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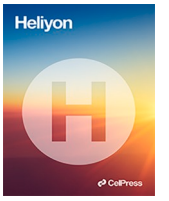

Review article

Unlocking the therapeutic potential of *Pelargonium sidoides* natural extract: A scoping review

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ABSTRACT

Pelargonium sidoides DC. (Geraniaceae) is a widely recognized medicinal plant whose natural extract exhibits therapeutic effects through a multi-target approach. Existing literature encompasses investigations of antimicrobial and cellular effects, including clinical trials. A comprehensive review is required to summary the substantial number of published investigations and to grasp the potentialities of this extract. The aim of this scoping review was to provide an overview of the antimicrobial, antiadhesive, immunomodulatory, and respiratory effects of the *P. sidoides* extract, along with a discussion of its mechanism of action, clinical safety, potential repurposing uses, and areas requiring further investigation. A systematic search of Medline (PubMED) and Scopus databases was conducted using the terms: EPs7630, *Pelargonium*, *Pelargonium sidoides*. The search process was finished on 5th, June 2024. Two researchers screened titles and abstracts according to the eligibility criteria, which included *in vitro*, *in vivo*, randomized, and non-randomized clinical trials. Out of 4367 publications identified, 134 studies were included in this review. A structured form was applied for data extraction. PRISMA-ScR was used to guide reporting of this review. Most of the studies were conducted *in vitro*, followed by human studies and animal models. The findings demonstrated a strong and broad-spectrum antimicrobial and antiadhesive effect against various bacterial, fungi, and virus species. Additionally, a strong immunomodulatory effect was observed, including the induction of pro-inflammatory cytokines during infection, and modulation of other immune response components. The effects on the respiratory system have been extensively examined, showing remarkable clinical efficacy against both bacterial and viral infections with no significant cytotoxicity or adverse effects. Furthermore, recent research showed an anti-COVID effect by direct antiviral and immunomodulation mechanisms. Nonetheless, the establishment of a concentration protocol to further studies is still challenging due to variations in extract origin, composition and extraction methods. In this sense, the use of a commercial extract such as EPs® 7630 is of great value to facilitate the standardization of the tested protocols. The noteworthy anti-infective potential of *P. sidoides* extract lies in its multifaceted mechanism of action, which encompasses direct microbicidal effects and

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modulation of the immune response. These unique properties establish *P. sidoides* extract as a promising alternative in the war against a wide range of infectious diseases.

1. Introduction

Several government reports, such as the Organization for Economic Co-operation and Development (OECD), the US Department of Health and Human Services (DHHS), and the World Health Organization, have been continuously warned about the rising of antimicrobial resistance as a global problem [1–3]. Antimicrobial-resistant infections are estimated to cause the annual deaths of more than 2.4 million people in Europe, North America, and Australia [2]. The unregulated and misuse of antimicrobials is considered one of the primary causes of the selective pressure that leads to microbial resistance [4,5]. Considering the high mortality rate and the decreased discovery of new antimicrobials, attention was brought to the repurposing of already existing drugs [6] and/or the search for other sources of antimicrobials, such as natural extracts [5–7]. In this scenario, investigating pluripotent natural extracts to apply and/or repurpose them into new applications is highlighted as a promising strategy to overcome the limitations of traditional antimicrobials [8].

The extract from the *Pelargonium sidoides* DC. (Geraniaceae) plant stands out due to its broad application in traditional African medicine and well documentation, being one of the firsts recorded in the 17th century [9]. Belonging to the *Pelargonium* genus, this perennial plant is primarily found in Southern Africa [10] and is characterized by its dark-colored flowers [9], yellowish pollen, and red tuberous rhizomes [11]. In African traditional medicine, *P. sidoides* was used mostly for the treatment of gastrointestinal and respiratory disorders, liver dysfunctions, menstrual complaints, and fever [9,10]. The popularization of this extract in Europe took place in the early 20th century and is related to Charles Henry Stevens, who received the natural extract to treat his tuberculosis [12,13]. It was only in the late 20th century that pharmacological research of a standardized extract of *P. sidoides*, EPs® 7630 (Umckaloabo®), was initiated at Munich University [9].

The rational basis investigation for the therapeutic use of EPs® 7630 comprised pharmacological characterization [14,15], *in vitro* [16], animal models [17], and clinical trials [18]. EPs® 7630 is an aqueous ethanolic extract from the roots of *P. sidoides* with a drug ratio 1:8–10 using 11 % ethanol as an extraction solvent [15,19]. EPs® 7630 has shown activity against a panel of microorganisms, including gram-negative and positive bacteria [16,20,21], and fungi [22], along with an antiviral effect [23,24]. The antimicrobial effects were also related to the antiadhesive and anti-invasion properties of the extract [25–27]. In addition, it was observed that EPs® 7630 exerts immunomodulatory properties towards cytokines and cell activity [28,29], as well as an antiproliferative effect on cancer cells of leukemic origin [30]. The anti-infective results from *in vitro* and *in vivo* were endorsed in clinical trials, where the EPs® 7630 promoted good clinical efficacy against different respiratory disorders and was well tolerated [31,32]. Herbal medicines developed from the EPs® 7630 extract have received approval from a regulatory agency and are commercially available [9,11].

It is believed that the variety of effects presented by the natural extract from *P. sidoides* is linked to its chemical composition. *Pelargonium sidoides* composition comprises primary metabolites, such as, carbohydrates, amino acids, peptides, and minerals, which represent about 30% of the composition of EPs® 7630 [15]. The secondary metabolites are mainly proanthocyanidins, which corresponds to approximately 40% of the extract's content, and it is believed to be the main responsible for the extract's effects [15]. Therefore, considering the vast amount of research around the natural extract from *P. sidoides*, this scoping review aims to summarize the available knowledge and promote a better understanding of the antimicrobial, antiadhesive, immunomodulatory, and respiratory effects of the extract. Yet, mechanism of action through a molecular biology approach, clinical safety, potential repurposing uses, and research gaps that need further survey will be discussed.

2. Materials and methods

This research was part of a doctoral thesis and the protocol for the review was prespecified in advance, but not published a priori. It is available in Portuguese, on request. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) to write this report [33].

2.1. Search strategy, eligibility criteria, and selection

Electronic databases included MEDLINE (PubMed) and Scopus. The search strategy was specific to each database and was constructed using the following keywords or terms related to *P. sidoides*: "EPs 7630"; "*Pelargonium*" and "*Pelargonium sidoides*". Also, the plant name has been checked with "World Flora Online" (on www.worldfloraonline.org). No restrictions on comparators, outcomes, or population were used to achieve a more sensitive search. In MEDLINE, the full electronic search strategy used was (("pelargonium"[MeSH Terms] OR "pelargonium"[All Fields]) OR ("EPs 7630"[Supplementary Concept] OR "EPs 7630"[All Fields] OR "eps 7630"[All Fields])) OR (("pelargonium"[MeSH Terms] OR "pelargonium"[All Fields]) AND "sidoides"[All Fields]). The search process was finished on 5th, June 2024. Although there was also no restriction on the publication date, only articles in English or Portuguese were selected. Reference lists of original studies were manually searched to identify articles that could have been missed during the initial online search. Grey literature (such as PhD theses) was not searched since we did not perform quality assessment or risk of bias analyses of the included studies. The search was performed by one of the researchers (SSM).

The following were the eligibility criteria for inclusion in this review: (a) studies investigating the effect of *P. sidoides* for medicinal

purposes; and (b) studies investigating the cytotoxicity or clinical safety of *P. sidoides*. *In vitro* designs, *in vivo* (animal models), and randomized and non-randomized trials were accepted. The exclusion criteria encompassed non-research articles, systematic reviews, non-systematic reviews, and *in silico* studies.

Initially, duplicate studies were removed using a reference manager (Mendeley Desktop version 1.19.4 ©2008–2019 Mendeley Ltd). Then, titles and abstracts were screened using the Rayyan software [34] by two reviewers (SSM, PFA) for the application of eligibility criteria. The software made it possible to classify each reference as included, excluded, or uncertain. All papers included by at least one reviewer or whose inclusion was uncertain were preliminarily accepted and left for full-text review. Three reviewers (SSM, BDR, SMV) read the full papers, and a form was filled in to guide the decision-making process. If a full-text version of an article was not available, an email was sent to its author or editor requesting full-text access. Disagreements were resolved with mutual consent and consulting a fourth reviewer when necessary.

Data extraction was carried out by three (SSM, BDR, SMV) previously trained investigators and with the aid of a standardized data pre-specified form. Discrepancies were resolved through discussion. The following items were extracted from included papers: first author, date of publication, country in which the study was conducted, study design, and type of effect investigated. For the antimicrobial effects, items extracted from the papers were microbial species tested, the resistance of the strain, microbial methodology used on the evaluations, adhesion to the biotic or abiotic surface, and type of antivirus effect. For the immunomodulatory effect, items investigated comprise effects on immune cells and levels of cytokines and/or other substances. For the clinical studies, the age of participants, treatment protocol, dosage of extract, and adverse effects assessment information were extracted. Also, data on efficacy, statistical analyses, mechanisms of action, type of extract utilized, chemical characterization of the extract, and effective concentrations were extracted.

