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REVIEW ARTICLE

Anti-bacterial efficacy of Aloe vera against *E. Faecalis* in comparison to other intracanal medicaments: A systematic review and *meta*-analysis

Rabia Tariq [a], **Zohaib Khurshid** [b,c,*], **Waqas Ahmed Farooqui** [d], **Nejdet Adanir** [e]

[a] *Department of Research, School of Public Health, Dow University of Health Sciences, Karachi 74200, Pakistan*
[b] *Department of Prosthodontics and Dental Implantology, College of Dentistry, King Faisal University, Al Ahsa 31982, Saudi Arabia*
[c] *Center of Excellence for Regenerative Dentistry, Department of Anatomy, Faculty of Dentistry, Chulalongkorn University, Bangkok 10330, Thailand*
[d] *School of Public Health, Dow University of Health Sciences, Karachi 74200, Pakistan*
[e] *Department of Restorative Dentistry, College of Dentistry, King Faisal University, Al Ahsa 31982, Saudi Arabia*

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KEYWORDS

Aloe vera;
Bacteria;
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E. faecalis;
Endodontic;
Intracanal medicament

Abstract *Introduction:* This review article aims to evaluate the antibacterial efficacy of Aloe vera against *Enterococcus faecalis* (*E. faecalis*) in comparison to other intracanal medicaments by assessing experimental in-vitro studies associated with the objective, many of which performed bacterial inoculation on extracted human teeth or directly on laboratory petri dishes.

Materials & Methods: Publications from 2012 to 2022 were retrieved from databases, including PubMed, Scopus, and Cochrane Library, and they were screened against our inclusion criteria, leading to the incorporation of 18 studies into the systematic review and nine into the *meta*-analysis. Colony-forming units (CFUs) in the Aloe vera group were compared with saline, sodium hypochlorite (NaOCl), chlorhexidine (CHX), and calcium hydroxide (CaOH) using a *meta*-analysis (Stata software version 16.0), and forest plots were computed to record the sample size, mean and standard deviation value of the outcome CFU, and 95% confidence intervals.

Results: This systematic review indicates that Aloe vera demonstrates bactericidal properties that are higher than or similar to those of saline and CaOH, but CHX, NaOCl, and propolis exhibited higher antibacterial properties against *E. faecalis* than Aloe vera. In a *meta*-analysis, Aloe vera

* Corresponding author at: Department of Prosthodontics and Dental Implantology, College of Dentistry, King Faisal University, Al-Ahsan 31982, Saudi Arabia.
E-mail addresses: zsultan@kfu.edu.sa, Zohaib.K@chula.ac.th (Z. Khurshid), waqas.ahmed@duhs.edu.pk (W. Ahmed Farooqui).
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showed a non-significantly lower CFU count than CaOH and saline ($p > 0.05$), while Aloe vera had a higher CFU count than CHX and NaOCl ($p > 0.05$).

Conclusion: In summary, Aloe vera exhibits antibacterial capabilities against *E. faecalis* that are superior or equal to those of saline and CaOH, respectively, while CHX and NaOCl showed greater antibacterial efficacy against *E. faecalis* than Aloe vera (PROSPERO registration no. CRD42022314790).

Contents

1. Introduction

The infective capability of endodontic microorganisms is responsible for the initiation and sustainment of periapical disease (Nair et al., 2005). In response, root canal treatment aims to eradicate bacterial counts and their by-products through chemo-mechanical cleaning and by shaping the root canal system (Peters et al., 1995). However, successful endodontic treatment requires countering persistent microbes with effective antimicrobial medicaments, in addition to overcoming common technical barriers, including the structural complexities of the root canal system, the unavailability of an appropriate instrument, and iatrogenic procedural errors (Byström et al., 1985; Tabassum and Khan, 2016). The key elements of different medicaments are responsible for variations in functional presentation, depending on the component concentration, biotic indicator, method, exposure interval, etc. Unfortunately, endodontists face challenges in identifying factors that support effective root canal treatment (Estrela et al., 2009; Sundqvist et al., 1998).

Enterococcus faecalis (*E. faecalis*) exists among the normal flora of the oral cavity, and it is primarily involved in the pathogenicity of recurrent infections (Love, 2001). It is an anaerobic gram-positive bacterium that contains virulence traits against host cells (Iii et al., 2001), and it can form a biofilm that resists high-pH saline solutions and intracanal medicaments (Janani et al., 2017; Kafil et al., 2013; Kristerson and Riis, n.d.). In a favorable atmosphere, the virulence and biofilm-productive nature of *E. faecalis* may lead to persistence and resilience in response to certain antimicrobial drugs (Aghdam et al., 2017).

Currently, evidence-based dentistry is gaining attention for its usage of herbal products in endodontics, which are recommended primarily for their biocompatibility and fewer side effects in contrast to artificial antimicrobials (Ríos and Recio, 2005). In fact, in the past several years, some studies assessed the antimicrobial activities of natural products for use against *E. faecalis* (Arunkumar and Muthuselvam, 2009; Gupta et al., 2013; Prabhakar et al., 2010; Vasudeva et al., 2017).

Aloe leaves (*Aloe barbadensis Miller*) are from the Liliaceae family, and their appearance resembles a cactus plant. Hypothetically, they can comprise 75 active components, such as vitamins, enzymes, sugars, minerals, lignin, saponins, amino

acids, and salicylic acids (Angerhofer, 2002), and they have significant anti-inflammatory, antibacterial, antiviral, antifungal, and anti-arthritic effects and produce positive hypoglycemic results (Arunkumar and Muthuselvam, 2009). Further, they have a strong history of usage in the fields of nutrition, medicine, and dentistry due to their multipurpose characteristics (Taheri et al., 2011). Yet, along with their anti-inflammatory and antibacterial properties, they allow the diffusion of hydroxyl ions through dentinal tubules to encourage curing and remineralization (Shabbir et al., 2022). As such, aloe leaves are now recommended in dental root canal treatment as an intracanal medicament due to their inhibitory effect on many oral pathogens, including the *Enterococci* species *E. faecalis* (Shahzad et al., 2009). Related in-vitro studies have shown effective outcomes of Aloe vera use against *E. faecalis* (Alemdar and Agaoglu, 2009; Athiban et al., 2012). However, a few studies have reported results that oppose Aloe vera use (Bhardwaj et al., 2013; Valera et al., 2013).

Conventional intracanal medicaments, such as sodium hypochlorite (NaOCl), chlorhexidine (CHX), calcium hydroxide (CaOH), and numerous saline and isotonic solutions (normal or sterile saline [NaCl], phosphate-buffered saline [PBS]) are still readily available for use during endodontic procedures. NaOCl is among the most widely used irrigants because of its potent antimicrobial properties, low cost, and long shelf life (Oliveira et al., 2007). Generally, CHX and CaOH are used more often against gram-positive than gram-negative bacterial infections, but these medicaments have weaknesses, including potential toxicity (NaOCl), minimal or no tissue-liquefying properties (CHX), and the ability to render the tooth structure susceptible to fractures (CaOH)(Panchal et al., 2020). Still, the persistent rise in antibiotic-resistant strains and side effects caused by synthetic medications has encouraged researchers to turn to herbal substitutes (de Almeida Gomes et al., 2006).

The actual goal of this systemic review and *meta*-analysis is to elaborate the final clinical decision for a proper recommendation when diverse clinical evidence has been reported. Seemingly, systemic assessments necessitate earlier adaptations of new evidence-based healthcare; therefore, this study aimed to review the antimicrobial efficacy of Aloe vera against *E. faecalis* as an endodontic infection treatment using a systematic review and *meta*-analysis.

2. Methods

2.1. Protocol registration

This systemic review was conducted in consideration of the following points: (a) the systemic review should match the population, intervention, comparator, outcome, and study design (PICOS) criteria, and the Measurement Tool to Assess Systemic Review-2 (AMSTAR-2) criteria should be adopted to provide a high-quality review article (Khurshid et al., 2021; Shea et al., 2017); (b) an advanced and up-to-date literature search should be provided; and (c) that no previous systemic reviews on a related subject have been published should be assured. The study protocol was registered on PROSPERO, the International Prospective Register of Systematic Reviews (Registration no. CRD42022314790), and the PRISMA 2020 statement was followed for recording this systemic review and *meta*-analysis (Page et al., 2021).

