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Plant secondary metabolites against *Candida auris*: mechanisms and evidence

Metabolitos secundarios de plantas contra *Candida auris*: mecanismos y evidencia

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ABSTRACT

Candida auris is an emerging multidrug-resistant fungal pathogen that poses a significant public health threat. This fungus has spread to more than 30 countries. This review was conducted aiming to search for *in vitro* studies on the antifungal actions of plant metabolites against *C. auris*. The review was constructed following the guidelines of the PRISMA statement. The research protocol was registered on the PROSPERO platform. A literature search was performed in the PubMed, Scopus, and Virtual Health Library databases, with no restrictions on year or language. Eligibility criteria were based on the PICO concept. Data were meta-analyzed using R software. The risk of bias assessment was performed using an adaptation of the CONSORT tool. A total of 11 of the 768 articles were included in the systematic review and meta-analysis, and 30 secondary metabolites of plant origin were analyzed. Of the 30 metabolites found, 26 presented results similar to the controls, and 4 showed superior results: palm leaf extract, *Syzygium samarangense* bark, *Cinnamomum zeylanicum* oil (bark) and *Cinnamomum zeylanicum* (leaf). Most plant secondary metabolites showed excellent antifungal potential against *C. auris*. As a limitation of the study, metabolites of very heterogeneous origin, extraction method, and distinct controls were grouped, which may have interfered with the interpretation of the results, increasing the risk of bias and imprecision. Therefore, further research is needed to confirm their clinical efficacy and safety and elucidate the mechanisms of action.

Keywords: antifungal activity; bioactive compounds; essential oils; fungal pathogens; natural extracts; phytochemicals

RESUMEN

Candida auris es un patógeno fúngico emergente, multirresistente a múltiples fármacos, que representa una amenaza significativa para la salud pública. Este hongo se ha propagado a más de 30 países. El objetivo de esta revisión fue buscar estudios *in vitro* sobre la acción antifúngica de metabolitos vegetales contra *C. auris*. La revisión se elaboró siguiendo las directrices de la declaración PRISMA. El protocolo de investigación fue registrado en la plataforma PROSPERO. Se realizó una búsqueda bibliográfica en las bases de datos PubMed, Scopus y Biblioteca Virtual en Salud, sin restricciones de año ni idioma. Los criterios de elegibilidad se basaron en el concepto PICO. Los datos fueron sometidos a metanálisis utilizando el software R. La evaluación del riesgo de sesgo se llevó a cabo mediante una adaptación de la herramienta CONSORT. Un total de 11 de los 768 artículos se incluyeron en la revisión sistemática y el metanálisis, y se analizaron 30

metabolitos secundarios de origen vegetal. De los 30 metabolitos identificados, 26 mostraron resultados similares a los controles y 4 mostraron resultados superiores: extracto de hoja de palma, corteza de Syzygium samarangense, aceite de Cinnamomum zeylanicum (corteza) y Cinnamomum zeylanicum (hoja). La mayoría de los metabolitos secundarios de plantas mostraron un excelente potencial antifúngico contra *C. auris*. Como limitación del estudio, se agruparon metabolitos de origen muy heterogéneo, diferentes métodos de extracción y controles distintos, lo que puede haber interferido en la interpretación de los resultados, aumentando el riesgo de sesgo e imprecisión. Por lo tanto, se necesitan más investigaciones para confirmar su eficacia y seguridad clínica, así como para elucidar sus mecanismos de acción.

Palabras clave: actividad antifúngica; compuestos bioactivos; aceites esenciales; patógenos fúngicos; extractos naturales; fitoquímicos.

INTRODUCTION

Candida are fungi, especially ascomycete yeasts, that belong to the phylum Ascomycota. It comprises approximately 300 species, of which more than 40 are recognized as pathogens capable of causing severe infections in humans, particularly in immunocompromised patients (Padmapriya *et al.*, 2015). Approximately 90% of infections are attributed to five significant species: *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei*. Three of these species (*C. albicans*, *C. tropicalis*, and *C. parapsilosis*) belong to the CTG clade. Phylogenetically, *Candida auris* is a member of the CTG clade, along with other multidrug-resistant *Candida* species (Turner *& Butler,* 2014).

Candida auris is an emerging multidrug-resistant fungal pathogen that poses a significant public health threat. Reported in more than 30 countries, it has been associated with several nosocomial outbreaks, with mortality rates ranging from 30% to 60% (Banik, 2023; Chowdhary *et al*., 2023). This fungus was first identified in 2009 in Japan from a patient's external ear canal (Satoh *et al*., 2009). Unlike many *Candida* species, it is not commonly found in colonizing mucosal surfaces and the gastrointestinal tract. However, it demonstrates a remarkable ability to persist and colonize human skin for months, potentially causing serious infections. The unique ability to persist on the skin and in the environment is a distinctive feature of *C. auris*, not identified in other *Candida* species (Huang *et al*., 2020; Benedict *et al*., 2023). High-level azole resistance is predominant among most *C. auris* strains (Eldesouky *et al*., 2020). The mechanisms underlying C. auris virulence factors remain poorly understood (Fatima *et al*., 2023). Genetic studies showed that this pathogen can adapt to different environments and form biofilms that confer protection against antifungal drugs, complicating treatment efforts (Ahmad & Alfouzan, 2021).

The literature highlights the importance of secondary metabolites as natural and traditional therapies in antifungal activity against *Candida* strains (Khan *et al*., 2022). A distinctive advantage of the approach centered on natural phytocompounds is their remarkable absence of mutagenic effects on host cells. This characteristic confers considerable safety when using these compounds as a basis for developing antifungal therapeutic alternatives (Lu *et al.,* 2017). These secondary metabolites are integral components of plant defense systems and play a crucial role in protection against fungal pathogens. They are biosynthesized through specialized metabolic pathways, including the shikimate, mevalonate, and phenylpropanoid pathways, and are frequently induced after pathogen recognition through pattern-triggered immunity (PTI) (Piasecka *et al*., 2015; Fisher *et al.*, 2012). After fungal attack, plants activate complex signaling cascades involving reactive oxygen species (ROS), in addition to regulatory pathways via jasmonic

acid and salicylic acid, terpenoids, and alkaloids. These compounds exert antifungal effects through multiple mechanisms, including disruption of fungal cell membrane integrity, interference with ergosterol biosynthesis, inhibition of cell wall synthesis, induction of oxidative stress, suppression of biofilm formation, and inhibition of efflux pumps (Piasecka *et al*., 2015).

This multi-target activity is particularly relevant in the context of multidrug-resistant pathogens such as *C. auris*, whose resistance mechanisms include overexpression of efflux pumps, biofilm formation, and adaptation to stress responses. Thus, the ecological function of these metabolites in plants provides a biologically plausible basis for their therapeutic application against emerging fungal pathogens (Smith *et al.,* 2017; Chowdhary *et a*l., 2023). This study aimed to review *in vitro* studies that investigated the antifungal potential of plant secondary metabolites, such as extracts, oils, or other compounds, against *C. auris*. The aim is to summarize the current scientific knowledge on the antifungal potential of these compounds against *C. auris*, identify the most promising plant metabolites with antifungal activity against this pathogen, elucidate the mechanisms of action of these metabolites, evaluate the potential synergies between plant metabolites and traditional antifungals, and discuss the challenges and opportunities for the development of new antifungal agents based on plant metabolites.

