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Review Article

Antifungal potential of Libyan medicinal plants: A systematic review with a focus on *Candida albicans* and other human pathogenic fungi

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Abstract

Objective: This systematic review aims to assess and summarize studies investigating the antifungal activity of Libyan medicinal plants, with emphasis on *Candida albicans* and other clinical relevance fungal species.

Materials and Methods: Electronic researches were conducted in PubMed, Dimensions and OpenAlex, supplemented with Libyan journals and Google Scholar to identify studies published between 1 January 2010 and 26 August 2025, only original *in vitro* studies assessing the antifungal activity of Libyan plants and those meeting the predefined inclusion criteria were selected. This review followed the PRISMA 2020 guidelines, study quality was assessed using a modified QUIN tool, and the protocol was registered in PROSPERO (CRD420251121497).

Results: A total of 45 articles were included with 51plant species evaluated. Several plants, particularly, *Malva parviflora, Satureja thymbra* L, *Arbutus pavarii* and *Phragmites australis* exhibited strong inhibitory activity against the most commonly targeted pathogen *C. albicans.* Additionally, several species tested against *Aspergillus* species including *Aspergillus fumigatus, Aspergillus niger* and *Aspergillus flavus* showed variable inhibition. The main active components identified were phenolic compounds such as flavonoids (especially catechin), thymol, tannins, saponins and terpenoids. The quality assessment indicated an overall acceptable methodological quality for most included studies.

Conclusion: This review highlights the potential of Libyan plants as a promising source of antifungal agents. Based on identified research gaps, this review recommends more innovative *in vitro* and *in vivo* studies, as well as elucidation of the action of the active compounds against fungi and evaluation their cytotoxicity.

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Introduction

Fungal infections are considered a growing global public-health concern, affecting more than 15 million cases and cause more than 1.5 million deaths annually worldwide (Bongomin et al. 2017).

These infections are most frequently associated with a compromised host immune system or health problems such as

chronic lung disease, prior tuberculosis (TB), human immunodeficiency virus (HIV) infection, cancer and diabetes mellitus (World Health Organization 2022). Azoles, echinocandins, polyenes and pyrimidine analogues are widely prescribed as first-line treatments against fungal infections; however, increased resistance to these drugs has complicated the issue (Hui et al. 2024). According to the Fungal Priority Pathogens List (FPPL) published by the World Health Organization (WHO) in 2022, 19 human pathogenic fungal species represent a major threat to health. The most critical species include *Candida albicans*, *Candida auris*, *Cryptococcus neoformans* and *Aspergillus fumigatus* due to their high ability to resist antifungal drugs (World Health Organization 2022). This increase in resistance has necessitated exploration of effective alternative therapies (Alajlani 2023). Among these, natural products, particularly plants are considered one of the main sources of new antifungal drugs (Dantas et al. 2025).

Plants in particular produce secondary metabolites, which have no direct function in essential processes such as photosynthesis, respiration, solute transport, protein synthesis, nutrient assimilation, the differentiation or formation of carbohydrates, proteins and lipids, but are essential for long-term survival and with numerous biological activities, making them also extremely important for human health and well-being (González Mera et al. 2019). These compounds are usually classified into three major chemical classes known for biological activity including antimicrobial properties: terpenoids, phenolics and alkaloids. In particular, terpenoids represent one of the most diverse secondary metabolite groups and include more than 50,000 known compounds (Chassagne et al. 2021). The wide variety of chemical components in plant extracts makes it severely challenging for microorganisms to develop resistance mechanisms against them; hence, investigation and screening of these plants for chemical compounds with considerable antimicrobial activity has been a continuous process (Alothyqi et al. 2016).

Libya occupies an area of about 1.7 million km^2, of which more than 90% is a desert. The climate is typically Mediterranean, with erratic rainfall. Libya has a number of advantages in medicinal plants production including low production costs, suitable climatic conditions, and large areas of wild medicinal species (Louhaichi et al. 2011). Medicinal plants are distributed all over the country, and about 450 species are reported to be of medicinal value; more than 100 species are utilized by local people in folk medicine; these plants have been widely used as drinks or chewed fresh or dry. They are also used to cure diseases and fungal, viral or bacterial infection (Auzi 2003). Despite the widespread use of medicinal plants in traditional therapeutics in Libya, scientific research on the medicinal value of these plants and especially their antifungal activity remains limited.

Therefore, this systematic review is considered to the best of our knowledge the first work aiming to summarize the available scientific evidence of Libyan medicinal plants against human pathogenic fungi covering studies published between 1 January 2010 to 26 August 2025. The review also aims to highlight existing knowledge gaps to assist in advancing future research on the antifungal potential of Libyan medicinal plants.

Materials and Methods

Study design

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines (Page et al. 2021), by providing a structured checklist descriptive details, databases, research strategies, eligibility criteria, data extraction and risk of bias assessments. The protocol for this review was registered with the International

Prospective Register of Systematic Reviews (PROSPERO) on 27 August 2025 (registration number: CRD420251121497).

Research strategy

Searches were conducted in the following bibliographic databases: PubMed, Dimensions and OpenAlex, supplemented with Libyan journals and Google Scholar. The electronic searches used keywords and employed the Boolean operators 'AND' and 'OR' to create search strings in Dimensions, OpenAlex, Google Scholar and PubMed. Manual searching of Libyan journal websites was also performed using the same keywords. Studies with publication dates were limited to between 1 January 2010 and 26 August 2025 were included. Only studies published in English and Arabic were considered. All search strategies and keywords used in this systematic review are shown in Table 1.

Table 1. Search strings used in electronic databases

Database	Search Strings	Date Searched
Dimensions	Antifungal agent OR antimicrobial AND plant extract AND Libya Antimicrobial OR *Candid albicans* AND plant extract AND in Libya Antimicrobial AND plant extract AND Libya	26 August 2025
OpenAlex	"Libyan AND medicinal plants OR plants extract AND antimicrobial OR antifungal" "Antimicrobial activity AND plant extract AND medicinal plant AND Libya"	26 August 2025
PubMed	Antifungal activity [Title/Abstract] OR antifungal inhibition [Title/Abstract] OR antimicrobial activity [Title/Abstract] AND plant extract [Title/Abstract] OR medicinal plants [Title/Abstract] AND in Libya [Title/Abstract] OR Libyan [Title/Abstract]	26 August 2025
Google Scholar	("Antifungal activity" OR "Antifungal properties" OR "Antifungal effect" OR" Antimicrobial activity" OR "inhibition of fungal growth" AND "medicinal plants" OR "herbal remedies" OR " Herbal treatment " AND " Libya " OR" grown in Libya")	20-26 August 2025
Libyan Journals (Manual search)	Titles and abstracts screened were manual	20-26 August 2025

Inclusion criteria

This review included only primary *in vitro* experimental studies that were published in scientific journals between 1 January 2010 to 26 August 2025. Eligible studies investigated medicinal plants which are growing in different regions of Libya, both cultivated and wild, and tested their efficacy against *C. albicans* and other human pathogenic fungi. Publications in both Arabic and English were included.

Exclusion criteria

Studies were excluded if they involved plants not growing in Libya, were *in vivo* experimental studies or were published before 1 January 2010 and after 26 August 2025 were excluded. Additionally, articles that investigated fungal species not pathogenic to human, articles written in languages other than Arabic or English, conference papers, theses, reviews, and book chapters were also excluded.

Study selection

The study selection process was conducted independently by the authors to identify potentially eligible studies and involved three stages. In the first stage, duplicates were removed using Rayyan software. The second stage involved screening by title and abstracts, and finally, full-text screening to ensure eligibility based on the predefined inclusion criteria.

Data extraction

All included articles were examined and information was extracted from each study using a standardized form that included the following columns: scientific name of the plant used in the study, part of the plant used, type of solvent, target fungi species,

measurement type, and the conclusion of each study.