2.2. Focused question

This review was conducted based on the following PICOS format with the assistance of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019). The research question was designed via a mutual discussion among a group of authors, who considered the availability, importance, and necessity of systemic reviews on related subjects. Thus, this review presents a comparison of an intervention (Aloe vera) with all other intracanal medicaments, and it includes in-vitro studies. As such, the final question was: "Does Aloe vera possess greater antimicrobial effectiveness as an intracanal medicament against *E. faecalis* when compared to other intracanal materials?"

2.3. Literature search strategies

PubMed, Scopus, and Cochrane Library were included as major search engines for publication retrieval with the aid of the following keywords: "Aloe vera," "endodontics," and "*E. faecalis*," and the following combination of search terms was used to explore articles: (Aloe OR "Aloe vera") AND (Endodontics OR "Regenerative Endodontics") AND (faecalis) using the All Fields function in PubMed, the Title-ABS-Key function in Scopus, and the Advance Search function with a Medical subheading (Mesh) in the Cochrane Library database. The organizations considered further for inclusion in the literature search were the FDI World Dental Federation, the Australian Dental Association, and the American Dental Association (ADA). Moreover, the ClinicalTrials.gov and the ISRCTN registries were accessed to review completed or ongoing trials. Further, the PROSPERO registry was also assessed initially to ensure that no other review on this subject has been registered. The electronic retrieval system and databases were searched for relevant articles without any restrictions, apart from being written in the English language, until September 30, 2022, and all article references were recorded and managed independently by two reviewers using the EndNoteX9 reference manager library (Hupe, 2019). Reference records were initially filtered according to the title and abstract of all papers that matched the inclusion criteria, and all articles meeting the inclusion criteria were considered relevant (Fig. 1).

2.4. Inclusion criteria

Studies performed on permanent teeth extracted from humans or in a laboratory (petri dish) to compare the antimicrobial activity of Aloe vera as an intracanal medicament against *E. faecalis* were included.

2.5. Exclusion criteria

In-vivo studies, randomized (or non-randomized) controlled trials (RCTs), studies executed on animal or bovine teeth, studies including primary teeth (deciduous teeth) extracted from humans, case reports, case series, review articles, commentaries, letters to the editor, and unpublished papers were excluded. Further, studies with a contact time with *E. faecalis* of less than 12 h before antibacterial valuation and studies that

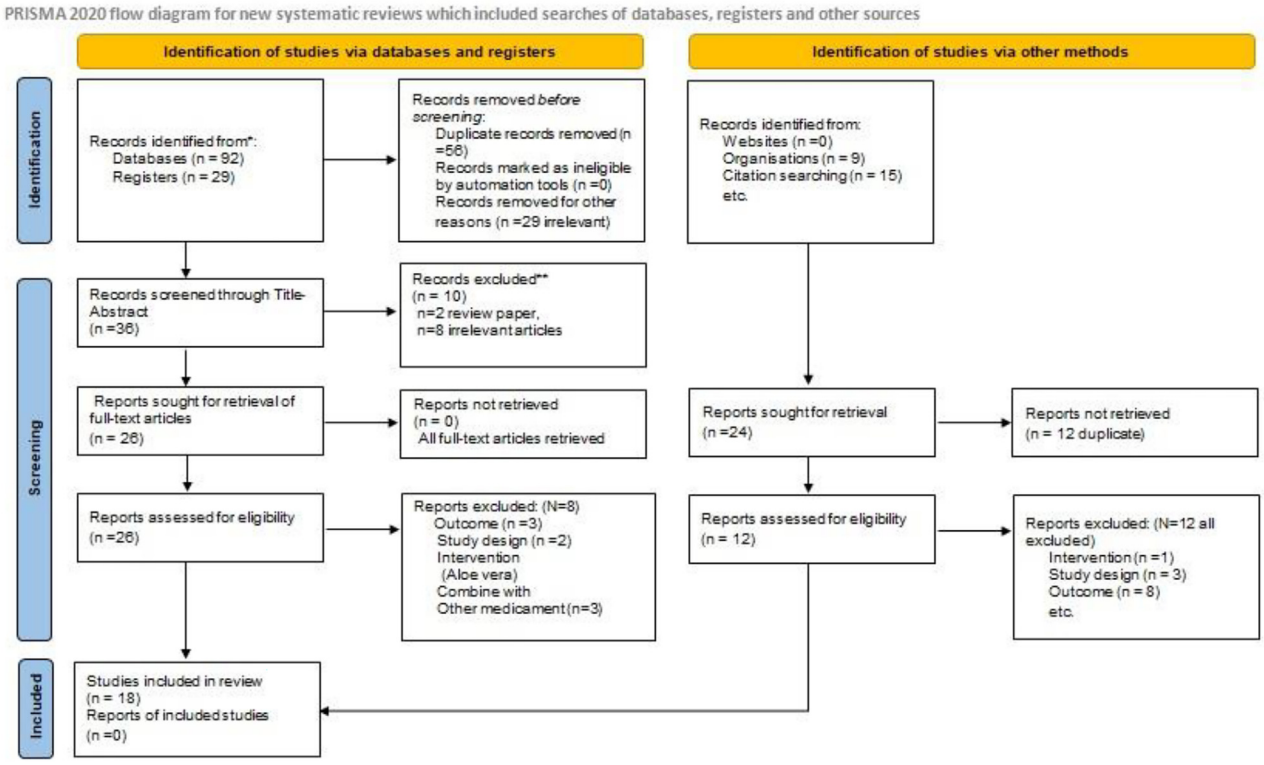

Fig. 1 Schematic representation of the PRISMA flowchart for literature search.

used Aloe vera exclusively—except when amalgamating with other medicaments—were also excluded to avoid selection bias.

2.6. Study selection and data extraction

Studies that met the above-mentioned eligibility criteria were selected with the mutual consent of all investigators, and the titles of all articles were explored through an online search and recorded on the EndNoteX9 reference manager library (Hupe, 2019) software separately by three investigators (ZK, RT, and WF). Later, the full titles and abstracts of the articles retrieved through the initial literature research were reviewed, and articles not meeting the eligibility criteria and duplicate articles were omitted from the study manually using the Endnote software. The abstracts of the remaining articles were screened individually, and the initial filtration files of both reviewers were cross-checked by the fourth reviewer (NA). In the case of any dissimilarities in or articles missing from the reference files, a search was carried out by a fourth author (NA), and modifications were made where needed. Further, the authors tried to obtain the full papers for all eligible studies.

Three separate computerized list records were created by the reviewers (RT, ZK, WF) consisting of included and excluded articles, and differences among all four reviewers in terms of the studies they identified as eligible were reviewed and resolved by mutual agreement. In addition, a citation analysis was performed manually via separate screenings of the reference list of included articles by RT and ZK. Additional articles from the reference list that matched the eligibility criteria were included, and the reference list was reviewed again by the other two authors (WF and NA) to avoid manual errors.

A schematic representation of the PRISMA 2020 flow diagram for the literature search (Fig. 1) describes the final filtration of full-text articles according to the PICOS criteria. The data were extracted from included studies and transferred to a pre-defined Microsoft Excel sheet containing specific columns to record data in the form of general information about the studies (Table 1). In Table 2, information related to the outcomes of the studies included in the systemic review and *meta*-analysis was noted, and data extraction was conducted by the four authors independently (RT, ZK, WF, and NA) on an Excel sheet to prevent information from being missed. The information of these three sheets was matched by RT and WF, and in the case of any discrepancies therein, ZK and NA again reviewed the data and made final modifications to the sheet, a final version of which was sent to all authors; any disagreements that arose between authors were resolved through discussion. Finally, a conclusive data extraction file was approved by all authors and sent to a biostatistician (WF) for further analysis.