MATERIALS AND METHODS

This systematic review followed the Cochrane Handbook for Systematic Reviews and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol. The protocol was previously registered with The International Prospective Register of Systematic Reviews -PROSPERO. (DRC42024531760) (Booth *et al*., 2012). The following research question was established to guide the literature search strategy and determine the variables considered in the meta-analysis: ‘’How can plant secondary metabolites be optimized to show efficacy against *C. auris*?’’

Search strategy

Three electronic databases were consulted to search for and identify potential studies for inclusion in this systematic review: PubMed, Scopus, and Virtual Health Library (BVS). There were no restrictions regarding the year of publication or language of the studies.

The MEDLINE search via PubMed was performed using MeSH terms and keywords as follows: ((*Candida auris*[Title/Abstract]) OR (*Candida auris*[MeSH Terms])) and ((((Essential oil[MeSH Terms]) OR (Essential oil[Title/Abstract])) OR (extract[Title/Abstract])) OR (extract[MeSH Terms])) and ((((fungus treatment[MeSH Terms]) OR (fungus treatment[Title/Abstract])) OR (Antifungal Agent[Title/Abstract])) OR (Antifungal Agent[MeSH Terms])). The following search terms were used for Embase and BVS: (*Candida auris*) and (Essential oil or extract) and (fungus treatment or Antifungal Agent); both searches were performed on April 17, 2024.

Screening and selection

Two blinded reviewers independently conducted the selection, eligibility assessment, and data extraction phases. In cases of disagreement, divergences were resolved through dialogue between the reviewers and, if necessary, by consulting a third researcher to reach a consensus.

The initial step consisted of selecting studies that met the eligibility criteria established by the PICO concept: (P) Population: *C. auris*; (I) Intervention: secondary metabolites; (C) Comparator: conventional treatment; and (O) Outcome: antifungal treatment. Exclusion criteria were also applied, excluding articles that did not correspond to PICO (duplicate studies, in vivo trials, soil-related, case reports, retrospective studies, prevalence studies, review studies, survey studies, observational, case-control, and evaluation studies). Study selection was conducted using the Rayyan platform (https://rayyan.ai/) (Ouzzani *et al*., 2016). Titles and abstracts were read for screening to discard studies that did not meet the PICO eligibility criteria and to remove irrelevant records.

Data extraction process

Data were collected from the full articles selected for inclusion using a standardized form in spreadsheet software (Office Excel 2013 Software, Microsoft Corporation, Redmond, WA, USA). Similar information was grouped based on the primary outcomes defined in the review, focusing on the primary outcome of the analysis: inhibition of *C. auris*. Data extracted from each study included the year of publication, type of study, type of components (extract, oil, or compounds), minimum inhibitory concentration, or inhibition zone. The collected data were used in subsequent analyses, such as meta-analyses.

Data tabulation

The data were carefully reviewed for accuracy and consistency, ensuring the robustness of subsequent analyses. Any inconsistencies or gaps were noted and addressed by referring to the original studies or by discussion with another researcher. The results are presented in narrative format and through descriptive statistics, supported by tables where appropriate, to illustrate and facilitate understanding of the data.

Quantitative analyses were grouped in terms of mean difference (MD) to evaluate the primary outcome, including the types of compounds of plant secondary metabolites and interventions and inhibitions used to summarize this work.

Data preparation

The methods used to prepare data for presentation and synthesis included a series of detailed steps to ensure data integrity and consistency. When included studies had missing data, several adjustment techniques were applied. Where specific control data were unavailable, available control data from other studies that used the same unit of measurement or type of inhibition were used. Attempts were made to contact the authors of the original studies to obtain missing data, especially when these data were critical for the analysis or synthesis of the results. In cases of non-response, data that could not be adjusted were not included in the meta-analysis. In some cases, the reported data needed to be converted to uniform units of measurement to enable meta-analysis. For example, the minimum inhibitory concentration reported in mg/mL was converted to µM when necessary.

Bias bisk assessment

The risk of bias was assessed by two reviewers using an adaptation of the Consolidated Standards of Reporting Trials (CONSORT) tool. This tool only includes in vitro studies, so items about clinical studies were not assessed, and the selected studies were examined according to a specific checklist to describe the established criteria. The analysis focused exclusively on items from the CONSORT list related to in vitro research.

Meta-analysis: data synthesis

Quantitative analyses of continuous variables of plant secondary metabolites and controls were grouped into MD with 95% confidence intervals (95% CI).

The meta-analyses expressed the results as MD 95% CI for the outcomes related to the inhibition zone in millimeters or minimum inhibitory concentration. The statistical analysis was performed using R software, version 4.3.1, for Windows 10, meta-package version 6.5.0. (R Core Team, 2023).

In the absence or presence of reduced heterogeneity (I^2 < 10% and p > 0.05), the fixed effect model was used with the Mantel-Haenszel method. When higher (I^2 > 10% and p < 0.05), the random effect model was used with the DerSimonian-Laird method (16). I^2 values close to 25%, 50%, and 75% indicated low, moderate, and high heterogeneity, respectively (Higgins & Thompson, 2002; Higgins *et al*., 2003). All possible heterogeneities found will be explained and justified.

Certainty of the evidence

Due to the nature of the reviewed studies, it was impossible to assess the certainty of the evidence, as the studies do not meet the certainty of evidence criteria of the GRADEpro (Grading of Recommendations Assessment, Development, and Evaluation) system used in systematic reviews of clinical trials.

RESULTS

Search strategy

The PubMed search strategy to identify studies on the antifungal potential of plant secondary metabolites against *Candida auris* involved using combinations of specific search terms. The search combined terms relevant to *C. auris*, such as "*Candida auris*" in the title or abstract or as a MeSH term, with terms related to essential oils ("Essential oil") and extracts ("Extract") in either the title, abstract or MeSH terms. When these terms were combined with "fungus treatment" or "Antifungal Agent" to filter results related to fungal treatment or antifungal agents, the final search (#1 AND #2 AND #3) yielded ten articles. The results of individual searches with each term can be found in Table 1.

Table 1. *Database search strategies*

	Database strategy	Results
PUBMED	**# 1** *Candida auris*[Title/Abstract] OR *Candida auris*[MeSH Terms]	1,418
	#2 Essential oil[MeSH Terms] OR Essential oil[Title/Abstract] OR extract[Title/Abstract] OR extract[MeSH Terms]	304,229
	#3 fungus treatment[MeSH Terms] OR (fungus treatment[Title/Abstract] OR Antifungal Agent[Title/Abstract] OR Antifungal Agent[MeSH Terms]	275,216
	#4 #1 AND #2 AND #3	10
EMBASE	(*Candida auris*) AND (Essential oil) OR (extract) AND (fungus treatment) OR (Antifungal Agent)	732
BVS	(*Candida auris*) AND (Essential oil) OR (extract) AND (fungus treatment) OR (Antifungal Agent)	26

The search strategies in the Embase and BVS platforms involved the combination of specific search terms related to the antifungal potential of plant secondary metabolites against *C. auris*. The search used the terms "*Candida auris"* combined with "Essential oil OR extract" and "fungus treatment OR Antifungal Agent."