Given the broad eligibility criteria, it was expected that different types of studies would be included. Thus, a critical appraisal of the

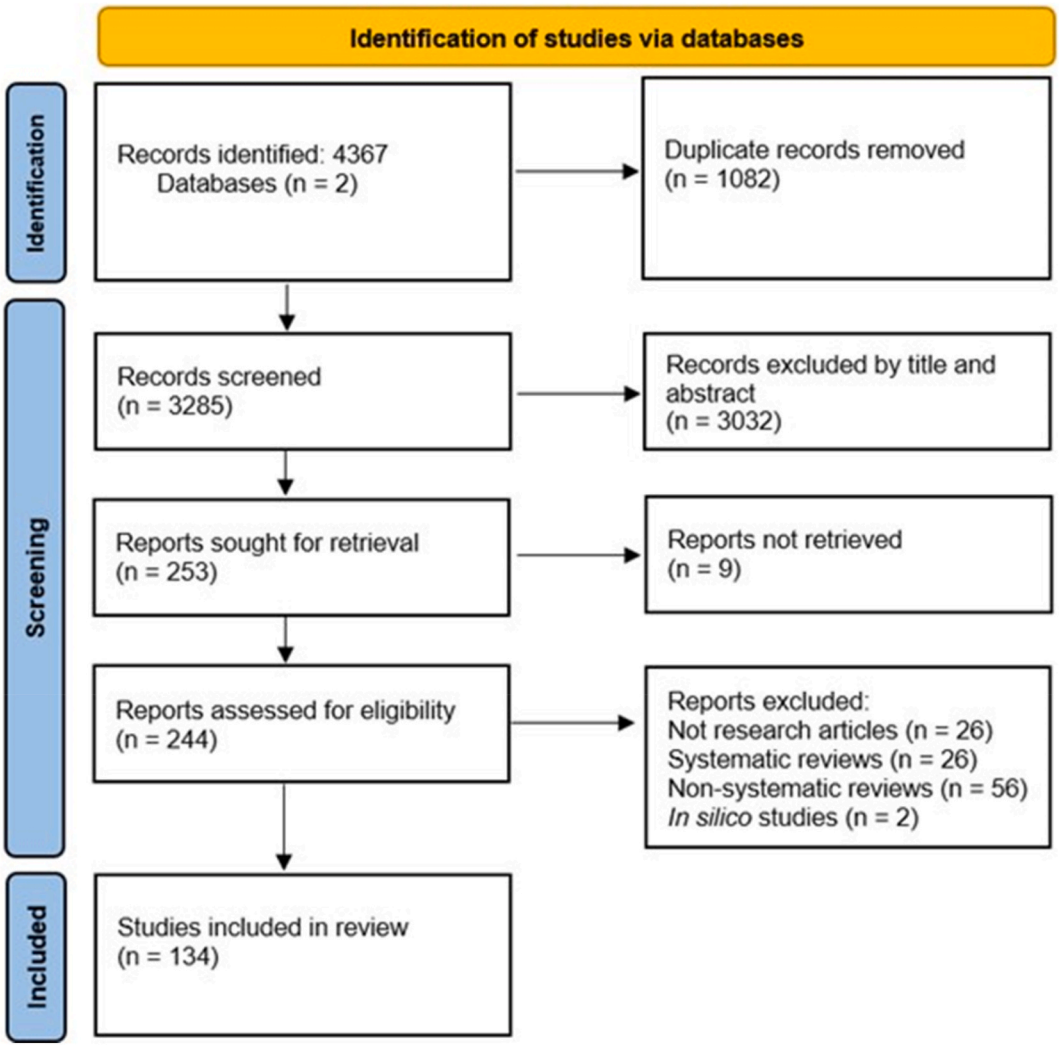

Fig. 1. PRISMA flowchart of the study selection procedure.

individual sources of evidence was not performed since it would have been difficult to compare evidence quality among the studies. Finally, the information obtained from the selected studies was tabulated.

3. Results and discussion

3.1. Identification of studies

Searches retrieved 4367 publications. After removing duplicates, the title and abstract of 3285 papers were screened for relevance for this review, resulting in the exclusion of 3032 publications. Then, 253 publications were evaluated for full-text eligibility. Of those, 110 papers were excluded (26 were not research articles [editorials, interviews, comments], 26 were systematic reviews, 56 were non-systematic reviews and 2 were *in silico* studies). The detailed flowchart of the review is presented in Fig. 1.

3.2. Characteristics of the included studies

A total of 134 studies were included in this review. Most of them were preclinical studies (Table 1), of which 53.96% were *in vitro* studies and 7.91% were animal models. Regarding the human studies, they accounted for 38.13% of the total, as presented in Table 2. The trend illustrated in Fig. 2 demonstrates a significant increase in clinical evidence in recent years, particularly for clinical trials. Notably, more than 40 studies are clinical trials, of which over 17 are double-blind. Although blinding is not the only potential source of bias, it was effectively controlled for in these studies.

3.3. Phytochemistry of P. sidoides extract

The wide antimicrobial and biological applications of *P. sidoides* extract in traditional and modern medicine [35] may represent an advancement in the standard of healthcare. It is believed that the combination of its components is responsible for the observed effects of the extract, potentially affecting a variety of targets in microbial and human cell pathways.

The chemical characterization of the extract was conducted in several studies by high performance liquid chromatography (HPLC) [16], ultra performance liquid chromatography (UPLC) [36], spectrometry [37]; oxygen radical absorbance capacity [36], nuclear magnetic resonance spectroscopy (NMR-spectra) [38], mass spectroscopy [38] and other techniques. The complexity of metabolites in *P. sidoides* is reflected in the presence of numerous coumarins, coumarin glycosides, coumarin sulfates, flavonoids, proanthocyanidins, phenolic acids, and phenylpropanoid derivatives [39].

One of the most important compounds found in EPs® 7630 is the highly oxygenated coumarins [37,40], such as 5,6,7-trimethoxycoumarin; 6,8-dihydroxy-5,7-methoxycoumarin, 7-Hydroxy-6-methoxycoumarin (scopoletin), 7-hydroxy-5,6-di-methoxycoumarin (umckalin) and others [16,39]. Coumarins belong to the class of benzopyrones and frequently occur as sulfate derivatives [19,38], which are lactones of o-hydroxy-cinnamic acid, derived from the amino acid phenylalanine. The latter converts to cinnamic acid, hydroxylates to form *p*-Coumaric acid (or hydroxycinnamic acid) [35,36] and can form derivatives or chalcones, which are precursors to all flavonoids.

Proanthocyanidins also significantly constitute the extract and are described as prodelphinidins, substances composed of gallocatechin and epigallocatechin subunits linked by type A or B bonds [19]. Proanthocyanidins in the *P. sidoides* extracts are characterized as complex molecules with a high degree of polymerization, comprising the class of oligomeric flavonoids. Flavonoids [35,36] represent a large group of secondary metabolites in the polyphenol class. Polyphenols [27,36], or phenolic compounds, are plant-derived substances that have one or more hydroxyls groups attached to an aromatic ring. Yet, the biological effects of the plant extract are believed to stem from the secondary metabolites, and it is crucial to note that the primary metabolites act as solubility modifiers, consequently altering the bioavailability of the drug in the body and, consequently, its effect [15]. It is important to note that the concentration, and even the presence of different components in the extract, can vary from aerial to root parts used in the extract preparation, leading to differences in the phytocomposition and, therefore, variations in the biological effects.

3.4. Therapeutic potential of P. sidoides

The body of literature concerning *P. sidoides* is extensive, indicating a broad spectrum of therapeutic effects. These documented effects encompass antimicrobial properties (including antibacterial, and antifungal), and antiviral activities, as well as effects on human cells (immunomodulatory effects, for example). Subsequent sections and Fig. 3 provide a detailed discourse on each of these effects, synthesizing evidence and possible mechanisms of action from various levels of evidence, including *in vitro* studies, *in vivo* experiments, and clinical trials.

3.5. Antibacterial effect

In 21 *in vitro* studies, *P. sidoides* were evaluated regarding its antibacterial effect. Several gram-positive bacterial species have been evaluated such as *Staphylococcus aureus* [41–43], *Streptococcus pneumoniae* [20,44,45], *Enterococcus faecalis* [36,43], *Streptococcus pyogenes* [10], *Mycobacterium tuberculosis* [14,46], *Staphylococcus epidermidis* [47]. Gram-negative bacteria *Escherichia coli* [48,49], *Klebsiella pneumoniae* [16,50], *Pseudomonas aeruginosa* [51] and *Porphyromonas gingivalis* [52] were also extensively evaluated. Fig. 4A shows the most used bacterial species in the antibacterial tests.

Table 1
List of the pre-clinical included studies and main characteristics summarized according to type of study, country, research effect, extract, and year.