2.7. Quality assessment of included studies

The Office of Health Assessment and Translation (OHAT) Risk of Bias Rating Tool for Human and Animal Studies (U.S. Department of Health and Human Services, 2018) was used to assess the internal validity/risk of bias of the included studies (National Institute of Environmental Health Sciences, 2015). The OHAT tool for experimental in-vitro studies contains 11 questions that consider seven different bias domains, including selection, confounder, performance, attrition/exclu-

Table 1 General characteristics of included studies.

Study Number	Authors	Year	Country	Test Group	Control Group	Outcome
1	Prakash P Athiban et al.	2012	India	Aloe vera	NaOCl (+ve control), Saline (-ve control)	Aloe vera produce effective (21 mm) zones of inhibition on agar plate. Nearly, similar bacterial effects to NaOCl even after 48hrs of incubation.
2	Leila Bazvand et al.	2013	Iran	*TAM, CHX gel, Propolis, Aloe vera gel,	Normal saline (+ve control), No inoculation (-ve control)	Aloe vera showed no significant difference t in comparison with other medicaments, it was less effective ($P < 0.05$). TAM was most effective.
3	Swati Ramesh Karkare et al.	2015	India	Hydro-alcoholic extract of Aloe vera and Garlic	NaOCl (+ve control)	Saturated hydro-alcoholic extract of Aloe vera showed the highest zone of inhibition against E. faecalis similar to NaOCl.
4	Sahebi S. et al.	2013	Iran	Aloe Vera gel, , NaOCl	May be Normal saline@	Inhibitory effect of NaOCl on E. faecalis was much greater than Aloe vera and normal saline ($p < 0.001$).
5	Anuj Bhardwaj et al.	2012	India	CaOH, Papain gel, Morinda citrifolia gel, Aloe vera, CHX	Saline (-ve control)	2% CHX produced 100% antimicrobial efficacy as compared to Aloe vera gel (78.9%).
6	Abbas Abbaszadegan et al.	2014	Iran	CaOH, Zataria multiflora, Aloe vera	Sterile Saline (+ve control), No inoculation (-ve control)	Herbal medicaments showed equal antimicrobial efficiency against *E. faecalis*, comparable to CaOH. Statistically significant difference between all medicaments noted after 1and 7 days but not after 14 days.
7	Prashant Babaji et al.	2016	India	NaOCl, *M. citrifolia*, Neem extract, Aloe vera	Distilled water	Highest inhibitory zone against E. faecalis was seen in NaOCl fallowed by *M. citrifolia* and Neem extract, and least by Aloe vera extract.
8	Maryam Ehsani et al.	2013	Iran	Propolis hydro-alcoholic extract, Aloe vera, CHX	Ethanol/ Distilled water (-ve control)	Aloe vera gel also showed significant antibacterial effect. However, Propolis is more potent than Aloe vera
9	Ikmal Hisham Ismail et al.	2020	Malaysia	MP[$], Aloe vera, MP + AV	CaOH (positive control), DMSO # (negative control	Propolis (mean = 6.21 mm ± 0.046) showed better antimicrobial activity compared to Aloe Vera (mean: 5.05 ± 0.012) alone against *E. faecalis*
10	Negin Ghasem et al.	2020	Iran	Aloe vera, CaOH	PBS=	Aloe vera showed significant antibacterial properties against *E. faecalis* in contrast to CaOH. Disregarded 4th and 6th week biofilms.
11	Pachalla M. Sailaja et al.	2020	India	Q Mix 2 in 1[+], NaOCl, chitosan, Aloe vera juice, Amla juice, Pancha tulsi	No medicament (positive control)No inoculation (negative control)	Pancha tulsi showed significant disinfectant action on the GP cones followed by Q Mix 2, Amla juice, NaOCl, Aloe vera
12	Thilla S Vinothkumar et al.	2012	India	Curcuma longa (CL), Azadiracta indica (AI), Aloebarbadensis (AV) , Myristica fragrans (MF), Terminalia chebula (TC)	saline (-ve control), NaOCl (+ve control)	The efficiency of the extracts against *E. faecalis* in descending order are as follows: AI, CL, MF, TC and AV with ($p < 0.0001$).
13	Ramamurthy Varshini et al.	2019	India	CaOH, Aloe vera, Ricinus communis (castor oil), Fresh lemon extract.	Normal saline	CaOH presented significantly greater antimicrobial ability than Aloe vera, Lemon, and R. communis ($P < 0.05$)
14	Marcia Carneiro Valera et al.	2013	Brazil	NaOCl, CHX Castor oil (Ricinus communis), Glycolic ginger, Glycolic Aloe vera	May be Sterile saline solution@	Reduction of bacterial count (CFU/mL) for groups NaOCl, CHX, Castor oil and Ginger was greater in comparison to Aloe vera and Saline
15	Soujanya Goud et al.	2018	India	NaOCl, CHX, Aloe vera	Saline (+ve control)	2% CHX showed highest antimicrobial effect. No significant difference was found between 3% NaOCl and Aloe vera

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Table 1 (*continued*)

Study Number	Authors	Year	Country	Test Group	Control Group	Outcome
						($p > 0.001$) against *E. faecalis*.
16	Agrima Vasudeva et al.	2017	India	CHX, Honey, Aloe vera gel, Curcuma longa, Propolis, CaOH	Saline (negative control)	2% Chlorhexidine gel was most effective followed by Propolis, Curcuma longa, Honey, CaOH, Aloe vera, and Saline.
17	M. C. Noushad et al.	2018	KSA	Aloe vera, Cashew apple extract, Guava leaf extract, Papaya leaf extract	NaOCl (+ve control)	A significant variance between the diameters of zones of inhibition of bacterial growth attained for 5.2% NaOCl, Aloe vera extract, Cashew apple extract, Papaya leaf extract, and Guava leaf extract against *E. faecalis* ($P < 0.05$)
18	Mahsa Eskandarinezhad et al.	2022	Iran	CaOH, Curcumin paste, Aloe vera gel	Normal saline (+ve control)	Aloe vera showed 98.79% antimicrobial effects than control group. However, no statistical difference ($P = 0.057$) between Aloe vera, CaOH, Curcumin paste.

@ not mentioned exactly about control group.
*Tri-antibiotic mixture (0.5 g of ciprofloxacin + 0.5 g of minocycline + 0.5 g of metronidazole mixed in normal saline 2:1 ratio).
* Morinda citrifolia juice.
$Malaysian geopropolis.
#Dimethyl sulfoxide.
= Phosphate-buffered saline.
+ QMix™ 2 in 1 is a mixture of (bisbiguanide antimicrobial agent, polyamine carboxylic acid calcium chelating agent, saline, and a surfactant).

sion, detection, and selective reporting bias, as well as adherence to the study protocol, use of appropriate statistical methods, etc. By employing validated classifications, each domain was rated on a scale of 1–4, where 1 denotes (++) "a definitely low risk of bias," 2 denotes (+) "a probably low risk of bias," 3 denotes (-) "a probably high risk of bias," and 4 denotes (--) "a definitely high risk of bias" (OHAT, 2015).

2.8. Measurement of effect and data synthesis

Comparative studies on Aloe vera, NaOCl, CHX, CaOH, and a variety of saline solutions—based on the bacterial counts in colony-forming units (CFUs) as an assessment method—were adequately available, but studies assessing the antimicrobial efficacy in the "zone of inhibition (ZOI)" were scarce. Thus, the studies that compared Aloe vera with NaOCl, CHX, CaOH, and different saline solutions were included in the *meta*-analysis. The heterogeneity of the *E. faecalis* count in CFUs was measured using a chi-squared test and I^2 statistics, because most studies that used ZOI as an assessment method did not mention mean and standard deviation (SD) values. The only study that used bacterial counts in CFUs as an outcome evaluation method was excluded from the *meta*-analysis because it reported a percentage reduction in CFUs instead of as a bacterial count (Abbaszadegan et al., 2016). To ensure data uniformity for the *meta*-analysis, the reported outcome was measured using a single scale, such as the duration in days, logged bacterial count, or unit in microliters, while the STATA version 16.0 software (Stata Corp, College Station, Texas, USA) was used for data analysis. Two models were used to pool the obtained data: a random effects model (REM) was used for the *meta*-analysis, as the I^2 value was higher than 50% and the level of significance for heterogeneity was fixed at a *p*-value of less than 0.05, while a forest plot was computed using the effect size and the standard error of 95% confidence interval (CI).