Quality assessment

The included studies were assessed for quality and risk of bias based on the 12 criteria (C1- C12) as shown in the Table 2. A modified version of the Quality Assessment Tool For *In Vitro* Studies (QUIN) tool (Sheth et al. 2024) was used to adapt it for the current review which focuses on *in vitro* antifungal studies of Libyan medicinal plants. The two authors independently evaluated each study and discussed any discrepancies. Each study was evaluated by assigning one of the following scores to every one of the twelve items 0-2 scale (0 = not reported, 1= partially reported, 2= clearly and completely reported). The scores were summed together to obtain an overall score for each *in vitro* study and utilized to determine the final percentage (%) score, according to this formula: Final score (%) = (overall score / 2 × number of pertinent criteria) × 100. The final percentage (%) scores obtained were used to classify each of the studies as high risk of bias (below 50 %) medium risk of bias (between 50% and 70%), and low risk of bias (70% and above).

Table 2. Quality Modified Criteria Checklist

S/N	Criteria Checklist
1	Clearly stated aims /objective
2	Identification of plant and collection description (Scientific name, family, part used, location, voucher specimen)
3	Detailed extraction
4	Clear description of test fungi
5	Detailed description of antifungal assay methods
6	Measurement of results methods
7	Use positive and negative control
8	Experiment replicated at least 3 times
9	Statistical analysis
10	Randomization
11	Presentation of results
12	Declaration of conflicts

Results

Study selection

The searches initially retrieved 2,982 records published between 1 January 2010 and 26 August 2025. In the first stage a total of 245 duplicate articles were removed using the Rayyan software. At the second stage, 2,737 articles were screened by title and abstract according to the predefined inclusion criteria, resulting in the exclusion of 2,600 and reducing the number of articles to 137 articles. Of these, five records were excluded because the full text was inaccessible. In the final stage, the 132 full-text articles were screened against all inclusion criteria. Of these, 45 peer-reviewed articles were included, whereas 87 were excluded. Reasons for exclusion were recorded. The study selection process is presented in PRISMA flow diagram (Figure 1).

Study characteristics

This systematic review included a total of 45 *in vitro* studies evaluating Libyan medicinal plants against human pathogenic fungi. These studies were published between 1 January 2010 and 26 August 2025. The following sections provide an overview of the 45 studies with the reported antifungal activity recorded, (Figure 2) illustrates their annual distribution, while Table 3 summarizes the main characteristics of each study.

Table 3. Data extraction from *in vitro* studies evaluating antifungal activity of medicinal plants.

Author /Year	Plant Name	Part Used	Target Fungi	Solvent Used	Measurement Type	Conclusion
(Abdelshafeek et al. 2010)	*Ballota andreuzziana* *Teucrium zanonii* *Verbena tenuisecta*	Flowers and Buds	*C. albicans*	Essential oil MeOH, n-BuOH, PE	IZD (mm)	MeOH and butanol extracts showed activity against *C. albicans*, whereas PE was inactive. Major constituents included caryophyllene (63.1%) in *B. andreuzziana*, germacrene-D in *T. zanonii* and 1-octen-3- ol (52.87%) in *V. tenuisecta.*
(Hasan et al. 2011)	*Myrtus communus* *Arbutus pavarii* *Pistacia lentiscus*	Leaves and Fruits	*C. albicans, A. flavus*	EtOH (98%)	IZD (mm)	All extracts showed low-to-moderate antifungal activity compared with nystatin. Contained flavonoids, tannins, and phenolic constituents.
(Giweli et al. 2012)	*Satureja thymbra*	Aerial parts	*A. flavus, A. fumigatus* *A. niger, C. albicans*	Essential oil	MIC, MFC (mg/mL)	Essential oil showed strong activity (MIC = 0.001-0.025 mg/mL; MFC =0.001–0.1 mg/mL) exceeding bifonazole (MIC=1.5; MFC = 2 mg/mL), likely linked to γ-terpinene, thymol, p-cymene and carvacrol.
(Abd-Alla et al. 2013)	*Daucus syrticus*	Aerial parts, Roots, and Seeds	*A. niger*; *C. albicans*	Essential oil, PE, acetone fraction	IZD (mm) MIC (µg/mL)	Volatile oil and fatty acid fractions showed moderate activity lower than nystatin, likely due to β-asarone and sterol/triterpene compounds.
(Abdelshafeek et al. 2013)	*Daucus syrticus*	Whole plant	*A. niger*; *C. albicans*	MeOH, EtOAc, n-BuOH, $CHCL_3$	IZD (mm) MIC (µg/mL)	Luteolin, 7,4- dimethoxy Luteolin, 6-hydroxy 4-methoxy apigenin, diosmetin-7-O-glucoside, Luteolin 3'-O- glucoside and 4'-methoxy Luteolin 7-O-rhamno-arabinoside were isolated. Luteolin was highly active against *A. niger*
(Alsabri et al. 2013a)	*Helianthemum lippii*	Aerial parts	*C. albicans*	PE→$CHCl_3$→ MeOH	IZD (mm) MIC (mg/mL)	MeOH extract inhibited *C. albicans* with (IZD 20 mm; MIC= 6.25 mg/mL), comparable to AmB (22 mm). Antifungal activity was likely related to flavonoids, tannins, saponins and simple phenolics; acute toxicity was low (safe up to 15,000 mg/kg).
(Alsabri et al. 2013b)	*Arbutus pavarii*	Aerial parts	*C. albicans*	MeOH, $CHCl_3$, n-hexane	IZD (mm) MIC (mg/mL)	MeOH extract showed strong IZD (21mm) comparable with AmB, likely linked to flavonoids, tannins, simple phenolics, triterpenes and sterols; n-hexane exhibited weak effect IZD (2mm); $CHCl_3$ was inactive. Antiproliferative activity was also observed.
(Giweli et al. 2013)	*Salvia fruticosa*	Aerial parts	*A. flavus, A. fumigatus* *A. niger , C. albicans*	Essential oil	MIC,MFC (mg/mL)	Essential oil exhibited antifungal activity (MIC = 0.125-1.0 mg/mL). *A. flavus* was most sensitive (MFC = 0.125 mg/mL), with activity exceeding bifonazole. *A. niger* was most resistant with higher MIC/MFC values. 1,8-cineole may be responsible for the antifungal activity
(Berfad et al. 2015)	*Posidonia oceanica*	Whole plant (seagrass)	*A.flavus*	AQ	Inhibition (%)	.AQ extract of P. oceanica showed 33.3% inhibition of *A. flavus* (5-15% w/v), likely associated with tannins, phlobatanins, terpenoids and saponins.
(Gamal and Atraiki 2015)	*Ferula communis*	Whole plant	*C. albicans, C. glabrata*	EtOAc, n-BuOH	MIC (mg/mL)	EtOAc extract showed moderate activity against *C. albicans* and *C. glabrata* (MIC= 0.8-1.0 mg/mL), lower than AmB, likely associated with flavonoids, alkaloids, terpenoids, diterpenes, glycosides and tannins.
(Sabry et al. 2016)	*Haplophyllum tuberculatum*	Aerial parts and Flowers	*A. fumigatus C. albicans*	Essential oil; percolation (95%) EtOH	IZD (mm) Potency (%) MIC (µg/mL)	The essential oil showed strong activity against *A. fumigatus* with (MIC = 0.49-1.95 µg/mL; IZD 20-22 mm; potency 93.6%) compared with AmB. EtOH showed moderate activity (MIC= 7.8 µg/mL; IZD 17.8 mm;75%). *C. albicans* was resistant. Acute toxicity was low (LD_{50} > 10 g/kg), indicating safety.