Study design	Country	Type of effect investigated	Type of extract	Year and Reference Number
In vitro study	Germany	Antibacterial effect	Self-produced *P. sidoides* extract	1997 [16]
In vitro study	Germany	Other	Self-produced *P. sidoides* extract	1998 [40]
In vitro study	Germany	Other	Other	2000 [150]
In vitro study	Germany	Immunomodulatory effect	Self-produced *P. sidoides* extract	2001 [84]
In vitro study	Germany	Antibacterial effect	EPs® 7630	2003 [14]
		Antiviral effect	Self-produced *P. sidoides* extract	
		Immunomodulatory effect		
In vitro study	United Kingdom	Antibacterial effect	Self-produced *P. sidoides* extract	2004 [53]
In vitro study	Germany	Immunomodulatory effect	EPs® 7630	2005 [80]
In vitro study	Germany	Other	Self-produced *P. sidoides* extract	2005 [37]
In vitro study	Germany	Other	EPs® 7630	2005 [129]
In vitro study	Germany	Immunomodulatory effect	EPs® 7630	2006 [28]
In vitro study	South Africa	Antibacterial effect	Self-produced *P. sidoides* extract	2006 [60]
		Antifungal effect		
In vitro study	South Africa	Antibacterial effect	Self-produced *P. sidoides* extract	2006 [47]
In vitro study	South Africa	Antibacterial effect	Self-produced *P. sidoides* extract	2006 [55]
		Antifungal effect		
In vitro study	Germany	Immunomodulatory effect	Self-produced *P. sidoides* extract	2007 [22]
In vitro study	Germany	Antiadhesive effect	EPs® 7630	2007 [25]
In vitro study	Germany	Antibacterial effect	EPs® 7630	2007 [54]
		Antiadhesive effect		
In vitro study	Germany	Antiadhesive effect	EPs® 7630	2007 [76]
		Biocompatibility/Cytotoxicity		
In vitro study	Germany	Antiadhesive effect	EPs® 7630	2007 [26]
In vitro study, Animal model	Germany	Other	EPs® 7630	2007 [19]
In vitro study	Egypt	Antibacterial effect	Self-produced *P. sidoides* extract	2007 [44]
		Immunomodulatory effect		
Animal model	Germany	Other	EPs® 7630	2007 [124]
Animal model	Germany	Immunomodulatory effect	EPs® 7630	2007 [17]
In vitro study	Germany	Immunomodulatory effect	EPs® 7630	2008 [78]
In vitro study	Germany	Other	Self-produced *P. sidoides* extract	2008 [15]
In vitro study	Germany	Antiviral effect	Self-produced *P. sidoides* extract,	2008 [23]
		Biocompatibility/Cytotoxicity		
In vitro study	UK	Antibacterial effect	Self-produced *P. sidoides* extract	2009 [56]
		Immunomodulatory effect		
In vitro study	Turkey	Antibacterial effect	Other	2009 [20]
In vitro study	Brazil	Other	Other	2010 [132]
In vitro study	Germany	Antiadhesive effect	EPs® 7630	2010 [75]
In vitro study	South Africa	Other	Other	2010 [133]
In vitro study	Turkey	Antibacterial effect	Self-produced *P. sidoides* extract	2010 [51]
		Antifungal effect		
In vitro study	Jordan	Other	Self-produced *P. sidoides* extract	2010 [134]
In vitro study	Germany	Antiviral effect	EPs® 7630	2011 [63]
		Biocompatibility/Cytotoxicity		
In vitro study	Germany	Immunomodulatory effect	EPs® 7630	2011 [77]
		Biocompatibility/Cytotoxicity		
In vitro study	Germany	Antiadhesive effect	EPs® 7630	2011 [27]
In vitro study	Germany	Immunomodulatory effect	EPs® 7630	2011 [79]
In vitro study	South Africa	Other	Self-produced *P. sidoides* extract	2011 [135]
In vitro study	South Africa	Other	Other	2012 [136]
In vitro study, Animal model	Luxembourg	Antiviral effect	EPs® 7630	2012 [24]
		Biocompatibility/Cytotoxicity		
In vitro study	South Africa	Antibacterial effect	Self-produced *P. sidoides* extract	2012 [46]
		Biocompatibility/Cytotoxicity		
In vitro study	South Africa	Antibacterial effect	Self-produced *P. sidoides* extract	2013 [36]
		Antifungal effect		
In vitro study	South Africa	Other	Self-produced *P. sidoides* extract	2014 [137]
In vitro study, Animal model	Germany	Immunomodulatory effect	EPs® 7630	2014 [91]
In vitro study	Germany	Antiviral effect	Self-produced *P. sidoides* extract	2014 [64]
In vitro study	South Africa	Antibacterial effect	Self-produced *P. sidoides* extract	2014 [50]
		Antifungal effect		
		Biocompatibility/Cytotoxicity		
Animal model	China	Immunomodulatory effect	EPs® 7630	2015 [87]
		Respiratory tract effect		
In vitro study	Germany	Immunomodulatory effect	EPs® 7630	2015 [29]
In vitro study	South Africa	Other	Other	2015 [138]
In vitro study	South Africa	Antitumor effect	Self-produced *P. sidoides* extract	2015 [95]
In vitro study	South Africa	Antitumor effect	Other	2016 [30]

(*continued on next page*)

Table 1 (*continued*)

Study design	Country	Type of effect investigated	Type of extract	Year and Reference Number
In vitro study	South Africa	Antibacterial effect	Self-produced *P. sidoides* extract	2017 [48]
In vitro study	South Africa	Antitumor effect	Other	2017 [93]
In vitro study	Turkey	Antitumor effect Biocompatibility/Cytotoxicity	Other	2017 [94]
In vitro study	Germany	Antiviral effect	EPs® 7630	2017 [70]
Animal model	Turkey	Immunomodulatory effect	Other	2018 [90]
In vitro study	Turkey	Immunomodulatory effect	EPs® 7630	2018 [81]
In vitro study	Lithuania	Antibacterial effect,	Self-produced *P. sidoides* extract	2018 [52]
In vitro study, Animal model	South Corea	Immunomodulatory effect	Other	2018 [82]
In vitro study	Egypt	Antibacterial effect Antifungal effect	Self-produced *P. sidoides* extract	2018 [49]
In vitro study	Switzerland	Antiviral effect Immunomodulatory effect	EPs® 7630	2019 [68]
In vitro study	South Africa	Antifungal effect Biocompatibility/Cytotoxicity	Self-produced *P. sidoides* extract	2019 [62]
In vitro study	Lithuania	Antibacterial effect Immunomodulatory effect	Other	2019 [41]
In vitro study	United Kingdom	Other	Other	2019 [139]
In vitro study	South Africa	Antibacterial effect	Self-produced *P. sidoides* extract	2019 [45]
Animal model	Republic of Korea	Immunomodulatory effect Respiratory tract effect	Other	2020 [89]
In vitro study	South Africa	Antibacterial effect	Self-produced *P. sidoides* extract	2020 [140]
In vitro study	Italy	Antibacterial effect Immunomodulatory effect	Other	2020 [43]
In vitro study, Animal model	Germany	Immunomodulatory effect	EPs® 7630	2020 [83]
In vitro study	Germany	Antiviral effect Biocompatibility/Cytotoxicity	Other	2020 [65]
In vitro study	Germany	Antiviral effect	EPs® 7630	2020 [141]
In vitro study	Italy	Antibacterial effect	Other	2021 [42]
In vitro study	Germany	Antiviral effect Immunomodulatory effect	EPs® 7630	2021 [71]
In vitro study	Turkey	Other	Other	2021 [85]
In vitro study	Switzerland	Antiviral effect Immunomodulatory effect	EPs® 7630	2021 [69]
In vitro study	Saudi Arabia	Antiviral effect	EPs® 7630	2022 [72]
In vitro study	United States of America	Antiviral effect	Other	2023 [73]
In vitro study *Animal model*	Germany	Antiviral effect Immunomodulatory effect	EPs® 7630	2023 [66]
In vitro study	Switzerland	Antiviral effect Immunomodulatory effect	EPs® 7630	2023 [67]

Antibacterial effect of *P. sidoides* and its components was evaluated through the inhibition zone diameter, colony forming units per milliliter (CFU/mL) count, optical density, fluorescence, colorimetric assays and minimum inhibitory concentration (MIC) assays, showing efficacy against gram-positive and gram-negative bacteria at varying concentrations between 1.6 μg/mL and 10 mg/mL, depending of the species, type of extract and treatment duration) [10,14,20,21,36,41,42,45–56]. Other studies using MIC assay showed the effectiveness of the extract when using butanol as a solvent, in which the MIC was 0.156 μg/mL [44] and in the crude extract of the root of *P. sidoides* at MIC concentrations between 5 and 7.5 mg/mL [16]. Fig. 5 describes the relation between the necessary concentration to verify antimicrobial effects depending on the type of extract.

The displayed results were derived from a descriptive analysis of data from data extraction form. The chart indicates the type of antimicrobial effect assessed in accordance with the study design (*in vitro* or animal study). Furthermore, the color of each bubble denotes the type of extract used in the study (commercial extract EPs® 7630, self-preparated extract, or other types of extracts). The bubble's size reflects the average concentration required to achieve the antimicrobial effect and the numbers inside the bubbles correspond to the papers listed on the side.

Also, some studies have utilized isolated components of *P. sidoides*, such as: proanthocyanidins, gallic acid, methyl-gallate, quercetin-3-O-b-d-glucoside, myricetin, umckalin, scopoletin, catechin, epigallocatechin, 6,8-Dihydroxy −5,7-dimethoxy2H-benzopyran-2-one, 6,8-Dihydroxy-7-methoxy2H-benzopyran-2-one [41,44,56]. These components have been proven effective in reducing bacterial load. According to studies, the inhibition of bacterial growth in different species can be primarily attributed to gallic acid and other phenolic compounds [9] from the extract, mostly at concentrations between 300 μg/ml and 2 mg/ml. According to a prior study using a bactericidal kinetic assay, the effect of some coumarins can be considered bacteriostatic against *E. coli* [16], likely through the interaction of the sulfated derivatives with biological processes necessary to replication. Also, bactericidal processes appear to be more active when constituents are extracted with polar solvents [56].

Indirect antibacterial effects were observed in a clinical trial involving adults (ages between 18 and 63) comparing EPs® 7630 with amoxicillin against acute bacterial rhinosinusitis. EPs® 7630 oral tablets, at a dosage of 3 × 20 mg/day, significantly decreased the frequency of patients with positive cultures of *S. pneumoniae* and *Haemophilus influenzae*. Results demonstrated superior clinical and

Table 2
List of the human included studies and main characteristics summarized according to type of study, country, research effect, extract, and year.