Search and selection

Figure 1 displays the flowchart outlining the study selection process according to the PRISMA guidelines. The search identified 768 potential studies, with 732 in Embase, 26 in BVS, and 10 in PubMed. Of these, 726 were excluded because they did not meet the inclusion criteria, while 10 were identified as duplicates. After the initial screening, 32 studies were selected for a complete textual analysis. Subsequently, 18 studies were discarded because they did not present compelling results, and another three studies were eliminated because they did not involve plant derivatives, according to the exclusion criteria. As a result, 11 remaining studies were included in the systematic review and meta-analysis. The characteristics of these included studies were summarized and presented in Table 2.

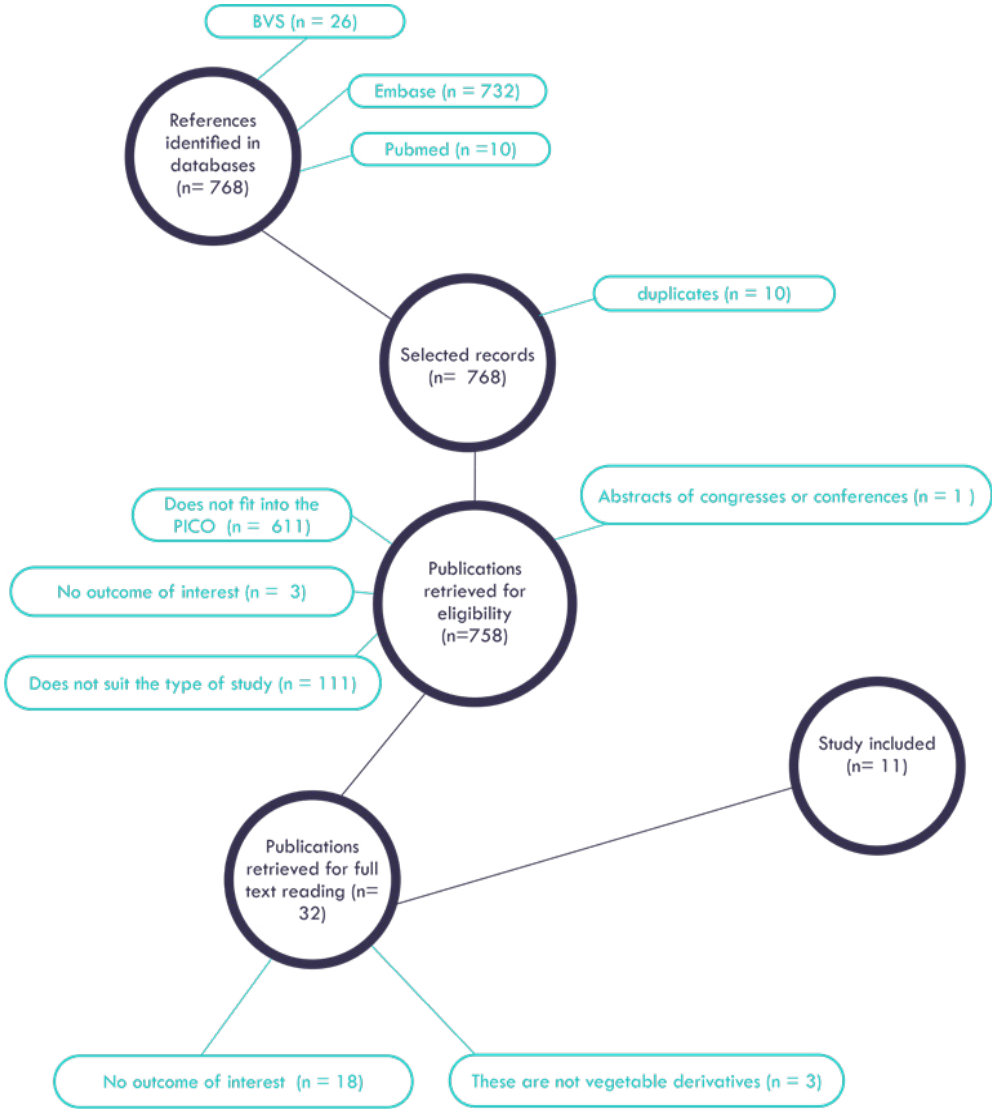


Figure 1. *Selection flowchart according to PRISMA*

After selecting the included studies, it was observed that of the 11 selected works, one was published in 2020, four in 2021, four in 2022, and two in 2023, as detailed in Table 2. This temporal panorama reflects the recent attention given to research on antifungal compounds against *C. auris*.

Characterization of included studies

Further analysis of the selected articles revealed a variety of plant secondary metabolites with antifungal potential against *C. auris*. These include essential oils, terpenes, and different types of extracts (methanolic, ethyl acetate, aqueous, ethanolic), totaling 14 tests related to extracts, 11 tests with essential oils, and five tests with terpenes derived from the essential oil of *Lippia origanoides* respectively, totaling 30 metabolites.

Most studies addressed more than one compound, extract, or vegetable oil, reflecting various approaches. Among the authors, Zapata-Zapata *et al*. (2022) stood out for investigating a notable number of active ingredients and including a significant diversity of microorganisms in his studies.

The characterization of the included studies revealed a remarkable diversity of plant genera with antifungal properties in combating *C. auris*, highlighting *Sarcochlamys*, *Coccinia*, *Myrcia*, *Eugenia*, *Beta*, *Syzygium*, *Cinnamomum*, *Athyrium*, *Fagus*, *Cynara*, and *Piper*, as detailed in Table 2.

