CATÓLICA
FACULDADE DE MEDICINA DENTÁRIA
VISEU

EXPLORING THE EFFECTS OF ISOLATED FLAVONOIDS OR FORMULATIONS AS ANTIMICROBIAL/ANTIBIOFILM AGENTS FOR ENDODONTIC TREATMENT

A SCOPING REVIEW

Dissertação apresentada à Universidade Católica Portuguesa

para obtenção do grau de Mestre em Medicina Dentária

Por:

Elise Lucie Saint-Etienne

Viseu, 2025

CATÓLICA
FACULDADE DE MEDICINA DENTÁRIA
VISEU

EXPLORING THE EFFECTS OF ISOLATED FLAVONOIDS OR FORMULATIONS AS ANTIMICROBIAL/ANTIBIOFILM AGENTS FOR ENDODONTIC TREATMENT:

A SCOPING REVIEW

Dissertação apresentada à Universidade Católica Portuguesa

para obtenção do grau de Mestre em Medicina Dentária

Por:

Elise Lucie Saint-Etienne

Orientador: Prof. Dr. Cristiane Duque

Coorientador: Prof. Dr. Renata Toledo Alves

Viseu, 2025

Remerciements

Au terme de ce long chemin, marqué par le travail, les incertitudes, les apprentissages et les découvertes, je souhaite exprimer ma profonde reconnaissance à toutes celles et ceux qui, de près ou de loin, ont contribué à l'accomplissement de cette thèse.

Tout d'abord, je tiens à remercier du fond du cœur la Prof. Cristiane Duque, Prof. Renata Toledo et Prof. Gabriel Pereira Nunes (UNESP, Brésil), pour leur patience, leur accompagnement rigoureux et bienveillant, et pour la confiance qu'ils m'ont accordé tout au long de ce travail. Leur exigence scientifique et leurs conseils toujours justes ont été des repères essentiels dans ma progression.

Je tiens également à exprimer ma reconnaissance à la Professeure Filomena Capucho, dont le soutien m'a accompagné dès les premiers pas de cette aventure. Sa disponibilité, sa capacité à écouter, à comprendre mes doutes, et à m'éclairer à chaque étape ont été d'une aide précieuse. Savoir qu'elle était là, constamment présente en cas de besoin, a été pour moi une sécurité et un réconfort inestimables tout au long de ce parcours.

Avant tout, je veux dédier cette thèse à ma famille, qui m'a portée depuis le tout début.

À ma grand-mère, l'âme la plus précieuse que je connaisse. Tu es faite d'un amour rare, de ceux qui réchauffent même à distance, d'une tendresse infinie et d'un cœur immense, tourné vers les autres avant toi-même. Même loin de toi, j'ai senti ton amour me porter, comme une force invisible mais constante. Ta sagesse, ta bonté et ta lumière m'accompagnent à chaque pas. Je te dois tant. Tu es et resteras pour moi un exemple de pureté, de générosité, et d'amour inconditionnel.

À ma mère, mon modèle de courage et de résilience, il n'y aura jamais assez de mots pour exprimer toute ma gratitude. Tu as toujours cru en mes rêves, même les plus fous, et tu n'as jamais cessé de me pousser à les poursuivre, à m'élever au-delà de mes peurs. Sans toi, rien de tout cela n'aurait été possible. Tu as su être à la fois une

mère, une meilleure amie, une confidente, une sœur… tout à la fois. Cette thèse, c'est aussi la tienne, car elle porte l'empreinte de tout ce que tu m'as transmis : la persévérance, la dignité, la capacité de toujours voir le positif, même dans les moments les plus sombres, et de ne jamais te laisser abattre. Merci d'être celle que tu es, et de m'avoir permis de devenir qui je suis.

À mes oncles, qui m'ont encouragée avec bienveillance et qui m'ont transmis, chacun à leur manière, des valeurs essentielles. Vous avez été là, toujours, sans y être obligés, avec une constance et une générosité qui m'ont profondément touchée. Vous m'avez soutenue comme une fille, entourée comme une nièce, et aimée comme une évidence. Un simple "merci" ne pourra jamais exprimer pleinement l'immense reconnaissance que je vous porte, ni mesurer l'importance que vous avez dans ma vie.

À mes frères et sœurs, ma plus grande richesse. Vous êtes les êtres les plus précieux de ma vie, ceux pour qui je donnerais tout, et grâce à qui je me suis toujours sentie complète, même loin de chez moi.

Je ne remercierai jamais assez la vie de m'avoir offert le privilège d'être votre sœur. C'est un cadeau immense, un privilège que je chéris chaque jour. Vous êtes ma fierté, mon ancrage, ce lien profond et indestructible qui m'accompagne partout, même à des milliers de kilomètres. Je vous porte en moi, toujours, et je vous aime d'un amour qui ne se dit pas, mais qui se ressent dans chaque battement.

Je voudrais ensuite dédier un mot très spécial à mon copain, mon meilleur ami, durant ces années d'études. Merci pour ta patience sans limite, ton soutien constant, et ta façon de toujours trouver les mots justes quand l'hésitation prenait trop de place. Merci aussi pour tous les moments passés ensemble qui ont fait passer le temps plus vite, qui ont allégé mes journées et rendu mes études plus belles à tes côtés. Ta manière d'être là, simplement et sincèrement, a fait toute la différence. Loin de chez moi, dans ce pays qui n'était pas le mien, c'est toi qui as été mon chez-moi.

Je pense aussi à mes amies, celles qui m'ont accompagnée dans cette aventure, de près comme de loin. À distance, Mathilde, Solène et Victoire ont toujours su trouver

les mots justes, les appels inattendus mais tellement nécessaires, et cette présence constante malgré les kilomètres. Merci pour votre écoute, votre humour, vos conseils, et pour être restées à mes côtés même quand nos quotidiens ne se croisaient plus. Il y a des liens qui ne s'expliquent pas, qui tiennent bon même dans le silence ou la distance. Le vôtre fait partie de ceux-là : solide, précieux, inébranlable.

Et puis, il y a celles que la vie m'a offertes ici, dans ce pays étranger où tout m'était inconnu et où l'absence de ma famille se faisait parfois lourdement sentir. Veronica et Michela, vous avez été bien plus que des amies : vous avez été ma famille de substitution. Grâce à vous, j'ai trouvé un cocon au milieu de l'inconnu, une chaleur humaine qui m'a portée bien plus que vous ne pouvez l'imaginer. Vous avez illuminé mon quotidien, soutenu mes silences, et rempli ce vide que seule l'amitié véritable peut combler. Merci.

Mon expérience Erasmus a aussi été une parenthèse inoubliable, pleine de découvertes, de rires et de liens précieux. Merci à Georgia, Vasylki et Marita pour ces instants partagés, votre énergie, et votre générosité qui ont marqué ce chapitre de ma vie.

Cette thèse est le fruit d'un travail personnel, mais elle est avant tout le reflet de tout l'amour, la patience et le soutien que j'ai reçus. À toutes et tous, merci du fond du cœur.

Acknowledgments

At the end of this long journey, marked by hard work, uncertainty, learning, and discovery, I would like to express my deep gratitude to all those who, from near or far, contributed to the completion of this thesis.

First and foremost, I wish to sincerely thank Prof. Cristiane Duque, Prof. Renata Toledo and Prof. Gabriel Pereira Nunes (UNESP, Brazil) for their patience, their rigorous and caring guidance, and the trust they placed in me throughout this work. Their scientific rigor and always sound advice were essential reference points along my path.

I also wish to express my heartfelt thanks to Prof. Filomena Capucho, whose support has been with me since the very first steps of this adventure. Her availability, her ability to listen, to understand my doubts, and to guide me at every stage were of great help. Knowing she was always there, constantly present if needed, gave me immeasurable security and comfort throughout this journey.

Above all, I dedicate this thesis to my family, who has supported me from the very beginning.

To my grandmother, the most precious soul I know. You are made of a rare kind of love — the kind that warms even from afar — of infinite tenderness and an immense heart, always putting others before yourself. Even far away, I felt your love carry me like an invisible yet constant force. Your wisdom, your kindness, and your light accompany me every step of the way. I owe you so much. You are, and always will be, for me, an example of purity, generosity, and unconditional love.

To my mother, my model of courage and resilience — there will never be enough words to express my full gratitude. You always believed in my dreams, even the wildest ones, and you never stopped pushing me to pursue them, to rise above my fears. Without

you, none of this would have been possible. You have been a mother, a best friend, a confidante, a sister… all at once. This thesis is yours too, as it carries the imprint of everything you taught me: perseverance, dignity, the ability to always see the positive, even in the darkest moments, and to never give up. Thank you for being who you are and for allowing me to become who I am.

To my uncles, who encouraged me with kindness and passed on essential values to me, each in their own way. You were always there, without ever being obligated, with a consistency and generosity that deeply moved me. You supported me like a daughter, surrounded me like a niece, and loved me as if it were obvious. A simple “thank you” could never fully express the immense gratitude I feel for you, nor the importance you hold in my life.

To my brothers and sisters, my greatest treasure. You are the most precious people in my life — those I would give everything for — and thanks to whom I have always felt whole, even far from home.

I will never thank life enough for giving me the privilege of being your sister. It is a tremendous gift, a privilege I cherish every day. You are my pride, my anchor, the deep and indestructible bond that follows me everywhere, even thousands of kilometers away. I carry you within me, always, and I love you with a kind of love that isn’t spoken, but is felt in every heartbeat.

Next, I would like to dedicate a very special word to my boyfriend, my best friend during these years of study. Thank you for your boundless patience, your constant support, and your ability to always find the right words when doubt took over. Thank you also for all the moments we spent together — moments that made time pass faster, that lightened my days and made my studies more beautiful by your side. Your way of simply and sincerely being there made all the difference. Far from home, in a country that wasn’t mine, you were my home.

I am also thinking of my friends, those who accompanied me throughout this adventure, both near and far. From a distance, Mathilde, Solène, and Victoire always knew how to find the right words, those unexpected but so necessary calls, and that constant presence despite the kilometers. Thank you for your listening, your humor, your advice, and for staying by my side even when our daily lives no longer crossed paths. Some bonds cannot be explained — they remain strong even in silence or distance. Yours is one of those: solid, precious, unshakable.

And then there are the ones life gifted me here, in this foreign country where everything was unfamiliar and where the absence of my family was sometimes deeply felt. Veronica and Michela, you were much more than friends — you were my substitute family. Thanks to you, I found a cocoon amidst the unknown, a human warmth that supported me far more than you could imagine. You brightened my daily life, supported me in my silences, and filled that void only true friendship can fill. Thank you.

My Erasmus experience was also an unforgettable chapter, full of discovery, laughter, and precious connections. Thank you to Georgia, Vasylki, and Marita for the moments we shared, your energy, and your generosity, which left a mark on this chapter of my life.

This thesis is the result of personal work, but above all, it reflects all the love, patience, and support I have received.

To all of you, thank you from the bottom of my heart.

Resumo

Esta revisão de escopo teve como objetivo mapear e resumir as evidências sobre a eficácia antimicrobiana e antibiofilme de soluções ou formulações à base de flavonoides para aplicações endodônticas. A revisão foi conduzida de acordo com as diretrizes PRISMA-ScR. Uma busca abrangente foi realizada em bases de dados para artigos publicados até abril de 2025. Os estudos elegíveis incluíram aqueles que avaliaram os efeitos antimicrobianos de flavonoides em microrganismos associados a infeções endodônticas. Dados relevantes foram extraídos e uma síntese descritiva dos achados foi realizada. Os resultados mostraram que quinze estudos preencheram os critérios de inclusão, demonstrando atividade antimicrobiana e antibiofilme significativa de vários flavonoides. A epigalocatequina-3-galato foi o composto mais extensivamente estudado, mostrando atividade dose-dependente contra *E. faecalis*, *F. nucleatum*, *A. israelii*, *S. mutans* e *C. albicans*, com eficácia aumentada quando combinada com agentes como o antibiótico fosfomicina ou peptídeo KR-12-a5. A quercetina também apresentou efeitos antibiofilme dependentes da concentração e modulação gênica em *E. faecalis*. A proantocianidina demonstrou eficácia superior em comparação aos irrigantes convencionais, especialmente em concentrações mais elevadas. A rutina, embora limitada em eficácia isolada, apresentou resultados promissores quando utilizada como fotossensibilizador. Outros polifenóis, como apigenina, teaflavina, isoquercitrina, ampelopsina, chalcona e crisina, também demonstraram graus variados de atividade antimicrobiana, frequentemente semelhantes ou superiores a agentes convencionais como clorexidina e hidróxido de cálcio em modelos específicos. Conclui-se que os flavonoides apresentam potencial significativo como agentes alternativos ou adjuvantes para a desinfeção endodôntica, especialmente em infeções relacionadas a biofilmes. Sua eficácia é influenciada pelo tipo de composto, concentração, formulação e combinações sinérgicas. Investigações adicionais, especialmente ensaios clínicos, são necessárias para validar sua aplicabilidade terapêutica e otimizar os sistemas de administração para uso clínico em endodontia.

Palavras-chave: flavonoides, atividade antimicrobiana, biofilme, medicação intracanal, endodontia

Abstract

This scoping review aimed to map and summarize the evidence on the antimicrobial and antibiofilm efficacy of flavonoid-based solutions or formulations for endodontic applications. The review was conducted in accordance with the PRISMA-ScR guidelines. A comprehensive search was performed across databases for articles published up to April 2025. Eligible studies included those evaluating the antimicrobial effects of flavonoids on microorganisms associated with endodontic infections. Relevant data were extracted, and a descriptive synthesis of the findings was carried out. The results showed that fifteen studies met the inclusion criteria, demonstrating significant antimicrobial and antibiofilm activity of various flavonoids. Epigallocatechin-3-gallate was the most extensively studied compound, showing dose-dependent activity against *E. faecalis*, *F. nucleatum*, *A. israelii*, *S. mutans*, and *C. albicans*, with enhanced efficacy when combined with agents such as fosfomycin or KR-12-a5. Quercetin also displayed concentration-dependent antibiofilm effects and gene modulation in *E. faecalis*. Proanthocyanidin showed superior efficacy compared to conventional irrigants, especially at higher concentrations. Rutin, although limited in standalone efficacy, showed promising results when used as a photosensitizer. Other flavonoids such as apigenin, theaflavin, isoquercitrin, ampelopsin, chalcone, and chrysin also demonstrated varying degrees of antimicrobial activity, often similar to or surpassing conventional agents like chlorhexidine and calcium hydroxide in specific models. In conclusion, flavonoids exhibit significant potential as alternative or adjunctive agents for endodontic disinfection, especially in biofilm-related infections. Their efficacy is influenced by compound type, concentration, formulation, and synergistic combinations. Further research, especially clinical trials, is warranted to validate their therapeutic applicability and optimize delivery systems for clinical use in endodontics.

Keywords: flavonoids, antimicrobial activity, biofilms, intracanal medication, endodontics.

List of Figures

List of Tables

List of acronyms

NaOCl : Sodium Hypochlorite

$Ca(OH)_2$: Calcium Hydroxide

CHX : Chlorhexidine

CFU : Colony Forming Units

CLSM : Confocal Laser Scanning Microscopy

DNA : Deoxyribonucleic Acid (Acide Désoxyribonucléique)

EGCG : Epigallocatechin Gallate

FIC : Fractional Inhibitory Concentration

MTT : 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (test de viabilité cellulaire)

ROS : Reactive Oxygen Species

SEM : Scanning Electron Microscopy

XTT : 2,3-Bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (test de viabilité cellulaire)

Índice geral

1. INTRODUCTION

1. Introduction

Extensive dental caries or traumatic injuries can cause pulp necrosis and infection of the root canal system (Smith, 2002). This system becomes a propitious habitat for the establishment of mixed, preponderantly anaerobic microbioma, which develops in complex biofilms (Smith, 2002; Gomes and Herrera, 2018). The microorganisms and their products move along the system and reach the apical apex, activating a coordinated immuno-inflammatory interaction among cells within the periapical area (Márton and Kiss, 2000). The intense host response to bacterial invasion triggers severe inflammation and damage to periapical tissues and can lead to apical periodontitis (Smith, 2002; Gomes and Herrera, 2018).