Study design	Country	Type of effect investigated	Type of extract	Year and Reference Number
Clinical trial	Germany	Respiratory tract effect Clinical Safety/Adverse Effects	EPs® 7630	2003 [106]
Clinical trial	Ukraine	Respiratory tract effect	EPs® 7630	2003 [99]
Clinical trial	Russia	Respiratory tract effect Clinical Safety/Adverse Effects	EPs® 7630	2005 [107]
Clinical trial	Germany	Respiratory tract effect Clinical Safety/Adverse Effects	EPs® 7630	2007 [100]
Clinical trial	Ukraine	Respiratory tract effect Clinical Safety/Adverse Effects	EPs® 7630	2007 [108]
Clinical trial	Germany	Respiratory tract effect Clinical Safety/Adverse Effects	EPs® 7630	2007 [31]
Clinical trial	Russia	Respiratory tract effect Clinical Safety/Adverse Effects	EPs® 7630	2007 [109]
Clinical trial	Germany	Respiratory tract effect Clinical Safety/Adverse Effects	EPs® 7630	2007 [110]
Clinical trial	Russia	Respiratory tract effect Clinical Safety/Adverse Effects	EPs® 7630	2008 [111]
Clinical trial	Ukraine	Respiratory tract effect Clinical Safety/Adverse Effects	EPs® 7630	2009 [18]
Clinical trial	Ukraine	Respiratory tract effect	EPs® 7630	2009 [101]
Clinical trial	Ukraine	Respiratory tract effect Clinical Safety/Adverse Effects	EPs® 7630	2010 [96]
Case report	Brazil	Clinical Safety/Adverse Effects	Other	2010 [126]
Cross section study	Brazil	Other	EPs® 7630	2010 [142]
Clinical trial	Germany	Respiratory tract effect	EPs® 7630	2010 [112]
Clinical trial	Ukraine	Respiratory tract effect	EPs® 7630	2010 [113]
Clinical trial	Ukraine	Respiratory tract effect Clinical Safety/Adverse Effects	EPs® 7630 Self-produced *P. sidoides* extract	2010 [114]
Clinical trial	Venezuela	Respiratory tract effect Clinical Safety/Adverse Effects	EPs® 7630	2011 [143]
Clinical trial	Brazil	Immunomodulatory effect	EPs® 7630	2011 [88]
Case report	Germany	Clinical Safety/Adverse Effects	Other	2012 [127]
Clinical trial	Russia	Respiratory tract effect Clinical Safety/Adverse Effects	EPs® 7630	2012 [97]
Clinical trial	Turkey	Respiratory tract effect	EPs® 7630	2012 [102]
Case report	United States of America	Other	Other	2013 [144]
Clinical trial	Turkey	Respiratory tract effect Clinical Safety/Adverse Effects	EPs® 7630	2013 [103]
Clinical trial	Ukraine	Respiratory tract effect	EPs® 7630 Self-produced *P. sidoides* extract	2013 [32]
Clinical trial	Ukraine	Respiratory tract effect	EPs® 7630	2015 [115]
Clinical trial	Ukraine	Respiratory tract effect	EPs® 7630	2016 [104]
Case series	Germany	Clinical Safety/Adverse Effects	Other	2016 [128]
Clinical trial	Ukraine	Respiratory tract effect	EPs® 7630	2018 [116]
Clinical trial	Ukraine	Respiratory tract effect Biocompatibility/Cytotoxicity	EPs® 7630	2019 [92]
Clinical trial	United Kingdom	Respiratory tract effect	EPs® 7630	2019 [117]
Clinical trial	Germany	Respiratory tract effect	EPs® 7630	2020 [121]
Clinical trial	Republic of Korea	Respiratory tract effect	EPs® 7630	2020 [118]
Clinical trial	Serbia	Respiratory tract effect	EPs® 7630	2020 [58]
Clinical trial	Serbia	Antibacterial effect Clinical Safety/Adverse Effects	EPs® 7630	2020 [57]
Clinical trial	Serbia	Immunomodulatory effect Respiratory tract effect	EPs® 7630	2020 [59]
Cohort study	Germany	Other	Other	2020 [121]
Clinical trial	Turkey	Respiratory tract effect	Other	2021 [145]
Clinical trial	United Kingdom	Respiratory tract effect	EPs® 7630	2021 [119]
Clinical trial	Austria	Antiviral effect Clinical Safety/Adverse Effects Respiratory tract effect	EPs® 7630	2021 [74]
Clinical trial	Germany	Clinical Safety/Adverse Effects	EPs® 7630	2021 [146]
Clinical trial	Republic of Korea	Other	Other	2022 [147]
Clinical trial	Italy	Respiratory tract effect	Other	2022 [123]
Clinical trial	Republic of Korea	Respiratory tract effect Clinical Safety/Adverse Effects	Self-produced *P. sidoides* extract	2022 [120]
Clinical trial	Germany	Clinical Safety/Adverse Effects	EPs® 7630	2022 [148]
Clinical trial	Germany	Immunomodulatory effect	EPs® 7630	2022 [149]
Clinical trial	Poland	Clinical Safety/Adverse Effects	EPs® 7630	2023 [98]
Clinical trial	Turkey	Clinical Safety/Adverse Effects	EPs® 7630	2024 [125]

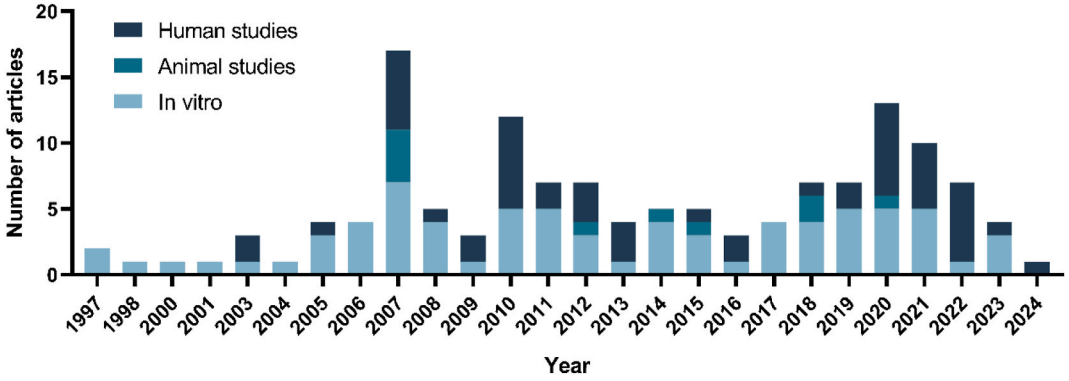

Fig. 2. A graphical representation of the timeline of publications concerning the antimicrobial effects of *P. sidoides* extract and the design of the studies included in this review. Different colored bars represent the number of manuscripts published in each year and their respective study designs.

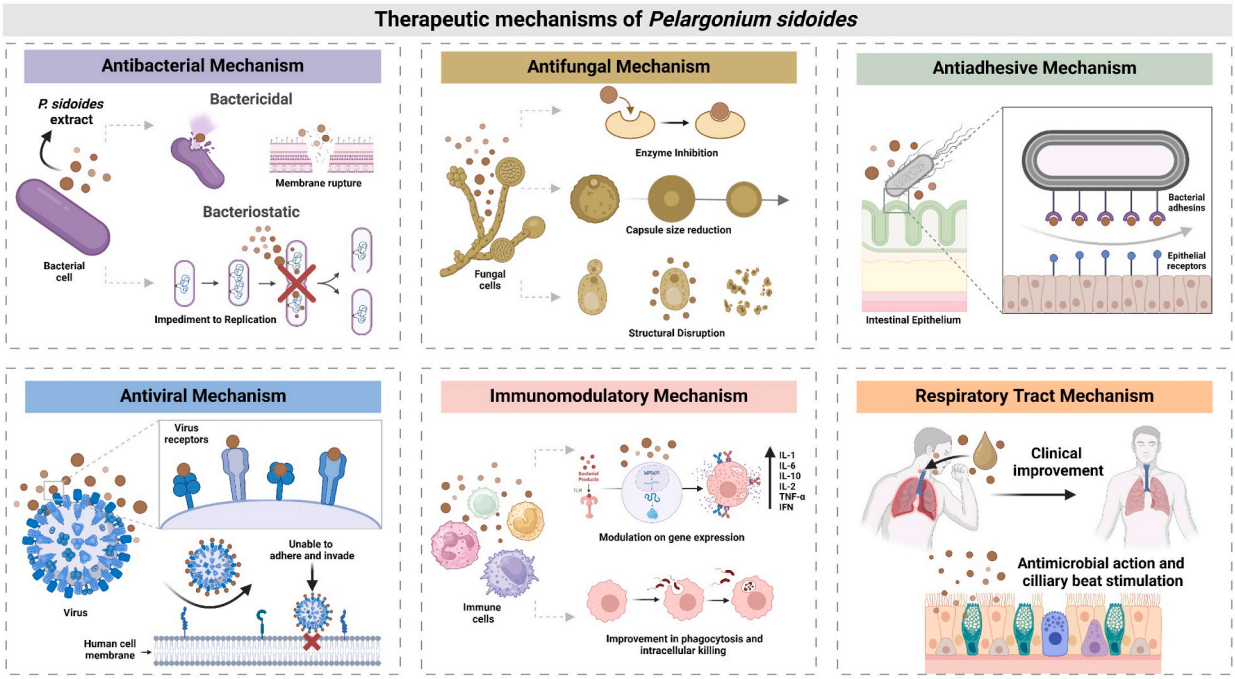

Fig. 3. Mechanism of action of *Pelargonium sidoides* extract. PS extract exhibits a range of effects, starting with its antibacterial action, which can be bacteriostatic against some species and bactericidal against others, through interaction with specific compounds. It also shows antifungal properties, such as inhibition of enzymes like laccase, inducing fungal cell death by structural disruption, and reducing capsule size. In terms of antiviral activity, the extract causes viral death and inhibits surface glycoproteins like hemagglutinin and neuraminidase, thereby preventing viral attachment and replication. Additionally, its antiadhesive effect prevents bacterial adhesion to human cells by interacting with bacterial adhesins and human cell membrane glycoproteins. Moreover, *P. sidoides* extract is known for its immunomodulatory effects, primarily through gene expression modulation, which leads to increased cytokine expression including IL-1, IL-6, IL-10, IL-2, TNF-α, and IFN. These changes enhance phagocytosis and intracellular killing. Furthermore, in the respiratory tract, the extract enhances ciliary beat frequency, facilitating mucus clearance. When combined with its antimicrobial effects, this contributes to clinical improvement. In conclusion, the multifaceted mechanism of *P. sidoides* extract underscores its therapeutic potential across bacterial, fungal, viral, immune modulation, and respiratory health domains. Created with BioRender (License number: BF26ZM77AI).