Table 2. *Characteristics of the included studies*

Author	Type of Components	Intervention	Risk of Bias	Results	Conclusion	Mechanism of Action
Akhtar *et al.* (2023)	**1.** methanolic extract of *Sarcochlamys pulcherrima* **2.** ethyl acetate extract of *S. pulcherrima* **3.** gallic acid compound from the leaves of *S. pulcherrima*	The fluconazole inhibition zone was 24 mm	Low	**1.** The zone of inhibition of the methanolic extract of *S. pulcherrima* against *C. auris* was 11 mm **2.** The zone of inhibition of the ethyl acetate extract of S. pulcherrima against C. auris was 15 mm **3.** The MIC of gallic acid against *C. auris* ranged from 1.6 to 3.2 mg/ml	• The plant extract of ethyl acetate has better antifungal activity against *C. auris*. • *S. pulcherrima* could serve as a potential source of new antifungal drugs, with gallic acid being one of the active molecules responsible for its antifungal properties	• The study suggests that gallic acid may bind to the active site residues of *C. auris* CA proteins
Alshahrani *et al.* (2022)	**1.** aqueous extract of *Coccinia indica* leaf **2.** ethanolic extract of *C. indica* leaf	The zone of inhibition of Anidulafungin was 18 mm	Low	**1.** The zone of inhibition of the aqueous extract was not observed **2.** The zone of inhibition of the ethanolic extract of *C. indica* was 18 mm at the minimum inhibitory contraction of 200 µg/mL	• The results of ethanolic extracts of *C. indica* were more active • *C. indica* could serve as a potential source of new natural medicines to combat resistance to common drugs	• Without knowledge of its exact mechanism of action
Bravo-Chaucanés *et al.* (2022)	**1.** ethanolic extract of *Piper nigrum* 2. activity of DCM (dichloromethane) fractions and EtOAc (ethyl acetate)	Caspofungin significantly reduced biofilm formation at 0.062 µg/mL	Low	**1.** Inhibition above 80% was observed at a concentration of 512 µg/mL 2. The minimum inhibitory concentrations observed were 2,048 µg/mL	• The ethanol extract was more effective • In addition, the ethanol extract of *P. nigrum* showed activity against biofilms in *C. auris*, even in drug-resistant strains.	• Without knowledge of its exact mechanism of action
Ferreira *et al.* (2021)	**1.** essential oils of three specimens of *Myrcia multiflora* (A, B and C) 2. essential oil of *Eugenia florida*	Nystatin	High	**1.** The zone of inhibition of the essential oil of *M. multiflora* (A) was 9 mm, *M. multiflora* (B) was 10 and *M. multiflora* (C) was 8 mm. Where the minimum inhibitory concentration for *M. multiflora* (A) was 3.12 µg/mL and for *M. multiflora* (C) was 5 µg/mL 2. The zone of inhibition of the essential oil of *E. florida* was 8 mm	• The *M. multiflora* specimen (B) was more effective • The fungicidal potential presented in the essential oils of *M. multiflora* may be promising for the development of natural agents	• Without knowledge of its exact mechanism of action

Author	Type of Components	Intervention	Risk of Bias	Results	Conclusion	Mechanism of Action
Kamli *et al.* (2021)	Ag-Fe bimetallic nanoparticles using aqueous extract of *Beta vulgaris* L.	Amphotericin B minimum inhibitory concentration ranged from 0.125 to 4 µg/mL	High	minimum inhibitory concentration ranging from 0.19 to 0.39 µg/mL against *C. auris* strains	Ag-Fe have intense anti-Candida activity against *C. auris* strains, and the non-toxic nature of Ag-Fe NPs makes them safe for in vivo studies.	Ag-Fe NPs have been shown to negatively affect the growth and survival of *C. auris*. The cumulative effects of Ag-Fe NPs were confirmed to be related to the modulation of crucial antioxidant enzymes, resulting in the generation of oxidative stress and cell cycle arrest in the G2/M phase, leading to programmed cell death of *C. auris*.
Malik *et al*. (2022)	silver nanoparticles (CC-AgNPs) biosynthesized with aqueous extract of *Cynara cardunculus*	Amphotericin B against *C. auris* MRL6057 the minimum inhibitory concentration was 4.0 µg/mL	High	CC-AgNPs were found to be active against *C. auris* MRL6057 with the minimum inhibitory concentration value of 50.0 µg/mL	The results demonstrated that the prepared silver nanoparticles had good antifungal performance against *C. auris* and could be exploited for exceptional and enhanced biomedical applications.	• The metabolite caused mitochondrial membrane disintegration in *C. auris*, and at higher concentrations of CC-AgNPs, it suggested DNA breakage in *C. auris* (DNA fragmentation) and directly inhibited the cell cycle and arrested the cells in the G2/M phase.
Mare *et al.* (2021)	**1.** Silver acetate salts (AgNP acetate BBE) biosynthesized with bark extract of *Fagus sylvatica* L. **2.** Silver nitrate salts (AgNP nitrate BBE) biosynthesized with bark extract of *F. sylvatica* L. **3.** Bark extract of *Fagus sylvatica* L.	Fluconazole	High	**1.** AgNP Ac BBE at a concentration of 50%, inhibition occurred at a minimum inhibitory concentration of 0.13 mg/mL **2.** AgNP Nit BBE at a concentration of 50%, inhibition occurred at a minimum inhibitory concentration of 0.14 mg/mL **3.** *F. sylvatica* L. bark extract at a concentration of 50%, inhibition occurred at 6.25%	• The effect of AgNP BBEs on *C. auris* was considered indifferent, as a small degree of inhibition was observed.	• Without knowledge of its exact mechanism of action
Raj *et al.* (2021)	*Syzygium samarangense* leaf extract	Clotrimazole at 20 µg, the diameter of the growth inhibitory zone against *C. auris* was 22.5 mm	High	The diameter of the growth inhibitory zone against *C. auris* was 13.4 mm in 15 mg of the extract	The results of the trial demonstrated that *C. auris* is less sensitive to the extract than other Candida strains tested.	For *C. albicans* treated with *Syzygium samarangense* leaf extract, it presented severe morphological defects (change in the morphology of the cell surface with undulations, breaks and dents) indicating its role as a potential antifungal agent against *Candida*.

Author	Type of Components	Intervention	Risk of Bias	Results	Conclusion	Mechanism of Action
Tran *et al*. (2020)	**1.** *Cinnamomum zeylanicum* bark oil **2.** *C. zeylanicum* leaf oil	The inhibitory zone of miconazole was 32.82 mm	Low	**1.** The inhibitory zone of the bark extract of *C. zeylanicum* was 70.4 mm in 2. The inhibitory zone of the leaf extract of *C. zeylanicum* was 39.67	• Both bark and leaf oil of *C. zeylanicum* have demonstrated fungicidal properties at very low concentrations.	• Triggers envelope damage, evident by shrinkage of cell surfaces and recoil of cytoplasm leading to cell lysis. Furthermore, the level of cell membrane damage in *Candida* correlated with the concentration of oils used.
Wadaan *et al*. (2023)	**1.** methanol extract of *Athyrium asplenioides* **2.** acetone extract of *A. asplenioides* **3.** ethyl acetate extract of *A. asplenioides* **4.** chloroform extract of *A. asplenioides*	The inhibitory zone of fluconazole was 11.50 mm	Uncertain	**1.** The inhibitory zone of methanol extract of *Athyrium asplenioides* was 7.6 mm **2.** Acetone extract of *A. asplenioides* was 8.1 mm **3.** Ethyl acetate extract of *A. asplenioides* was 9.5 mm **4.** Chloroform extract of *A. asplenioides* was 6.8 mm	• The crude methanol extract demonstrated excellent antifungal activity against *Candida* species • The ethyl acetate extract of *A. asplenioides* was better on *C. auris*	• The crude methanol extract has significant α-amylase and α-glucosidase inhibitory activity (antihyperglycemic activity)
Zapata-Zapata *et al*. (2022)	**1.** *Lippia origanoides* essential oil (carvacrol + thymol chemotype) **2.** *L. origanoides* essential oil (carvacrol +p-cymene) **3.** *L. origanoides* essential oil (thymol chemotype) 14. *L. origanoides* essential oil (thymol chemotype) 2 **5.** *L. origanoides* essential oil (thymol + p-cymene) **6.** Terpene thymol **7.** Terpene Limonene **8.** Terpene carvacrol **9.** Terpene p-Cymene **10.** Terpene Perillyl alcohol	The minimum inhibitory concentration of amphotericin B was 0.07 µg/mL The minimum inhibitory concentration of itraconazole was 0.04 µg/mL The minimum inhibitory concentration of fluconazole was 1.4 µg/mL The minimum inhibitory concentration of caspofungin was 0.5 µg/mL	Low	**7.** The best activity was observed with limonene (with the minimum inhibitory concentration of 64 µg/mL)	• Strains resistant to the main antifungal agents in clinical use (*C. tropicalis* ATCC 200956, *C. parapsilosis* Synlab 406 and *C. auris*) were the most susceptible to the studied EOs and to commercial terpenes.	• information about its mechanism is missing