The treatment of apical periodontitis involves the chemical-mechanical instrumentation of root canal and application of an intracanal medication for promoting disinfection of root canal system (Arias et al., 2023). The endodontic management of immature permanent teeth, which have open apices, large root canals, thin dentinal walls, and short roots, becomes even more challenge, considering root canal therapy should disinfect root canal system and parallelly, promote complete root formation (Kahler et al., 2024).

Traditional treatment approaches, such as apexification with calcium hydroxide ($Ca(OH)_2$) and apical plug/barrier with mineral trioxide aggregate (MTA), have been employed to manage these infected teeth, however, these techniques do not result in further root maturation (Kahler et al., 2024). $Ca(OH)_2$ apexification includes the disinfection of the teeth with highly concentrated sodium hypochlorite (NaOCl) (2.5 – 6%) and $Ca(OH)_2$ placing within the root canal. This procedure requires a long-term treatment (9-14 months) and periodical changes of $Ca(OH)_2$. As a consequence of multiple appointments, tooth structure can become weak, increasing the risk of cervical root fractures and potentially compromising the long-term prognosis of the treated tooth (Asgary et al., 2024). The MTA-apical plug technique proposes to create an artificial barrier placing MTA or other silicate-based cement at the root apex to facilitate root canal obturation (Asgary et al., 2024). Despite the advantages of the apical-plug therapy, such as shorter treatment time and better biocompatibility, neither of them do not enhance root formation, and tooth discoloration remains a drawback (Możyńska et al., 2017).

Then, a current of researchers have been searched for biological materials that present multiple biological activities, including the ability of reducing microorganisms and inflammation in endodontically-compromised teeth, in addition to preserve Hertwig epithelial sheath (responsible for guiding the radicular dentin formation), the dental papilla and the odontoblast layer in the apical area, allowing the continuity in the root formation (Iguesias-Linares et al., 2013; Xie et al., 2021). Flavonoids are the most important classes of polyphenols, with more than 6000 compounds already described in the literature (Dias et al., 2021). They are present in small amounts in fruits, seeds, and vegetables, generally as secondary metabolites and play important roles in plants specially against biotic and abiotic stresses (Dias et al., 2021). Studies have pointed out several pharmacological properties of polyphenols for humans, such as antimicrobial, antioxidant, anti-inflammatory, osteogenic, antiosteoclastogenic and other properties (Yahfouf et al., 2018; Dias et al., 2021, Intharuksa et al., 2024).

Flavonoids have a common basic chemical structure (flavone), consisting of a 2-phenyl-1,4-benzopyrone nucleus with two aromatic rings (A and B) joined by three carbons that form a heterocyclic ring, called ring C. According to the variations in ring C, flavonoids are divided into flavones, flavonols, flavanones (3-hydroxy-flavone), flavanonol (2,3-dihydroflavonol), flavanols (or catechins), anthocyanidins and chalcones. Other types of compounds are included in the flavonoid group, the isoflavonoids and the neoflavonoids. Substitutions in the A and B rings give rise to different compounds within each class of flavonoids and flavonoids with the open C ring are called chalcones (Dias et al., 2021). Examples of flavonoids are: flavonols - quercetin, morin, myricetin, rutin, kaempferol, fisetin and isorhamnetin; flavanones – naringenin and hesperidin; flavones – luteolin, acacetin, vitexin and apigenin; isoflavone – genistein and diadzin; flavanols – catechin and epigallocatechin-3-gallate (EGCG), anthocyanidins – cyanidin and delphinidin (Nath et al., 2024).

The potential use of polyphenols for the prevention and treatment of oral diseases, especially dental caries and periodontitis, have been explored by many investigators (Carneiro et al., 2024; Beckman et al., 2024, Castellanos et al., 2024, Nunes et al., 2024). In Endodontics, the majority of the studies were focused on testing antimicrobial and antibiofilm effect of different crude extracts containing flavonoids as potential agents for irrigation and intracanal medication (Borzini et al., 2026; Febvey et al., 2023). Few studies evaluated the antimicrobial activity of pure flavonoids against

putative endodontic pathogens, particularly *Enterococcus faecalis (E. faecalis)* and *Candida albicans (C. albicans)* are in vitro or ex-vivo (in root dentin specimens) (Yang et al., 2020; Caiaffa et al., 2021; Graciani et al., 2023, Duque et al., 2023). In addition, flavonoids have shown low cytotoxicity and positive effects on dental stem cells, reducing reactive oxygen species production and inflammatory response stimulating, as well as, stimulating odontogenic differentiation and reparative dentin formation (Duque et al., 2022; Liu et al., 2022; Mendes-Soares et al., 2024; Elhakim et al., 2025).

Although flavonoids could be promising multifunctional agents for dental application, their low water solubility and degradability by oral fluids reduce their stability, bioavailability and bioefficacy when applied in solution. Therefore, natural or synthetic polymers have been used as drug carriers to promote the controlled release of compounds and extend their biological effect. Advantages of these carriers include reduction of doses or frequent exposure to antimicrobials, and the risk of bacterial resistance (Braga et al., 2022). Antimicrobial and antibiofilm effect of flavonoids-loaded drug delivery systems, such as hydrogels and nanoparticles, have been recently observed in in vitro and ex-vivo studies, showing an interesting strategy to reduce bacterial infection in root canals (Minhaco et al., 2023; Braga et al., 2022, Ferreira et al., 2025). The objective of this study was to conduct a scoping review on the efficacy of solutions or formulations containing flavonoids as antimicrobial/antibiofilm agents for endodontic treatment.

2. MATERIAL AND METHODS

2. Material and Methods

2.1 Study Protocol

This scoping review was carried out in accordance with the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (Tricco et al., 2018), incorporating methodologies from recent publications (Seron et al., 2024; Nunes et al., 2024).

2.2 Eligibility criteria

To define the research question, the Patient, Concept, and Context (PCC) framework (Peters et al., 2015) was utilized, leading to the formulation of the following question: “Do flavonoids promote antimicrobial/antibiofilm effects when used in endodontic treatment?”

PCC Framework Details:

- Population: Studies evaluating the effects of flavonoids on microorganisms associated with endodontic infections. These include microbial samples/biofilms collected from the root canals of patients undergoing endodontic treatment, in vitro models using extracted teeth, infected root discs, dentin/dentin tubules, or direct exposure to planktonic microorganisms or biofilms.
- Concept: The application of flavonoids, in various forms−such as treatment solutions, incorporated formulations, irrigants, or intracanal medications. Comparison groups include negative controls (e.g., placebo or untreated samples) or positive controls using standard endodontic agents (e.g., NaOCl, chlorhexidine (CHX), $Ca(OH)_2$, or other substances commonly employed in endodontic dental practice).
- Context: The primary outcomes of interest focus on antimicrobial efficacy, measured through: The total bacterial count. Positive bacterial culture results quantified as colony-forming unit (CFU/mL) or equivalent methods.

The inclusion criteria for this scoping review comprised in *vitro*, *in silico*, *in situ,* and *in vivo* (animal or human) studies assessing the antimicrobial or antibiofilm effects of flavonoids (excluding plant extracts) in solution or injectable carrier systems for

endodontic treatment. Eligible studies used pure flavonoids or those diluted in a vehicle, ensuring that the intervention differed only by the presence of flavonoids. There were no restrictions on publication period or language. Exclusion criteria encompassed studies without a control group, those evaluating multiple antimicrobial agents that obscured the specific effects of flavonoids, and studies using plant extracts without isolating the tested flavonoid. Reviews and expert opinions were also excluded. In short, any study failing to meet these predefined criteria was excluded from the review.

2.3 Search strategy

The electronic search was conducted across the following databases: PubMed (MEDLINE), Scopus, Web of Science, Embase, and Cochrane Library, up to April 10, 2025. Additionally, gray literature (produced by government, academic, business, and industrial sectors, in either print or electronic format, but not controlled by commercial publishers) was explored using the OpenGrey database (http://www.opengrey.eu/). Medical Subject Headings (MeSH) terms, developed with the assistance of a specialized librarian, were employed to construct the search strategy (see Appendix #S1) to enhance the sensitivity of the search. Free terms that were not available as descriptors in the databases were also included.

The search strategy was developed without restrictions on publication dates. To ensure comprehensive coverage, a manual search was performed to identify manuscripts potentially missed by the electronic search, focusing on articles published in key journals in the field, including: *Journal of Endodontics, International Endodontic Journal, Australian Endodontic Journal, Iranian Endodontic Journal, European Endodontic Journal, Restorative Dentistry and Endodontics, Journal of Dental Research, Clinical Oral Investigations, Journal of Dentistry, Dental Materials, International Dental Journal, Odontology,* and *Brazilian Oral Research*. Additionally, a manual screening of the reference lists of all included studies was conducted to capture any relevant articles that might have been overlooked.

2.4 Study selection

The article selection process began with a systematic evaluation of titles and abstracts, followed by a full-text evaluation of potentially eligible studies. In the first

step, two independent reviewers (E.S.T. and G.P.N.) conducted an initial screening, importing all references retrieved from the databases into an online reference manager (EndNote Web; Thomson Reuters Inc., Philadelphia, PA, USA) to remove duplicates. If titles and abstracts provided insufficient information, the corresponding full texts were retrieved for a comprehensive review. Disagreements during this stage were resolved through discussion or consultation with a third reviewer (C.D.).

In the second step, after duplicates were removed, potentially relevant articles were screened for eligibility based on their titles and abstracts. Studies meeting the inclusion criteria underwent a detailed full-text review, with reasons for exclusion systematically documented. Final study selection was independently performed by the two reviewers, with a third reviewer resolving any conflicts to achieve consensus.

2.5 Data extraction and synthesis

Details of the studies were extracted using customized forms designed to capture comprehensive information, including the following parameters: authorship and year of publication, country of origin, study design, sample characteristics, details of study groups, evaluated microorganisms, assessment methods, results (outcomes), conclusions, and the effects of the interventions. Specific data regarding the types of flavonoids evaluated were systematically recorded (Table 1). When additional details were required, the corresponding authors were contacted via email for clarification.

The extracted data were synthesized into a narrative summary, highlighting experimental protocols, intervention characteristics, main findings, and conclusions, ensuring a concise and structured presentation of the results.

3. RESULTS

3. Results

3.1 Study selection, and characteristics of the included studies

A total of 478 studies were identified through database searches: PubMed (281), Scopus (79), Web of Science (64), Embase (35), and Cochrane Library (19). After the removal of 112 duplicates, 366 titles and abstracts were screened based on the predefined eligibility criteria. Nineteen articles were selected for full-text evaluation, and four were excluded for not meeting the inclusion criteria. As a result, 15 *in vitro* studies were included in this scoping review (Chrisostomo et al., 2025; Aqabat et al., 2024; Pourhajibagher et al., 2024; Wang et al., 2024; Duque et al., 2023; Graciani et al., 2023; Huang et al., 2023; Kim et al., 2023; Braga et al., 2022; Alipour et al., 2021; Caiaffa et al., 2021; Liu et al., 2021; Yang et al., 2020; Qayyum et al., 2019; Lee et al., 2015). (**Figure 1**).

The analyzed fifteen articles were published between 2015 and 2025, and their characteristics are summarized in **Table 1**. The eligible studies originated from various countries, including Egypt (Aqabat et al., 2024), Iran (Pourhajibagher et al., 2024; Alipour et al., 2021), China (Wang et al., 2024; Huang et al., 2023; Kim et al., 2023; Liu et al., 2021; Yang et al., 2020), Brazil (Chrisostomo et al., 2025 ; Duque et al., 2023; Graciani et al., 2023; Braga et al., 2022; Caiaffa et al., 2021), India (Qayyum et al., 2019), and Singapore (Lee et al., 2015). All studies utilized an *in vitro* model to assess antimicrobial effects in endodontics.

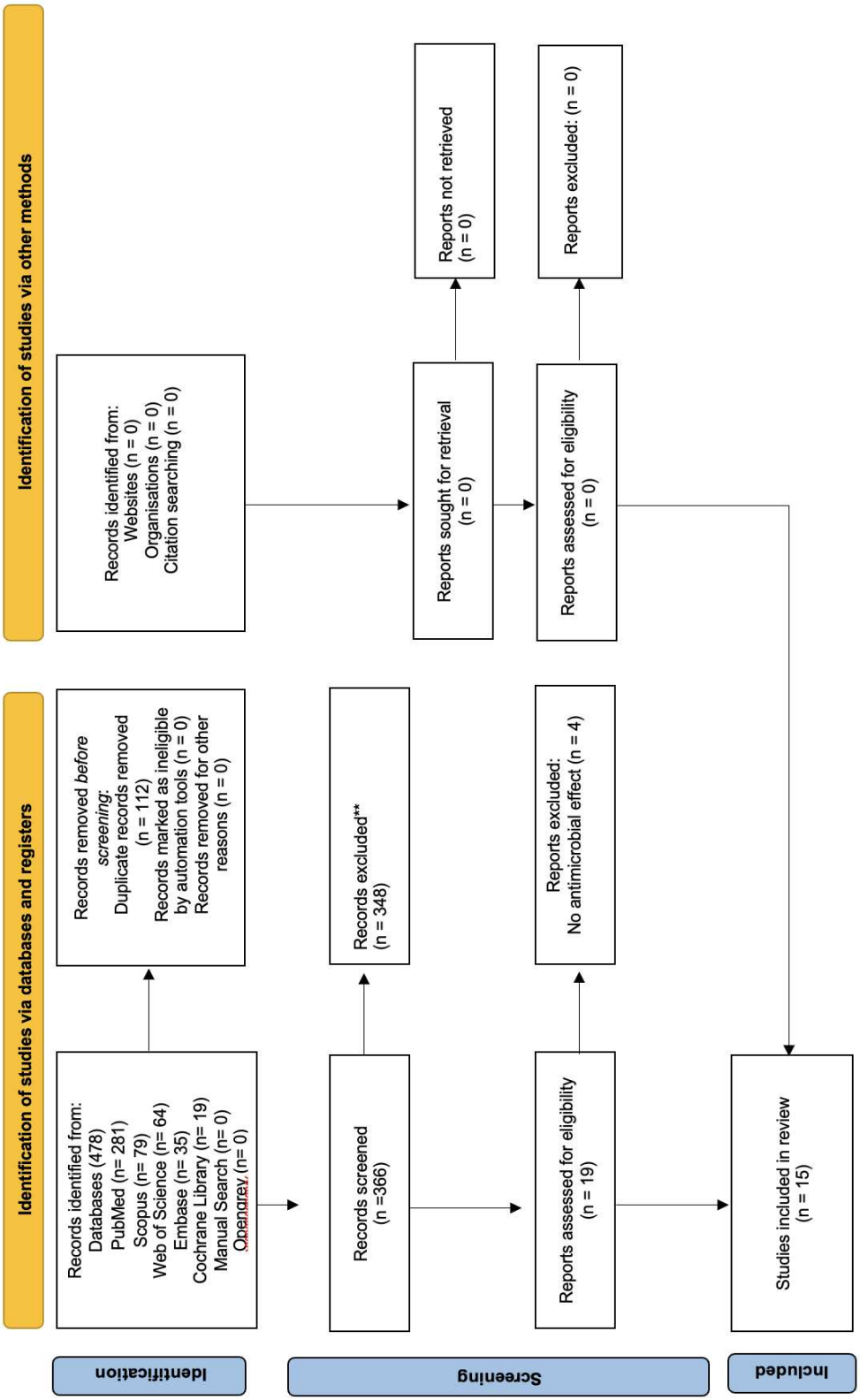

Figure 1. Flow diagram presenting the identification of studies for the scoping review.