Due to the heterogeneity in the primary outcome-measuring unit and the selective reporting of statistical parameters, we were unable to include all selected studies in the *meta*-analysis. Hence, we restricted the *meta*-analysis to studies that provided data on outcomes in the form of mean and SD values. However, all selected studies were included in the qualitative analysis. As less than 10 studies were eligible for the heterogeneity assessment, a funnel plot was not reported.

3. Result

3.1. Study selection

The PRISMA 2020 flow diagram in Fig. 1 determined the studies to be included through a preliminary literature search, which retrieved 92 studies in total after an initial search of the three main databases (PubMed = 75, Scopus = 15, Cochrane Library = 2), as well as 29 studies from registers. All references were imported to the Endnote X9 reference manager library, and after eliminating 56 duplicate references and 29 irrelevant references, such as books, protocols, conference reports, etc., 36 reference articles underwent an initial thorough screening based on title and abstract. A further 11 irrelevant articles were excluded (two review papers, nine human clinical trials or studies with an unrelated topic and abstract). After reading the full texts of the 25 selected articles, seven were excluded because three produced different outcome variables, one was a human RCT design, and three involved an intervention (Aloe vera) combined with other medications. Other methods of reference retrieval were also used, from which 24 sources were imported to the EndnoteX9 library initially (nine references from different organizations and 15 ref-

Table 2 Outcomes of studies included in systematic review and *meta*-analysis.

No	Author, Year	Total Sample	TestGroup (sample/plate)	Control Group	Sample Medium	Medicaments	Last Medicament Duration	Last Inoculation Period	Outcome Measure	Outcome Evaluation Method	Result
1	Athiban et al, 2012	1plate/3parts	1part	2parts	Agar diffusion plate	NaOCl, Aloe vera, Normal saline	24 h	24 h	Zone of inhibitory	diameters of the zones in millimeter (mm)	**Mean inhibition diameter (mm)** Aloe vera = 21 mm NaOCl = 23 mm Saline = 0.0 mm
2	Leila Bazvand et al, 2013	90 samples	60 (15each)	30 (15each)	Extracted single rooted teeth	*TAM, CHX gel, Propolis, Aloe vera gel, Normal saline	7 days	21 days	colony-forming units	Colonies counted by blinded microbiologist	**Mean colony count (Cfu/μL)** TAM = 73.3 ± 310.4 CHX = 880 ± 574.7 Propalis = 2933.3 ± 2880.1 Aloe vera = 9200 ± 4601.2 Saline = 33333.3 ± 9759
3	Karkare et al, 2015	3plates/ 3parts	6parts	3parts	Agar diffusion plate	NaOCl, Hydro-alcoholic extract of Aloe vera and Garlic	24 h	24 h	Zone of inhibitory	diameters of the zones in millimeter (mm)	**Mean inhibition region (mm)** Aloe vera (saturated) = 13 ± 0.81Garlic (saturated) = 10.66 ± 0.942 NaOCl = 16.33 ± 2.49
4	Sahebi S. 2013	60 Samples	40 (20each)	20 (20each)	Extracted single rooted teeth	Aloe Vera gel, Normal Saline, NaOCl	48 h	48 h	colony-forming units	Bacterial colonies counted	**Mean colony count** (Cfu/mL) Aloe vera = 2.21×10^8 ± 0.98×10^8 Saline = 2.27×10^8 ± 0.95×10^8 NaOCl = 0.0
5	Bhardwaj et al, 2012	180 samples	150 (30each)	30 (30each)	Extracted single rooted teeth	CaOH, Saline, Papain gel, Morinda citrifolia gel, Aloe vera, CHX	5 days	21 days	colony-forming units	Bacterial colonies counted	**Mean colony count at 5 day (400 μm depth, Cfu/μL)** CHX = 0.0 Morinda citrifolia = 0.52×10^5 Aloe vera = 1.04×10^5 Papain = 1.31×10^5 CaOH = 1.24×10^5 Saline = 3.84×10^5
6	Abbas Abbaszadegan et al, 2014	108 samples	90 (10each/ per 14 days)	18 (3each/ per 14 days)	Extracted single rooted teeth	CaOH, Zataria multiflora, Aloe vera, sterile saline	14 days	21 days	colony-forming units	Bacterial colonies counted	**Median Percentage reduction of the $\log_{10}$ c.f.u./mL** Ataria Multiflora Bois = 89% CaOH = 86% Aloe vera = 85% Saline = 1%
7	Babaji et al, 2016	60 samples	48 (12each)	12 (12each)	Agar diffusion plate	NaOCl, M. citrifolia, Neem extract, Aloe vera, Distilled water	24 h	24 h	Zone of inhibitory	diameters of the zones in millimeter (mm)	**Mean of inhibition zone in mm** NaOCl = 28.6 ± 1.15 M Citrifolia = 22.7 ± 1.12 Naeem = 18.3 ± 1.06 Aloe vera = 14.7 ± 1.04

(*continued on next page*)

Table 2 (*continued*)

No	Author, Year	Total Sample	TestGroup (sample/plate)	Control Group	Sample Medium	Medicaments	Last Medicament Duration	Last Inoculation Period	Outcome Measure	Outcome Evaluation Method	Result
											Distilled water = 0
8	Ehsani et al. 2013	24 well plates	Not given	Not given	Agar diffusion plate	Propolis hydro-alcoholic extract, Aloe vera, CHX, Distilled water, Ethanol	24 h	24 h	Minimal inhibitory concentration (MIC)/ minimum bactericidal concentration (MBC)	Serial dilution and plated method	**Mean of inhibition zone in mm** CHX = 8.7 ± 0.5Propalis (aqueous extract) = 0.0 Aloe vera = 17.3 ± 1.3
9	Ismail et al, 2020	3plates/divided into 5 portions	9portion	6portion	Agar diffusion plate	MP[$], Aloe vera, MP + AV, CaOH, DMSO[#]	18-24 h	18-24 h	Minimal inhibitory concentration (MIC)/ minimum bactericidal concentration (MBC)	Turbidity measured through micro-plate reader/sub-culturing on plates	**Mean of inhibition zone in mm (*)** MP extract = 6.21 ± 0.046 CaOH = 5.51 ± 0.006 Aloe Vera = 5.05 ± 0.012
10	Ghasem et al, 2020	130 samples	40 (20each)	20 (20each)	Extracted single rooted teeth	Aloe vera, CaOH, PBS[=]	24 h	6 weeks	colony-forming units	colony count machine	**Mean colony count at 6 week interval (Cfu/mL)** Aloe vera = $136.36x10^8$ ± $323.33 x10^8$ CaOH = $27501.66 x10^8$ ± $36570.34 x10^8$ PBS = $95000 x10^8$ ± $12247.44 x10^8$
11	Sailaja et al, 2020	80 samples	60 (10each)	20 (10 each)	Contaminated GP cones	Q Mix 2 in 1^+, NaOCl, chitosan, Aloe vera juice, Amla juice, Pancha tulsi	9 days	23 h	colony-forming units	Digital colony counter.	**Mean colony count in Cfu/mL** Q Mix 2 in 1 = $5.6 x10^{-1}$ NaOCl = $15.6x10^{-1}$ Chitosan = $79.2 x10^{-1}$ Aloe vera = $69.00x10^{-1}$ Amla Juice = $8.90 x10^{-1}$ PanchaTulsi = $2.80x10^{-1}$
12	Thilla S Vinothkumar et al, 2012	42 samples	30 (6each)	12 (6each)	Extracted single rooted teeth	Curcuma longa (CL), Azadiracta indica (AI), Aloebarbadensis (AV) , Myristica fragrans (MF), Terminalia chebula (TC)	24 h	21 days	qPCR*	Thermal cycler	Mean cells/ mL CL = $32.16 x10^8$ ± $1.27 x10^8$ AL = $33.94 x10^8$ ± $0.70 x10^8$ TC = $32.44 x10^8$ ± $0.88 x10^8$ MF = $31.84 x10^8$ ± 0.62 Saline = $24.01x10^8$ ± $0.96 x10^8$ NaOCl = $34.20 x10^8$ ± $0.83 x10^8$ Aloe vera = $28.58 x10^8$ ± $1.11 x10^8$ TC = 23.6%