Based on the data provided in Table 2 of the included studies, five needed to provide detailed information on the mechanism of action of the tested compounds. For example, Alshahrani *et al*. (2022) studied *Coccinia indica* extracts, and Bravo-Chaucanés *et al*. (2022) on *Piper nigrum* extract, which showed antifungal activities. However, they did not elucidate the underlying mechanisms. Similarly, Ferreira, Silva *et al*. (2021) investigated the essential oils of *Myrcia multiflora* specimens (A, B, and C) and *Eugenia florida* essential oil, while Mare *et al*. (2021) studied biosynthesized silver salts with *Fagus sylvatica* extract, without providing specific information on how these compounds exert their antifungal action against *C. auris*. Zapata-Zapata *et al*. (2022) evaluated ten compounds but did not present details on the mechanisms of action associated with these compounds.

On the other hand, six studies provided detailed information on the mechanisms of action of the tested compounds against *C. auris*. Akhtar *et al.* (2023) suggested that gallic acid may bind to the active site residues of CA proteins (which are responsible for virulence and several other critical biological functions) of *C. auris*, contributing to its antifungal action. Kamli *et al*. (2021) demonstrated that Ag-Fe bimetallic nanoparticles negatively affect the growth and survival of *C. auris*. The cumulative effects of Ag-Fe NPs are related to the modulation of crucial antioxidant enzymes, resulting in the generation of oxidative stress and cell cycle arrest at the G2/M phase, leading to programmed cell death.

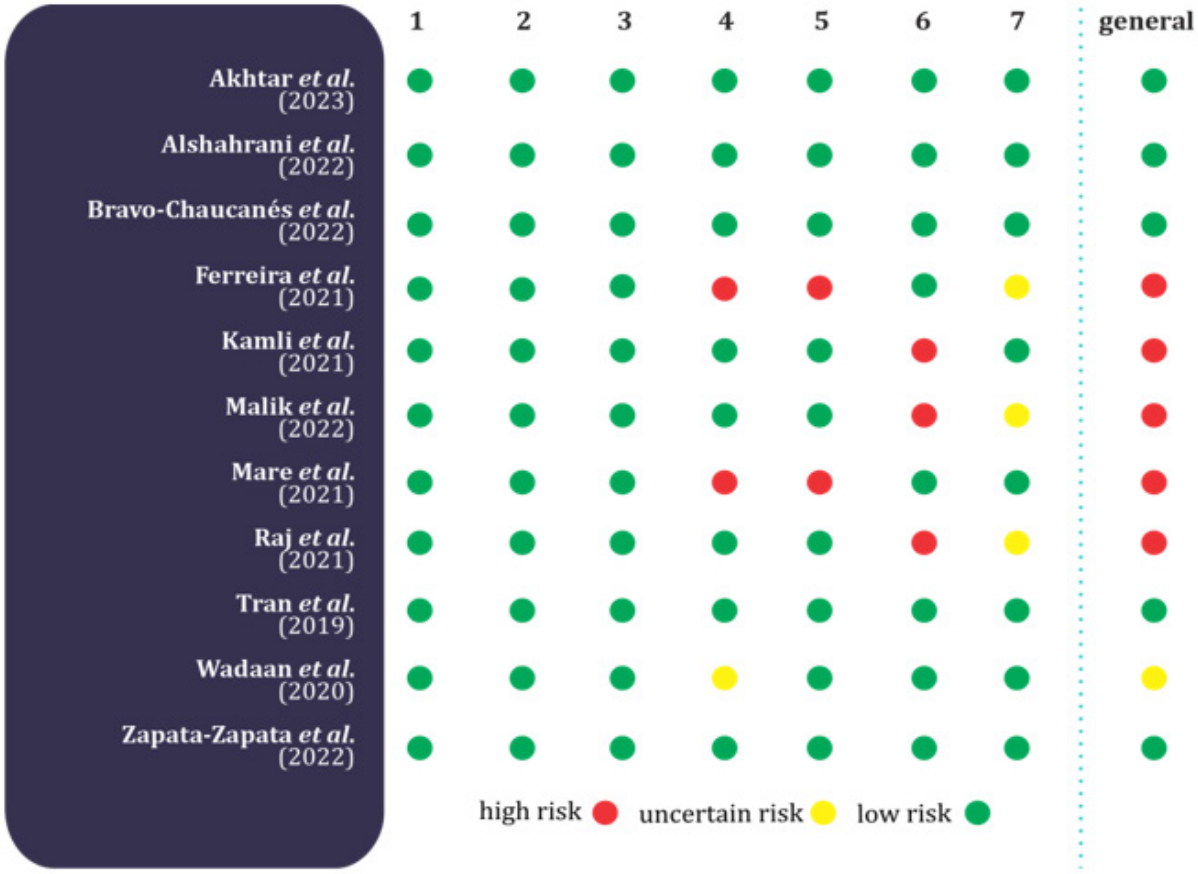
Malik *et al.* (2022) found that silver nanoparticles biosynthesized with aqueous extract of *Cynara cardunculus* caused mitochondrial membrane disintegration in *C. auris*. At higher concentrations, these nanoparticles suggested DNA breakage (DNA fragmentation) and directly inhibited the cell cycle by arresting cells in the G2/M phase in *C. auris*. Raj *et al*. (2021) observed that *Syzygium samarangense* leaf extract caused severe morphological defects in *C. albicans*, such as dimpling, breaks, and dents on the cell surface, indicating its role as a potential antifungal agent against other *Candida* species.

Tran *et al*. (2020) reported that *Cinnamomum zeylanicum* oils trigger cell envelope damage, which is evident by the shrinkage of cell surfaces and cytoplasmic indentation, leading to cell lysis. The membrane damage level correlated with the oil concentration. Wadaan *et al*. (2023) reported that the crude methanol extract of *Athyrium asplenioides* possesses significant α-amylase and α-glucosidase inhibitory activity, indicating relevant antihyperglycemic activity.

These studies highlight the diversity of mechanisms of action of the investigated compounds, showing different strategies to combat *C. auris*. This variety of mechanisms and the observed efficacy illustrate the complexity of the interactions between plant secondary metabolites and *C. auris*.