Table 1. General data from the studies included in the scoping review.

Author/ year (Country)	Design study	Flavonoid (s)	Control (s)	Microorganism examined	Form of Administration or use (Protocol)	Assessment Method	Main results	Intervention Effect
Chrisostomo *et al.,* 2025 (Brazil)	*In vitro* Infected bovine dentin roots specimens	EGCG 0.625 mg/mL associated with fosfomycin at 0.156 mg/mL in polyethylene glycol 400 (PEG400)	Triantibiotic combination of metronidazole, ciprofloxacin and fosfomycin (TRI, all at 0.625 mg/mL), calcium hydroxide (CH, 1mg/mL), PEG, and negative control (untreated cells)	*E. faecalis* (ATCC 51299), *S. mutans* (ATCC 25175), *A. israelii* (ATCC 12102), *C. albicans* (ATCC 26790)	Endodontic application, tested with antibiotics. 500 µL of the medications for 48 h and 7 days	Biofilms assays and analysis of dead/live cells by CLSM	After 48 h of treatment, the EGCG/FOSFO, TRI and CH groups had more than 80% dead cells in the multi-species biofilms, indicating an effective short-term antibiofilm effect, with no statistical differences between them. After 7 days of treatment, EGCG/FOSFO maintained the highest efficacy, with 82.9% of cells killed, followed by TRI (64.9%) and CH (54.5%), showing a superior long-term antibiofilm effect for EGCG/FOSFO.	Positive
Aqabat *et al.,* 2024;	*In vitro* Infected human dentin roots specimens	Quercetin 3%, 1.25% and 5% in hydrogels	Calcium hydroxide (CH) and untreated biofilms	*E. faecalis* *(ATCC 29212)*	Carbopol hydrogels The root canals of the experimental groups were medicated with either an aqueous CH paste or quercetin hydrogels and sealed coronally with sticky wax for 7 days, while the root canals of the positive control group were sealed without being medicated.	MIC, MBC, CFU count, and dead/live bacterial viability by CLSM	CH and quercetin used in the treatment model to reduce microbial load in infected root canals fulfilled the ideal requirements of intracanal medications as being both potent antibacterial and, at the same time, non-cytotoxic.	Positive

Pourhajibagher *et al.,* 2024 (Iran)	*In vitro* Infected human dentin roots specimens	Rutin-Ga (III) complex at from 6.25 to 50 µmol/mL	Sodium hypochlorite (NaOCl), and untreated cells	*E. faecalis* *(ATCC 29212)*	Antimicrobial photodynamic therapy (LED at 150 and 75 J/cm^2) with rutin-Ga (III) complex. The samples were incubated at 37°C for 24 h, and the log_{10} CFU/mL values were calculated.	Minimum biofilm eradication concentration, minimum biofilm eradication dose, CFU count, SEM	Rutin-Ga (III) complex–mediated aPDT could effectively reduce the growth of biofilms formed by *E. faecalis*. Concentrations of this complex lower than 50 µmol/L had no significant effect in reducing the viability of microbial biofilms.	Positive
Wang *et al.,* 2024 (China)	*In vitro* Biofilms were formed on 10 × 10 mm^2 glass coverslips	Theaflavin 7.81 µg/mL, 15.63 µg/mL and 31.25 µg/mL	Ethanol (0.016–4%) and sterile water	*E. faecalis* *(ATCC 29212)*	Theaflavin at different concentrations (7.81–2000 µg/mL) was added to 96-well plates containing the bacterial cultures, and incubated for 24 h.	MBC, Crystal violet staining assay, CLSM, FE-SEM, transcriptomic analysis, qRT-PCR	Theaflavin significantly inhibited *E. faecalis* biofilm formation in a dose-dependent manner, altered transcriptomic profiles, downregulated quorum-sensing pathways, and suppressed key virulence genes (gelE, sprE, secY).	Positive
Duque *et al.,* 2023 (Brazil)	*In vitro* Infected bovine dentin roots specimens	EGCG at 0.625 mg/mL associated or not with FOSFO at 0.078 mg/mL	CHX 0.5 mg/mL Negative control (untreated biofilms)	*E. faecalis* *A. israelii* *S. mutans* *F. nucleatum*	Treatment of monospecies and multispecies biofilms with EGCG, EGCG-FOSFO, CHX for 48 h	MIC, MBC, CFU/mL count, CLSM, SEM	EGCG and FOSFO showed strong antimicrobial activity, with a synergistic effect when combined. particularly against *A. israelii*, *F. nucleatum*, and *E. faecalis*. In mono- and multispecies biofilms, EGCG+FOSFO was as effective or superior to CHX in reducing bacterial load and disrupting the biofilm matrix. In the intratubular model, EGCG+FOSFO achieved the highest percentage of dead cells (84.85%), outperforming EGCG (78.49%) and CHX (50.6%).	Positive
Graciani *et al.,* 2023 (Brazil)	*In vitro* Biofilms were formed on hydroxyapatite (HA) disks	Aminochalcone: 7.8 µg/mL to 156 µg/mL	CHX 2%; Sodium hypochlorite at 1% Negative control (untreated biofilm)	*E. faecalis* *C. albicans*	Endodontic irrigant containing aminochalcone tested on mono- and dual-species biofilms for 72 h	MIC, MBC, MFC, CFU/ml count	The chalcone-based irrigant significantly reduced biofilm formation and viability, with MIC values of 7.8 µg/ml for *E. faecalis* and 15.6 µg/ml for *C. albicans*, without showing toxicity. In biofilm formation on hydroxyapatite, chalcone at 156 µg/mL significantly reduced *E. faecalis* and *C. albicans* biofilms, both in monoculture and coculture, showing similar efficacy to 1% sodium hypochlorite. However, 2% chlorhexidine demonstrated superior antibiofilm activity.	Positive
Huang *et al.,* 2023 (China)	*In vitro*	Proanthocyanidin 6.5%	0.9% normal saline; and 17% EDTA + 3% NaOCl	*E. faecalis* *(ATCC 29212)*	Endodontic irrigant Each irrigation was used for 10 min – 5mL	SEM, CLSM	Proanthocyanidin showed significantly higher *E. faecalis* biofilm removal than the control group as examined by CLSM. In addition, proanthocyanidin and carboxymethyl chitosan/amorphous calcium phosphate nanocomplexes	Positive

	Infected human dentin roots specimens						preserved root dentin structural integrity, showed significant antibacterial effects (P < 0.05). The novel irrigation strategy demonstrated a favorable antimicrobial effect.	
Kim *et al.,* 2023 (China)	*In vitro* Biofilms were formed on hydroxyapatite (HA) disks (1.2 cm in diameter)	Apigenin 200-1000 µg/mL	Reduced Graphene Oxide (rGO) (180µg/mL), Negative control (untreated biofilm)	*E. faecalis* *(ATCC 47077)*	The biofilms treated with apigenin with/without RGO for 1h, and were washed with PBS three times	MIC, MBC, CLSM, SEM, CFU/mL count	Apigenin reduced *E. faecalis* biofilm viability in a dose-dependent manner, showing bactericidal effects at higher concentrations (MBIC 1,000–2,000 µg/mL; MBBC 3,000–5,000 µg/mL), though with limited impact on biomass. When combined with reduced graphene oxide (RGO), its antimicrobial activity was significantly enhanced. RGO promoted biomass reduction and biofilm disruption, leading to superior effects compared to apigenin alone.	Positive
Braga *et al.,* 2022 (Brazil)	*In vitro* Infected bovine dentin roots specimens	Ampelopsin (AMP) at 2.5 mg/mL (Eligible Hydrogel), Isoquercitrin and Rutin 1 to 0.0001 mg/mL serially diluted (MIC-MBC)	Calcium hydroxide (CH) at 1 mg/mL, and chlorhexidine (CHX) at 0.5 mg/mL	*E. faecalis* *(ATCC51299),* *A. israelii* *(ATCC12102),* *Lactobacillus casei* *(IAL#523),* *S. mutans* *(ATCC 25175),* *F. nucleatum* *(NCTC 11326)*	PNVCL hydrogels were incubated for 48 h	MIC, MBC, SEM, CLSM	AMP showed the strongest antimicrobial activity among the tested flavonoids (MIC: 0.125–1 mg/mL; MBC: 0.25–1 mg/mL), while ISO and RUT were effective only against *F. nucleatum*. In multispecies biofilms, PNVCL hydrogel with AMP disrupted biofilm structure, reduced bacterial cells and extracellular matrix, with efficacy comparable to CHX and calcium hydroxide hydrogels. CLSM confirmed a higher proportion of dead intratubular cells in the PNVCL+AMP group (73.8%) versus CH (58.8%) and CHX (50.6%).	Positive
Alipour *et al.,* 2021 (Iran)	*In vitro* Infected human dentin roots specimens	Chrysin	PCL/Gel: control scaffolds without chrysin	*E. faecalis (ATCC 13048), Cinetobacter baumannii (ATCC BAA-747), Pseudomonas aeruginosa (ATCC 27853),*	Chrysin incorporated into a poly-ε-caprolactone-gelatin solution (5% w/w) and mixed with a gelatin solution at a 1:1 ratio, using 1% polyvinyl alcohol to prevent phase separation. Scaffolds	Agar diffusion test and live/dead assay.	The chrysin-loaded scaffolds reported antimicrobial effects against evaluated bacterial strains.	Positive

				Staphylococcus aureus (ATCC 6538)	were incubated at 37 °C for 24 h to assess the inhibition zones.			
Caiaffa *et al.,* 2021 (Brazil)	*In vitro* Infected bovine dentin roots specimens	Epigallocatechin -3-gallate 0.6 mg/mL 4 mg/mL	Chlorhexidine (CHX) 0.05 and 0.5 mg/mL Negative control (untreated biofilm)	*E. faecalis* *(ATCC 51299),* *A. israelii* *(ATCC 12102),* *S. mutans (UA159),* *F. nucleatum* *(NCTC 11326)*	All antimicrobial agents were serially diluted in sterile deionized water. The microbial suspensions were inoculated in each well/infected disc containing the previously diluted flavonoids and peptides. Incubation at 37 °C for 24 h for all microorganisms, except *F. nucleatum*, which was incubated for 48 h**.**	MIC, MBC, CLSM, CFU/mL count	EGCG showed antibacterial activity in dentinal tubules, though less effective than CHX. When combined with the antimicrobial peptide KR-12-a5, EGCG exhibited synergistic or additive effects against various bacteria, outperforming the individual agents. In biofilm models, the EGCG + KR-12-a5 combination achieved bacterial reduction comparable to CHX. In dentinal tubules, this combination resulted in similar efficacy to CHX 0.5 mg/mL, indicating strong therapeutic potential.	Positive
Liu *et al.,* 2021 (China)	*In vitro* Infected human dentin roots specimens	Quercetin 1, 2, and 4 %	Control: Sterile water, and ethanol	*E. faecalis* *(ATCC 29212)*	Quercetin powder was directly added to 100% ethanol, followed by water-bath heating at 37 °C for 15 min. A droplet (50 µL) of irrigant was placed on the pulp side of the dentin pieces for 3 min. Then, the specimens were rinsed with sterile water for 1 min.	CLSM	Quercetin exhibited anti-biofilm activity. Both the pure ethanol and quercetin solutions showed obvious anti-biofilm effects, and as the concentration of the quercetin solution increased, the proportion of dead volumes of *E. faecalis* raised from 19.13% to 57.8%, with a statistically significant difference. The 4 % group (57.8%) showed the strongest anti-biofilm activity.	Positive
Yang *et al.,* 2020 (China)	*In vitro* Infected human dentin roots specimens	Proanthocyanidi n 5% and 10%	Sterile water, Chlorhexidine 2%	*E. faecalis* *(ATCC 29212)*	Proanthocyanidin as an auxiliary irrigant. A droplet of 50 µL of each disinfecting solution was placed on the root canal wall of the specimens for 3 min. Then, the specimens were washed with sterile water for 1 min.	CLSM	CLSM images of *E. faecalis*-infected dentinal tubules revealed that none of the irrigants achieved complete disinfection after instrumentation. CHX and PA showed significant antibacterial effects ($P < 0.05$), with 10% PA resulting in the highest percentage of dead cells. Lower concentrations of PA (2% and 5%) were comparable to CHX, while 10% proved more effective.	Positive

Qayyum *et al.,* 2019 (India)	*In vitro*	Quercetin 64 to 512 mg/mL	Negative control (untreated biofilm)	*E. faecalis* *(MTCC 2729)*	Biofilm growth and stress conditions with quercetin exposure. Incubation for 24 h at 37 °C.	MIC, SEM, CLSM, qRT-PCR	Quercetin inhibited *E. faecalis* biofilm formation in a dose-dependent manner at sub-MIC concentrations (64–256 mg L^{-1}), reducing biofilm by up to 95% without affecting bacterial viability. CLSM and SEM confirmed decreased biofilm thickness without morphological damage. Proteomic analysis revealed 19 differentially expressed proteins linked to glycolysis, translation elongation, and protein folding, supporting quercetin's potential as a non-bactericidal antibiofilm agent and identifying molecular targets for future studies.	Positive
Lee *et al.,* 2015 (Singapore)	*In vitro* Infected human dentin roots specimens	Epigallocatechin -3-gallate (125 µg/mL to 500 µg/mL) – Screening 5 to 20 µg/mL Selection	Control (untreated biofilm)	*E. faecalis* *(ATCC 29212)*	Treatment solution: media containing EGCG: 7 days at 37°C anaerobically without changing the media during treatment.	CFu/mL Count, CLSM, Flow cytometry, RNA extraction and quantitative polymerase chain reaction (qPCR),	EGCG exhibited strong antimicrobial activity against *Enterococcus faecalis*, with a MIC of 5 µg/mL and MBC of 20 µg/mL after 24 h. At 500 µg/mL, EGCG completely eradicated mature biofilms on dentin discs. Cell viability analysis showed a significant reduction in live cells after 7 days, confirmed by bacterial culture. Additionally, even at subinhibitory concentrations (2.5 µg/mL), EGCG suppressed over 75% of the expression of key virulence genes (*ace*, *cylA*, *gelE*, and *sprE*), highlighting its potential as an anti-virulence agent.	Positive

Abbreviations: *A. israelii: Actinomyces israelii;* CFU: Colony forming unit; *C. albicans : Candida albicans,* CLSM: Confocal laser scanning microscopy; CH: Calcium hydroxide ; CHX: Chlorhexidine digluconate; *E. f*

aecalis: Enterococcus faecalis; EGCG: Epigallocatechin-3 gallate; FE-SEM : Field Emission-Scanning Electron Microscopy ; FOSFO: Fosfomycin; *F. nucleatum: Fusobacterium nucleatum;* MBC: Minimum bactericidal concentration; MIC: Minimum inhibitory concentration; MFC: minimum fungicidal concentration; PA: Proanthocyanidin; QCT: Quercetin; qRT-PCR: Quantitative real-time polymerase chain reaction; SEM: Scanning electron microscopy; *S. mutans: Streptococcus mutans*

3.2 Flavonoids and control agents

Several flavonoids were evaluated in the included studies, such as epigallocatechin-3- gallate (Chrisostomo et al., 2025; Duque et al., 2023; Caiaffa et al., 2021; Lee et al., 2015) quercetin (Aqabat et al., 2024; Liu et al., 2021; Qayyum et al., 2019), proanthocyanidin (Huang et al., 2023; Yang et al., 2020), rutin (Pourhajibagher et al., 2024; Braga et al., 2022), apigenin (Kim et al., 2023), theaflavin (Wang et al., 2024), chalcone (Graciani et al., 2023), chrysin (Alipour et al., 2021), ampelopsin (Braga et al., 2022), and isoquercitrin (Braga et al., 2022). The main control agents used in the included studies were CHX (Duque et al., 2023; Graciani et al., 2023; Braga et al., 2022; Caiaffa et al., 2021; Yang et al., 2020), NaOCl (Pourhajibagher et al., 2024; Graciani et al., 2023; Huang et al., 2023), $Ca(OH)_2$ (Chrisostomo et al., 2025; Aqabat et al., 2024), ethanol (Wang et al., 2024; Liu et al., 2021), and triple antibiotic paste (Chrisostomo et al., 2025). In addition, all studies included a negative control, consisting of untreated biofilms or those exposed only to sterile water.