Table 3. Continued

(El-Hawary et al. 2016)	*Arbutus pavarii* *Sarcopoterium spinosum* L.	Aerial parts	*A. fumigatus, A. niger, C. albicans, C. tropicalis*	MeOH (90%)	IZD (mm)	*A. pavarii* showed strong activity against *A.fumigatus* (33.3 mm) exceeding AmB (23.7 mm) and *A. niger* (21.1 mm ≈ AmB 21.8 mm), moderate activity against *C. tropicalis* and no activity against *C. albicans*. *S. spinosum* extract was moderately comparable with AmB all species; inactive against *C. tropicalis*. MeOH extracts were rich in phenolics and flavonoids. *A. pavarii* extract proved to be highly effective IC_{50} 19.7±2.8 and 19±0.65 (µg/ml) on HEPG2 and T47D cell lines.
(El Zalabani et al. 2017)	*Artemisia monosperma* Del.	Aerial parts	*A. fumigatus, C.albicans*	Essential oil	IZD (mm) MIC (µg/mL)	Essential oil samples (A_1-A_3) showed moderate activity against *A. fumigatus, C. albicans* compared with AmB. Major compounds included sabinene, β-pinene, β-cis-ocimene, bornyl acetate and β-eudesmol. Median lethal dose (LD_{50}) was greater than 0.05 mL/kg body weight.
(Elghwaji et al. 2017)	*Ferula tingitana* L.	Flower and Leaves	*C. albicans* (ATCC 26555) *A. flavus*	Essential oil	IZD (mm) Potency (%)	Essential oil samples (leaves and flowers) showed no activity against two species. The main constituents of both flowers and leaves derived oil samples were α-thujene, elemol, eudesmol and cadinol. Cytotoxicity against breast (MCF7), cervical (HeLa), liver (HePG2) carcinoma cell lines with IC_{50} (6.9, 4.8), (8.6, 10.9), (4.4, 4.3) for the flower and leaves respectively.
(El-tawaty et al. 2018)	*Capparis spinosa* subsp orientalis (Duh.)	Leaves and Bark	*C. albicans*	MeOH, EtOH, $CHCl_3$, AQ	IZD (mm) MIC (mg/mL)	MeOH bark and leaf extracts showed moderate activity against *C. albicans* (IZD16 mm ± 0.71; MIC = 50 mg/mL). EtOH leaf and bark extracts recorded IZD (15 -18 mm). These activities may be contributed to the high content of flavonoids and tannins. $CHCl_3$ leaf and bark extracts were weakly active, whereas AQ was inactive.
(Duletić-Laušević et al. 2018)	*Salvia fruticosa* Mill. *Salvia lanigera* Poir.	Aerial parts	*C. krusei, C. albicans, C. parapsilosis, A. fumigatus A. flavus T. mentagrophytes*	EtOH, AQ	MIC, MFC (mg/mL)	EtOH extract of *S. fruticosa* was inactive against all *Candida* species. *S. lanigera* showed low-to-moderate inhibition (MIC =16-64 mg/mL) compared with ketoconazole. The AQ extract was active only against *C. parapsilosis* (MIC = 32 mg/mL). The plants contained phenolic and flavonoid. Cytotoxicity was evaluated (IC_{50} 375.96 µg/mL) for *S. fruticosa* EtOH extract.
(El-Jalel et al. 2018)	*Thymus capitatus* L.	Aerial parts	*C. albicans, A. niger*	Essential oil	IZD (mm)	Low and high altitudes oils showed activity against *C. albicans* IZD (40, 34 mm respectively), while moderate activity against *A. niger* compared with nystatin. Antifungal activity was attributed to high carvacrol content, supported by b-caryophyllene, caryophyllene oxide and phenolic compounds.
(Elgubbi et al. 2019)	*Acacia raddiana*	Leaves	*C. albicans*	EtOH (80%); Fractiona (PE, $CHCl_3$, EtOA, EtOH)	Inhibition (%)	Inhibition percentage of the flavonoids extract against *C. albicans* was 70% compared with 100% for nystatin. Crude EtOH extract was inactive.

Table 3. Continued

(Elmarimi et al. 2019)	*Syzygium cumini* L.	Leaves	*C. albicans*	MeOH decoction; PE, $CHCl_3$, MeOH, EtOAc	IZD (mm)	Only MeOH extract showed antifungal activity against *C. albicans*. Phytochemical screening revealed flavonoids, anthocyanin, triterpenes, glycosides, tannins, saponins, alkaloids, steroids and coumarins.
(Othman et al. 2019)	*Pistacia atlantica*Desf.	Leaves	*C. albicans*	n-hexane, EtOAc, MeOH	IZD (mm)	MeOH extract inhibited *C. albicans* (IZD 18.5 mm), while EtOAc was inactive. It contained six polyphenols: gallic acid (1), ellagic acid (2), 3,3'-dimethoxyellagic acid (3) and three gallotannins, 2,3-di-O-galloyl-(α/β)-4C1 glucopyranose, nilocitin (4),1,3-di-O-galloyl-β-D-4C1-glucopyranose (5), 1,2,3,4,6- penta-O galloyl-β-D-4C1-glucopyranose (6).
(Bengleil et al. 2020)	*Globularia alypum*	Aerial parts	*A. flavus*, *C. albicans*	MeOH (70%)	IZD (mm)/ % potency	The MeOH extract showed activity against *A. flavus* (10 mm; 59%), *C. albicans* (14 mm; 74%), which was lower than AmB (17-19 mm; 100%). Phytochemical screening showed condensed tannins, flavonoids and phenolic compounds.
(Zargoun et al. 2020)	*Arum cyrenaicum*	Herbs, Seeds and Roots	*C. albicans A. flavus A. niger*	AQ, MeOH, PE, $CHCl_3$, EtAc, n-BuOH	IZD (mm)	All extracts (AQ, MeOH, PE, $CHCl_3$, EtAc, n-BuOH) were inactive against *C. albicans*, *A. niger* and *A. flavus*.
(Khalil et al. 2020)	*Satureja thymbra* L.	Aerial parts	*C. albicans A. niger*	Essential oil	IZD (mm), MIC/ MLC (µg/mL)	Low-altitude oil showed strong antifungal activity compared to those at high-altitudes oil. *A. niger* was least responsive. The major compounds were thymol in the low-altitude and carvacrol in the high-altitude. cytotoxicity on (MCF-7) and (HCT-116) cells; showed activity specially against HCT-116 with IC50 2.45 ± 0.21 µg/ml.
(Alshalmania et al. 2020)	*Ephedra alata*	Aerial parts	*A. flavus*, *C. albicans*	MeOH (70%)	IZD (mm)	MeOH extract showed weak antifungal activity compared with AmB. MeOH extract revealed the presence of alkaloids, flavonoids, steroids, tannins, and phenolic compounds. The extract exhibited a significant cytotoxic effect on MCF7 with IC50 and IC90 comparing with doxorubicin
(Miloud and Senussi 2021)	*Euphorbia paralias* L. *Melilotus sulcatus* Desf.	Leaves	*A. flavus*, *A. niger*	MeOH, AQ	IZD (mm)	MeOH extracts moderate activity (IZD 9 mm) against *A. flavus*, *A. niger* which was lower than fluconazole (14 mm). AQ extracts were inactive.
(Elkady et al. 2021)	*Pinus halepensis* L. *Pinus pinea* Mill.	Aerial parts	*C. albicans*	Eeesntial oil	IZD (mm)	*P. halepensis* showed moderate activity against *C. albicans* (IZD 10-15 mm) compared with nystatin (18 mm). *P. pinea* oil was inactive. Major compounds in two species included α-pinene, thunbergol, aromadendrene oxide, limonene, β-Caryophyllene.
(Alamami et al. 2021)	*Cistus salviifolius*	Aerial parts	*A.niger*, *A fumigatus*, *C. tropicalis*, *C. albicans*	MeOH (70%)	IZD (mm) MIC(µg/mL)	MeOH extract showed strong against *A.fumigatus* (22.2 mm; MIC= 0.98 µg/mL), *A. niger* (20.6 mm; MIC =1.95 µg/mL) and moderate against *C. albicans* (18.3 mm; MIC= 7.81 µg/mL). It was inactive against *C. tropicalis*. Catechin and gallic acid were the major constituents in the extract.
(Tayeb et al. 2021)	*Laurus nobilis*	Leaves and Stem	*A. niger*	MeOH (80%)	IZD (mm)	No antifungal activity was reported at any concentration.