Table 2 (*continued*)

No	Author, Year	Total Sample	TestGroup (sample/plate)	Control Group	Sample Medium	Medicaments	Last Medicament Duration	Last Inoculation Period	Outcome Measure	Outcome Evaluation Method	Result
13	Ramamurthy Varshini et al, 2019	80 samples	64 (16each)	16 (16each)	Extracted single rooted teeth	Normal saline, CaOH, Aloe vera, Ricinus communis (castor oil), fresh lemon extract.	7 days	21 days	Fluorescent stained scan	Observed under confocal laser scanning microscope with x20 magnification	**Mean remaining live bacterial count/μL** Saline = 49849.60 ± 14664.13 Ca $(OH)_2$ = 4717.20 ± 1877.59 Aloe vera = 10528.60 ± 11403.08 Castor oil = 38771.40 ± 22977.22 Lemon = 11574.40 ± 14757.77
14	Valera et al, 2013	72 samples	60 (12each)	12 (12each)	Extracted single rooted teeth	NaOCl, CHX Castor oil (Ricinus communis), Glycolic ginger, Glycolic Aloe vera, Sterile saline solution	7 days	21 days	colony-forming units	Bacterial colonies counted	**Mean log colony count in Cfu/mL** NaOCl = 0.0 CHX = 0.0 Castor oil = 3.49 $x10^8$ Ginger = 3.49 $x10^8$ Aloe vera = 5.73 $x10^8$ Saline = 5.46 $x10^8$
15	Goud et al, 2018	80 samples	60 (20 each)	20 (20 each)	Extracted single rooted teeth	NaOCl, CHX, Aloe vera, Saline	24 h	3 days	colony-forming units	Bacterial colonies counted	**Mean log colony-forming units in Per mL** NaOCl = 2.76 ± 0.18 CHX = 1.36 ± 1.18 Aloe vera = 2.88 ± 0.09 Saline = 3.20 ± 0.08
16	Vasudeva et al, 2017	210 samples	180 (30each)	30 (30each)	Extracted single rooted teeth	Saline, CHX, Honey, Aloe vera gel, Curcuma longa, Propolis, CaOH	5 days	21 days	colony-forming units	Colonies counted at two depths of dentin block (200 and 400 mm)	**Mean count in Cfu/mL at 5 day, (400 μm depth)** CHX = 0.10 ± 0.31 Propolis = 2.80 ± 0.632 Curcuma longa = 3.10 ± 0.567 Honey = 8.40 ± 0.84 CaOH = 9.30 ± 1.05 Aloe vera = 12.90 ± 0.73 Saline = 20.30 ± 0.48
17	M. C. Noushad et al, 2018	5 plate/ 25parts	20 parts	5parts	Disc Diffusion/ Agar culture plates	Aloe vera, Cashew apple extract, Guava leaf extract, Papaya leaf extract, NaOCl	24 h	24 h	zones of inhibition	diameters of the zones in millimeter (mm)	**Means diameter in mm** NaOCl = 25.4 ± 1.19 Cashew apple = 14.1 ± 0.41 Guava leaf = 12.5 ± 0.5 Aloe vera = 7.2 ± 0.75 Papaya leaf = 6.3 ± 0.83
18	Eskandarinezhad et al, 2022	72 samples	54 (18each)	18 (18each)	Extracted single rooted teeth	CaOH, Curcumin paste, Aloe vera gel, Normal saline	1 week	6 week	colony-forming units	Bacterial colonies counted	**Mean colony-forming unit per ml** CaOH = $7.4 \times 10^2 \pm 5.2 \times 10^2$ Curcumin = $6.3 \times 10^2 \pm 4.6 \times 10^2$ Aloe vera = $1.5 \times 10^3 \pm 1.1 \times 10^3$ Saline = $1.2 \times 10^5 \pm 8.1 \times 10^2$

*Quantitative polymerase chain reaction.
(*) To avoid confounder effect results of combine MP + AV excluded (mean = 8.11 ± 0.015).

erences from a manual citation analysis of a full-text article). After the removal of 12 duplicate studies from other resources, the file of articles retrieved from sources other than the main search engines was named the "other method reference" folder.

In total, 12 full-text articles were read thoroughly according to the inclusion criteria from the other method reference folder, and the remaining 18 studies that met the eligibility criteria adequately were from the main databases; no study from the "other method reference" folder was included. The final 18 studies were included in the qualitative analysis (Abbaszadegan et al., 2016; Athiban et al., 2012; Babaji et al., 2016; Bazvand et al., 2014; Bhardwaj et al., 2012; Ehsani et al., 2013; Eskandarinezhad et al., 2022; Ghasemi et al., 2020; Goud et al., 2018; Ismail et al., 2020; Karkare et al., 2015; Noushad et al., 2017; Ramamurthy et al., 2017; Sahebi et al., 2014; Sailaja et al., 2020; Valera et al., 2013; Vasudeva et al., 2017; Vinothkumar et al., 2013), and nine studies were included in the *meta*-analysis (Bazvand et al., 2014; Bhardwaj et al., 2012; Eskandarinezhad et al., 2022; Ghasemi et al., 2020; Goud et al., 2018; Sahebi et al., 2014; Sailaja et al., 2020; Valera et al., 2013; Vasudeva et al., 2017). The agreement between reviewers was evaluated with the support of statistics (Landis and Koch, 1977), which showed a high agreement (0.75) among them.

3.2. Study characteristics

All studies included in the review were in-vitro or ex-vivo designs, and they were performed in a laboratory setup and published between 2012 and 2022. Meanwhile, the test medicaments included Aloe vera contrasted with other intracanal medicaments, e.g., Propolis, CHX, CaOH, *Curcuma longa*, NaOCl, tri-antibiotic paste, honey gel, glycolic ginger extracts, CaOH plus metronidazole, etc. Half of the studies used the bacterial count in CFUs as an outcome measure (Abbaszadegan et al., 2016; Bazvand et al., 2014; Bhardwaj et al., 2012; Eskandarinezhad et al., 2022; Ghasemi et al., 2020; Goud et al., 2018; Sahebi et al., 2014; Sailaja et al., 2020; Valera et al., 2013; Vasudeva et al., 2017), while the other half was assessed according to bacterial ZOIs (Athiban et al., 2012; Babaji et al., 2016; Karkare et al., 2015; Noushad et al., 2017) and underwent antimicrobial sensitivity testing according to the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) (Ehsani et al., 2013; Ismail et al., 2020), quantitative polymerase chain reaction (qPCR)(Vinothkumar et al., 2013), and confocal laser scanning microscopy after fluorescent staining (Ramamurthy et al., 2017). The included studies used saline as a positive or negative control group (Abbaszadegan et al., 2016; Athiban et al., 2012; Bazvand et al., 2014; Bhardwaj et al., 2012; Eskandarinezhad et al., 2022; Ghasemi et al., 2020; Goud et al., 2018; Ramamurthy et al., 2017; Vasudeva et al., 2017; Vinothkumar et al., 2013). Further, while Sahebi et al. (2014) used saline for comparison in their studies, they did not mention the use of saline as a control, but a few studies employed a variety of materials as controls, including distilled water, CaOH, NaOCl, dimethyl sulfoxide, ethanol, etc. (Ehsani et al., 2013; Ismail et al., 2020; Karkare et al., 2015; Noushad et al., 2017; Vinothkumar et al., 2013).