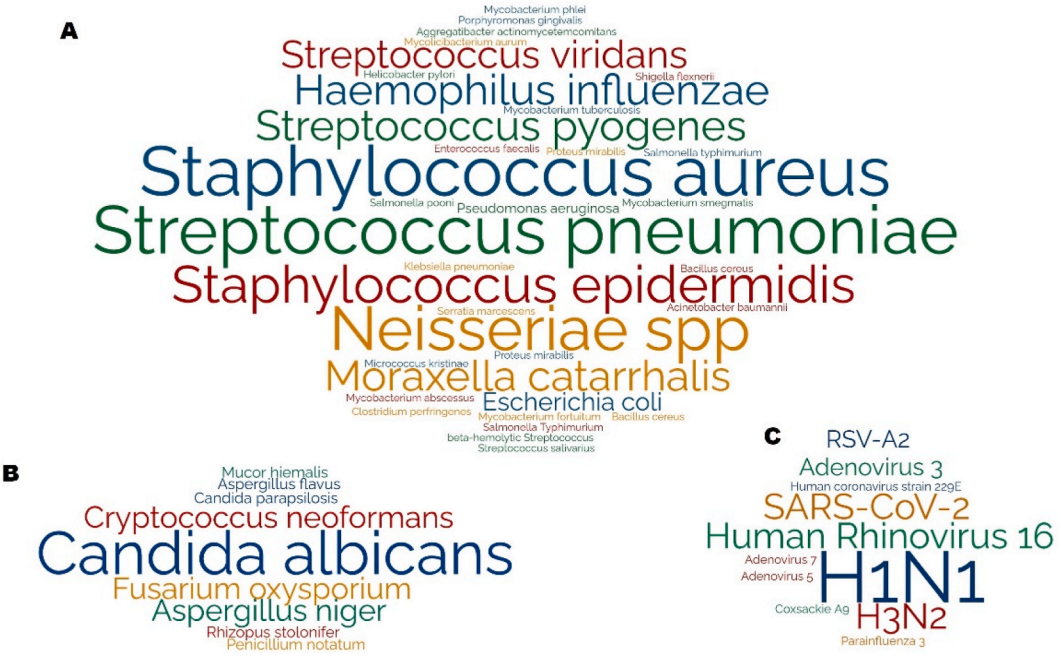

Fig. 4. Word cloud representing the microbial species in the included studies and the frequency of use indicated by the font size. **A)** Bacteria species. **B)** Fungi species. **C)** Viruses.

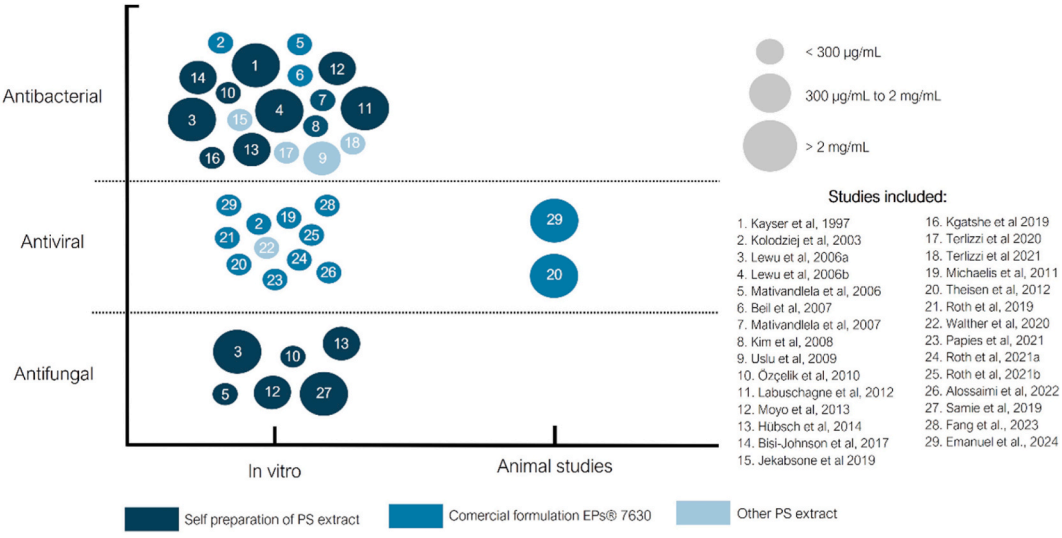

Fig. 5. Bubble chart illustrating studies evaluating the antimicrobial effects of *P. sidoides* extract.

antimicrobial efficacy of EPs® 7630 compared with amoxicillin. Therefore, EPs® 7630 has proven to be a potent agent and a potential alternative to antibiotics for treating local symptoms of uncomplicated acute bacterial rhinosinusitis [57–59].

3.6. Antifungal effect

Regarding the antifungal effect, seven *in vitro* studies were identified. In these studies, the zone of inhibition diameter and MIC assays were used against various antifungal species (Fig. 4B). The results of the studies suggest that *P. sidoides* demonstrates efficacy against several fungal strains [36,49–51,60,61]. Effective concentrations of ethanolic extract of *P. sidoides* that significantly inhibited the growth of *Aspergillus niger* and *Fusarium oxysporum* were around 5×10^3 mg/L [55]. Additionally, the growth of *Rhizopus stolonifer* was suppressed by the ethanolic extract of *P. sidoides* at 1×10^3 mg/L [60]. Further effective concentrations and types of used extracts

can be seen in Fig. 5. No animal or clinical study analyzing the antifungal effect of *P. sidoides* was retrieved in our search.

Although the antifungal effect is not as well understood as the antibacterial effect, some studies have already demonstrated that *P. sidoides* extract is able to promote fungal death, inhibition of laccase (an important fungal enzyme), and reduction of capsule size [62]. The reduction in capsule size is related to a virulence-attenuating effect, probably caused by capsule dehydration or destruction mediated by the high content of phenolic compound in the *P. sidoides* extract [62]. For the enzyme activity disturbance, the mechanism behind it is not clear, but some possible explanations can be considered. For example, *P. sidoides* extract can interrupt the melanisation cascade or inhibition of substrate binding, leading to enzyme inhibition. Another possibility is that the *P. sidoides* extract can promote an antioxidant effect, preventing oxidation caused by the enzymes [62].

3.7. Antiviral effect

Among the 16 studies that evaluated the antiviral effect of *P. sidoides* extract, the viruses most extensively studied can be seen in Fig. 4C [23,63–67]. The antiviral protective action against encephalomyocarditis viruses and the impact of EPs® 7630 on the expression of virus anchoring proteins were assessed [68]. Additionally, rhinovirus infection [14,69] and the action of the extract on neuraminidase and/or hemagglutinin were also investigated [70]. The cytopathogenic effect reduction assay (CPE) and colorimetric tests were used for these studies. The most effective concentrations of the extract promoting direct action against viruses ranged between 1 and 100 μg/mL.

Two animal studies were conducted. In the first one, the extract was used on an oseltamivir resistant seasonal H1N1 strain. In the *in vitro* part of the study, the half-maximum antiviral concentration of EPs® 7630 was determined to be 6.6 μg/ml, corresponding to a selectivity index of 84.4. Concentrations above 50 μg/ml completely inhibited virus growth [24]. In the animals, inhalation treatment with 5 mg/mL of EPs® 7630 promoted no signs of the disease after 14 days of monitoring. Fig. 5 illustrates the necessary concentrations to achieve antiviral effects in *in vitro* and animal studies and the type of extract used. No clinical studies evaluating the direct antiviral effect of the extract have been found.

The direct virucidal effect is present only for some viruses at concentrations below 300 μg/ml. However, other indirect effects of EPs® 7630 extract may exist, such as the inhibition of surface glycoproteins hemagglutination and neuraminidase, which are crucial for virus anchorage and replication, thereby inhibiting the human cell infection process further [68]. The reduced infection after EPs® 7630 treatment may be related to the downregulation of cell surface calreticulin (C1qR), a membrane cell receptor related to the virus phagocytosis and intracellular killing, and by a reduction of the viral docking protein ICOS on host cells through a compartmental location change within the host cells [68].