Table 3. Continued

(Jamaa et al. 2022)	*Rosmarinus officinalis* *Lippia citriodora*	Leaves	*C. albicans, C. glabrata,* *C. parapsilosis*	Essential oil	IZD (mm)	*R. officinalis* showed inhibition (≤15 mm) against Candida species, while *L. citriodora* showed weak activity.
(Fadl and Khalfallah 2022)	*Lawsania inemis*	Leaves	*T. rubrum* *T. mentagrophytes*	EtOH, AQ	IZD (mm)	AQ extract (40%) stronger than EtOH; synergy with miconazole greater than clotrimazole.
(Mohammed et al. 2022)	*Jasonia glutinosa*	Whole plant	*C. albicans*	MeOH (70%)	IZD (mm)	Despite the presence of active compound in the extract, such as phenolics and flavonoids, the MeOH extract demonstrated no antifungal activity. The plant was considered a weak cytotoxic effect when compared to the standard anticancer agent, doxorubicin (DOX).
(Abushiba et al. 2023)	*Drimia maritime*	Leaves and Tubers	*C. albicans A. niger*	AQ ,EtOH, benzene	IZD (mm)	AQ tuber extract was active against *C. albicans* (IZD 18 mm) but inactive against *A. niger*. Leaves: EtOH and benzene extract were inactive. The cytotoxicity tests showed that the leaves had moderate toxicity, while the tubers did not exhibit any toxic effects.
(Dakhil et al. 2023)	*Malva parviflora*	Leaves	*A. fumigatus, C. albicans*	PEF, AQ, EtOAc, MeOH, MF	Inhibition IC_{50}	PEF fraction strongest (94.96%) against *A. fumigatus.* AQ extract (96.48%) against *C. albicans.* EtOAc least effective (77.8%), and MeOH fraction (lowest IC_{50}). Total phenolic and flavonoids were found to PEF extract
(Fathallah et al. 2023)	*Pinus halepensis* *Pinus pinea*	Aerial parts	*C. albicans*	EtOH (95%) fraction; n-hexane, $CHCl_3$ EtOH	IZD (mm)	Total EtOH and hexane extracts of both plants: showed moderate activity against *C. albicans* (≤ 10 mm) compared with AmB, while $CHCl_3$ and EtOH fractions were inactive. The cytotoxicity was evaluated against breast and colon cell lines, where the Pp-W locality showed the strongest cytotoxic activity against both cell lines.
(Miloud 2023)	*Cistus incans* L. *Cistus salvifolius* L. *Cistus parviflorus*	Leaves	*A. flavus, A. niger*	MeOH	IZD (mm)	MeOH extracts of the three species yielded IZD (9-12 mm), which was slightly lower than fluconazole (14 mm).
(Miloud and Senussi 2023)	*Silene gallica* L. *Silene succulent* Forsk. *Silene apetala* Willd.	Aerial parts	*A. flavus A. niger*	MeOH, EtOH, acetone	IZD (mm), MIC, MFC (mg/mL)	Acetone extracts of *S. gallica* L and *S. apetala* low-to-moderate against *A. niger* and *A. flavus*. EtOH and MeOH were less active, while *S. succulenta* extracts were inactive.
(Elshibani et al. 2023)	*Thymbra linearifolia*	Aerial parts	*C. albicans*	AQ, EtOH (95%)	IZD (mm), MIC (mg/mL)	EtOH extract yielded (IZD =17 mm; MIC= 0.63 mg/ mL). Extract had strong cytotoxic effects on three types of cancer cell lines (MCF-7, HepG2, and Panc-1, with IC_{50} values of 24.023, 22.94, and 33.30 g/mL, respectively). The plant extract revealed the presence phenolic acids and flavonoids.
(El-tawaty et al. 2023)	*Pistacia lentiscus* L.	Fruits	*C. albicans*	$CHCl_3$, MeOH	IZD (mm)	$CHCl_3$ (IZD10 mm), MeOH (IZD 8 mm) extracts showed weak activity compared with fluconazole (26.1±1.2 mm). Active compounds chloroform extract were phenol,3-pentadecyl, benzene,1-(1,1-dimethylpropoxy)-4 methyl and isobutyl-3-methylpyrazine, whereas methanol extract compounds were 1,2,3-benzenetriol, benzoic acid,3-hydroxy and quinic acid.
(Adem and Auzi 2024)	*Cynomorium coccineum* L.	Aerial parts	*C. albicans C. neoformans, A. niger, A. flavus*	MeOH (97%)	IZD (mm) MIC (mg/mL)	MeOH extract showed activity against *C. albicans* and *C. neoformans.* (MIC 125-250 mg/mL) but it was inactive against *A. niger* and *A. flavus.* The extract contained flavonoids, terpenoids, saponins, tannins, cardiac glycosides and phenols.

Table 3. Continued

(Elshibani et al. 2024)	*Haplophyllum tuberculatum*	Aerial parts	*A. niger, C. albicans*	Essential oil	IZD (mm)	The essential oil was active against *C. albicans* (IZD 22 mm), and weaker against *A. niger* (IZD 12 mm). The major volatile constituents were δ-3-carene, bornyl acetate and limonene aldehyde. The oil also exhibited *in vitro* anti-cancer activities.
(Alkabou et al. 2024)	*Mesembryanthemum crystallinum* L.	Leaves	*C. albicans*	AQ, EtOH (70%), MeOH (50%)	IZD (mm)	EtOH extract was the most active (IZD 17 mm) followed by MeOH (16 mm) and AQ (15 mm). The EtOH extract contained saponins and resins, alkaloids, glycosides, flavonoids and tannins in the AQ extract.
(Zubi et al. 2024)	*Cyclamen rohlfsianum*	Tubers	*C. albicans, C. tropicalis, C. krusei*	EtOAc, $CHCl_3$, EtOH n-hexane	IZD (mm)	$CHCl_3$ and hexane extracts were active against *C. albicans, C. krusei*, but inactive against *C. tropicalis.*
(Fouad et al. 2024)	*Arbutus pavarii* *Rosmarinus officinalis* L.	Leaves	*C. albicans, A. niger*	Maceration (MeOH, $CHCl_3$, n-hexane)	IZD (mm)	Both extracts demonstrated no antifungal activity. Chemical constituents included phenolics, terpenoids, flavonoids, and fatty acids. *A. pavarii* showed moderate toxicity against cancer cells, while *R. officinalis* L demonstrated low toxicity against lung cells and colon cells.
(Hasan et al. 2024)	*Cistus salviiflius* *Cistus parviiflous*.	Leaves, Root, Stem	*A. niger*	AQ, EtOH	IZD (mm)	AQ and EtOH extracts of both species were inactive against *A. niger* Chemical screening included glycosides, tannins, flavonoids, triterpenes, saponins, and anthraquinones
(Abdulla et al. 2025)	*Phragmites australis*	Aerial parts	*C. albicans* (ATCC 10221)	EtOH	IZD (mm)	EtOH extract showed strong activity against *C. albicans* (IZD =33 mm). Flavonoids such as rutin, quercetin, luteolin-7-O-glucoside, caffeic acid, and apigenin-6-C-glucoside, as well as phenolic acids such as protocatechuic acid, coumaric acid, and feruloyl-quinic acid derivatives were identified. *In vitro* cytotoxic activity particularly against MCF-7 and Caco-2 cells.