Most of the studies were performed in India (Athiban et al., 2012; Babaji et al., 2016; Bhardwaj et al., 2012; Goud et al., 2018; Karkare et al., 2015; Ramamurthy et al., 2017; Sailaja et al., 2020; Vasudeva et al., 2017; Vinothkumar et al., 2013) and Iran (Abbaszadegan et al., 2016; Bazvand et al., 2014; Ehsani et al., 2013; Eskandarinezhad et al., 2022; Ghasemi et al., 2020; Sahebi et al., 2014), but three were conducted in Malaysia (Ismail et al., 2020), Brazil (Valera et al., 2013), and Saudi Arabia (Noushad et al., 2017). In total, 13 of the 19 studies used the *E. faecalis* strain ATCC 29212 (Babaji et al., 2016; Bazvand et al., 2014; Bhardwaj et al., 2012; Eskandarinezhad et al., 2022; Ghasemi et al., 2020; Goud et al., 2018; Ismail et al., 2020; Noushad et al., 2017; Ramamurthy et al., 2017; Sailaja et al., 2020; Valera et al., 2013; Vasudeva et al., 2017; Vinothkumar et al., 2013), but some used other *E. faecalis* strains, including Karkare et al. (2015), who used ATCC11420; Sahebi et al. (2014), who used ATCC 11700; Abbaszadegan et al. (2016), who used KF465681; Ehsani et al. (2013), who used PTCC 1394; and Athiban et al. (2012), who obtained *E. faecalis* from the Department of Microbiology, JIPMER, Puducherry, but did not mention the strain used. In addition to *E. faecalis*, other microbes were used to assess the antimicrobial activity of different intracanal medicaments in contrast to Aloe vera, including *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans* (Athiban et al., 2012; Noushad et al., 2017; Sailaja et al., 2020; Valera et al., 2013; Vinothkumar et al., 2013). Eleven studies used single-rooted extracted teeth for bacterial inoculation, while six used disc diffusion agar plates (Athiban et al., 2012; Karkare et al., 2015). Further, only Sailaja et al. (2020) used contaminated gutta-percha (GP) cones as the study medium for examination, where the antimicrobial efficacy of Aloe vera and other comparators was assessed after 24–48 h of minimal incubation between 7 and 14 days (Table 2).

3.3. Main study outcome

Seven included studies concluded that Aloe vera possesses potent antibacterial properties similar to other intracanal medicaments (Abbaszadegan et al., 2016; Athiban et al., 2012; Bazvand et al., 2014; Ghasemi et al., 2020; Goud et al., 2018; Karkare et al., 2015), while the results of six included studies concluded that CHX exhibits better antibacterial properties than Aloe vera against *E. faecalis* (Bazvand et al., 2014; Bhardwaj et al., 2012; Ehsani et al., 2013; Goud et al., 2018; Valera et al., 2013; Vasudeva et al., 2017). Moreover, six studies included in the review argued that NaOCl was more effective against *E. faecalis* than other intracanal medicaments, including Aloe vera, CHX, CaOH, propolis, saline, ginger extract, turmeric, etc. (Babaji et al., 2016; Noushad et al., 2017; Sahebi et al., 2014; Valera et al., 2013; Vinothkumar et al., 2013), but Aloe vera demonstrated significant antibacterial effects, as reported in all studies that used saline as a control (Abbaszadegan et al., 2016; Athiban et al., 2012; Bazvand et al., 2014; Bhardwaj et al., 2012; Ghasemi et al., 2020; Goud et al., 2018; Ramamurthy et al., 2017; Vasudeva et al., 2017; Vinothkumar et al., 2013). Lastly, all four studies that used propolis as a comparative intracanal medicament found that it was superior to Aloe vera (Bazvand et al., 2014; Ehsani et al., 2013; Ismail et al., 2020; Vasudeva et al., 2017).

Table 3 OHAT (Office of Health Assessment and Translation) tool for Risk of bias and methodological quality assessment.

Vitro-studies	Selection Bias		Performance Bias		Attrition/Exclusion Bias	Detection Bias		Selective Reporting Bias	Other Sources of Bias
Authors, Years	1. Was random allocation present?	2. Was allocation to study groups adequately concealed?	5. Were the experimental conditions identical across study groups?	6. Were the research personnel Blinded to the study group?	7. Were outcome data complete without attrition or exclusion from analysis?	8. Can we be confident in the intervention characterization?	9. Can we be confident in the outcome assessment?	10. Were all measured outcomes reported?	11. Statistical methods were appropriate, or researchers adhered to the study protocol?
Athiban et al, 2012	- **NR**	- **NR**	+ +	- **NR**	+ +	+	+	–	–
Leila Bazvand et al, 2013	+	–	+ +	–	+ +	+ +	+ +	+ +	+ +
Karkare et al, 2015	- **NR**	- **NR**	+ +	- **NR**	+	+ +	–	+ +	+ +
Sahebi S. 2013	+ +	–	–	- **NR**	+	+	**NR**	+	+
Bhardwaj et al, 2012	**NR**	–	+	- **NR**	+	+	–	–	+
Abbas Abbaszadegan et al, 2014	+ +	+	+ +	+	+ +	+ +	–	+ +	+ +
Babaji et al, 2016	- **NR**	- **NR**	+	- **NR**	+ +	+ +	–	+ +	+
Ehsani et al, 2013	- **NR**	- **NR**	+	- **NR**	+	+	–	+	+
Ismail et al, 2020	–	+	+	- **NR**	+ +	+	–	+ +	+
Ghasem et al, 2020	- **NR**	- **NR**	+ +	- **NR**	+ +	+ +	+	+ +	+ +
Sailaja et al, 2020	- **NR**	- **NR**	+ +	- **NR**	+ +	+	–	+ +	+
Thilla S Vinothkumar et al, 2012	- **NR**	- **NR**	+ +	- **NR**	+ +	+ +	–	+ +	+ +
Ramamurthy Varshini et al, 2019	+	- **NR**	+ +	- **NR**	+	+ +	–	+	+
Valera et al, 2013	- **NR**	- **NR**	+ +	- **NR**	+	+	–	+	+
Goud et al, 2018	+	- **NR**	+ +	- **NR**	+ +	+ +	–	+ +	+
Vasudeva et al, 2017	- **NR**	- **NR**	+ +	- **NR**	+	+ +	–	+ +	+

(*continued on next page*)

Table 3 (*continued*)

Vitro-studies	Selection Bias		Performance Bias		Attrition/Exclusion Bias	Detection Bias		Selective Reporting Bias	Other Sources of Bias
Authors, Years	1. Was random allocation present?	2. Was allocation to study groups adequately concealed?	5. Were the experimental conditions identical across study groups?	6. Were the research personnel Blinded to the study group?	7. Were outcome data complete without attrition or exclusion from analysis?	8. Can we be confident in the intervention characterization?	9. Can we be confident in the outcome assessment?	10. Were all measured outcomes reported?	11. Statistical methods were appropriate, or researchers adhered to the study protocol?
M. C. Noushad et al, 2018	-	–	+ +	–	+ +	+	–	+ +	+
	NR								
Eskandarinezhad et al, 2022	+ +	-	+ +	-	+ +	+	+	+ +	–
		NR		**NR**					

Q#3&Q#4 do not apply for vitro studies.
+ + Definitely low risk of bias.
+ Probably low risk of bias.
- Probably high risk of bias.
– Definitely high risk of bias.
NR = not reported.

Concerning the outcome measurement, 10 included studies used CFUs as an assessment method for *E. faecalis*, while the second most common outcome assessment method used the ZOI. Most studies using CFUs reported that Aloe vera demonstrated a greater efficacy than saline, apart from the study conducted by Valera et al. (2013), which reported in favor of saline. Moreover, all studies that employed the bacterial count in CFUs claimed that CHX had a higher antibacterial effect than Aloe vera (Bazvand et al., 2014; Bhardwaj et al., 2012; Goud et al., 2018; Valera et al., 2013; Vasudeva et al., 2017), while one study used the MIC/MBC (Ehsani et al., 2013). Moreover, six studies reported that Aloe vera possesses an ability greater than or similar to that of CaOH to reduce the bacterial count in CFUs (Abbaszadegan et al., 2016; Bhardwaj et al., 2012; Eskandarinezhad et al., 2022; Ghasemi et al., 2020; Vasudeva et al., 2017) and inhibit high bacteria zones (Ismail et al., 2020), except Ramamurthy et al. (2017), who reported in favor of CaOH by using laser scanning microscopy following fluorescence staining. All studies using the ZOI reported a significant effect of NaOCl in contrast to Aloe vera (Athiban et al., 2012; Babaji et al., 2016; Karkare et al., 2015; Noushad et al., 2017), though Athiban et al. identified Aloe vera as an alternative to NaOCl.