Risk of bias

The results of this analysis are detailed in Figure 2, showing that almost half of the studies (45.45%) were classified as having a low risk of bias in multiple domains. Most studies demonstrated a low risk of bias in several methodological aspects of results, discussions, abstract structure, and scientific basis, including how and when it was administered.



criteria:
1 structured summary of study desing, methods, results, and conclusions
2 scientific basis and rationale
3 specific objectives and hypotheses
4 details of the intervention, including how and when it was administered, ensuring reproducibility
5 presence of a control group
6 inclusion of comparable specimens that received similar treatment or care besides the exposure or intervention of interest
7 use of appropriate statistical analysis

Note. The information regarding the following parameters was judged: (Red) indicates a high risk of bias, (Green) indicates a low risk of bias, and (Yellow) for uncertain answers.

Figure 2. *Assessment of risk of bias using the adapted CONSORT checklist*

While some studies demonstrated rigorous implementation of methods, ensuring the minimization of potential biases, others presented significant methodological flaws, such as failures in the detailing of the control, the methods used, and differential exposure between some specimens, which may compromise the reliability of the results.

Ferreira, Silva *et al*. (2021) and Mare *et al*. (2021), in general terms, presented a high risk of bias, as they presented a high risk of bias in items 4 and 5 due to the lack of sufficient details in the description of the intervention and the absence of a control group in their study, which could compromise the interpretation of the results. Ferreira, Silva *et al*. (2021) also presented an uncertain risk in item 7 due to the need for more clarity in describing the statistical analysis performed.

Similarly, the studies by Kamli *et al*. (2021), Malik *et al*. (2022), and Raj *et al.* (2021) also demonstrated a high overall risk of bias. This risk is mainly related to item 6, which investigates whether the samples included in the comparisons received similar

treatments/care beyond the intervention or exposure of interest. Notably, the study by Wadaan *et a*l. (2023) was the only one to receive an unclear risk of bias in item 4, indicating areas where descriptions of the interventions could be more detailed.

Despite the presence of studies with a high risk of bias and uncertainty in critical domains, the overall analysis suggests that the results of this review are reliable and accurate. These limitations maintain the integrity of the findings, especially given the diversity of approaches and the complexity of the interactions between investigated plant metabolites and *C. auris*. The methodological variety supports the results' robustness, which contributes to a more comprehensive understanding of the phenomenon studied.

Meta-analysis

Inhibition halo performance. Of the nine extracts and five vegetable oils (Tran *et al*., 2020; Ferreira, Silva *et al*., 2021; Raj *et al*., 2021; Alshahrani *et al*., 2022; Akhtar *et al*., 2023; Wadaan *et al*., 2023), two demonstrated better results than the controls [Tran 2020a, 2020b], and the others did not present significant differences. The outcome of the meta-analysis demonstrated that the extracts/oils presented similar results to the controls (MD: 0.71 mm) [95% CI −6.46; 7.88] (Figure 3).

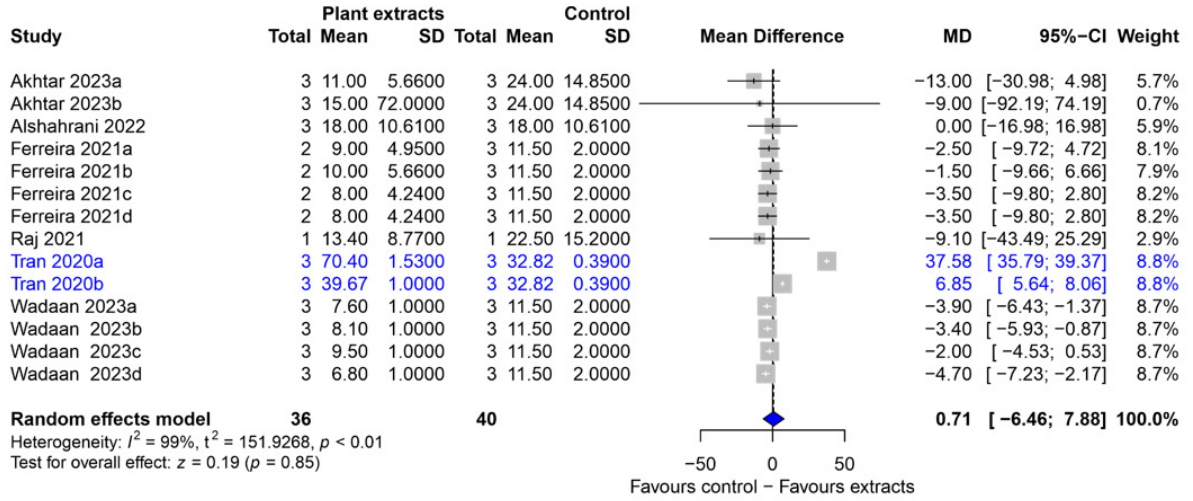


Figure 3. *Inhibitory effect of plant extracts and essential oils against Candida auris*

The figure shows the inhibition zone (mm) observed in *Candida auris* cultures exposed to methanolic extract from *Sarcochlamys pulcherrima* [Akhtar, 2023a], ethyl acetate extract from *Sarcochlamys pulcherrima* [Akhtar, 2023b], aqueous extract from *Coccinia indica* leaf [Alshahrani, 2022a], leaf extract from *Syzygium samarangense* [Raj, 2021], and methanolic, acetone, ethyl acetate, and chloroform extracts from *Athyrium asplenioides* [Wadaan, 2023a, 2023b, 2023c, 2023d]. Vegetable essential oils from *Myrcia multiflora* [Ferreira, Silva, 2021a, 2021b, 2021c] and *Eugenia florida* [Ferreira, Silva, 2021d] were also tested *in vitro*. For each treatment group, mean (MD), standard deviation (SD), and confidence interval (CI) are presented.

The high heterogeneity observed (I^2 = 99%) can be attributed to differences in the types of extracts and oils used and the study methodologies. Akhtar *et al*. (2023) used two types of extracts: methanolic (a) and ethyl acetate (b) from *Sarcochlamys pulcherrima*. Alshahrani *et al*. (2022) evaluated the ethanolic and aqueous extract of *Coccinia indica* leaf, and the aqueous extract was not included in this meta-analysis

because it did not demonstrate inhibition of *C. auris*. Ferreira, Silva *et al*. (2021) tested *Myrcia multiflora* oils (a, b, and c) and *Eugenia florida* oil (d), and the control data were incorporated from the article by Raj *et al*. (2021) due to the lack of specific control and the botanical similarity between the plants. Raj *et al*. (2021) studied the leaf extract of *Syzygium samarangense*. Tran *et al*., (2020) investigated bark (a) and leaf (b) oils of *Cinnamomum zeylanicum*. Wadaan *et al*. (2023) evaluated methanol (a), acetone (b), ethyl acetate (c), and chloroform (d) extracts of *Athyrium asplenioides*.