Abbreviations: C*: Candida;* C: *Cryptococcus;* A*: Aspergillus*, IZD: Inhibition Zone Diameter; MIC: Minimum Inhibitor Concentration; MFC: Minimum Fungicidal Concentration; MF: Methanol Fraction;MeOH: Methanol; PE: Petroleum Ether; EtOH: Ethanol; EtAc: Ethyl Acetate; AQ: Aqueous; $CHCl_3$; Chloroform, n-BuOH: n-Butanol; PEF: Petroleum Ether Fraction; NR: Not Reported; ATCC: American Type Culture Collection; RCMB: Regional Center for Mycology and Biotechnology; IMRU: Waksman Institute of Microbiology Culture Collection (Rutgers University); AmB: Amphotericin B; < Lower than; > Higher than; VS: Versus/against; LC_{50} : Lethal Concentration 50%.

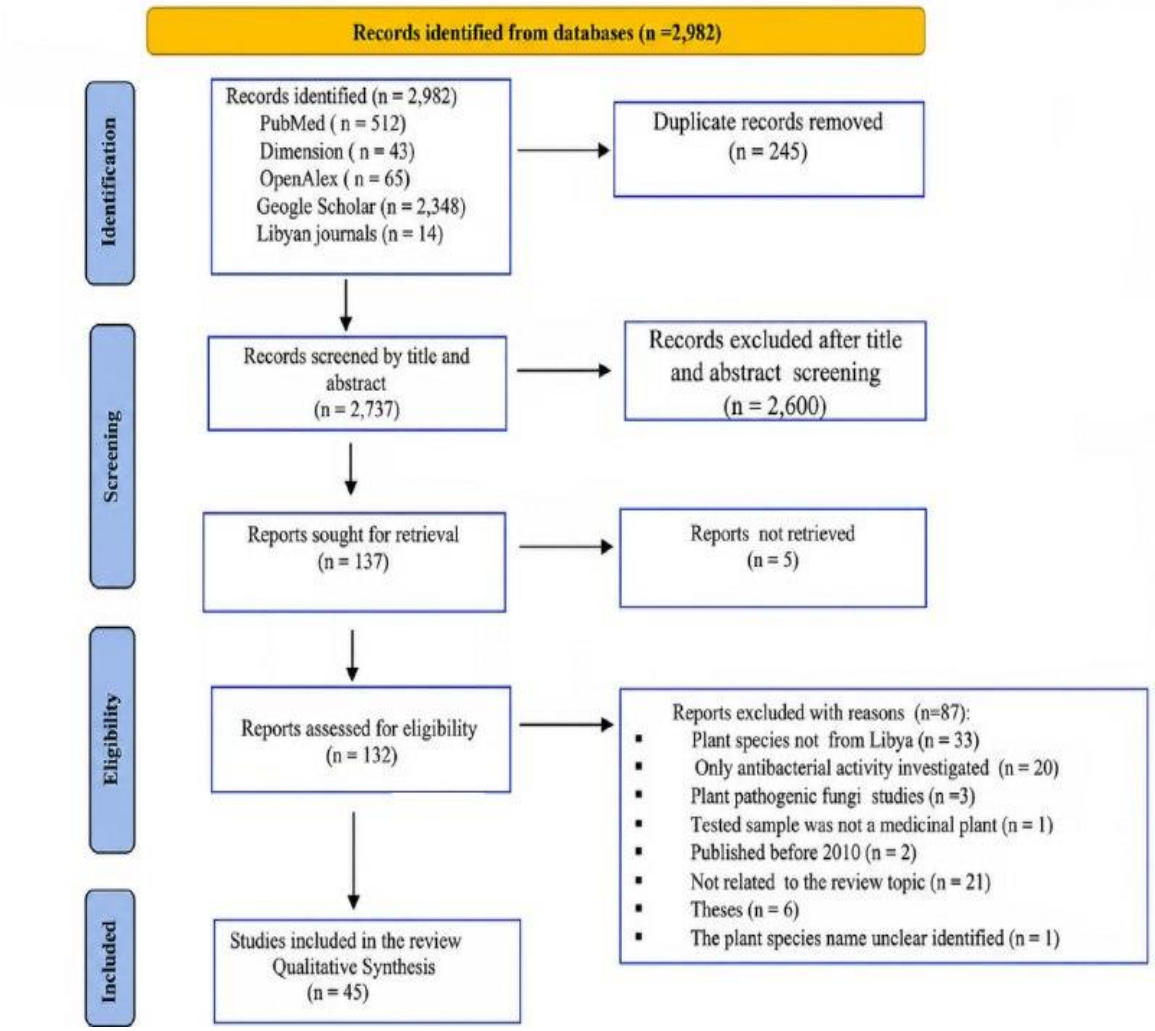


Figure 1. PRISMA flow diagram of articles screened for inclusion in the systematic review.

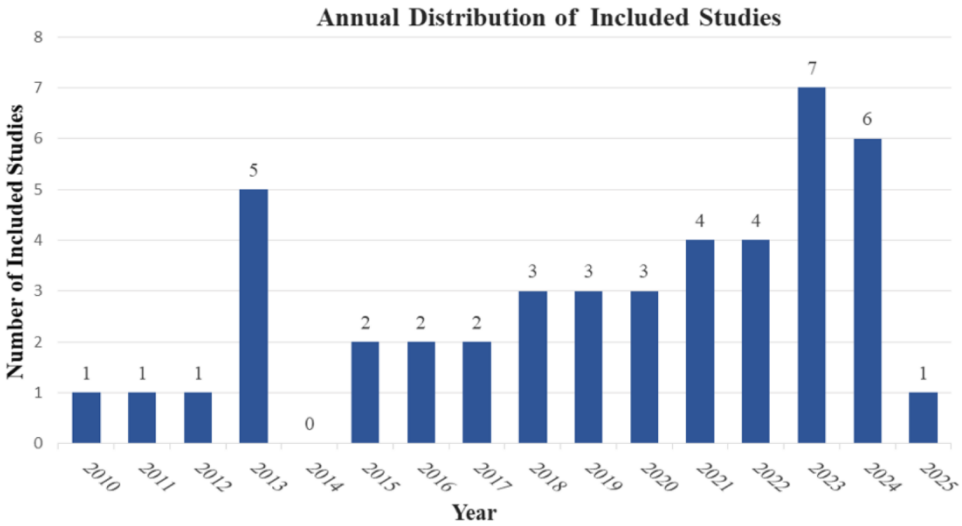


Figure 2. Annual distribution of the included studies (2010-2025).

Medicinal plants and parts used

In total, 61 medicinal plant species were documented across the 45 studies included in this systematic review. Of these, 51 species were reported in single studies only, whereas ten species were assessed in several studies and appeared more than once in this review. For example, *Arbutus pavarii* was evaluated in four separate studies (Hasan et al. 2011; Alsabri et al. 2013b; El-Hawary et al. 2016; Fouad et al. 2024). Likewise, *Rosmarinus officinalis* L. was tested in two studies (Jamaa et al. 2022; Fouad et al. 2024). *Haplophyllum tuberculatum* was assessed in two separate studies (Sabry et al. 2016; Elshibani et al. 2024). In addition, *Cistus salvifolius* L. and *Cistus parviflorus* (Alamami et al. 2021; Miloud 2023; Hasan et al. 2024), *Salvia fruticosa* (Giweli et al. 2013; Duletić-Laušević et al. 2018), *Satureja thymbra* L. (Giweli et al. 2012; Khalil et al. 2020), as well as *Pinus halepensis* and *Pinus pinea* (Elkady et al. 2021; Fathallah et al. 2022), were each evaluated in more than one investigation (Table 3). Regarding plant parts, aerial parts were investigated in 21 studies, followed by leaves in 16 studies, while whole plants, flowers, roots, seeds, tubers, fruits, buds and stems were examined only in a few studies (Figure 3 and Table 3).