The concentrations of flavonoids tested varied across studies. Reported concentrations ranged from 12.5 to 50 µg/mL (Pourhajibagher et al., 2024; Wang et al., 2024; Graciani et al., 2023), 100 to 500 µg/mL (Lee et al., 2015; Kim et al., 2023), and 500 to 4000 µg/mL (Chrisostomo et al., 2025; Duque et al., 2023; Kim et al., 2023; Braga et al., 2022; Caiaffa et al., 2021). Higher ranges were also tested, including 64 to 512 mg/mL (Qayyum et al., 2019), 1–2% (Aqabat et al., 2024; Liu et al., 2021), 3–6.5% (Aqabat et al., 2024; Huang et al., 2023; Alipour et al., 2021; Liu et al., 2021; Yang et al., 2020), and up to 10% (Yang et al., 2020). The concentrations of the main positive controls were as follows: CHX at 50 to 500 µg/mL (Braga et al., 2022; Caiaffa et al., 2021; Duque et al., 2023), and 2% (Graciani et al., 2023; Yang et al., 2020); $Ca(OH)_2$ at 41.667 µg/mL (Aqabat et al., 2024) and 1000 µg/mL (Chrisostomo et al., 2025; Braga et al., 2022); and NaOCl at 1% (Graciani et al., 2023) and 2.5–3% (Pourhajibagher et al., 2024; Huang et al., 2023).

The majority of the studies (80%, n = 12) evaluated the antimicrobial activity of flavonoids applied in solution form (Chrisostomo et al., 2025; Pourhajibagher et al., 2024; Wang et al., 2024; Duque et al., 2023; Graciani et al., 2023; Huang et al., 2023; Kim et al., 2023; Caiaffa et al., 2021; Liu et al., 2021; Yang et al., 2020; Qayyum et al.,

2019; Lee et al., 2015). In contrast, only three studies incorporated flavonoids into delivery systems, such as hydrogels and scaffolds, targeting regenerative endodontic applications (Aqabat et al., 2024; Braga et al., 2022; Alipour et al., 2021). The exposure time of biofilms to flavonoids varied according to the proposed therapeutic purpose. When evaluated as alternative endodontic irrigants, shorter exposure times were used, ranging from 3 min (Liu et al., 2021; Yang et al., 2020), to 10 min (Huang et al., 2023), and up to 60 min (Kim et al., 2023). In contrast, when flavonoids were investigated as intracanal medicaments, higher treatment durations were adopted, including 24 h (Pourhajibagher et al., 2024; Wang et al., 2024; Alipour et al., 2021; Caiaffa et al., 2021; Qayyum et al., 2019), 48 h (Chrisostomo et al., 2025; Duque et al., 2023; Braga et al., 2022; Caiaffa et al., 2021), 72 h (Graciani et al., 2023), and up to 7 days (Chrisostomo et al., 2025; Aqabat et al., 2024; Lee et al., 2015).

3.3 Microorganisms and assessments

Regarding oral pathogens, all included studies evaluated the antimicrobial activity of flavonoids against *E. faecalis*. In addition, effects on other microorganisms were investigated, such as *Fusobacterium nucleatum* (*F. nucleatum)* (Duque et al., 2023; Braga et al., 2022; Caiaffa et al., 2021), *Actinomyces israelii* (*A. israelii*) (Chrisostomo et al., 2025; Duque et al., 2023; Braga et al., 2022; Caiaffa et al., 2021), *Streptococcus mutans* (*S. mutans*) (Chrisostomo et al., 2025; Duque et al., 2023; Braga et al., 2022; Caiaffa et al., 2021), *C. albicans* (Chrisostomo et al., 2025; Graciani et al., 2023), *Staphylococcus aureus* (S. aureus), *Acinetobacter baumannii* (*A. baumannii*), and *Pseudomonas aeruginosa* (*P. aeruginosa*) (Alipour et al., 2021), as well as *Lactobacillus casei* (*L. casei*) (Braga et al., 2022).

The experimental models varied in terms of biofilm complexity, including monospecies biofilms (Aqabat et al., 2024; Pourhajibagher et al., 2024; Wang et al., 2024; Huang et al., 2023; Kim et al., 2023; Alipour et al., 2021; Liu et al., 2021; Yang et al., 2020; Qayyum et al., 2019; Lee et al., 2015), multispecies biofilms (Chrisostomo et al., 2025; Braga et al., 2022), and both models (Duque et al., 2023; Graciani et al., 2023; Caiaffa et al., 2021). The biofilm development time also varied across studies: 24 h (Pourhajibagher et al., 2024; Wang et al., 2024; Braga et al., 2022; Alipour et al., 2021; Qayyum et al., 2019; Lee et al., 2015), 48 h (Duque et al., 2023; Braga et al., 2022; Caiaffa et al., 2021), 72 h (Duque et al., 2023; Graciani et al., 2023), and, in

infected dentin root specimen models, 7 days (Chrisostomo et al., 2025; Aqabat et al., 2024; Pourhajibagher et al., 2024; Huang et al., 2023; Liu et al., 2021; Yang et al., 2020; Lee et al., 2015), 14 days (Duque et al., 2023; Braga et al., 2022; Caiaffa et al., 2021), and 21 days (Alipour et al., 2021).

The methods employed to evaluate the antimicrobial activity of flavonoids included both quantitative and qualitative approaches. The most commonly used techniques were: minimum inhibitory concentration (MIC) assays (Aqabat et al., 2024; Pourhajibagher et al., 2024; Duque et al., 2023; Graciani et al., 2023; Kim et al., 2023; Braga et al., 2022; Caiaffa et al., 2021; Qayyum et al., 2019), minimum bactericidal concentration (MBC) assays (Aqabat et al., 2024; Duque et al., 2023; Graciani et al., 2023; Kim et al., 2023; Braga et al., 2022; Caiaffa et al., 2021), live/dead staining combined with confocal laser scanning microscopy (CLSM) (Chrisostomo et al., 2025; Aqabat et al., 2024; Wang et al., 2024; Duque et al., 2023; Huang et al., 2023; Kim et al., 2023; Braga et al., 2022; Alipour et al., 2021; Caiaffa et al., 2021; Liu et al., 2021; Yang et al., 2020; Qayyum et al., 2019; Lee et al., 2015), colony-forming unit (CFU/mL) counts (Aqabat et al., 2024; Pourhajibagher et al., 2024; Duque et al., 2023; Graciani et al., 2023; Kim et al., 2023; Caiaffa et al., 2021; Lee et al., 2015), agar diffusion tests (Alipour et al., 2021), quantitative real-time polymerase chain reaction (qRT-PCR) (Wang et al., 2024; Qayyum et al., 2019; Lee et al., 2015), and scanning electron microscopy (SEM) (Pourhajibagher et al., 2024; Wang et al., 2024; Duque et al., 2023; Huang et al., 2023; Kim et al., 2023; Braga et al., 2022; Qayyum et al., 2019).

3.4. Effects of flavonoids on oral pathogens associated with endodontic infections

The 15 studies included in this scoping review demonstrated the antimicrobial activity of flavonoids against microorganisms commonly associated with endodontic infections. The specific characteristics of each flavonoid evaluated are detailed below, including their effects and comparisons with the respective positive and negative controls used in the assays.

3.4.1 Epigallocatechin-3- gallate (EGCG)

Epigallocatechin-3-gallate has stood out for its antimicrobial and antibiofilm properties against clinically relevant oral pathogens, including *E. faecalis*, *F. nucleatum*, *A. israelii*, *C. albicans*, and *S. mutans* (Chrisostomo et al., 2025; Duque et

al., 2023; Caiaffa et al., 2021). All studies evaluating EGCG reported significant antimicrobial activity compared to negative controls (Chrisostomo et al., 2025; Duque et al., 2023; Caiaffa et al., 2021; Lee et al., 2015), with a dose-dependent effect demonstrated by Lee et al. (2015). When compared to conventional antimicrobial agents, EGCG showed similar efficacy to the triple antibiotic paste and $Ca(OH)_2$ in reducing colony-forming units (CFU/mL) (Chrisostomo et al., 2025), and similar activity to CHX (Duque et al., 2023; Caiaffa et al., 2021). In dentin disk infection models with *E. faecalis*, EGCG outperformed CHX at concentrations 10× and 100× the MIC (Duque et al., 2023), while another study reported similar efficacy to CHX at 0.05 mg/mL (Caiaffa et al., 2021).

Moreover, available studies indicate that the antimicrobial efficacy of EGCG can be significantly enhanced when combined with other agents, especially fosfomycin (FOSFO) and the synthetic peptide KR-12-a5, leading effects similar or superior to CHX in various experimental models (Chrisostomo et al., 2025; Duque et al., 2023; Caiaffa et al., 2021). The EGCG+FOSFO combination exhibited potent antibiofilm activity against multispecies biofilms, with cell death rates exceeding 80% after 48 h of exposure and reaching 82.9% after 7 days – outperforming conventional formulations such as the triple antibiotic paste (64.9%) and $Ca(OH)_2$ (54.5%) (Chrisostomo et al., 2025). In an intratubular biofilm model, this combination achieved 84.85% dead cells, a performance similar to that of EGCG alone (78.49%) and significantly higher than CHX at 100× MIC (50.6%) (Duque et al., 2023). These findings were supported by CLSM and SEM analyses, which revealed biofilm structural disruption and a marked reduction in the extracellular matrix.

Another investigated approach was the antimicrobial activity of EGCG, either alone or in combination with cationic peptides such as LL-37 and its analog KR-12-a5 (Caiaffa et al., 2021). EGCG showed significant antimicrobial effects, particularly against *A. israelii* and *F. nucleatum*. However, its effect against *E. faecalis* in intratubular biofilms was less pronounced when used alone. Despite this, a significant reduction in microbial viability was observed across all groups: 37.93% dead cells with EGCG alone and 88.04% with the EGCG + KR-12-a5 combination, compared to 49.72% and 89.41% achieved with CHX at concentrations of 0.05 and 0.5 mg/mL, respectively. The EGCG + KR-12-a5 combination demonstrated statistically superior efficacy compared to the isolated compounds and was equivalent to CHX at 0.5

mg/mL. Notably, the synergism promoted by KR-12-a5 was evidenced by low Fractional Inhibitory Concentration (FIC) values, significantly enhancing EGCG's antimicrobial action. This combination eliminated *S. mutans*, reduced *E. faecalis* by 5.52 log units, and achieved 88.04% dead cells in dentinal tubules – similar to 0.5 mg/mL CHX (89.41%) and superior to the individual agents.

3.4.2 Quercetin

Quercetin has demonstrated significant activity in inhibiting *E. faecalis* biofilms (Aqabat et al., 2024; Liu et al., 2021; Qayyum et al., 2019). The minimum inhibitory concentration of quercetin was 250 µg/mL – approximately six times higher than that of $Ca(OH)_2$ (41.667 µg/mL) – while the minimum bactericidal concentration, at 125 µg/mL, was equivalent to that of $Ca(OH)_2$, suggesting that both compounds exhibit similar bactericidal potential at higher concentrations. Furthermore, quercetin outperformed $Ca(OH)_2$ in inhibiting biofilm formation, although it was less effective in reducing the total viable bacterial count (Aqabat et al., 2024).

In dentinal tubules infected with *E. faecalis*, quercetin exhibited a concentration-dependent antibiofilm effect, with cell death rates increasing from 19.13% to 57.8% as the concentration rose from 1% to 4%. The 4% concentration showed the highest antibiofilm efficacy, significantly outperforming both the negative control and ethanol (Liu et al., 2021). Additionally, quercetin demonstrated dose-dependent inhibition of biofilm formation, with MIC at 512 mg/L, achieving 70%, 85%, and 95% inhibition at concentrations of 64, 128, and 256 mg/mL, respectively. CLSM and SEM images at 64 mg/L confirmed disruption of the biofilm matrix and reduction in biofilm thickness, although no bactericidal activity was observed at subinhibitory concentrations. At the molecular level, quercetin also downregulated five genes associated with bacterial stress response, suggesting a potential modulatory effect on gene expression in *E. faecalis* (Qayyum et al., 2019).

3.4.3 Proanthocyanidin (PA)

The reviewed studies indicate that proanthocyanidin exhibits significant antibiofilm activity against *E. faecalis*, with efficacy directly related to the concentration used, demonstrating a clear dose-dependent effect (Huang et al., 2023; Yang et al., 2020).

In infected dentin disk models assessed by CLSM, 6.5% PA showed significantly greater antibiofilm activity against *E. faecalis* biofilms than 0.9% saline solution (control group) (Huang et al., 2023). When used alone, PA outperformed the conventional irrigation protocol combining 17% ethylenediaminetetraacetic acid (EDTA) and 3% NaOCl, indicating superior bacterial viability reduction. Furthermore, combining PA with EDTA and NaOCl enhanced the antibiofilm effect even more, surpassing the outcomes observed with either PA or the irrigants used in isolation. These findings were statistically confirmed by integrated optical density analysis, which revealed the highest antibiofilm activity in the combination group, followed by PA alone, and lastly by the conventional irrigants alone (Huang et al., 2023).

Additionally, in a similar experimental model, PA was compared with 2% CHX, considered the gold standard among endodontic irrigants. Results showed that 10% PA was the most effective solution in inactivating *E. faecalis* within dentinal tubules, significantly outperforming CHX. Moreover, 2% and 5% PA concentrations demonstrated antibacterial efficacy similar to CHX. CLSM analysis corroborated these findings, showing a higher proportion of dead bacterial cells in PA-treated groups, mainly at the 10% concentration (Yang et al., 2020).

3.4.4 Rutin

Rutin has demonstrated selective antibacterial activity against *F. nucleatum*, with a minimum inhibitory concentration of 0.5 mg/mL and a minimum bactericidal concentration of 1 mg/mL, while showing no efficacy against other tested pathogens such as *E. faecalis*, *A. israelii*, *L. casei*, and *S. mutans* (Braga et al., 2022). In contrast, when rutin was employed as a photosensitizer in photodynamic therapy, it significantly and dose-dependently reduced the viability of *E. faecalis* biofilms. Notably, concentrations of 12.5 µmol/L and 25 µmol/L resulted in reductions of 3.6 and 4.2 $\log_{10}$ CFU/mL, respectively ($p < 0.05$) (Pourhajibagher et al., 2024). Conversely, lower concentrations (6.2 µmol/L) did not significantly affect biofilm viability ($p > 0.05$). These outcomes were supported by field emission scanning electron microscopy (FESEM) analyses, which revealed marked biofilm disorganization and removal at higher rutin concentrations and longer irradiation times, whereas lower doses induced only mild morphological changes in bacterial cells (Pourhajibagher et al., 2024).