Moreover, even if the virus can infect the cell, the virus released from the host cells after one life cycle is prevented from entering new host cells to initiate its next life cycle, suggesting that EPs® 7630 may have a therapeutic effect and limit the spread of infection [24]. This result may differ from other studies due to the varying sensitivity of viruses to the components of the extract and the chemical structure of the main antiviral compound, the prodelphinidins. For example, gallocatechin carrying a trihydroxylation at the B-ring along with a pyrogallol in position 3 appears to have a higher antiviral effect [24]. Also, the limited antiviral effect verified in mice can be explained by the cleavage of polyphenols, especially oligo/polymers, after the oral uptake. However, monomers and dimers still possess an effect, and along with a small amount of low molecular weight cathecins absorbed by oral mucosa, a lower but still present antiviral effect can be verified [24].

3.8. Anti-COVID effects

Considering the antiviral effect of *P. sidoides* extract and the high mortality rates of COVID-related infections, four *in vitro*, one *in vivo* and one clinical study investigated the effect of extracts against SARS-CoV-2 and its associated acute respiratory tract infections. A study showed that at 10 and 100 μg/mL, EPs® 7630 significantly inhibited propagation and infection, respectively, of SARS-CoV-2. These antiviral effects were also maintained against SARS-CoV-2 variants, such as alpha and beta, by a reduction of virus RNA levels. In addition to the direct antiviral effects, EPs® 7630 inhibits virus entry in two different cell lines. Further investigations revealed that concomitant treatment of infected cells with EPs® 7630 led to a reduction of important inflammatory cytokines related to the cytokine storm associated with COVID-19 infection, especially after 48h [71]. These findings were corroborated by another *in vitro* study that indicated that EPs® 7630 demonstrates limited antiviral activity against SARS-CoV-2 B.1, but exhibits a substantial immunomodulatory effect, contributing to the prevention of excessive pro-inflammatory cytokine release [67]. In this same study, the *in vivo* evaluations showed that EPs® 7630 decreased viral load at the early stages of infection and demonstrated notable immunomodulatory effects, which positively impacted the progression of the disease in hamsters [67].

Another *in vitro* study corroborated the abovementioned results, showing that IC_{50} (concentration required to cause a 50 % fall in the viral-induced cytopathic effect) was around 14 μg/mL. Yet, specific compounds from the *P. sidoides* extract promoted variable antiviral effects, being scopoletin the one with the lowest IC_{50} and highest selectivity index [72]. Another study showed that not only *P. sidoides* extract (Bi121 commercial extract) showed activity against various strains of SARS-CoV-2, but also against the Omicron strain, a very important and dominant one. This activity was related to a more than 5 log reduction in viral copies. The antiviral activity was also related to interference with the early stages of entry and replication of the viruses, since this effect appeared in a variety of strains, the results suggest a broad inhibitory effect [73].

In vitro data demonstrated that the release of several cytokines and growth factors associated with the critical progression of COVID-19 was attenuated by EPs® 7630 in SARS-CoV-2-infected human lung cells and it is believed that this process is intermediate by low molecular weight compounds, such as low-polymerized prodelphinidins, purine derivates and benzopyranones. Treatment with

EPs® 7630 elevated levels of SARS-CoV-2 RNA in cells, highlighting its broad antiviral activity and the potential to inhibit newly emerging variants of SARS-CoV-2. A reduced number of spreading variants of concern (VOC) were detected at low concentrations, possibly due to the reported reduction in replication for SARS-CoV-2 alpha and beta [71]. Yet, the possible effect of flavonoids on the inhibition of human serine proteases and glycosaminoglycans synthesis can explain the inhibition of virus entry in lung cells [71]. Despite presenting several properties and effects of *P. sidoides*, more studies are needed to further substantiate its efficacy in the fight against COVID-19.

Nevertheless, a clinical study with adults indicated that treatment with EPs® 7630 tablet three times a day reduced the symptoms throughout the analysis time but did not promote any superior effect in patients with respiratory infections related to the coronaviruses compared to non-corona viruses' respiratory infections [74].

3.9. Anti-adhesive effect

The anti-adhesive effect of *P. sidoides* extract was investigated *in vitro* on various biotic surfaces, including human laryngeal epithelial cells (Hep-2 cells) [27,75], gastric cancer cell line A-streptococci [54], deparaffinized sections of human stomach [76], deparaffinized sections of animal organs [26] and cultured epithelial cells from the lung [25].

When utilizing EPs® 7630 extract at different concentrations, clear dose-dependent anti-adhesive activity was demonstrated [26,54,76]. Moreover, a model of infection using bacteria and human cells, involving the pre-treatment of bacteria with EPs® 7630 showed that the extract exerts an anti-adhesive effect by interacting with the bacterial cell. The effect was concentration-dependent, with 30 μg/mL promoting more than 40% reduction in the adhesion of bacteria to epithelial cells. Yet, when analyzing the adhesion kinetics, at the same concentration of 30 μg/mL, the kinetic curve decreased more rapidly after 180 min of co-incubation. However, when the same evaluation was conducted with buccal epithelial cells, the opposite behavior was found, suggesting a difference depending on the substrate. Moreover, a trend toward a reduction in streptococcal invasion was observed [25].

The proposed mechanism behind this effect is the interaction of the extracted compound with adhesins present in the outer cell wall of bacteria, causing a blockage/inactivation of their adhesion to mucosal glycoproteins and epithelial mucins [76]. Another hypothesis proposed is that the proanthocyanidins in the extract can form hydrogen bonds with bacterial adhesins and block adhesion through a process known as tannin-type astringent [26]. An *in vitro* study supported this hypothesis by showing that EPs® 7630 can antagonize specific, but not non-specific, adhesion of Group A Streptococci to human epithelial cells. Pretreatment of epithelial cells had no effect, while pretreatment of bacteria resulted in reduced adhesion. This suggests a specific antagonism developed during the pretreatment of bacteria that was not reversed by the subsequent washing step [22].

3.10. Immunomodulatory effect

Of the 31 studies that investigated the immunomodulatory effects of *P. sidoides*, 20 were *in vitro* and used colorimetric tests, radiometric assays, and assessment of intracellular death by macrophages to determine possible immunomodulation.

On a molecular level, studies identified induction of expression of the following cytokines: interleukin (IL) 08 [77], IL-1, IL-6 [41], IL-10 [29], IL-2 [78], IL-18, tumor necrosis factor (TNF)-α, Interferon (IFN) [67,79], and other products from immune response, such as immunoreactive cells COX-2 and induced nitric oxide synthase (iNOS) [80–82]. The inductive action appears to be time-dependent for IL-17, IFN-γ, and mainly for IL-22 when detection occurs already after 24 h of stimulation with EPs® 7630 [83]. Also, the augmented synthesis of IFN-β by *P. sidoides* was only found in the presence of a viral chemical analog acting as an inducing substance [14].

On a cellular basis, *P. sidoides* extract improves phagocytosis, oxidative burst, and intracellular killing ability of human peripheral blood phagocytes [22]. Also, a significant reduction of rhinovirus (RV)-16 infection and viral docking proteins in the human bronchial epithelium was found after treatment with EPs® 7630 [68]. Studies using cells infected with *Leishmania donovani* have shown that the immunomodulatory effect of *P. sidoides* extract depends on the solvent extract, concentration, and components. Compounds such as gallic acid promoted a nonspecific immune response in terms of parasite killing intracellularly and release of nitric oxides and TNF [84]. However, the direct inhibitory effects of the promastigote were verified in a concentration-dependent manner [85]. On the contrary, a second study with a similar evaluation did not find any effect of *P. sidoides* compounds on infected macrophage cells [44]. Yet, reductions in IL-1β and levels of reactive oxygen species (ROS) and nitrite produced by macrophages were also verified [43].

Another study conducted on human airway epithelial cells demonstrated that EPs® 7630 modulates intracellular signaling, extracellular matrix composition, and wound repair in human bronchial epithelial cells. Data obtained from cell lines and primary bronchial epithelial cells suggest that EPs® 7630 also enhances tissue recovery following rhinovirus infection, which in turn contributes to the improved clinical recovery observed in patients with respiratory tract infections. Overall, EPs® 7630 regulates epithelial cell proliferation through cAMP (cyclic AMP) and p38 MAPK pathways, modifies the extracellular matrix composition of epithelial cells, affects epithelial cell tight junction protein expression, increases epithelial cell differentiation and host defense mechanisms, and enhances wound repair [66].

The immunomodulatory effects are related to an alteration of gene expression, modulation of cytokine release, and alteration of immune cell activity. EPs® 7630 strongly induced gene expression of mRNAs of iNOS and several cytokines; more interestingly, this effect occurs only in the presence of an infectious agent, preventing tissue damage when it is not necessary [28]. Furthermore, EPs® 7630 has been proven to enhance the release of antimicrobial peptides from polymorphonuclear neutrophils and to increase the phagocytic activity of macrophages against bacteria [86]. Gene expression experiments showed that after treatment with EPs® 7630, macrophages are activated at the transcriptional level [86].

Because the host response to infection involves the synthesis and release of pro-inflammatory cytokines (IL-1, TNF-alpha, IL-6), which induce symptoms of unhealthy behavior, pretreatment with EPs® 7630 before infection dose-dependently counteracted lipopolysaccharide-induced morbidity. However, although EPs® 7630 is very active in preventing unhealthy behaviors, the molecular basis of this effect is unclear [17]. In another animal study with cough models, the extract significantly and dose-dependently reduced cough frequency and exerted secretolytic activity. This protective effect seems to be mediated by an upregulation of superoxide dismutase and a subsequent protective effect against oxidative stress as indicated by a reduced serum level of malondialdehyde [87]. Also, reduced IL-6 and IL-15 production can attenuate the allergic/inflammatory response by interfering with the regulation and differentiation of Th2 effector cells [88].