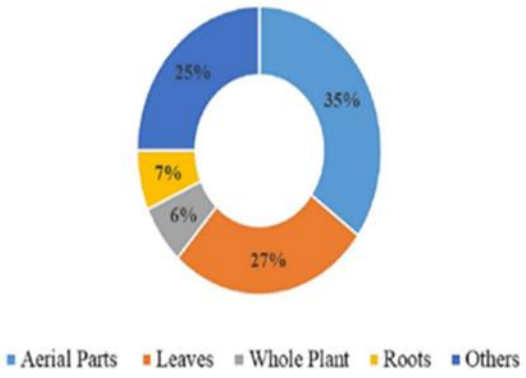
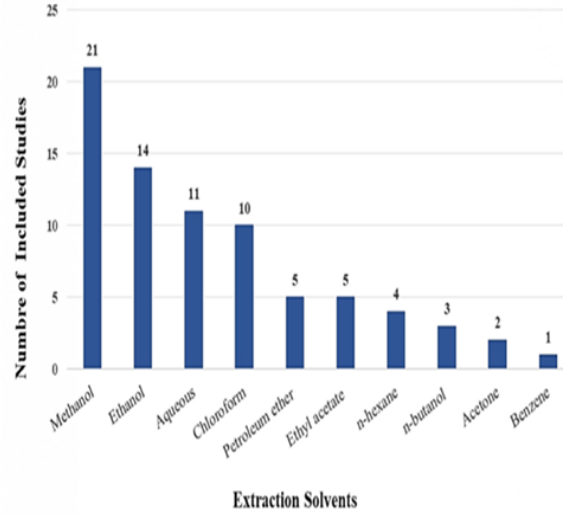


Figure 3. Plant parts extracted for antifungal investigation.

Plant extracts preparation

Methanol was the most commonly used solvent in the 45 studies, reported in 21of the included studies. It was employed in the primary extraction methods through cold maceration and Soxhlet extraction. This was followed by ethanol, which was used in 14 studies, and aqueous preparations in 11 studies. Other solvents used include chloroform in ten studies, ethyl acetate and petroleum ether in five studies, n-hexane in four studies, n-butanol in three studies, acetone in two studies and benzene in one study (Figure 4). The extraction techniques used in the literature comprised cold maceration, Soxhlet extraction, successive fractionation with various solvents. In addition, hydrodistillation was commonly used for essential oils. Throughout the included studies, the fractionated extracts were generally weak or inactive compared to crude extracts. An exception was the petroleum ether fraction used on leaves of *Malva parviflora*, which markedly exhibited strong antifungal activity against *A. fumigatus* (Dakhil et al. 2023) (Table 3).



Figur.4. Distribution of solvents used for plant extraction in the included studies

Targeted fungi and evaluation methods

Of the total 45 included studies, 38 targeted *C. albicans*, followed by19 studies on *A. niger*, 12 studies on *A. flavus* and eight studies targeted *A. fumigatus*, while other fungi such as *C. krusei*, *C. parapsilosis*, *C. glabrata*, *C. tropicalis*, *Cryptococcus neoformans* and Dermatophytes spp. had limited appearances in the studies, the distribution of fungal species tested in the included studies is illustrated in Figure 5. The agar well or disk diffusion with inhibition zone diameter (IZD) was the primary method used in 38 studies. Four studies mainly utilized broth microdilution or macrodilution assays on essential oils, providing minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) values. Twelve studies combined both approaches, while a few studies reported inhibition percentages or IC_{50} values. In most of the included studies, the positive controls were amphotericin B and nystatin, with occasional use of azoles such as ketoconazole, fluconazole and miconazole (Table 3).

Quality assessment of included studies

The quality of the included studies was assessed using the modified Quality Evaluation Instrument for *In Vitro* Studies (QUIN; 12 criteria, 0-2) (Sheth et al. 2024). The overall scores of individual studies were converted into percentages, as shown in Table 4, 23 studies (51.1%) were classified as having a low risk of bias, with percentage scores ranging from 70.8-91.6%, whereas 18 studies (40 %) had a medium risk of bias, with percentage scores ranging 50-66.6%, while four studies (8.8 %) fell into the high risk of bias with a percentage (45.8%).

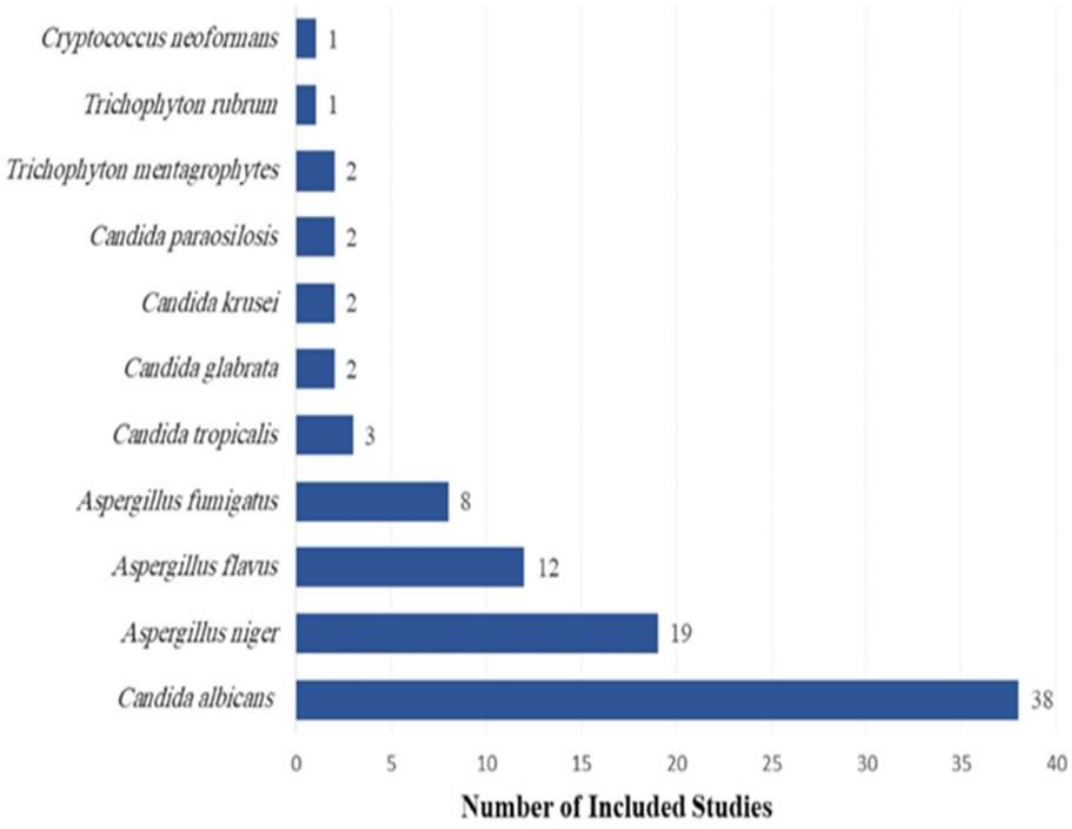


Figure 5. Distribution of fungal species tested in the included studies.

Table 4. Quality assessment and risk of bias for the included studies.