3.4.5 Other flavonoids: findings from isolated studies

Apigenin exhibited concentration-dependent bactericidal effects against *E. faecalis* biofilms, with minimum biofilm inhibitory concentrations (MBICs) ranging from 1to 2 mg/mL and minimum biofilm bactericidal concentrations (MBBCs) between 3 and 5 mg/mL. However, when used alone, its impact on biofilm biomass was limited. The combination of apigenin with reduced graphene oxide significantly enhanced its antimicrobial activity and biofilm-disrupting capacity, as confirmed by CLSM and MEV analyses, allowing comparable effects at reduced doses (Kim et al., 2023).

Theaflavin also demonstrated promising activity, significantly inhibiting *E. faecalis* biofilm formation even at subinhibitory concentrations (sub-MICs). At 50% of the MIC (31.25 µg/mL), biofilm formation was suppressed by 97.53%. These findings were corroborated by CLSM and SEM analyses, which revealed reduced biofilm density and deformed bacterial cells. In addition, transcriptomic analyses identified differential expression of 248 genes, notably a downregulation of quorum sensing-related genes (*gelE*, *sprE*, and *secY*), suggesting that inhibition of bacterial virulence may be a potential mechanism of action (Wang et al., 2024).

Isoquercitrin and Ampelopsin (Amp) exhibited antibacterial activity against *F. nucleatum*. Isoquercitrin showed a MIC of 0.25 mg/mL and a MBC of 1 mg/mL, while Ampelopsin presented MIC values ranging from 0.125 to 1 mg/mL and MBC values between 0.25 and 1 mg/mL, indicating substantial antimicrobial potential (Braga et al., 2022). Ampelopsin demonstrated antimicrobial efficacy similar to 1 mg/mL CH and 0.5 mg/mL CHX in multispecies biofilms. In SEM and CLSM analyses, hydrogels composed of poly(N-vinylcaprolactam) (PNVCL) combined with Amp induced significant biofilm disorganization, characterized by reductions in bacterial cells and extracellular matrix, similar to the effects observed for PNVCL + $Ca(OH)_2$ and PNVCL + CHX. Quantitative analysis revealed a significant reduction in biofilm-associated bacteria in all treated hydrogel groups, with Ampelopsin resulting in the greatest reduction (73.8%), followed by $Ca(OH)_2$ (58.8%) and CHX (50.6%) (Braga et al., 2022).

Another compound evaluated was chalcone, which demonstrated potent antimicrobial activity against *E. faecalis*. MIC and MBC/MFC values ranged from 7.8 to 15.6 µg/mL, indicating a microbicidal effect. In hydroxyapatite disc biofilm models, chalcone at 10× MIC significantly reduced *E. faecalis* and *C. albicans* biofilms in both

mono- and co-culture settings ($p < 0.05$), showing efficacy similar to 1% NaOCl, although 2% CHX exhibited superior effectiveness (Graciani et al., 2023).

Finally, chrysin incorporated into poly-ε-caprolactone (PCL) scaffolds demonstrated relevant antimicrobial activity against various strains – including *E. faecalis*, *A. baumannii*, *P. aeruginosa*, and *S. aureus* – with the highest efficacy observed against *E. faecalis*. Bacterial viability was reduced to below 16% ($p < 0.05$), in contrast to control PCL scaffolds without chrysin, which showed no significant antimicrobial effect (Alipour et al., 2021).

4. DISCUSSION

4. Discussion

Antimicrobial activity is a determining factor in the success of endodontic therapy, especially in control of persistent microorganisms such as E. faecalis, which is frequently associated with treatment failure (Sharma et al., 2025; Alghamdi et al., 2020). This scoping review, by compiling available evidence for the first time, highlighted the potential of flavonoids in inhibiting biofilms formed by pathogens involved in endodontic infections. Compounds such as EGCG, quercetin, proanthocyanidin and others have shown significant antimicrobial and antibiofilm action in different experimental models, often equaling or surpassing conventional agents such as NaOCl, CHX and $Ca(OH)_2$. In addition, studies evaluating the combination of flavonoids with other molecules, such as cationic peptides or antibiotics, revealed promising synergistic effects, expanding therapeutic possibilities against resistant strains and mature biofilms.

Medical research has increasingly focused on the impact of novel antimicrobial agents on biofilms, given their critical role in the persistence and progression of various bacterial infections. This includes endodontic infections, which are particularly challenging to eliminate due to the protective and resilient nature of biofilm communities, often limiting the effectiveness of conventional antimicrobial treatments (Hall & Mah, 2017). Flavonoids are plant-derived compounds synthesized in response to microbial infection, which accounts for their documented *in vitro* antimicrobial activity against a broad range of microorganisms. Extracts from various flavonoid-rich plant species have demonstrated antimicrobial effects (Wu et al., 2024; Xu et al., 2024; Mishra et al., 2013; Pandey et al., 2010). Several flavonoids, including apigenin, galangin, flavone and flavonol glycosides, isoflavones, flavanones, and chalcones, have shown potent antibacterial activity (Wu et al., 2024; Salatin et al., 2022; Cushnie & Lamb, 2005). Their antimicrobial efficacy likely stems from the ability to act on multiple cellular targets rather than a single specific site. One proposed mechanism involves the formation of complexes with proteins through non-specific interactions such as hydrogen bonding and hydrophobic forces, as well as covalent bonding. Consequently, flavonoids may inactivate microbial adhesins, enzymes, and membrane transport proteins, disrupting essential microbial functions (Wu et al., 2024; Chagas et al., 2022). Lipophilic flavonoids, in particular, can disrupt microbial membranes, compromising cell integrity (Mishra et al., 2009; Cowan et al., 1999). Additional

mechanisms described in the literature and relevant to the findings of this review include inhibition of nucleic acid synthesis, increased membrane permeability, disruption of energy metabolism, and modulation of virulence factors (Chagas et al., 2022; Cushnie & Lamb, 2005). The convergence of these mechanisms may account for the favorable outcomes reported across multiple studies, especially those evaluating the antibiofilm efficacy of isolated flavonoids or their combinations with other antimicrobial agents.

Furthermore, several antimicrobial mechanisms have been attributed to the main flavonoids evaluated in the studies included in this review, all of which show promising activity against oral pathogens associated with endodontic infections. EGCG primarily exerts its effects through cytoplasmic membrane disruption, increasing membrane permeability and causing leakage of intracellular contents (Capasso et al., 2025). It also inhibits bacterial enzymes such as DNA gyrase and induces oxidative stress via the generation of reactive oxygen species (ROS) (Capasso et al., 2025; Lee et al., 2015). Quercetin, in turn, interferes with nucleic acid and protein synthesis, compromises bacterial membrane integrity, and exhibits anti-inflammatory properties that contribute to modulation of the host response (Nguyen & Bhattacharya, 2022; Qayyum et al., 2019). Proanthocyanidins destabilize bacterial membranes, inhibit microbial adhesion, and block the activity of extracellular enzymes such as matrix metalloproteinases (Huang et al., 2023; Yang et al., 2020; Rauf et al., 2019).

The findings of this scoping review reveal that flavonoids exhibit remarkable antimicrobial efficacy under various experimental conditions that mimic the complexity of endodontic infections. Included studies demonstrated that these natural compounds are effective against both monospecies biofilms – commonly formed by *E. faecalis* (Aqabat et al., 2024; Pourhajibagher et al., 2024; Wang et al., 2024; Huang et al., 2023; Kim et al., 2023; Alipour et al., 2021; Liu et al., 2021; Yang et al., 2020; Qayyum et al., 2019; Lee et al., 2015) – and multispecies biofilms, which better represent the microbial diversity typically found in infected root canals (Chrisostomo et al., 2025; Braga et al., 2022; Duque et al., 2023; Graciani et al., 2023; Caiaffa et al., 2021). Furthermore, flavonoids showed significant activity against both early-stage biofilms (Pourhajibagher et al., 2024; Wang et al., 2024; Braga et al., 2022; Alipour et al., 2021; Qayyum et al., 2019; Lee et al., 2015) and mature biofilms (Duque et al., 2023; Graciani et al., 2023; Caiaffa et al., 2021), which are known to be more resistant to antimicrobial

penetration and frequently associated with treatment failure. Notably, even in the presence of infected dentin roots – a biological substrate that can reduce the efficacy of conventional irrigants – flavonoids maintained their antimicrobial activity. This is particularly relevant considering the structural organization of biofilms and the inherent properties of dentin, such as its ability to absorb and neutralize active agents (Da Silva et al., 2013), potentially compromising clinical efficacy. Another noteworthy finding is the effectiveness of flavonoids at low concentrations (Pourhajibagher et al., 2024; Wang et al., 2024; Graciani et al., 2023; Braga et al., 2022; Caiaffa et al., 2021; Lee et al., 2015), with studies reporting bactericidal or viability-reducing effects at doses significantly lower than those required for conventional agents. Moreover, dose-dependent responses were observed (Huang et al., 2023; Braga et al., 2022; Liu et al., 2021; Yang et al., 2020), suggesting a favorable and adjustable therapeutic window. Collectively, these results support the potential of flavonoids as versatile and effective agents, capable of acting at various stages of endodontic infection and under challenging clinical scenarios, including mature biofilms and infected dentin substrates.

Moreover, studies in this review, when evaluating the combined effect of flavonoids with other antimicrobials, such as antibiotics (e.g., fosfomycin) (Chrisostomo et al., 2025; Duque et al., 2023), synthetic peptides (e.g., KR-12-a5) (Caiaffa et al., 2021) and smart delivery systems (e.g., hydrogels or scaffolds) (Braga et al., 2021; Alipour et al., 2021), potentiate their antimicrobial effects through proven synergisms, as demonstrated by FIC indices, CLSM, and SEM analyses. Beyond their direct antimicrobial activity, flavonoids have also been shown to modulate bacterial gene expression, including stress response and quorum sensing genes, which may contribute to reducing microbial virulence and the formation of persistent biofilms (Liu et al., 2025). In advanced formulations such as nanoemulsions or controlled-release complexes, these natural compounds have demonstrated improved penetration into biofilms (Tran & Hadinoto, 2021; Braga et al., 2022), establishing themselves as multifunctional alternatives for the management of endodontic infections. Moreover, although not the primary focus of this review, 8 out of the 15 included studies investigated the biocompatibility of flavonoids through cytotoxicity assays on various cell lines, showing either no cytotoxic effects (Chrisostomo et al., 2025; Duque et al., 2023; Graciani et al., 2023; Braga et al., 2022; Alipour et al., 2021; Caiaffa et al., 2021; Liu et al., 2021) or only a slight reduction in cell viability when higher concentrations of

the compounds were used (Aqabat et al., 2024). These findings are highly relevant to contemporary endodontic therapy, which seeks effective, biocompatible, and sustainable alternatives to address treatment failures related to endodontic infection. Thus, the use of flavonoids represents an innovative strategy, offering advantages such as low cytotoxicity, multifactorial mechanisms of action, and a reduced likelihood of inducing bacterial resistance–highlighting their potential as adjuncts to conventional antimicrobials in the development of novel endodontic treatment protocols.

E. faecalis is frequently reported as one of the main microorganisms associated with endodontic treatment failure, largely due to its remarkable ability to form resistant biofilms and survive in hostile environments, even after instrumentation and irrigation procedures (Yang et al., 2024). In this review, it was noted that although widely used irrigants such as NaOCl and CHX exhibit recognized antimicrobial activity, the data analyzed indicate that these agents are not fully effective in eliminating mature *E. faecalis* biofilms (Clegg et al., 2006). Similarly, conventional intracanal medicaments like $Ca(OH)_2$ have also shown limited efficacy against microorganisms organized in biofilms (Tronstad et al., 1981). Moreover, while NaOCl exhibits strong antimicrobial and tissue-dissolving properties, it is also highly cytotoxic and irritating to periapical tissues, with no residual antimicrobial effect or regenerative capabilities (Gomes et al., 2023; Yesilsoy et al., 1995). CHX, although less toxic and known for its substantivity to dentin, lacks the ability to dissolve necrotic tissue and is less effective against deeper biofilm layers due to its interaction with the extracellular polymeric substances that protect the microbial community (Gomes et al., 2023; Ruiz-Linares et al., 2017; Carrilho et al., 2010; Yesilsoy et al., 1995). In contrast, flavonoids represent a promising therapeutic alternative due to their multifaceted properties (Liu et al., 2025; Intharuksa et al., 2024; Salatin et al., 2022). Beyond their potent antimicrobial effects against resistant strains, flavonoids have demonstrated several biological activities not found in conventional irrigants and medicaments. Importantly, they stimulate alkaline phosphatase activity – a classical marker of osteoblastic differentiation – and promote mineralized nodule formation in human dental pulp cells and osteoblast-like cells (Duque et al., 2025; Rabelo et al., 2025; Braga et al., 2023), indicating a potential role in tissue regeneration. These regenerative effects, combined with anti-inflammatory and antioxidant properties, may provide a favorable microenvironment for pulp and periapical tissue repair. Another key advantage of flavonoids is their superior

biocompatibility, marked by low cytotoxicity and a reduced risk of inducing bacterial resistance, owing to their multitarget mechanisms of action. Furthermore, when formulated as nanoparticles or in controlled-release systems, flavonoids have shown improved biofilm penetration, enhanced stability, and sustained antimicrobial activity (Kopka et al., 2023; Braga et al., 2022; Alipour et al., 2021). Therefore, the incorporation of flavonoids into endodontic protocols represents an innovative strategy that addresses several limitations of conventional antimicrobial substances. By combining effective antimicrobial action with regenerative and immunomodulatory potential, flavonoids offer a biocompatible, multifunctional approach to managing endodontic infections and supporting pulp tissue regeneration.

This scoping review identified several limitations, particularly regarding methodological variability among the included studies. Differences were noted in flavonoid concentrations, exposure durations, delivery methods, antimicrobial assessment techniques, and experimental models. The antimicrobial activity was evaluated using diverse approaches, including assays on planktonic cultures, biofilm inhibition tests, CFU quantification, colorimetric metabolic assays (e.g., MTT, XTT), and structural analyses via CLSM or SEM. While CFU counts provide quantitative insights into microbial viability, they do not distinguish between bacteriostatic and bactericidal effects. Likewise, metabolic assays can be affected by residual compound activity, potentially misrepresenting microbial death. Although biofilm-based models are more representative of endodontic infections, only a minority of studies employed multispecies biofilms or clinically relevant settings. In many cases, studies relied on simplified *in vitro* models and focused on isolated microorganisms, which may not fully represent the complexity of actual endodontic infections, which are generally polymicrobial in composition. In addition, fewer investigations addressed the mechanisms of action of flavonoids, their biocompatibility, and their performance under simulated clinical conditions. Future studies could benefit from the use of models that better reflect clinical practice, including multispecies biofilms, cytotoxicity assessments, and well-designed in vivo and clinical trials. Moreover, a promising area to be explored involves the development of novel therapeutic strategies based on the combination of flavonoids with conventional medications and irrigants, as well as the incorporation of controlled-release systems and nanotechnology to enhance their efficacy and safety as adjuncts in endodontic treatment.

5. CONCLUSION

5. Conclusion

Flavonoids have demonstrated promising antimicrobial and antibiofilm activity against microorganisms associated with endodontic infections, especially *E. faecalis*. Although the *in vitro* results are encouraging and enable new antimicrobial advances, the available data are not yet sufficient to robustly support flavonoids as clinically effective interventions. Further standardized and clinical studies are needed to validate their efficacy and safety as therapeutic agents in the endodontic field.

