Low risk of bias: The study is judged to be at low risk of bias with "Yes" answered for all domains for this result • Some concerns: The study is judged to raise some concerns if it is insufficiently reported in at least one domain for this result, with any "No" reported for any domain. •High risk of bias: The study is judged to be at high risk of bias with at least one "No" answered for a domain, or the study is judged to have insufficiently reported information for multiple domains in a way that substantially lowers confidence in the result									



APÊNDICE E – Checklist PRISMA

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	45
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	NA
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA

	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	43
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	48
Study characteristics	17	Cite each included study and present its characteristics.	31
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NA
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	NA
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			

Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	12
	23b	Discuss any limitations of the evidence included in the review.	18
	23c	Discuss any limitations of the review processes used.	18
	23d	Discuss implications of the results for practice, policy, and future research.	18
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	19
Competing interests	26	Declare any competing interests of review authors.	19
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	45