	Criteria /Checklists														
Authors/Year	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	Overall score	Score (%)	Risk of bias
Abdelshafeek et al. (2010)	1	1	2	1	1	1	0	1	1	0	2	2	13	54.1%	Moderate
Hasan et al. (2011)	2	1	2	1	2	1	2	0	0	0	2	0	12	50%	Moderate
Giweli et al.(2012)	2	2	2	2	2	2	2	0	0	0	2	0	16	66.6%	Moderate
Abd Alla et al. (2013)	1	1	2	1	2	2	1	1	0	0	2	2	15	62.5%	Moderate
Abdelshafeek et al. (2013)	1	1	2	1	2	2	0	0	0	0	2	0	11	45.8%	High
Alsabri et al. (2013a)	1	1	2	2	2	2	2	2	1	0	2	0	17	70.8%	Low
Alsabri et al. (2013b)	1	1	2	2	2	2	1	2	2	0	2	0	17	70.8%	Low
Giweli et al. (2013)	2	2	2	2	2	2	2	1	1	0	2	0	18	75%	Low
Berfad et al. (2015)	2	1	2	1	1	1	1	0	0	0	2	0	11	45.8%	High
Gamal and Atraiki (2015)	1	1	2	2	1	2	2	1	1	0	2	0	13	54.1%	Moderate
Sabry et al. (2016)	2	2	2	2	2	2	2	2	2	0	2	0	20	83.3%	Low
El Hawary et al.(2016)	1	1	2	2	2	1	2	2	2	1	2	0	18	75%	Low
El Zalabani et al. (2017)	2	2	2	2	2	2	2	2	2	0	2	2	22	91.6%	Low
Elghwaji et al. (2017)	1	2	2	1	1	1	0	1	0	0	2	2	13	54.1%	Moderate
Eltawaty et al. (2018)	1	1	2	2	2	2	1	1	2	0	2	0	16	66.6%	Moderate
Duletić-Laušević et al. (2018)	1	2	2	2	1	2	2	2	2	0	2	0	18	75%	Low
El-Jalel et al. (2018)	1	2	2	1	2	1	2	2	2	0	2	0	17	70.8%	Low
Elgubbi et al. (2019)	2	1	2	1	1	1	2	1	0	0	2	0	13	54.1%	Moderate
Elmarimi et al. (2019)	1	2	2	2	2	1	2	1	0	0	2	2	17	70.8%	Low
Othman et al. (2019)	1	1	2	2	1	1	1	0	1	0	2	0	12	50%	Moderate
Bengleil et al. (2020)	1	1	2	1	2	1	1	0	1	0	2	2	14	58.3%	Moderate
Zargoun et al. (2020)	1	1	2	1	1	1	1	0	0	0	2	2	12	50%	Moderate
Khalil et al. (2020)	1	2	2	2	2	2	2	2	1	0	2	2	20	83.3%	Low
Alshalmani et al. (2020)	1	1	2	1	1	1	2	0	0	0	2	0	11	45.8%	High
Miloud and Senussi (2021)	2	1	2	1	1	1	2	2	1	0	2	2	17	70.8%	Low
Elkady et al. (2021)	1	2	2	2	2	1	2	2	1	0	2	2	19	79.1%	Low
Alamam et al. (2021)	1	1	2	2	2	2	2	2	1	0	2	2	19	79.1%	Low
Tayab et al. (2021)	2	1	2	1	1	2	0	2	0	0	2	0	13	54.1%	Moderate
Jamaa et al. (2022)	2	1	2	1	1	1	2	2	2	0	2	0	16	66.6%	Moderate

Table 4. Continued

Fadl and Khalfallah (2022)	2	1	2	2	1	1	2	0	1	0	2	0	14	58.3%	Moderate
Mohammed et al. (2022)	1	1	2	2	2	1	1	2	2	0	2	2	18	75%	Low
Abushiba et al. (2023)	2	1	2	2	2	1	1	2	1	0	2	0	16	66.6%	Moderate
Dakhil et al. (2023)	2	1	2	2	2	2	1	1	1	0	2	0	16	66.6%	Moderate
Fathallah et al. (2023)	1	1	2	1	2	1	2	0	0	1	2	2	15	62.5%	Moderate
Miloud (2023)	2	1	2	1	2	2	2	2	1	0	2	0	17	70,8%	Low
Miloud and Senussi (2023)	2	1	2	1	2	2	2	2	1	0	2	2	19	79.1%	Low
Elshibani et al. (2023)	1	2	2	2	2	2	1	2	2	0	2	2	20	83.3%	Low
Eltawaty et al.(2023)	1	2	2	2	2	1	2	2	2	0	2	2	20	83.3%	Low
Adem and Auzi (2024)	2	2	2	2	2	2	2	2	2	0	2	0	20	83.3%	Low
Elshibani et al. (2024)	1	2	2	2	2	1	2	2	2	0	2	2	20	83.3%	Low
Alkabou et al. (2024)	2	1	2	1	1	1	2	2	1	0	1	0	14	58.3%	Moderate
Zubi et al. (2024)	2	1	2	2	2	1	2	2	1	0	2	0	17	70.8%	Low
Fouad et al. (2024)	1	1	2	2	2	1	2	2	2	0	2	0	17	70.8%	Low
Hasan et al. (2024)	2	1	1	1	1	1	0	0	0	0	2	2	11	45.8%	High
Abdulla et al. (2025)	1	1	2	2	2	1	2	2	2	0	2	2	19	79.1%	Low

Abbreviations: C1: Clearly stated aims /objective; C2: Identification of plant and collection description (Scientific name, family, part used, location, voucher specimen C3: Detailed extraction; C4: Clear description of test fungi; C5: Detailed description of antifungal assay methods; C6: Measurement of results methods; C7: Use positive and negative control; C8: Experiment replicated at least 3 times; C9; Statistical analysis; C10: Randomization; C11: Presentation of results; C12: Declaration of conflicts.

Discussion

The primary aim of this systematic review was to highlight the potential of Libyan medicinal plants against human pathogenic fungi with a particular emphasis on *C. albicans* and fungal species with clinical relevance listed in the WHO Fungal Priority Pathogens List (2022), as well as recent antifungal resistance reports and published studies as a guiding framework for selection the clinically relevant fungal pathogens, whereas fungal species with limited pathogenicity were not included in this review due to insufficient evidence of their clinical relevance (World Health Organization 2022; Arendrup et al. 2024; Casalini et al. 2024; Hui et al. 2024; Hussain et al. 2024). This review synthesized the findings of 45 *in vitro* studies involving a wide range of Libyan plant species these studies collectively represent the available evidence on the antifungal activity of Libyan medicinal plants. The results demonstrated that several medicinal plants and their extracts possess inhibitory effects, in some cases approaching the efficacy of standard antifungal drugs. However, marked variation in study designs, particularly in extraction solvents, fungal strains tested, assay protocols and plant parts used, restricted direct comparability and may explain inconsistencies in the reported antifungal potency.

Among the included studies, *C. albicans* was the most frequently

investigated fungal species. Many species such as *A. pavarii*, *Ferula communis*, *Syzygium cumini* L., *Globularia alypum*, *M. parviflora* and *Phragmites australis* demonstrated strong-to-moderate inhibition when alcoholic solvents were utilized for extraction methods (Alsabri et al. 2013b; Gamal and Atraiki 2015; Elmarimi et al. 2019; Bengleil et al. 2020; Dakhil et al. 2023; Abdulla et al. 2025). This may be attributed to the ability of these solvents to solubilize a broad spectrum of polar compounds, including flavonoids, anthocyanins and phenolic compounds, which are known for their efficiency as antimicrobial (Lee et al. 2024).

Two studies examined the essential oil of *S. thymbra* L. collected from the Green Mountain region in Libya against *C. albicans*. The sample evaluated by Giweli et al. (Giweli et al. 2012) demonstrated strong antifungal activity (MIC= 0.025-0.05 mg/mL), whereas Khalil et al. (Khalil et al. 2020) showed even greater potency (MIC = 0.125 µg/mL). Despite the plant species originated from the same geographical region, the reported antifungal activity varied substantially, this variation may be attributed to micro- environmental differences within the Green Mountain, such as altitude, soil composition, rainfall, stage of plant development, harvest time, and potential shifts in essential oil chemotypes, particularly thymol and carvacrol (El-Beyrouthy et al. 2013).

Some plant species including, *A. pavarii*, *R. officinalis* L. and *H. tuberculatum*, manifested heterogeneous results, displaying positive antifungal activity against *C. albicans* (Alsabri et al. 2013b; Jamaa et al. 2022; Elshibani et al. 2024). Conversely, the same species demonstrated inconsistent results in other studies (Sabry et al. 2016; Fouad et al. 2024), which may be explained by geographical factors or genetic variation among plant species, or differences in the fungal strains tested.