One animal study evaluated the antiasthmatic effects of *P. sidoides* extract when combined with *Coptis Rhizoma* extract. C57BL/6J mice with ovalbumin- (OVA-)-induced asthma, presented significant increases in total bronchoalveolar lavage fluid (BALF) cells, levels of IL-4 and 5, and lung weight. Experimental intervention was conducted by the administration of 300 and 1000 mg/kg of *P. sidoides* + *C. rhizoma* extract once a day for 16 days. The treatment proved to be significantly and dose-dependently effective in reducing the total count of inflammatory cells in BALF. Yet, levels of cytokines IL-4 and IL-5 were reduced with an effect equivalent to 3 mg/kg of dexamethasone. Based on this animal model results, *P. sidoides* + C. rhizoma was considered an interesting treatment option for asthma, presenting similar effects to dexamethasone, but with no side effects detected [89].

Another animal study utilizing CEVASTIM, a tablet forms herbal drug combining 500 mg of *Echinacea purpurae* and 135 mg of *P. sidoides*, was conducted in calves for 5 or 10 days. Determination of interferon-ɣ and immunoglobulin G levels and IL-4, IL-1β, and TNF-α gene expression were conducted 9 and 30 days after the beginning of the regimen, showing that the use of ½ tablet for 5 days can promote a modulation and upregulation of cytokine gene expression. However, this effect can be related to concentration and regimen [90]. Another study suggests the antioxidant effect of EPs® 7630 (40–100 μg/mL) in the animal model *C. elegans* since the extract was able to reduce intracellular expression of genes related to oxidative stress and therefore augmented by 22–24% the survival rate of worms [91]. A study with mice, rats, and guinea pigs (concentrations varying from 10 to 120 mg/kg/day) with induced acute bronchitis showed a significant and dose-dependent reduction of cough frequency, a prolongation of cough latency time, and a bronchosecretolytic activity. In animals with acute bronchitis, although the number of leukocytes was not altered, histopathological examination revealed a reduced degree of lesions in animals treated with EPs® 7630 at doses of 30 and 60 mg/kg [87].

A clinical trial was conducted to evaluate the immunomodulatory potential of *P. sidoides*. For this, participants ingested 30 drops of a solution of approximately 800 mg/mL of *P. sidoides* 3 times a day for 28 days. *Pelargonium sidoides* altered the synthesis of IL-6 and IL-15 in serum and nasal epithelium, essential cytokines to trigger allergic processes [88].

Although many compounds have been proposed to be responsible for the immunomodulatory effect, there is still no consensus as to whether the highly oxygenated coumarins or other polyphenolic compounds are responsible [25]. All secondary endpoints demonstrated a more favorable disease course and faster disease recovery under treatment with EPs® 7630 compared to placebo. The time to onset of treatment effect was significantly shorter in the EPs® 7630 group than in the placebo group [92]. In general, all studies reported a positive effect of *P. sidoides* treatment, regardless of age, sex, and type of respiratory infection, showing that research on *P. sidoides* related to the respiratory tract is well consolidated in the literature.

3.11. Antitumor effect

Four studies included in this review evaluated the antitumor effect of *P. sidoides*. One of the studies showed that *P. sidoides* was most effective in decreasing cancer cell growth in the Jurkat human leukemic T-cell lymphoblast cell line with a concentration required to inhibit cell growth by 50% (GI_{50}) equal to 6.2 μg/ml. The SF-268 (human glioblastoma) and NCI-H460 (human lung large cell carcinoma) cell lines were more resistant presenting GI_{50} values of 60 and 80 mg/mL, respectively. Using a higher concentration of 10 mg/mL, the *P. sidoides* extract was able to not only arrest Jurkart cells in the early stages of cell division, but also promote cell apoptosis and death [30]. In another study, the *P. sidoides* compounds besides inhibiting the growth of the tumor cells through regulation of the PI3K-AKT and Ras–MAPK pathways may also inhibit the process of angiogenesis through the attenuation of the PI3K-AKT and Ras–MAPK pathways in the cells of the vascular system [93]. Along with a direct effect of the extract on cancerous cells, *P. sidoides* extract also presented a statistically significant protective effect against 2-aminofluorene, a well-known carcinogenic substance [94].

Not only does the complete extract present antiproliferative effects on leukemia-like cancer cells, but also its polyphenolic compounds as well [30]. For example, specific fractions composed of gallic acid, proanthocyanidins, dihydroxycoumarin sulfates, and others were promising due to the inhibition of four cancer cell lines [95].

3.12. Effects on the respiratory tract

Regarding the upper and lower respiratory tract disorders, 41 papers were found, comprising clinical trials, case reports, and case series. The main respiratory disorders investigated were acute rhinosinusitis, common cold, acute bronchitis, acute non-streptococcal tonsillopharyngitis, tonsillitis, and chronic obstructive pulmonary disease.

Clinical trials were conducted in children, adolescents [31,96–105] and adults [18,32,57,86,106–120], ranging in age from 0 to 93 years. All studies reported a positive effect of treatment with *P. sidoides* regardless of age, gender, and type of respiratory infection. Also, a retrospective cohort study demonstrated that the use of phytopharmaceuticals, such as *P. sidoides* extract promoted a reduced use of antibiotics in the treatment of acute respiratory infections [121]. It is noteworthy that a recent meta-analysis of two clinical trials involving children and adolescents with acute bronchitis highlighted that treating with EPs® 7630 for 7 days significantly shortens the average duration of illness and increases the number of patients able to resume normal activities within a week [122]. Although the

literature review conducted prior to the meta-analysis was not a systematic one, and the authors declared a potential conflict of interest, the paper deserves attention as it suggests significant evidence of efficacy in the treatment of bronchitis in children.

Treatment regimens varied depending on the pharmaceutical formulation and age of the patient. For adults ingesting tablets, doses comprised from 1 to 3 pills per day of 10 mg, 20 mg, or 30 mg, thus totaling 3 pills a daily dose of 30, 60 and 90 mg, which were effective in the treatment of respiratory diseases [58,59,112–114]. In other studies, in adults, *P. sidoides* (EPs® 7630) was evaluated with a drop formulation where patients ingested 3 × 30 drops or 3 × 60 drops daily [18,32,106–111,115,116]. In children and adolescents (age 1–18 years), *P. sidoides* (EPs® 7630) effective doses were applied differing the age ranges in the following manner: 3 x 10 drops (patients aged 1–6 years) [96], 3 x 20 drops (patients >6–12 years) [93,94,98] or 3 x 30 drops (patients >12–18 years) [31,97,103]. In general, treatment duration was 7–10 days in most of the studied disorders, apart from studies treating COPD, in which the duration of the protocol was 24 weeks. Yet, 1 study used a gummy formulation of *P. sidoides* associated with *Malva sylvestris* three times a day for 10 consecutive days and verified a significant improvement in daytime and nighttime cough scores [123].

3.13. Cytotoxicity/clinical safety

The cytocompatibility and clinical safety of *P. sidoides* extract were evaluated in 38 studies. Cytotoxicity was evaluated by eleven *in vitro* studies using cell viability tests, such as the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) test [16,23,24,63,77] XTT (2,3-bis-(2-methoxy-4-nitro-5-sulphenyl)-(2H)-tetrazolium-5-carboxanilide) [46], BSLA [50], hemolysis test [62], crystal violet [65] and gene mutagenicity test (Ames MPFTM) [94].

One study tested the EPs® 7630 cytotoxicity by adding quadruplicate serial dilutions of the extract to lung carcinoma epithelial cells and measuring cell viability after 24 h of incubation by XTT assay. The half-maximal cytotoxic concentration of EPs® 7630 (CC_{50}) was 557 μg/ml [24]. Two other studies verified that EPs® 7630 did not decrease the viability of all cell types investigated at concentrations up to 100 μg/ml [63] and only limited the growth of HNSCC cell lines to 35% compared to control at a concentration of 25 μg/mL [77]. A hemolysis test was also conducted to evaluate the potential cytotoxicity of *P. sidoides* extract to blood cells. The study showed that no red blood cells were lysed, demonstrating that α-hemolytic activity (green discoloration) and β-hemolytic activity (clear zones of lysis) were absent from the *P. sidoides* extract [62].

Biocompatibility using animal models was investigated in two studies. Inhalation of 5 mg/mL of EPs® 7630 for 10 days did not produce any differences in body and organs weight, and temperature, indicating a good safety profile of the extract [24]. In ovariectomized rats, administration of 300 mg/kg of *P. sidoides* extract for 16 days did not alter the body weight [89]. Since EPs® 7630 is a coumarin-rich extract, its interaction with coumarin-type anticoagulants was also investigated in rats. The administration of 10–500 mg/kg of EPs® 7630 for two weeks did not cause any changes in the thromboplastin time or thrombin time. Yet, the concomitant use of the extract and an anticoagulant did not alter the action and pharmacokinetics of warfarin [124].