6. REFERENCES

6. References

1. Alghamdi F, Shakir M. The Influence of Enterococcus faecalis as a Dental Root Canal Pathogen on Endodontic Treatment: A Systematic Review. *Cureus*. 2020;12(3):e7257. doi:10.7759/cureus.7257
2. Alipour M, Pouya B, Aghazadeh Z, et al. The Antimicrobial, Antioxidative, and Anti-Inflammatory Effects of Polycaprolactone/Gelatin Scaffolds Containing Chrysin for Regenerative Endodontic Purposes. *Stem Cells Int*. 2021;2021:3828777. doi:10.1155/2021/3828777
3. Aqabat HMA, Abouelseoud M, Rafaat SN, et al. Cytocompatibility, Antibacterial, and Anti-Biofilm Efficacy of Grape Seed Extract and Quercetin Hydrogels Against a Mature Endodontic Biofilm Ex Vivo Model. *J Clin Med*. 2024;13(21):6464. doi:10.3390/jcm13216464
4. Arias Z, Nizami MZI, Chen X, Chai X, Xu B, Kuang C, Omori K, Takashiba S. Recent Advances in Apical Periodontitis Treatment: A Narrative Review. *Bioengineering* (Basel). 2023 Apr 19;10(4):488. doi: 10.3390/bioengineering10040488.
5. Asgary S, Shamszadeh S, Nosrat A, Aminoshariae A, Sabeti M. Management Strategies for Immature Teeth with Pulp Necrosis: An Umbrella Review of Systematic Reviews. *Iran Endod J.* 2024;19(4):242-253. doi: 10.22037/iej.v19i4.46292.
6. Beckman CKC, de Lima Costa T, Puppin-Rontani RM, de Castilho ARF. Exploring the role of flavonoids in caries-affected dentin adhesion: A comprehensive scoping review. *Arch Oral Biol.* 2024 Jun;162:105942. doi: 10.1016/j.archoralbio.2024.105942. Epub 2024
7. Borzini L, Condò R, De Dominicis P, Casaglia A, Cerroni L. Root Canal Irrigation: Chemical Agents and Plant Extracts Against *Enterococcus faecalis*. *Open Dent J.* 2016 Dec 19;10:692-703. doi: 10.2174/1874210601610010692.
8. Braga GPA, Caiaffa KS, Pereira JA, et al. Microbiological Properties and Cytotoxicity of PNVCL Hydrogels Containing Flavonoids as Intracanal Medication for Endodontic Therapy. *J Funct Biomater*. 2022;13(4):305. doi:10.3390/jfb13040305

9. Braga GPA, Caiaffa KS, Rabelo RL, et al. Cytotoxicity and Biomineralization Potential of Flavonoids Incorporated into PNVCL Hydrogels. *J Funct Biomater*. 2023;14(3):139. doi:10.3390/jfb14030139.
10. Caiaffa KS, Dos Santos VR, Abuna GF, et al. Cytocompatibility and Synergy of EGCG and Cationic Peptides Against Bacteria Related to Endodontic Infections, in Planktonic and Biofilm Conditions. *Probiotics Antimicrob Proteins*. 2021;13(6):1808-1819. doi:10.1007/s12602-021-09830-3
11. Capasso L, De Masi L, Sirignano C, et al. Epigallocatechin Gallate (EGCG): Pharmacological Properties, Biological Activities and Therapeutic Potential. *Molecules*. 2025;30(3):654. doi:10.3390/molecules30030654
12. Carneiro BT, de Castro FNAM, Benetti F, Nima G, Suzuki TYU, André CB. Flavonoids effects against bacteria associated to periodontal disease and dental caries: a scoping review. *Biofouling.* 2024 Feb;40(2):99-113. doi: 10.1080/08927014.2024.2321965.
13. Carrilho MR, Carvalho RM, Sousa EN, et al. Substantivity of chlorhexidine to human dentin. *Dent Mater*. 2010;26(8):779-785. doi:10.1016/j.dental.2010.04.00
14. Castellanos JS, Betancourt DE, Díaz-Báez D, Baldión PA. Effect of flavonoids from grape seed and cranberry extracts on the microbiological activity of *Streptococcus mutans*: a systematic review of in vitro studies. *BMC Oral Health.* 2024 Jun 5;24(1):662. doi: 10.1186/s12903-024-04263-0.
15. Chagas MDSS, Behrens MD, Moragas-Tellis CJ, Penedo GXM, Silva AR, Gonçalves-de-Albuquerque CF. Flavonols and Flavones as Potential anti-Inflammatory, Antioxidant, and Antibacterial Compounds. *Oxid Med Cell Longev*. 2022;2022:9966750. doi:10.1155/2022/9966750
16. Chrisostomo DA, Pereira JA, Scaffa PMC, et al. Antibiofilm properties, cytotoxicity, and effect on protease activity of antibiotics and EGCG-based medications for endodontic purposes. *J Dent*. 2025;156:105660. doi:10.1016/j.jdent.2025.105660
17. Clegg MS, Vertucci FJ, Walker C, Belanger M, Britto LR. The effect of exposure to irrigant solutions on apical dentin biofilms in vitro. *J Endod*. 2006;32(5):434-437. doi:10.1016/j.joen.2005.07.002
18. Cowan MM. Plant products as antimicrobial agents. *Clinical Microbiology Reviews.* 1999;12(4):564–582. doi: 10.1128/cmr.12.4.564.
19. Cushnie TPT, Lamb AJ. Antimicrobial activity of flavonoids. *Int J Antimic Agents* 2005;26(5):343–356. doi: 10.1016/j.ijantimicag.2005.09.002.

20. Da Silva L, Finer Y, Friedman S, Basrani B, Kishen A. Biofilm formation within the interface of bovine root dentin treated with conjugated chitosan and sealer containing chitosan nanoparticles. *J Endod*. 2013;39(2):249-253. doi:10.1016/j.joen.2012.11.008
21. Dias MC, Pinto DCGA, Silva AMS. Plant Flavonoids: Chemical Characteristics and Biological Activity. *Molecules*. 2021 Sep 4;26(17):5377. doi: 10.3390/molecules26175377.
22. Duque C, Hussein H, Bortolatto J, Prakki A, Kishen A. Effect of taxifolin and epigallocatechin-3-gallate on biomineralization potential of stem cells from dental apical papilla. *Arch Oral Biol.* 2022 Jun;138:105413. doi: 10.1016/j.archoralbio.202
23. Duque C, Rabelo RL, Braga GPA, et al. EGCG and Taxifolin Modulate Secretory Activity and Expression of Dentinogenesis Markers in Odontoblast-Like Cells. *Scientifica (Cairo)*. 2025;2025:3233536. doi:10.1155/sci5/3233536
24. Duque C, Souza ACA, Aida KL, Pereira JA, Caiaffa KS, Santos VRD, Cosme-Silva L, Prakki A. Synergistic antimicrobial potential of EGCG and fosfomycin against biofilms associated with endodontic infections. *J Appl Oral Sci.* 2023 Mar 27;31:e20220282. doi: 10.1590/1678-7757-2022-0282.
25. Elhakim A, Kim U, Kim E, Lee S, Lee JM, Jung HS, Kim S. Effects of icariin on dental pulp stem cells and its potential applications in dentin repair. *Arch Oral Biol.* 2025 Jan;169:106112. doi: 10.1016/j.archoralbio.2024.106112.
26. Febvey A, Silva F, Henriques B, Özcan M, Teughels W, Souza JCM. Root canal disinfection and maintenance of the remnant tooth tissues by using grape seed and cranberry extracts. *Odontology.* 2023 Jul;111(3):541-553. doi: 10.1007/s10266-022-00766-w.
27. Ferreira S, Grenho L, Fernandes MH, Lima SAC. Curcumin-Loaded Lipid Nanoparticles: A Promising Antimicrobial Strategy Against *Enterococcus faecalis* in Endodontic Infections. *Pharmaceutics.* 2025 Jan 14;17(1):108. doi: 10.3390/pharmaceutics17010108.
28. Gomes BPFA, Aveiro E, Kishen A. Irrigants and irrigation activation systems in Endodontics. *Braz Dent J*. 2023;34(4):1-33. doi:10.1590/0103-6440202305577
29. Gomes BPFA, Herrera DR. Etiologic role of root canal infection in apical periodontitis and its relationship with clinical symptomatology. *Braz Oral Res.* 2018 Oct 18;32(suppl 1):e69.

30. Graciani J, Rosalen PL, de Oliveira Chaves Dos Santos E, et al. Evaluation of efficacy of new chalcone-based endodontic irrigant against dual biofilm Enterococcus faecalis and Candida albicans: a study in vitro. *Odontology*. 2023;111(3):573-579. doi:10.1007/s10266-022-00764-y
31. Graciani J, Rosalen PL, de Oliveira Chaves Dos Santos E, Rocha KAP, Balen BRT, Garcia MAR, Lazarini JG, da Silva DR, Carvalho SG, Regasini LO, Chorilli M, Orlandi Sardi JC. Evaluation of efficacy of new chalcone-based endodontic irrigant against dual biofilm *Enterococcus faecalis* and *Candida albicans*: a study in vitro. *Odontology.* 2023 Jul;111(3):573-579. doi: 10.1007/s10266-022-00764-y.
32. Hall CW, Mah TF. Molecular mechanisms of biofilm-based antibiotic resistance and tolerance in pathogenic bacteria. *FEMS Microbiol Rev.* 2017;41:276–301. doi: 10.1093/femsre/fux010.
33. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.5 (updated August 2024). Cochrane, 2024. Available from www.training.cochrane.org/handbook.
34. Huang Y, Zhang Y, Liu Q, et al. Evaluation of structural integrity effect on adhesion strength of root dentin with a multi-functional irrigation strategy. *Clin Oral Investig*. 2023;27(4):1465-1472. doi:10.1007/s00784-022-04765-7
35. Iglesias-Linares A, Yáñez-Vico RM, Sánchez-Borrego E, Moreno-Fernández AM, Solano-Reina E, Mendoza-Mendoza A. Stem cells in current paediatric dentistry practice. *Arch Oral Biol.* 2013 Mar;58(3):227-38. doi: 10.1016/j.archoralbio.2012.11.008.
36. Intharuksa A, Kuljarusnont S, Sasaki Y, Tungmunnithum D. Flavonoids and Other Polyphenols: Bioactive Molecules from Traditional Medicine Recipes/Medicinal Plants and Their Potential for Phytopharmaceutical and Medical Application. *Molecules.* 2024 Dec 5;29(23):5760. doi: 10.3390/molecules29235760.
37. Kahler B, Lu J, Taha NA. Regenerative endodontic treatment and traumatic dental injuries. *Dent Traumatol.* 2024 Dec;40(6):618-635. doi: 10.1111/edt.12979.
38. Kim MA, Min KS. Combined effect of apigenin and reduced graphene oxide against Enterococcus faecalis biofilms. *J Oral Sci*. 2023;65(3):163-167. doi:10.2334/josnusd.22-0459
39. Kopka B, Kost B, Wrześniewska J, Rajkowska K, Kadłubowski S, Kunicka-Styczyńska A, Baryga A, Gonciarz W, Basko M, Brzeziński M. Supramolecular

poly(vinyl alcohol)-based hydrogels containing quercetin for bacterial and fungal elimination. *Eur Polymer J.* 2023; 187:111881, https://doi.org/10.1016/j.eurpolymj.2023.111881.

40. Lee P, Tan KS. Effects of Epigallocatechin gallate against Enterococcus faecalis biofilm and virulence. *Arch Oral Biol*. 2015;60(3):393-399. doi:10.1016/j.archoralbio.2014.11.014
41. Liu G, Yang Y, Min KS, Lee BN, Hwang YC. Odontogenic Effect of Icariin on the Human Dental Pulp Cells. *Medicina* (Kaunas). 2022 Mar 16;58(3):434. doi: 10.3390/medicina58030434.
42. Liu Y, Zhu J, Liu Z, Zhi Y, Mei C, Wang H. Flavonoids as Promising Natural Compounds for Combating Bacterial Infections. *Int J Mol Sci*. 2025;26(6):2455. doi:10.3390/ijms26062455
43. Liu Z, Feng X, Wang X, Yang S, Mao J, Gong S. Quercetin as an Auxiliary Endodontic Irrigant for Root Canal Treatment: Anti-Biofilm and Dentin Collagen-Stabilizing Effects In Vitro. *Materials (Basel)*. 2021;14(5):1178. doi:10.3390/ma14051178
44. Márton IJ, Kiss C. Protective and destructive immune reactions in apical periodontitis. *Oral Microbiol Immunol.* 2000 Jun;15(3):139-50. doi: 10.1034/j.1399-302x.2000.150301.x.
45. Mendes Soares IP, Anselmi C, Ribeiro RAO, Mota RLM, Pires MLBA, Fernandes LO, de Souza Costa CA, Hebling J. Flavonoids modulate regenerative-related cellular events in LPS-challenged dental pulp cells. *J Dent.* 2024 Dec;151:105424. doi: 10.1016/j.jdent.2024.105424.
46. Minhaco VMTR, Maquera Huacho PM, Mancim Imbriani MJ, Tonon CC, Chorilli M, Rastelli ANS, Spolidorio DMP. Improving antimicrobial activity against endodontic biofilm after exposure to blue light-activated novel curcumin nanoparticle. *Photodiagnosis Photodyn Ther.* 2023 Jun;42:103322. doi: 10.1016/j.pdpdt.2023.103322
47. Mishra A, Sharma AK, Kumar S, Saxena AK, Pandey AK. Bauhinia variegata leaf extracts exhibit considerable antibacterial, antioxidant, and anticancer activities. *Biomed Res Int*. 2013;2013:915436. doi:10.1155/2013/915436
48. Mishra AK, Mishra A, Kehri HK, Sharma B, Pandey AK. Inhibitory activity of Indian spice plant Cinnamomum zeylanicum extracts against Alternaria solani and

Curvularia lunata, the pathogenic dematiaceous moulds. *Annals Clin Microbiol Antimicr.* 2009;8, article 9 doi: 10.1186/1476-0711-8-9.

49. Możyńska J, Metlerski M, Lipski M, Nowicka A. Tooth Discoloration Induced by Different Calcium Silicate-based Cements: A Systematic Review of In Vitro Studies. *J Endod.* 2017 Oct;43(10):1593-1601. doi: 10.1016/j.joen.2017.04.002
50. Nath R, Manna S, Panda S, Maity A, Bandyopadhyay K, Das A, Khan SA, Debnath B, Akhtar MJ. Flavonoid Based Development of Synthetic Drugs: Chemistry and Biological Activities. *Chem Biodivers.* 2024 Oct 27:e202401899. doi: 10.1002/cbdv.202401899.
51. Nguyen TLA, Bhattacharya D. Antimicrobial Activity of Quercetin: An Approach to Its Mechanistic Principle. *Molecules*. 2022;27(8):2494. Published 2022 Apr 12. doi:10.3390/molecules27082494
52. Nunes GP, de Oliveira Alves R, Ragghianti MHF, Dos Reis-Prado AH, de Toledo PTA, Martins TP, Vieira APM, Peres GR, Duque C. Effects of quercetin on mineralized dental tissues: A scoping review. *Arch Oral Biol.* 2025 Jan;169:106119. doi: 10.1016/j.archoralbio.2024.106119.
53. Page MJ, McKenzie JE, Bossuyt PM, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. *J Clin Epidemiol*. 2021;134:103-112. doi:10.1016/j.jclinepi.2021.02.003
54. Pandey AK, Mishra AK, Mishra A, Kumar S, Chandra A. Therapeutic potential of C. zeylanicum extracts: an antifungal and antioxidant perspective. *Int J Biol Med Res*. 2010;1:228–233.
55. Peters MDJ, Godfrey CM, Khalil H, et al. 2015. Methodology for JBI scoping reviews. The Joanna Briggs Institute reviewers' manual. Adelaide, South Australia: The Joanna Briggs Institute; 2015.
56. Pourhajibagher M, Ghafari HA, Bahrami R, Bahador A. Photoinactivation of Enterococcus faecalis Biofilm: In Vitro Antimicrobial Effect of Photoexcited Rutin-Gallium(III) Complex via Visible Blue Light. *J Endod*. 2024;50(5):602-611. doi:10.1016/j.joen.2024.01.007
57. Qayyum S, Sharma D, Bisht D, Khan AU. Identification of factors involved in Enterococcus faecalis biofilm under quercetin stress. *Microb Pathog*. 2019;126:205-211. doi:10.1016/j.micpath.2018.11.013
58. Rabelo RL, Nunes GP, Peres GR, et al. Comparison of dose and time effects of flavonoids, alone or in combination, on the induction of mineralization markers in

human osteoblast-like cells. *Arch Oral Biol*. Published online May 5, 2025. doi:10.1016/j.archoralbio.2025.106285.