In addition, the duration of intracanal medicament placement revealed some influential effects. Studies reported promising results of Aloe vera as an intracanal medicament when exposed to microbes for more than 48 h in comparison to saline, CaOH, lemon, papine, amla, and castor oil. However, other medicaments, such as CHX, NaOCl, TAM, propolis, *Morinda citrifolia*, tulsi, QMix 2in1, *C. longa*, honey, ginger, etc., were better at reducing the *E. faecalis* count than Aloe vera, but these outcomes were reported by few studies, as shown in Table 2 (Abbaszadegan et al., 2016; Bazvand et al., 2014; Bhardwaj et al., 2012; Eskandarinezhad et al., 2022; Ramamurthy et al., 2017; Sailaja et al., 2020; Valera et al., 2013; Vasudeva et al., 2017).

3.4. Risk of bias and quality assessment

In the 18 publications that qualified, the bias risk and methodological quality of the research were evaluated using the OHAT tool (Table 3), where items 1 and 2, which deal with group allocation and concealment, demonstrated that a greater likelihood of bias might exist, as most authors failed to mention established procedures used for participant randomization. Further, items 3 and 4 were not included, as they do not apply to in-vitro and animal investigations, but concerning item 5, all studies demonstrated sound classifications of and identical characteristics among all groups, except Sahebi (2013), who did not offer information on the control group used. Item 6, referring to blinding investigators, was underlined in most studies with the NR option, as none of the authors of the 14 studies mentioned this information. That said, most studies received a good rating on items 7 and 8, relating to complete outcome data without attrition or exclusion from analysis and to the link between bias detection and intervention characteristics. Further, concerning item 9, related to the outcome assessment protocol, most studies were either unable to ensure blinding of the outcome assessment or failed to mention it in their articles, except Bazvand et al. (2014). Finally, items 10 and 11, which refer to possible threats

or internal validation, did not apply to most articles, and while two studies were likely at a high risk of bias due to selective reporting or the application of inappropriate statistical tests (Athiban et al., 2012; Bhardwaj et al., 2012), the scoring criteria specific to these items depend on many issues and, simultaneously, the included articles did not contain enough detail to clarify correctly the risk of bias. It is essential to emphasize that these experimental studies are distinct from RCTs, as random allocation is not a standard practice in all these experimental study designs. In addition, because the sample size in these studies is usually small, estimates of the high risk of bias may be justified, while evaluating the outcome also requires information regarding the circumstances surrounding the management, distribution, bacterial strain type, dose or concentration of intervention, timing of the experimental and control groups during the experiments, etc. To improve the internal validity of the investigations, it was evident that the methodological processes used in the experiments required more explication and detail. Although, with the differences in and heterogeneity of the results of the included studies, it is possible to carry out a *meta*-analysis of the similarities in CFU outcome measurements and to use the control (saline) in five studies.

3.5. Meta-Analysis

Non-significant heterogeneity was observed in the mean *E. faecalis* count in CFUs when Aloe vera was compared with saline (H^2 = 105.99, I^2 = 99.06%), CaOH (H^2 = 36.03, I^2 = 97.22%), CHX (H^2 = 192.80, I^2 = 99.48%), and NaOCl (H^2 = 2.61 × 10^9, I^2 = 100%), while the overall mean differences in *E. faecalis* CFUs between Aloe vera and saline (Overall = -2.18 [-5.01, 0.66] z = -1.50; p = 0.13), Aloe vera and CaOH (Overall = 0.94 [-0.99, 2.86] z = 0.95; p = 0.34), Aloe vera and CHX (Overall = -1.96 [-7.33, 3.40] z = -0.72; p = 0.47), and Aloe vera and NaOCl (Overall = 12,291.74 [-1.2 × 10^4, 37,027.30] z = 0.97; p = 0.33) were statistically non-significant, indicating that Aloe vera did not exhibit a substantial change in the CFU count when compared to saline, CaOH, CHX, and NaOCl (Fig. 2).

4. Discussion

Aloe vera is gaining popularity as a natural treatment and alternative therapy in evidence-based dentistry for numerous diseases, and quite a few studies have assessed the curative, cosmetic, and nutritious benefits of this plant (Dal'Belo et al., 2006; Heggers et al., 1996). Aloe vera has also been reported to possess antibacterial and anti-inflammatory activities, leading to its recommendation as an alternative medicament in endodontics (Arunkumar and Muthuselvam, 2009). The outcomes of the laboratory in-vitro or ex-vivo trials included herein demonstrate that Aloe vera is efficacious as an intracanal medicament, but the duration of exposure may affect its potency.

Aloe vera can be considered an effective therapeutic replacement for low-efficacy saline (Abbaszadegan et al., 2016; Athiban et al., 2012; Bazvand et al., 2014; Bhardwaj et al., 2012; Ghasemi et al., 2020; Goud et al., 2018; Ramamurthy et al., 2017; Vasudeva et al., 2017; Vinothkumar et al., 2013), cytotoxic or harsh NaOCl (Athiban et al., 2012; Goud et al., 2018; Karkare et al., 2015), and CaOH (Abbaszadegan et al., 2016; Ghasemi et al., 2020), but some studies reported contradictory results in favor of NaOCl (Babaji et al., 2016; Noushad et al., 2017; Sahebi et al., 2014; Valera et al., 2013) and CaOH (Bhardwaj et al., 2012; Ramamurthy et al., 2017; Vasudeva et al., 2017). The included studies that used CHX (Bhardwaj et al., 2012; Goud et al., 2018; Valera et al., 2013; Vasudeva et al., 2017) and propolis (Ehsani et al., 2013; Ismail et al., 2020; Vasudeva et al., 2017) to compare to Aloe vera claimed they were more effective in decreasing the bacterial count in CFUs or in increasing the ZOI, except for Bazvand et al. (2014), who reported results in favor of Aloe vera. Based on the overall review and analysis of the included studies, the results revealed that the antibacterial efficacy of Aloe vera as

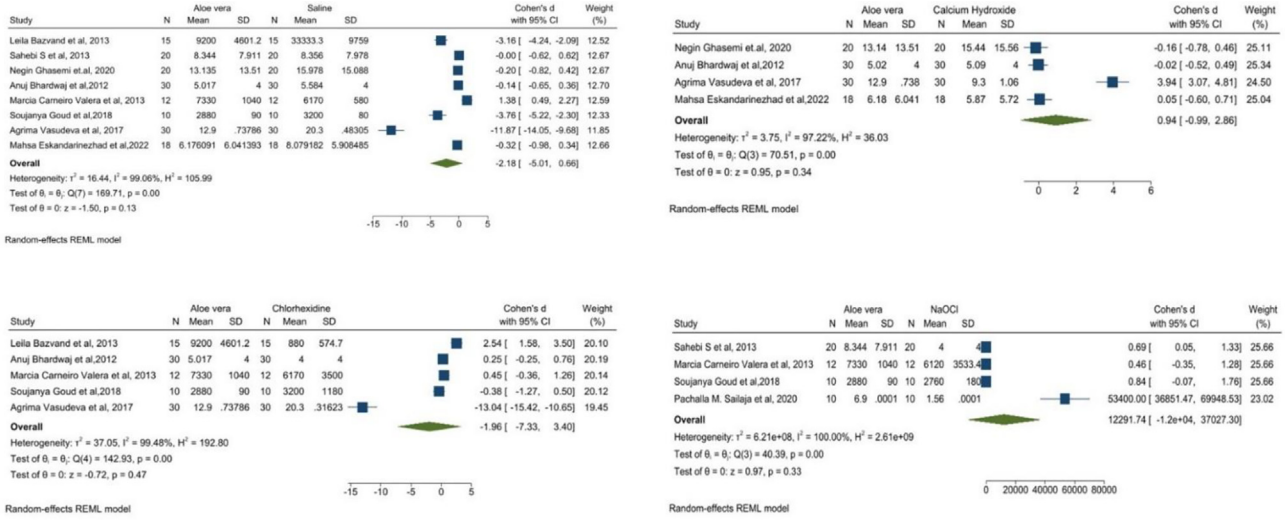

Fig. 2 Forest plot showing mean, standard deviation between Aloe vera and Saline, CaOH, CHX, NaOCl (comparative groups) in the reduction of *E. Faecalis* colony forming unit.