Clinical safety investigation was conducted in 25 clinical trials. In clinical trials carried out in children and adolescents, the safety of the experimental drug was documented concerning the frequency, nature, and severity of adverse events (AEs) [91,97] The frequency of adverse events in the experimental group was between 1.1 and 19.3%, in samples varying from 400 to 742 participants, and was similar to the frequency found in the placebo group. The most frequent AEs were gastrointestinal disorders, other events include rash, psychomotor instability, dyspnea, and diarrhea. in which a causal relationship with the test drug could not be excluded. 5 patients had to stop the treatment and only 3 patients presented an intensification of pre-existing respiratory symptoms [100]. None of the AEs were classified as severe [96]. As for tolerability, it was evaluated by the patient or parent and the physician on a four-point scale, ranging from “very good” to “unsatisfactory”. Tolerability was rated as good or very good in 94.9% of cases [100]. In another study involving 104 children taking EPs® 7630, no side effects were observed except for an unpleasant taste [125]. Overall, the results suggest that the study medication is a safe and well-tolerated treatment in children and infants [31].

In clinical trials conducted in adults, experimental drug safety was also evaluated in relation regarding the frequency, severity, and severity of adverse events (AE's) [18,106,111,120]. AEs occurred in five patients (9.4%) in the EPs® 7630 group and 7 patients (13.5%) in the placebo group. All adverse events were of mild intensity, except for 3 events in the placebo group, which were classified as moderate. None of the AEs were classified as severe in intensity [92]. Tolerability was assessed by a four-point verbal scale and results of laboratory tests, including leukocytes, erythrocyte sedimentation rate, -glutamyl transpeptidase, aspartate aminotransferase, alanine aminotransferase, rapid test and partial thromboplastin time (PTT). Very good or good tolerability was reported by 98.4% of patients in the EPs® 7630 group and by 96.7% of patients in the placebo group. All AEs were assessed as non-serious [107,108]. Other studies showed similar frequency rates of AE (around 10–20%) and in the majority of them, they were related to the gastrointestinal tract [109]. Serious adverse events did not occur; therefore, *P. sidoides* was assessed as safe and well-tolerated for acute bronchitis or acute exacerbation of chronic bronchitis [110]. In general, all patients had vital signs and laboratory tests considered good and/or normal during all studies, suggesting that *P. sidoides* has a very tolerable safety in the treatment of adult patients [57,114].

The clinical safety of *P. sidoides* was also evaluated through clinical case reports (1 study), clinical case series (1 study), and a case-control study. In the case report, notifications of adverse effects from ANVISA from 1999 to 2009 were verified. The only adverse effect related to *P. sidoides* was a notification of constipation and oliguria. The patient was concomitantly using a syrup of Hedera Helix [126]. In the case series, the hepatotoxicity of the extract was evaluated by data from 15 cases and the causality was assessed by an algorithm that considered temporal association, criteria of hepatotoxicity, and definition of liver injury (step 2), application of a liver-specific causality assessment method (step 3), and exclusion of alternative diagnoses (step 4). This study concluded that there is a lack of evidence for a hepatotoxic risk associated with *P. sidoides* treatment when *P. sidoides* was used as recommended and that *P. sidoides* did not show a highly probable causality in any of the cases [127]. In the case-control study the suspected association between herbal drug use and liver damage was investigated. A single case of a patient that used *P. sidoides* was included in this study,

the possible etiology of the symptoms was attributed to *P. sidoides*, however, possible causality does not prove clinical significance. Therefore, studies in this area are needed [128].

3.14. Other effects

An *in vitro* study showed stimulation of ciliary beat frequency of cultured cells isolated from respiratory mucosa [129]. Animal models showed that *P. sidoides* extract fractions have a moderate effect on the central nervous system of treated animals [19]. These results can be related to the findings of another study showing that animals that received an application of LPS and were pretreated with 400 mg/kg of EPs® 7630 showed similar behavior to control animals, instead of sickness behavior [17]. As EPs® 7630 contains a variety of polar compounds of structural diversity, perhaps this is why the extract is efficient for variations in species of bacteria, and viruses and has beneficial effects on LPS-induced sickness behavior, being under the control of the central nervous system (CNS), in which all its fractions were tested and moderately influenced animal behavior [19].

The possible interference of *P. sidoides* extract with blood coagulation parameters was investigated. The study showed that EPs® 7630 caused no effect in the studied parameters, even after 2 weeks of administration in different concentrations. Also, the extract did not interfere with the pharmacokinetics of warfarin, an anticoagulant, even with 2 weeks of concomitant administration [124]. This can be justified by the fact that EPS 7630 does not influence the metabolization of markers by human recombinant CYP450 isoenzymes and does not influence their expression in human hepatocytes [124]. In a clinical study conducted with pediatric patients suffering from the viral disease named 'hand, foot, and mouth disease' (HFMD), who exhibited symptom onset within the last 48 h (including fever, enanthemas, or rash), the administration of EPs® 7630 significantly reduced complaint scores [125]. According to the authors, the relief in symptoms promoted by EPs® 7630 could be attributed to its antiviral action in the early stages of virus replication and cell attachment [125].

3.15. Limitations and future perspectives

One main limitation of studies, not only using *P. sidoides* extract but also employing phytomedicines in general, is the variability in concentrations required to achieve proper effects. For *P. sidoides* extract, effective concentrations to achieve antimicrobial and immunomodulatory results ranged from less than 300 μg/mL to more than 2 mg/mL. This difference can be attributed, mainly, to the use of different extracts from the same plant. The method of extraction, the post-processing, and the weather conditions in which the plant was cultivated can influence the composition profile, leading to differences in the extract effect. In this sense, the use of a commercial extract such as EPs® 7630 is of great value because of the possibility of not total, but more control over the composition. Clinical studies, for example, are stricter in this sense because they employ specific formulations with predetermined concentrations. This fact can explain a greater homogeneity of the effects observed among the clinical studies that use the same concentration of the extract compared to *in vitro* studies.

A Cochrane systematic review and meta-analysis published in 2013 [130] concluded that *P. sidoides* showed potential benefits for acute bronchitis in both adults and children, as well as for sinusitis and the common cold in adults. In summary, the review indicated that *P. sidoides* may offer symptomatic relief for certain acute respiratory infections, but there was a need for more high-quality research to establish its efficacy and safety in different respiratory conditions. Since then, however, additional clinical studies have been published evaluating the efficacy of *P. sidoides*, suggesting that the extract's effectiveness may be broader than previously thought. Considering that the systematic review was published more than 10 years ago, and more than 20 new clinical studies were published since then, our paper can underscore the importance of updating the existing systematic review. This update is necessary not only to obtain more current and robust conclusions but also to critically evaluate the quality of these recently published clinical studies and identify areas for improvement.

The repurposing of already approved or experimental drugs brought a lot of attention to the field of phytotherapeutics [5,6]. Considering the extensive research on *P. sidoides* and its diverse therapeutical effects, this extract could find utility in various biomedical applications. For example, a recent pharmacovigilance survey highlighted the off-label use of EPs® 7630 for COVID-19. Most reports (over 75%) detailed its application for treating COVID-19, while the remainder focused on post-COVID-19 syndrome or prophylaxis. Since most reports did not indicate any complications, this suggests that EPs® 7630 could potentially be used for other applications [131]. For instance, in dentistry, numerous infectious diseases such as candidiasis, periodontitis and peri-implantitis can inflict substantial damage to patients' lives. Many of these diseases, however, have an immunological aspect associated with tissue damage. Therefore, the use of an extract, such as *P. sidoides*, with both antimicrobial and immunomodulatory effects would be highly relevant for controlling such diseases. Nevertheless, even for broader applications, the *P. sidoides* natural extract, with its diverse mechanisms of action, would likely pose a lower risk of antimicrobial resistance when compared to a single mechanism of action antibiotic.

However, it is important to mention that a significant number of studies included in this review did not present a robust statistical analysis, which made difficult the process of analysis and confidence in the scientific evidence. For example, many studies only presented descriptive analysis without any type of inferential statistics. In other cases, the data presented was not clear regarding the data acquisition method. This may lead to setbacks in further analysis of the various effects, which may delay the advancement of knowledge to more robust models, such as *in vivo* and clinical trials. Therefore, it is necessary that studies using natural compounds, and here more specifically *P. sidoides*, standardize the composition of its extract and pay attention to the analysis and report of their data to assure advances in phytotherapy research.

4. Conclusions

Within the limitations of this review, it is possible to understand that *P. sidoides* extract is a promising strategy for the treatment of a diverse range of infectious diseases, particularly for upper and lower respiratory tract disorders, for which a substantial volume of clinical evidence already exists. Furthermore, considering the information gathered here regarding potential cytotoxicity and clinical safety, along with the fact that the EPS extract has received approval and registration from health regulatory authorities in various countries, there appears to be sufficient data supporting its safety and tolerability, especially in children and infants. Its long medical history and recent evidence of therapeutic success suggest that more research can be conducted to deepen the knowledge specifically of antimicrobial and immune mechanisms of action and to explore new applications of the extract. Rising problems such as antimicrobial resistance and the emergence of new infections (e.g. coronavirus) require more sophisticated and innovative approaches, and in this sense, natural extracts can be an excellent strategy.

CRediT authorship contribution statement

Bárbara Donadon Reina: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Samuel Santana Malheiros:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis. **Sâmmea Martins Vieira:** Writing – review & editing, Validation, Methodology, Formal analysis. **Paula Ferreira de Andrade:** Writing – original draft, Validation, Methodology. **Lívia Nordi Dovigo:** Writing – review & editing, Visualization, Validation, Supervision, Data curation, Conceptualization.

Ethical statement

This is a literature review; therefore, the ethical statement is not applicable.

Data availability statement

This is a literature review, in which no original data were created. For this reason, no data were deposited in a publicly repository. The information extracted from the primary studies has been summarized, and the tables containing all the collected data can be made available by the corresponding author upon request with reasonable justification.

Declaration of competing interest

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

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