59. Rauf A, Imran M, Abu-Izneid T, et al. Proanthocyanidins: A comprehensive review. *Biomed Pharmacother*. 2019;116:108999. doi:10.1016/j.biopha.2019.108999
60. Ruiz-Linares M, Aguado-Pérez B, Baca P, Arias-Moliz MT, Ferrer-Luque CM. Efficacy of antimicrobial solutions against polymicrobial root canal biofilm. *Int Endod J*. 2017;50(1):77-83. doi:10.1111/iej.12598.
61. Salatin S, Bazmani A, Shahi S, Naghili B, Memar MY, Dizaj SM. Antimicrobial Benefits of Flavonoids and their Nanoformulations. *Curr Pharm Des*. 2022;28(17):1419-1432. doi:10.2174/1381612828666220509151407
62. Seron MA, Nunes GP, Ferrisse TM, et al. Influence of bioceramic sealers on dentinal tubule penetration and antimicrobial effectiveness: a systematic review and meta-analysis of in vitro studies. *Odontology*. 2024;112(3):672-699. doi:10.1007/s10266-024-00904-6
63. Sharma J, Jhamb S, Mehta M, Bhushan J, Bhardwaj SB, Kaur A. Prevalence of Enterococcus faecalis in refractory endodontic infections: A microbiological study. *J Cons Dent Endod.* 2025; 28(5): 462-467. doi: 10.4103/JCDE.JCDE_871_24
64. Sheehy EC, Roberts GJ. Use of calcium hydroxide for apical barrier formation and healing in non-vital immature permanent teeth: a review. *Br Dent J.* 1997 Oct 11;183(7):241-6. doi: 10.1038/sj.bdj.4809477.
65. Smith AJ. Pulpal responses to caries and dental repair. *Caries Res.* 2002 Jul-Aug;36(4):223-32.
66. Tran TT, Hadinoto K. A Potential Quorum-Sensing Inhibitor for Bronchiectasis Therapy: Quercetin-Chitosan Nanoparticle Complex Exhibiting Superior Inhibition of Biofilm Formation and Swimming Motility of *Pseudomonas aeruginosa* to the Native Quercetin. *Int J Mol Sci*. 2021;22(4):1541. Published 2021 Feb 3. doi:10.3390/ijms22041541
67. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med*. 2018;169(7):467-473. doi:10.7326/M18-0850
68. Tronstad L, Andreasen JO, Hasselgren G, Kristerson L, Riis I. pH changes in dental tissues after root canal filling with calcium hydroxide. *J Endod*. 1981;7(1):17-21. doi:10.1016/S0099-2399(81)80262-2

69. Wang S, Deng S, Wang Y. Theaflavin-3,3'-digallate effectively attenuates biofilm formation by *Enterococcus faecalis* via the targeting of specific quorum sensing pathways. *Microb Pathog*. 2024;193:106739. doi:10.1016/j.micpath.2024.106739
70. Wu Y, Jiang L, Ran W, Zhong K, Zhao Y, Gao H. Antimicrobial activities of natural flavonoids against foodborne pathogens and their application in food industry. *Food Chem*. 2024;460(Pt 1):140476. doi:10.1016/j.foodchem.2024.140476
71. Xie Z, Shen Z, Zhan P, Yang J, Huang Q, Huang S, Chen L, Lin Z. Functional Dental Pulp Regeneration: Basic Research and Clinical Translation. *Int J Mol Sci.* 2021 Aug 20;22(16):8991.
72. Xu S, Kang A, Tian Y, et al. Plant Flavonoids with Antimicrobial Activity against Methicillin-Resistant *Staphylococcus aureus* (MRSA). *ACS Infect Dis*. 2024;10(9):3086-3097. doi:10.1021/acsinfecdis.4c00292
73. Yahfoufi N, Alsadi N, Jambi M, Matar C. The Immunomodulatory and Anti-Inflammatory Role of Polyphenols. *Nutrients.* 2018 Nov 2;10(11):1618. doi: 10.3390/nu10111618.
74. Yang S, Meng X, Zhen Y, et al. Strategies and mechanisms targeting *Enterococcus faecalis* biofilms associated with endodontic infections: a comprehensive review. *Front Cell Infect Microbiol*. 2024;14:1433313. doi:10.3389/fcimb.2024.1433313
75. Yang SY, Liu Y, Mao J, et al. The antibiofilm and collagen-stabilizing effects of proanthocyanidin as an auxiliary endodontic irrigant. *Int Endod J*. 2020;53(6):824-833. doi:10.1111/iej.13280
76. Yang SY, Liu Y, Mao J, Wu YB, Deng YL, Qi SC, Zhou YC, Gong SQ. The antibiofilm and collagen-stabilizing effects of proanthocyanidin as an auxiliary endodontic irrigant. Int Endod J. 2020 Jun;53(6):824-833. doi: 10.1111/iej.13280.
77. Yesilsoy C, Whitaker E, Cleveland D, Phillips E, Trope M. Antimicrobial and toxic effects of established and potential root canal irrigants. *J Endod*. 1995;21(10):513-515. doi:10.1016/s0099-2399(06)80524-8

SUPPLEMENTARY FILES

Supplementary File 1. Search strategies used for the electronic databases

Search Strategy
PUBMED/MEDLINE: 281
(((Flavonoid) OR (Flavonoids) OR (Bioflavonoids) OR (Bioflavonoid) OR (Flavon) OR (Isoflavones) OR (Flavanones) OR (Flavanols) OR (Flavanonols) OR (2-Phenyl-Chromene) OR (2 Phenyl Chromene) OR (2-Phenyl-Benzopyran) OR (2 Phenyl Benzopyran) OR (2-Phenyl-Benzopyrans) OR (2 Phenyl Benzopyrans) OR (2-Phenyl-Chromenes) OR (2 Phenyl Chromenes) OR (Proanthocyanidin) OR (Polyhydroxyflavan-3-ol) OR (Naringenin) OR (4',5,7-trihydroxyflavanone) OR (myricetin) OR (3,3',4',5,5',7-hexahydroxyflavone) OR (Hesperitin) OR (Hesperidin) OR (Taxifolin) OR (Dihydroquercetin) OR (Quercetin) OR (Quercetine) OR (Dikvertin) OR (3,3',4',5,7-Pentahydroxyflavone) OR (Isoquercitrin) OR (Quercetin-3-O-glucoside) OR (isoquercetin) OR (isoquercitin) OR (isotrifoliin) OR (epigallocatechin-3-gallate) OR (epigallo-catechin gallate) OR (epigallocatechin-3-O-gallate) OR (EGCG) OR (Ampelopsin) OR (Rutin) OR (Rutoside) OR (Morina) OR (Kaempferol) OR (Kaempferols) OR (Myricetin) OR (Epicatechin) OR (Catechin) OR (Isorhamnetin) OR (Fisetin) OR (3,3',4',7-Tetrahydroxy-flavone) OR (Chrysin) OR (chrysene) OR (5,7-dihydroxyflavone) OR (Pinocembrin) OR (eriodictyol) OR (Abyssinones) OR (Theaflavin) OR (Genistein) OR (Genestein) OR (Daidzein) OR (Theaflavin) OR (Macluraxanthone) OR (Scopoletin) OR (Luteolin) OR (3',4',5,7-Tetrahydroxyflavone) OR (Luteoline) OR (Apigenin)) AND ((Root Canal Therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontic therapy) OR (endodontic treatment) OR (root canal treatment) OR (RCT) OR (endodontic procedure) OR (Root Canal Irrigants) OR (Canal Irrigant, Root) OR (Canal Irrigants, Root) OR (Irrigant, Root Canal) OR (Irrigants, Root Canal) OR (Root Canal Irrigant) OR (Root Canal Medicament) OR (Root Canal Medicaments) OR (Canal Medicament, Root) OR (Canal Medicaments, Root) OR (Medicament, Root Canal) OR (Medicaments, Root Canal) OR (Root Canal Preparation) OR (Canal Preparation, Root) OR (Canal Preparations, Root) OR (Preparation, Root Canal) OR (Preparations, Root Canal) OR (Root Canal Preparations) OR (Therapeutic Irrigation) OR (Irrigation, Therapeutic) OR (Irrigations, Therapeutic) OR (Therapeutic Irrigations) OR (Lavage) OR (Lavages) OR (Douching) OR (Douchings) OR (Endodontics) OR (Endodontology) OR (Dentinal Tubule) OR (Tubule Penetration) 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 (Endodontic retreatment) OR (Root channel retreatment) OR (Root canal retreatment) OR (Endodontic, Regenerative) OR (Endodontics, Regenerative) OR (Regenerative Endodontic))) AND ((Antimicrobial activity) OR (Antimicrobial effectiveness) OR (Antimicrobial effect) OR (Antibacterial Affect) OR (Antibacterial Effectiveness) OR (Anti-biofilm Activity) OR (Anti-biofilm Effectiveness) OR (Bacteria) OR (Eubacteria) (antimicrobial) OR (disinfection) OR (bacterial reduction) OR (microbial reduction) OR (microbial outcome) OR (molecular microbial) OR (antimicrobe) OR (Infections) OR (Infection Control Dental) OR (Microbiology) OR (Biofilm) OR (Enterococcus faecalis) OR (Streptococcus faecalis) OR (Streptococcus Group D) OR (Fusobacterium nucleatum) OR (Fusobacterium) OR (Propionibacterium) OR (Klebsiella) OR (Enterococcus klebsiella) OR (Streptococcus spp.) OR (Tannerella forsythia))

(http://www.ncbi.nlm.nih.gov/pubmed)

SCOPUS: 79

(TITLE-ABS-KEY ((flavonoid) OR (flavonoids) OR (bioflavonoids) OR (bioflavonoid) OR (flavon) OR (isoflavones) OR (flavanones) OR (flavanols) OR (flavanonols) OR (2-phenyl-chromene) OR (2 phenyl AND chromene) OR (2-phenyl-benzopyran) OR (2 phenyl AND benzopyran) OR (2-phenyl-benzopyrans) OR (2 phenyl AND benzopyrans) OR (2-phenyl-chromenes) OR (2 phenyl AND chromenes) OR (proanthocyanidin) OR (polyhydroxyflavan-3-ol) OR (naringenin) OR (4',5,7-trihydroxyflavanone) OR (myricetin) OR (3,3',4',5,5',7-hexahydroxyflavone) OR (hesperitin) OR (hesperidin) OR (taxifolin) OR (dihydroquercetin) OR (quercetin) OR (quercetine) OR (dikvertin) OR (3,3',4',5,7-pentahydroxyflavone) OR (isoquercitrin) OR (quercetin-3-o-glucoside) OR (isoquercetin) OR (isoquercitin) OR (isotrifoliin) OR (epigallocatechin-3-gallate) OR (epigallo-catechin AND gallate) OR (epigallocatechin-3-o-gallate) OR (egcg) OR (ampelopsin) OR (rutin) OR (rutoside) OR (morina) OR (kaempferol) OR (kaempferols) OR (myricetin) OR (epicatechin) OR (catechin) OR (isorhamnetin) OR (fisetin) OR (3,3',4',7-tetrahydroxy-flavone) OR (chrysin) OR (chrysene) OR (5,7-dihydroxyflavone) OR (pinocembrin) OR (eriodictyol) OR (abyssinones) OR (theaflavin) OR (genistein) OR (genestein) OR (daidzein) OR (theaflavin) OR (macluraxanthone) OR (scopoletin) OR (luteolin) OR (3',4',5,7-tetrahydroxyflavone) OR (luteoline) OR (apigenin)) AND TITLE-ABS-KEY ((root AND canal AND therapy) OR (canal AND therapies, AND root) OR (canal AND therapy, AND root) OR (root AND canal AND therapies) OR (therapies, AND root AND canal) OR (therapy, AND root AND canal) OR (endodontic AND therapy) OR (endodontic AND treatment) OR (root AND canal AND treatment) OR (rct) OR (endodontic AND procedure) OR (root AND canal AND irrigants) OR (canal AND irrigant, AND root) OR (canal AND irrigants, AND root) OR (irrigant, AND root AND canal) OR (irrigants, AND root AND canal) OR (root AND canal AND irrigant) OR (root AND canal AND medicament) OR (root AND canal AND medicaments) OR (canal AND medicament, AND root) OR (canal AND medicaments, AND root) OR (medicament, AND root AND canal) OR (medicaments, AND root AND canal) OR (root AND canal AND preparation) OR (canal AND preparation, AND root) OR (canal AND preparations, AND root) OR (preparation, AND root AND canal) OR (preparations, AND root AND canal) OR (root AND canal AND preparations) OR (therapeutic AND irrigation) OR (irrigation, AND therapeutic) OR (irrigations, AND therapeutic) OR (therapeutic AND irrigations) OR (lavage) OR (lavages) OR (douching) OR (douchings) OR (endodontics) OR (endodontology) OR (dentinal AND tubule) OR (tubule AND penetration) OR (tooth, AND nonvital) OR (nonvital AND tooth) OR (tooth, AND devitalized) OR (devitalized AND tooth) OR (tooth, AND pulpless) OR (pulpless AND tooth) OR (teeth, AND pulpless) OR (pulpless AND teeth) OR (teeth, AND devitalized) OR (devitalized AND teeth) OR (teeth, AND nonvital) OR (nonvital AND teeth) OR (teeth, AND endodontically-treated) OR (endodontically-treated AND teeth) OR (teeth, AND endodontically AND treated) OR (tooth, AND endodontically-treated) OR (endodontically-treated AND tooth) OR (tooth, AND endodontically AND treated) OR (endodontic AND retreatment) OR (root AND channel AND retreatment) OR (root AND canal AND retreatment) OR (endodontic, AND regenerative) OR (endodontics, AND regenerative) OR (regenerative AND endodontic)) AND TITLE-ABS-KEY ((antimicrobial AND activity) OR (antimicrobial AND effectiveness) OR (antimicrobial AND effect) OR (antibacterial AND affect) OR (antibacterial AND effectiveness) OR (anti-biofilm AND activity) OR (anti-biofilm AND effectiveness) OR (bacteria) OR (eubacteria) (

antimicrobial) OR (disinfection) OR (bacterial AND reduction) OR (microbial AND reduction) OR (microbial AND outcome) OR (molecular AND microbial) OR (antimicrobe) OR (infections) OR (infection AND control AND dental) OR (microbiology) OR (biofilm) OR (enterococcus AND faecalis) OR (streptococcus AND faecalis) OR (streptococcus AND group AND d) OR (fusobacterium AND nucleatum) OR (fusobacterium) OR (propionibacterium) OR (klebsiella) OR (enterococcus AND klebsiella) OR (streptococcus AND spp.) OR (tannerella AND forsythia)))