an intracanal medicament against *E. faecalis* is not greater than or equal to conventional medicaments, though it could be considered an alternative drug during endodontic treatments, especially intracanal therapeutic replacement against saline, NaOCl, and CaOH. Therefore, the hypothesis was not rejected, but there is a possibility of result variations due to the dissimilarities in materials and methods, the use of different measuring outcome units (ZOIs, CFU count, laser scanning microscopy after fluorescence staining, MIC/MBC, etc.), or varied drug exposure intervals. Different techniques, including the dentin powder model, dentin block model, agar diffusion method, and broth dilution method, have been utilized to define the antibacterial properties of intracanal medications, and these commonly used in-vitro and ex-vivo models have a "carryover" or buffering effect on antimicrobial agents, have difficulty creating microbial film, and lack consideration of the differences between bactericidal and bacteriostatic agents as disadvantages (Haapasalo, 2008; Siqueira and de Uzeda, 1997). Moreover, sometimes, while using dentin block models, the microanatomy of dentinal tubules provides resistance to the penetration of antimicrobial agents, apparently favoring bacteria. Thus, due to these concerns, reconstructing the microanatomy, encouraging a favorable chemical environment, and confirming microbial film establishment are important steps during in-vitro trials, though more common features include the variation in concentration or dose, though contact between intracanal medications and *E. faecalis* was also included, which may affect the efficacy of Aloe vera. That said, studies with intracanal medicaments used less than 24 h during the procedure, and Aloe vera mixed with other medicaments was excluded to avoid bias and a confounding effect (Bhardwaj et al., 2013; Farhadian et al., 2020; Ismail et al., 2020; Jaidka et al., 2017; Tonea et al., 2017).

The current systemic review identified a few studies that placed Aloe vera for more than 48 h, reporting effective results compared to saline and CaOH (Abbaszadegan et al., 2016; Bazvand et al., 2014; Bhardwaj et al., 2012; Ramamurthy et al., 2017). The possible reasons for the low efficacy of saline and CaOH include lesser bactericidal activity and the development of resistance to *E. faecalis* (Eskandarinezhad et al., 2022; Vasudeva et al., 2017). Seemingly, the most plausible effects of CHX and NaOCl include their broad-spectrum bacteriostatic and bactericidal activities against gram-positive and -negative microbes (Bazvand et al., 2014; Karkare et al., 2015). A comparison between Aloe vera and such materials as TAM, MCJ, *M. citrifolia* gel, propolis, neem extract, ginger extract, honey, *C. longa*, moxifloxacin, ciprofloxacin, curcumin, metronidazole, ethylenediaminetetraacetic acid (EDTA), *Azadiracta indica*, *Myristica fragrans*, *Terminalia chebula*, tulsi, castor oil, cashew apple extract, and guava and papaya leaf extract found in the included studies was not completed, because most of the above are either outdated or not considered an intracanal medicament. Though, researchers have begun using propolis in different dental procedures and have recommended its use in endodontic treatments as a medicament (Botushanov et al., 2001; González-Serrano et al., 2021). Moreover, half of the studies measured the bacterial count in CFUs, which were included in the *meta*-analysis, except for Abbas Abbaszadegan et al., who reported their results as a median percentage reduction. Non-significant heterogeneity was observed in the mean *E. faecalis* count in CFUs when Aloe vera was compared to saline, CHX, NaOCl, and CaOH. The plausibility of large heterogenic outcomes and a lack of meaningful results from systemic reviews and *meta*-analyses, where the absence of valid studies with identical measuring units, drug exposure times, study designs, inoculation times, study samples, and sample media, is mentioned in Table 2.

Furthermore, we used the OHAT score to assess the methodological quality of the in-vitro trials, where most of the studies reviewed had methodological flaws within the acceptable range. Of all 18 studies included in this review, only two demonstrated a low risk of bias (Abbaszadegan et al., 2016; Bazvand et al., 2014). Meanwhile, the remaining studies were scored as having (Athiban et al., 2012; Bhardwaj et al., 2012; Ehsani et al., 2013; Ismail et al., 2020; Noushad et al., 2017; Sahebi et al., 2014; Valera et al., 2013; Vasudeva et al., 2017) or developing a high risk of bias (Babaji et al., 2016; Eskandarinezhad et al., 2022; Ghasemi et al., 2020; Goud et al., 2018; Karkare et al., 2015; Ramamurthy et al., 2017; Sailaja et al., 2020; Vinothkumar et al., 2013). The prevalent limitations in most studies included the absence of randomization, a method to generate randomization sequences, and double or triple blinding, as well as differences in the reported total and group sample sizes, selective reporting, the use of inappropriate statistical methods, etc., thus making it challenging to draw well-founded conclusions from this review.

In effect, after assessing all the results of the in-vitro studies, it was determined that the effect of Aloe vera is not cytotoxic at the precise therapeutic dose (Shah et al., 1989), but it possesses bactericidal properties against *E. faecalis* and other microbes of endodontic origin and promotes angiogenesis or cell growth, though its mechanism of action is still unclear (Yagi et al., 1997). Moreover, the results of the included in-vitro trials may assure that Aloe vera has anti-inflammatory and antimicrobial effects in root canal treatment. Besides all procedural limitations and active efficiency debates, Aloe vera reduced the bacterial count or developed a ZOI against *E. faecalis*. While Aloe vera could be considered a suitable replacement for standard intracanal medicaments, further in-vitro trials are necessary to succeed in scoring all standard guidelines to avoid bias.

5. Strength and limitations

The current systematic review demonstrated that Aloe vera has antimicrobial properties against resistive *E. faecalis* in endodontic treatment, though the diverse outcomes of this study cannot be applied clinically because of the inclusion of in-vitro studies, thus motivating researchers to carry out in-vivo RCTs to investigate the efficacy of Aloe vera as a root canal medicament against *E. faecalis*. Second, the quality assessment of the included studies revealed the categories of probable risk and high risk, according to which the conclusions were constructed. Consequently, the validation of the findings may be questionable, but publication bias was not reported due to the availability of fewer than 10 studies.

6. Conclusion

As an intracanal medication, Aloe vera exhibited a better bactericidal capability against *E. faecalis* than saline and a bactericidal capability similar to CaOH, but CHX and NaOCI showed a greater antibacterial efficacy against *E. faecalis* than

Aloe vera. However, complete elimination of the bacterial count has not likely been achieved by any medicament. Further in-vivo RCTs with a parallel methodology and study design are recommended to validate the efficacy of Aloe vera as an intracanal medicament against *E. faecalis*.

Ethical statement

The systematic review was registered in PROSPERO (International Prospective Register of Systematic Reviews) CRD42022314790, and it was directed as per PRISMA 2020 statement, with detailed information provided in the manuscript.

CRediT authorship contribution statement

Rabia Tariq: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. **Zohaib Khurshid:** Conceptualization, Data curation, Formal analysis, Project administration, Supervision, Validation, Writing – original draft. **Waqas Ahmed Farooqui:** Formal analysis, Project administration, Supervision, Validation, Writing – original draft. **Nejdet Adanir:** Conceptualization, Formal analysis, Project administration, Supervision, Validation, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None

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