Minimum inhibitory concentration performance. Of the six extracts and ten vegetable oils (Mare *et al*., 2021; Kamli *et al*., 2021; Zapata-Zapata *et al*., 2022; Malik *et al*., 2022; Bravo-Chaucanés *et al*., 2022; Wadaan *et al*., 2023), three demonstrated results similar to the controls [Mare, 2021a, 2021b; Kamli, 2021], two showed worse results than the controls [Bravo-Chaucanés, 2022a, 2022b] and the others showed no significant differences. The outcome of the meta-analysis demonstrated that the extracts/oils showed worse results than the controls (MD: 53.10 µg/mL) [95% CI 25.14–81.16] (Figure 4).

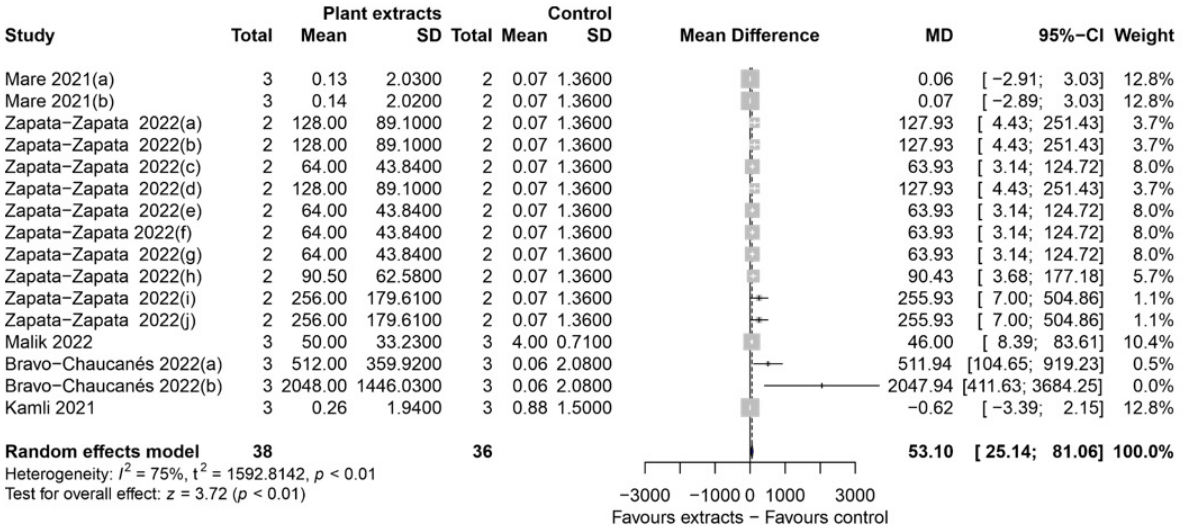


Figure 4. *Inhibitory effect of plant extracts, essential oils, and nanoparticles against Candida auris*

In the figure above, the minimum inhibitory concentration (MIC, µg/mL) observed in *Candida auris* cultures exposed to silver acetate salts combined with *Fagus sylvatica* L. bark extract [Mare, 2021a], silver nitrate salts with *Fagus sylvatica* L. bark extract [Mare, 2021b], and silver nanoparticles synthesized with *Cynara cardunculus* aqueous extract [Malik, 2022] is presented. Ethanolic extract of *Piper nigrum* [Bravo-Chaucanés, 2022a], dichloromethane (DCM) and ethyl acetate (EtOAc) fractions [Bravo-Chaucanés, 2022b], and bimetallic nanoparticles obtained from *Beta vulgaris* L. aqueous extract [Kamli, 2021] were also evaluated. Furthermore, essential oils and terpenes from *Lippia origanoides* carvacrol + thymol chemotypes [Zapata-Zapata, 2022a], carvacrol + p-cymene [Zapata-Zapata, 2022b], thymol chemotype 1 [Zapata-Zapata, 2022c], thymol chemotype 2 [Zapata-Zapata, 2022d], thymol + p-cymene [Zapata-Zapata, 2022e] and individual terpenes such as thymol [Zapata-Zapata, 2022f], carvacrol [Zapata-Zapata, 2022g], p-cymene, and perillyl alcohol [Zapata-Zapata, 2022h] were tested *in vitro*. For each treatment group, the mean (MD), standard deviation (SD), and confidence interval (CI) are presented.

The observed heterogeneity (I^2 = 75%) can be attributed to differences in the types of extracts and oils used and the study methodologies. Mare *et al*. (2021) investigated silver acetate salts (a) and silver nitrate salts (b) biosynthesized with *Fagus sylvatica* L. bark extract. Control data were incorporated from the study by Malik *et al*. (2022), and the units of measurement in mg were converted to µL to maintain consistency between studies. Zapata-Zapata *et al*. (2022) evaluated a wide range of essential oils from *Lippia origanoides*, including carvacrol + thymol (a), carvacrol + p-Cymene (b), thymol chemotype 1 (c), thymol chemotype 2 (d), and thymol + p-Cymene (e), in addition to individual terpenes such as thymol (f), Limonene (g), carvacrol (h), p-Cymene (i), and Perillyl alcohol (j). Malik *et al*. (2022) investigated biosynthesized silver nanoparticles with aqueous extract of *Cynara cardunculus*. Bravo-Chaucanés *et al*. (2022) studied the ethanolic extract of Piper nigrum (a) and the dichloromethane and ethyl acetate fractions (b). Kamli *et al*. (2021) evaluated Ag-Fe bimetallic nanoparticles using an aqueous extract of *Beta vulgaris* L.

DISCUSSION

Natural plant products are essential sources for drug innovation, and the selection and validation of extracts, essential oils, and molecules with relevant pharmacological action require effective strategies for the selection of bioproducts. This systematic review evaluates the inhibitory effect of in vitro studies on plant secondary metabolites, such as essential oils and extracts that act specifically against *C. auris* (Silva *et al*., 2020; Meirelles *et al*., 2023). The inhibitory effect of plant metabolites depends on the chemical composition of the oils and extracts, which are affected by several factors, including the origin of the plant, location, environmental conditions, and phenotypic variation. This variation is intensified when comparing species of the same genus or completely different species. Thus, the predominance of certain chemical constituents can determine these metabolites' greater or lesser effectiveness (Meirelles *et al*., 2023).

The in vitro antifungal inhibitory effect is determined using different techniques, such as the broth method, with results expressed in % (v/v) µg/mL and mg/mL. Due to the lack of standardization of the techniques to determine the MIC, it was observed that some studies use the agar dilution technique or the broth microdilution technique. These variations in methodologies and the lack of standardization of results between in vitro studies are limitations that can negatively influence the evidence of antifungal activity. This methodological heterogeneity makes comparison difficult and allows variable results to be presented (Perez & Clímaco, 2023; Liñán-Atero *et al*., 2024; Ostrosk *et al*., 2008). Another limitation identified when reviewing the studies included in the meta-analysis is the variation in methodological quality. While some studies present robust methodologies with adequate extraction techniques and controls, others need a solid experimental design and proper control. This discrepancy in methodological quality may introduce bias in the results and compromise the reliability of the conclusions obtained in the meta-analysis (Martins & Ernst, 2004).