(http://www.scopus.com)

EMBASE: 35

(flavonoid:ti,ab,kw OR flavonoids:ti,ab,kw OR bioflavonoids:ti,ab,kw OR bioflavonoid:ti,ab,kw OR flavon:ti,ab,kw OR isoflavones:ti,ab,kw OR flavanones:ti,ab,kw OR flavanols:ti,ab,kw OR flavanonols:ti,ab,kw OR '2 phenyl chromene':ti,ab,kw OR '2 phenyl benzopyran':ti,ab,kw OR '2 phenyl benzopyrans':ti,ab,kw OR '2 phenyl chromenes':ti,ab,kw OR proanthocyanidin:ti,ab,kw OR 'polyhydroxyflavan 3 ol':ti,ab,kw OR naringenin:ti,ab,kw OR '4,5,7 trihydroxyflavanone':ti,ab,kw OR '3,3,4,5,5,7 hexahydroxyflavone':ti,ab,kw OR hesperitin:ti,ab,kw OR hesperidin:ti,ab,kw OR taxifolin:ti,ab,kw OR dihydroquercetin:ti,ab,kw OR quercetin:ti,ab,kw OR quercetine:ti,ab,kw OR dikvertin:ti,ab,kw OR '3,3,4,5,7 pentahydroxyflavone':ti,ab,kw OR isoquercitrin:ti,ab,kw OR 'quercetin 3 o glucoside':ti,ab,kw OR isoquercetin:ti,ab,kw OR isoquercitin:ti,ab,kw OR isotrifoliin:ti,ab,kw OR 'epigallocatechin 3 gallate':ti,ab,kw OR 'epigallo-catechin gallate':ti,ab,kw OR 'epigallocatechin 3 o gallate':ti,ab,kw OR egcg:ti,ab,kw OR ampelopsin:ti,ab,kw OR rutin:ti,ab,kw OR rutoside:ti,ab,kw OR morina:ti,ab,kw OR kaempferol:ti,ab,kw OR kaempferols:ti,ab,kw OR myricetin:ti,ab,kw OR epicatechin:ti,ab,kw OR catechin:ti,ab,kw OR isorhamnetin:ti,ab,kw OR fisetin:ti,ab,kw OR '3,3,4,7 tetrahydroxy flavone':ti,ab,kw OR chrysin:ti,ab,kw OR chrysene:ti,ab,kw OR '5,7 dihydroxyflavone':ti,ab,kw OR pinocembrin:ti,ab,kw OR eriodictyol:ti,ab,kw OR abyssinones:ti,ab,kw OR genistein:ti,ab,kw OR genestein:ti,ab,kw OR daidzein:ti,ab,kw OR theaflavin:ti,ab,kw OR macluraxanthone:ti,ab,kw OR scopoletin:ti,ab,kw OR luteolin:ti,ab,kw OR '3,4,5,7 tetrahydroxyflavone':ti,ab,kw OR luteoline:ti,ab,kw OR apigenin:ti,ab,kw) AND ('root canal therapy':ti,ab,kw OR 'canal therapies, root':ti,ab,kw OR 'canal therapy, root':ti,ab,kw OR 'root canal therapies':ti,ab,kw OR 'therapies, root canal':ti,ab,kw OR 'therapy, root canal':ti,ab,kw OR 'endodontic therapy':ti,ab,kw OR 'endodontic treatment':ti,ab,kw OR 'root canal treatment':ti,ab,kw OR rct:ti,ab,kw OR 'endodontic procedure':ti,ab,kw OR 'root canal irrigants':ti,ab,kw OR 'canal irrigant, root':ti,ab,kw OR 'canal irrigants, root':ti,ab,kw OR 'irrigant, root canal':ti,ab,kw OR 'irrigants, root canal':ti,ab,kw OR 'root canal irrigant':ti,ab,kw OR 'root canal medicament':ti,ab,kw OR 'root canal medicaments':ti,ab,kw OR 'canal medicament, root':ti,ab,kw OR 'canal medicaments, root':ti,ab,kw OR 'medicament, root canal':ti,ab,kw OR 'medicaments, root canal':ti,ab,kw OR 'root canal preparation':ti,ab,kw OR 'canal preparation, root':ti,ab,kw OR 'canal preparations, root':ti,ab,kw OR 'preparation, root canal':ti,ab,kw OR 'preparations, root canal':ti,ab,kw OR 'root canal preparations':ti,ab,kw OR 'therapeutic irrigation':ti,ab,kw OR 'irrigation, therapeutic':ti,ab,kw OR 'irrigations, therapeutic':ti,ab,kw OR 'therapeutic irrigations':ti,ab,kw OR lavage:ti,ab,kw OR lavages:ti,ab,kw OR douching:ti,ab,kw OR douchings:ti,ab,kw OR endodontics:ti,ab,kw OR endodontology:ti,ab,kw OR 'dentinal tubule':ti,ab,kw OR 'tubule penetration':ti,ab,kw OR 'tooth, nonvital':ti,ab,kw OR 'nonvital tooth':ti,ab,kw OR 'tooth, devitalized':ti,ab,kw OR 'devitalized tooth':ti,ab,kw OR 'tooth,

pulpless':ti,ab,kw OR 'pulpless tooth':ti,ab,kw OR 'teeth, pulpless':ti,ab,kw OR 'pulpless teeth':ti,ab,kw OR 'teeth, devitalized':ti,ab,kw OR 'devitalized teeth':ti,ab,kw OR 'teeth, nonvital':ti,ab,kw OR 'nonvital teeth':ti,ab,kw OR 'teeth, endodontically-treated':ti,ab,kw OR 'endodontically-treated teeth':ti,ab,kw OR 'teeth, endodontically treated':ti,ab,kw OR 'tooth, endodontically-treated':ti,ab,kw OR 'endodontically-treated tooth':ti,ab,kw OR 'tooth, endodontically treated':ti,ab,kw OR 'endodontic retreatment':ti,ab,kw OR 'root channel retreatment':ti,ab,kw OR 'root canal retreatment':ti,ab,kw OR 'endodontic, regenerative':ti,ab,kw OR 'endodontics, regenerative':ti,ab,kw OR 'regenerative endodontic':ti,ab,kw) AND (('antimicrobial activity':ti,ab,kw OR 'antimicrobial effectiveness':ti,ab,kw OR 'antimicrobial effect':ti,ab,kw OR 'antibacterial affect':ti,ab,kw OR 'antibacterial effectiveness':ti,ab,kw OR 'anti-biofilm activity':ti,ab,kw OR 'anti-biofilm effectiveness':ti,ab,kw OR bacteria:ti,ab,kw OR eubacteria:ti,ab,kw) AND antimicrobial:ti,ab,kw OR disinfection:ti,ab,kw OR 'bacterial reduction':ti,ab,kw OR 'microbial reduction':ti,ab,kw OR 'microbial outcome':ti,ab,kw OR 'molecular microbial':ti,ab,kw OR antimicrobe:ti,ab,kw OR infections:ti,ab,kw OR 'infection control dental':ti,ab,kw OR microbiology:ti,ab,kw OR biofilm:ti,ab,kw OR 'enterococcus faecalis':ti,ab,kw OR 'streptococcus faecalis':ti,ab,kw OR 'streptococcus group d':ti,ab,kw OR 'fusobacterium nucleatum':ti,ab,kw OR fusobacterium:ti,ab,kw OR propionibacterium:ti,ab,kw OR klebsiella:ti,ab,kw OR 'enterococcus klebsiella':ti,ab,kw OR 'streptococcus spp.':ti,ab,kw OR 'tannerella forsythia':ti,ab,kw)

(https://www.embase.com)

WEB OF SCIENCE: 64

(Flavonoid) OR (Flavonoids) OR (Bioflavonoids) OR (Bioflavonoid) OR (Flavon) OR (Isoflavones) OR (Flavanones) OR (Flavanols) OR (Flavanonols) OR (2-Phenyl-Chromene) OR (2 Phenyl Chromene) OR (2-Phenyl-Benzopyran) OR (2 Phenyl Benzopyran) OR (2-Phenyl-Benzopyrans) OR (2 Phenyl Benzopyrans) OR (2-Phenyl-Chromenes) OR (2 Phenyl Chromenes) OR (Proanthocyanidin) OR (Polyhydroxyflavan-3-ol) OR (Naringenin) OR (4',5,7-trihydroxyflavanone) OR (myricetin) OR (3,3',4',5,5',7-hexahydroxyflavone) OR (Hesperitin) OR (Hesperidin) OR (Taxifolin) OR (Dihydroquercetin) OR (Quercetin) OR (Quercetine) OR (divertin) OR (3,3',4',5,7-Pentahydroxyflavone) OR (Isoquercitrin) OR (Quercetin-3-O-glucoside) OR (isoquercetin) OR (isoquercitrin) OR (isotrifoliol) OR (epigallocatechin-3-gallate) OR (epigallo-catechin gallate) OR (epigallocatechin-3-O-gallate) OR (EGCG) OR (Ampelopsin) OR (Rutin) OR (Rutoside) OR (marina) OR (Kaempferol) OR (kaempferol3) OR (Myricetin) OR (Epicatechin) OR (Catechin) OR (Isorhamnetin) OR (Fisetin) OR (3,3',4',7-Tetrahydroxy-flavone) OR (Chrysin) OR (chrysene) OR (5,7-dihydroxyflavone) OR (Pinocembrin) OR (eriodictyol) OR (abyssinone) OR (Theaflavin) OR (Genistein) OR (Genestein) OR (Daidzein) OR (Theaflavin) OR (Macluraxanthone) OR (Scopoletin) OR (Luteolin) OR (3',4',5,7-Tetrahydroxyflavone) OR (luteolin) OR (Apigenin) (Topic) and (Root Canal Therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontic therapy) OR (endodontic treatment) OR (root canal treatment) OR (RCT) OR (endodontic procedure) OR (Root Canal Irrigants) OR (Canal Irrigant, Root) OR (Canal Irrigants, Root) OR (Irrigant, Root Canal) OR (Irrigants, Root Canal) OR (Root Canal Irrigant) OR (Root Canal Medicament) OR (Root Canal Medicaments) OR (Canal Medicament, Root) OR (Canal Medicaments, Root) OR (Medicament, Root Canal) OR (Medicaments, Root Canal) OR (Root Canal Preparation) OR (Canal Preparation, Root) OR (Canal Preparations, Root) OR (Preparation, Root Canal)

OR (Preparations, Root Canal) OR (Root Canal Preparations) OR (Therapeutic Irrigation) OR (Irrigation, Therapeutic) OR (Irrigations, Therapeutic) OR (Therapeutic Irrigations) OR (Lavage) OR (Lavages) OR (Douching) OR (douching) OR (Endodontics) OR (Endodontology) OR (Dentinal Tubule) OR (Tubule Penetration) 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 (Endodontic retreatment) OR (Root channel retreatment) OR (Root canal retreatment) OR (Endodontic, Regenerative) OR (Endodontics, Regenerative) OR (Regenerative Endodontic) (Topic) and (Antimicrobial activity) OR (Antimicrobial effectiveness) OR (Antimicrobial effect) OR (Antibacterial Affect) OR (Antibacterial Effectiveness) OR (Anti-biofilm Activity) OR (Anti-biofilm Effectiveness) OR (Bacteria) OR (Eubacteria) (antimicrobial) OR (disinfection) OR (bacterial reduction) OR (microbial reduction) OR (microbial outcome) OR (molecular microbial) OR (antimicrobes) OR (Infections) OR (Infection Control Dental) OR (Microbiology) OR (Biofilm) OR (Enterococcus faecalis) OR (Streptococcus faecalis) OR (Streptococcus Group D) OR (Fusobacterium nucleatum) OR (Fusobacterium) OR (Propionibacterium) OR (Klebsiella) OR (Enterococcus klebsiella) OR (Streptococcus spp.) OR (Tannerella forsythia)

(https://clarivate.com/webofsciencegroup/solutions/web-of-science-core-collection)

LIBRARY COCHRANE: 19

(Flavonoid) OR (Flavonoids) OR (Bioflavonoids) OR (Bioflavonoid) OR (Flavon) OR (Isoflavones) OR (Flavanones) OR (Flavanols) OR (Flavanonols) OR (Proanthocyanidin) OR (Naringenin) OR (myricetin) OR (Hesperitin) OR (Hesperidin) OR (Taxifolin) OR (Dihydroquercetin) OR (Quercetin) OR (Quercetine) OR (Dikvertin) OR (Isoquercitrin) OR (isoquercetin) OR (isoquercitin) OR (isotrifoliin) OR (EGCG) OR (Ampelopsin) OR (Rutin) OR (Rutoside) OR (Morina) OR (Kaempferol) OR (Kaempferols) OR (Myricetin) OR (Epicatechin) OR (Catechin) OR (Isorhamnetin) OR (Fisetin) OR (Chrysin) OR (chrysene) OR (Pinocembrin) OR (eriodictyol) OR (Abyssinones) OR (Theaflavin) OR (Genistein) OR (Genestein) OR (Daidzein) OR (Theaflavin) OR (Macluraxanthone) OR (Scopoletin) OR (Luteolin) OR (Luteoline) OR (Apigenin) in Title Abstract Keyword AND (Root Canal Therapy) OR (Canal Therapies, Root) OR (Canal Therapy, Root) OR (Root Canal Therapies) OR (Therapies, Root Canal) OR (Therapy, Root Canal) OR (Endodontic therapy) OR (endodontic treatment) OR (root canal treatment) OR (RCT) OR (endodontic procedure) OR (Root Canal Irrigants) OR (Canal Irrigant, Root) OR (Canal Irrigants, Root) OR (Irrigant, Root Canal) OR (Irrigants, Root Canal) OR (Root Canal Irrigant) OR (Root Canal Medicament) OR (Root Canal Medicaments) OR (Canal Medicament, Root) OR (Canal Medicaments, Root) OR (Medicament, Root Canal) OR (Medicaments, Root Canal) OR (Root Canal Preparation) OR (Canal Preparation, Root) OR (Canal Preparations, Root) OR (Preparation, Root Canal) OR (Preparations, Root Canal) OR (Root Canal Preparations) OR (Therapeutic Irrigation) OR (Irrigation, Therapeutic) OR (Irrigations, Therapeutic) OR (Therapeutic Irrigations) OR (Lavage) OR (Lavages) OR (Douching) OR (Douchings) OR (Endodontics) OR (Endodontology) OR (Dentinal Tubule) OR (Tubule Penetration) 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 (Endodontic retreatment) OR (Root channel retreatment) OR (Root canal retreatment) OR (Endodontic, Regenerative) OR (Endodontics, Regenerative) OR (Regenerative Endodontic) in Title Abstract Keyword AND (Antimicrobial activity) OR (Antimicrobial effectiveness) OR (Antimicrobial effect) OR (Antibacterial Affect) OR (Antibacterial Effectiveness) OR (Anti-biofilm Activity) OR (Anti-biofilm Effectiveness) OR (Bacteria) OR (Eubacteria) (antimicrobial) OR (disinfection) OR (bacterial reduction) OR (microbial reduction) OR (microbial outcome) OR (molecular microbial) OR (antimicrobe) OR (Infections) OR (Infection Control Dental) OR (Microbiology) OR (Biofilm) OR (Enterococcus faecalis) OR (Streptococcus faecalis) OR (Streptococcus Group D) OR (Fusobacterium nucleatum) OR (Fusobacterium) OR (Propionibacterium) OR (Klebsiella) OR (Enterococcus klebsiella) OR (Streptococcus spp.) OR (Tannerella forsythia)

(https://www.cochranelibrary.com)