Although the search strategy was comprehensive, resulting in a total of 11 included studies after thorough screening, it is still possible that not all trials that met the inclusion criteria established in the PICO were located, which may limit the comprehensiveness of the review and the generalizability of the results. The lack of access to all relevant studies, especially *in vitro* studies without flaws in the methodology regarding the control group and replicable methods, may have resulted in an incomplete view of the

body of evidence available on the topic. This highlights the importance of future review updates as new evidence becomes available (Ferreira, Rosalen *et al*., 2021; Pinto *et al*., 2024). After analyzing the studies included in the meta-analysis, the results suggest that plant oils and extracts have potential as antifungal agents against *C. auris*. Data analysis revealed a significant reduction in fungicidal activity compared to the control groups, indicating the ability of these compounds to inhibit growth.

Similarly, Akhtar *et al*. (2023) reported that a compound potentially responsible for antifungal activity acts on the active site of the CA protein in *C. auris*. This finding highlights its efficacy against a defined molecular target and its ability to interact directly with fluconazole-resistant clinical isolates. Furthermore, the authors emphasize the potential of several essential oils (EOs), plant extracts, and terpenes as promising candidates for the development of new antifungal agents.

In addition to the qualitative synthesis of previous studies, a quantitative meta-analysis was performed to pool the antifungal effects reported in the literature. For the inhibition zone outcome (Figure 3), 14 treatments derived from 6 independent studies were included. For the minimum inhibitory concentration (MIC) analysis (Figure 4), 16 treatments from 5 studies were evaluated. The pooled effects were calculated using mean difference (MD) with 95% confidence intervals (CI), considering inhibition zone (mm) and MIC (µg/mL) as outcome measures. These analyses provide a structured quantitative synthesis of the individual results, including cases in which the same study evaluated multiple essential oils or extracts under different experimental conditions.

The meta-analysis presented in Figure 3 evaluated the inhibitory effect of EOs and extracts against *C. auris* through the inhibition halo, covering 14 treatments. The results showed an overall mean inhibition of 0.71 mm and a 95% CI with a variation of -6.46 and 7.88 mm, with no statistically significant differences. Given the above, the treatments that obtained excellent performance in inhibiting *C. auris* were the oils from the bark of *C. zeylanicum* [Tran, 2020a], with an average of 37.58 mm [95% CI 35.79–39.37] and from the leaf of *C. zeylanicum* [Tran, 2020b], with an average of 6.85 mm [95% CI 5.64–8.06]. Both presented superior results to the controls used in the tests, indicating considerable efficacy in inhibiting fungal growth (Tran *et al*., 2020).

Similar results were reported by Di Vito *et al*. (2023), who found that *C. zeylanicum* bark at a concentration of 0.06 µg/mL was able to eliminate *C. auris* by 90%, confirming the efficacy of *C. zeylanicum* essential oils in inhibiting *C. auris*. Furthermore, studies demonstrate that Cinnamomum cassia essential oil (extracted from a more accessible species compared to the more valuable *C. zeylanicum*), whether in its pure form or formulated in polycaprolactone nanoparticles, is effective against *C. auris* and that the essential oil encapsulation process may contribute to better distribution and reduced toxicity (Rosato *et al*., 2023). This superior performance of oils, especially from *C. zeylanicum*, suggests that these natural compounds are an alternative in antifungal treatments. This is especially relevant given the difficulties encountered in conventional treatments, which employ hooks, echinocandins, and amphotericin B, which face challenges due to the resistance of *C. auris*.

The other studies analyzed in this meta-analysis, except the methanolic extract of *Sarcochlamys pulcherrima* [Akhtar, 2023a], presented inhibition rates similar to those of the controls used (fluconazole, amphotericin B, and clotrimazole), which indicates that, although they do not demonstrate superior inhibition to conventional medicines, the oils and extracts have an effective antifungal action, with significant inhibition capacity when compared to traditional methods (Akhtar *et al*., 2023). In the studies described

in Figure 4, the inhibitory effect of 16 treatments with extracts, EOs, and terpenes was evaluated regarding the minimum inhibitory concentration (µg/mL). The overall result of the analysis revealed an average inhibition of 53.10 µg/mL, with a 95% CI ranging from 25.14 to 81.06 µg/mL. These data indicate that in some treatments the inhibition values were lower than those observed in the control, suggesting a greater need to optimize the use of extracts, oils, and terpenes to achieve effective inhibition, as described by Zapata-Zapata *et al*. (2022) in treatments [2022i, 2022j] and by Bravo-Chaucanés *et al*. (2022) in treatments [2022a, 2022b].

Similar findings were observed by Manohar *et al*. (2001) when investigating the inhibition of *C. albicans* with origanum essential oil, noting that the inhibitory efficacy increased proportionally with increased administrative concentrations. These results corroborate the relationship between concentration and efficacy in inhibiting the fungus. The other results of the meta-analysis showed that treatments in concentrations close to the controls could inhibit the development of the fungus, demonstrating that its effectiveness can be compared to that of conventional medications. In addition to oil extracts, treatments by Zapata-Zapata *et al*. (2022) with terpenes also achieved inhibition at concentrations similar to the control. It has been observed in previous studies that oxygenated terpene compounds, such as carvacrol, are often identified as the primary agents responsible for inhibiting the germination of other *Candida* species and mycelial elongation. These compounds act through chemical reactions with amino and hydroxylamine groups in membrane proteins (Palmeira-de-Oliveira *et al*., 2009). Furthermore, Shaban *et al*. (2020) consolidated these findings by demonstrating a significant reduction in proteinase production in vivo after carvacrol treatment in *C. auris*.

CONCLUSIONS

Given the growing public health threat posed by *C. auris*, the reviewed studies reveal a promising outlook for the potential of plant secondary metabolites as effective antifungal agents. The diversity of compounds explored, from extracts to essential oils of different plants, demonstrates significant antifungal activity against this resistant strain. The results showed that many of these plant compounds could inhibit the growth of *C. auris*, some with minimum inhibitory concentrations comparable to or even better than conventional antifungals. This finding paves the way for promising therapeutic alternatives, especially when traditional antifungals are ineffective. However, it is essential to emphasize that many studies require further investigation to confirm the clinical efficacy of these compounds, in addition to fully elucidating their mechanisms of action. Despite the challenges, the reviewed studies provide a solid basis for future investigation and development of novel antifungal therapies based on plant compounds. With a deeper understanding of their mechanisms of action and potential synergies with traditional antifungals, these compounds may represent a valuable addition to the therapeutic arsenal in combating *C. auris* and other resistant fungal pathogens.

AUTHOR CONTRIBUTIONS

Conceptualization, S. H. S. and M. G. S.; Methodology, S. H. S. and G. R. S.; Investigation, S. H. S. and O. F. S.; Data Curation, S. H. S., H. C. J. and C. E. L. R.; Formal Analysis, T. G. S. C. and V. B. S.; Writing—Original Draft Preparation, S. H. S. and O. F. S.; Writing—Review & Editing, M. P. S. S., G. R. S., O. F. S., and M. G. S.; Visualization, V. B. S.; Supervision, R. W. S. A., and A. S. R. C.; Project Administration, A. S. R. C. and M. G. S.; Funding Acquisition, M. G. S.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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