The antifungal activity of Libyan medicinal plants also extended to clinically relevant non-*C. albicans* species (*C. tropicalis*, *C. glabrata*, *C. krusei* and *C. parapsilosis*), which have become a major concern due to their increasing resistance to available antifungal agents. Together with *C. albicans*, these species account for about 90% of overall fungal infections (Akwongo et al. 2024). The chloroform and hexane extracts of *Cyclamen rohlfsianum* demonstrated moderate activity against *C. krusei*, whereas no inhibitory effect was observed against *C. tropicalis* (Zubi et al. 2024). Similarly, the extracts of both *Sarcopoterium spinosum* L. and *C. salviifolius* showed no activity against these fungal species (El-Hawary et al. 2016; Alamami et al. 2021). In contrast, plants belonging to the Lamiaceae family such as *Salvia lanigera* Poir., *S. fruticosa* Mill. and *R. officinalis*, exhibited weak or inconsistent inhibition against non-*albicans* strains (Duletić-Laušević et al. 2018; Jamaa et al. 2022). Overall, the evidence suggests that while some Libyan medicinal plants have promising broad-spectrum activity against *C. albicans*, their effects against non-*C. albicans* species appear to be limited.

In this review, *Aspergillus* spp. represented the second most commonly evaluated group of human pathogenic fungi, following *Candida* spp. Among species within this genus, *A. fumigatus*, according to WHO Fungal Priority Pathogens List published in 2022, it was classified within Critical Priority Group it considered the primary causative invasive aspergillosis azole-resistance (World Health Organization 2022). This has driven the researchers to focus on identifying alternatives from plants to synthetic antifungal drugs, including those targeting *A. fumigatus* (Tan et al. 2022). In general, most of the plants included in this review demonstrated inhibitor activity against *A. fumigatus* (Sabry et al. 2016; El Zalabani et al. 2017; Alamami et al. 2021). Among the medicinal plants examined, *A. pavarii* methanolic extract recorded a large inhibition zone reaching (33.3 mm) which

was higher than amphotericin B (23.7mm) (El-Hawary et al. 2016). This activity may be attributed to the high solubility of methanol, which enables extraction of a broad spectrum of polar compounds (Lee et al. 2024). Similarly, *S. thymbra* essential oil exhibited strong antifungal activity (MIC = 0.025 mg/ml) which was lower than bifonazole (MIC =1.5 mg/mL) (Giweli et al. 2012). The potency of the this oil can be to explained by the presence of phenolic content in the plant particularly, thymol and carvacrol (Adam et al. 1998). In line with these findings, a study from Serbia reported that *S. thymbra* oil inhibited same fungus with (MIC =1.25 µg/mL), which was lower than ketoconazole (MIC = 2.5 µg/mL) (Markovic et al. 2011). These findings may indicate the ability of *S. thymber* to exert antifungal activity comparable to the synthetic drugs.

In addition to *A. fumigatus*, this review covered other clinically relevant species, including *A. flavus* and *A. niger*, which also pose challenges due to their inherent resistance (Djenontin et al. 2025). Overall, most of the plants tested against both *A. niger* and *A. flavus* showed low-to-moderate activity. For instance, extracts of *Euphorbia paralias* L., *Melilotus sulcatus* Desf. and *Cistus* species exhibited small inhibition zones ranging from (9-11mm) (Miloud 2023; Miloud and Senussi 2023), whereas *A. pavarii* Pampan recorded conflicting antifungal activity against *A. niger*. In one study, the methanolic extract from aerial parts recorded an inhibition zone of (21.1± 1.5 mm), which was nearly equal to that of amphotericin B (El-Hawary et al. 2016). Conversely, another study testing same plant's leaf extracts prepared with different solvents (hexane, chloroform and methanol) reported no detectable activity against *A. niger* (Fouad et al. 2024). Several factors could be responsible for this discrepancy, including differences in the extraction method, plant sample size and solvent type (Zaïri et al. 2019).

Similarly, other species, such as *S. thymbra* and *S. fruticosa*, have demonstrated inhibitory activity. Giweli et al (2012) reported that the essential oil extracted from aerial parts of *S. thymbra* using hydrodistillation exhibited high antifungal activity against *A. niger* and *A. flavus*, with MIC 0.025 mg/mL and MFC 0.05 mg/mL, which was markedly lower than bifonazole (MIC =1.5-2 mg/mL). However, 33 compounds were identified by using GC and GC-MS analyses, suggesting that its composition may be responsible for the antifungal effect. In the same context, the essential oil of *S. fruticose* showed considerable activity against *A. flavus* (MIC and MFC = 0.125 mg/mL) compared with the positive control bifonazole (MIC and MFC=2-1.5 mg/mL) (Giweli et al. 2013), while exhibiting weak activity against *A. niger* (MIC=1.0 mg/mL; MFC=1.5 mg/mL) (Duletić-Laušević et al. 2018). Conversely, some plant extracts showed no remarkable antifungal activity against either species. Examples include *Daucus syrticus*, *G. alypum*, *Arum cyrenaicum*, *Laurus nobilis*, *Drimia maritima* tubers, *Cynomorium coccineum* L. and *R. officinalis* L. (Abdelshafeek et al. 2013; Bengleil et al. 2020; Zargoun et al. 2020; Tayeb et al. 2021; Abushiba et al. 2023; Adem and Auzi 2024; Fouad et al. 2024). The resistance of these fungal species may be due to the cell wall structure, which is mainly composed of polysaccharides including α-glucans (mainly α-1,3-glucan), β-glucans (β-1,3-glucan with β-1,6- branches), chitin and galactomannan, forming a defence barrier; resistance may also result from degradation of bioactive substances by fungal enzymes or the removal of it by efflux systems (Yoshimi et al. 2016; Gacem et al. 2019).

Two studies focused on dermatophytes. In one, the aqueous and alcoholic extracts of *Lawsonia inermis* leaves were examined against *Trichophyton rubrum* and *Trichophyton mentagrophytes* isolated from foot infections. The aqueous extract exhibited moderate-to-strong activity with inhibition zones ranging from (20-30 mm) against *T. mentagrophytes* and *T. rubrum.*

When the aqueous extract was combined with miconazole, it resulted in a marked increase in the activity against *Trichophyton* species. The synergistic effect is likely due to the presence of various compounds in the henna plant, which might act synergistically with the antifungal drug (Fadl and Khalfallah 2022). Similarly, Haroun and Al-Kayali (2016) reported the ability of some plant extracts to act synergistically with antibiotics in bacteria, which might operate through similar mechanisms against fungi, whereas in the second study, assessed *S. lanigera* Poir. and *S. fruticosa* Mill. extracts, exhibited weak-to-moderate inhibition (MIC = 8-32 mg/mL) against clinical isolates of *T. mentagrophytes* compared with ketoconazole (Duletić-Laušević et al. 2018). In general, the antifungal trends observed for *L. inermis* and *S. fruticosa* were consistent with findings of some previous studies (Adam et al. 1998; Jain and Sharma 2016; Bello 2020). In the present review, only one study investigated the methanolic extract of *C. coccineum* against *C. neoformans*, revealing that the extract had moderate inhibitory activity. However, further investigations of Libyan medicinal plants are necessary to confirm these results, the need for broader evaluation of this clinically relevant pathogen (Adem and Auzi 2024).

In this systematic review, numerous active compounds have been identified as active against pathogenic fungi with several exhibiting remarkable antifungal activity (Table 3).

Phenolic compounds are a major class of plant secondary metabolites that can be found in various plant organs and exhibit multiple effects, such as antioxidant, anti-microbial, anti-carcinogenic and anti-inflammatory (Zhang et al. 2022). This review included flavonoids, tannins, and phenolic acid, as well as saponins and terpenoids, along with other related active compounds.

Flavonoids are widely present in most plants encompassing over 9,000 recognized natural molecules. Various kinds of flavonoids have been ascribed with anti-inflammatory, antioxidant, anti-infective and anti-depressant effects (El-Saadony et al. 2025). In the present review, flavonoids were the most frequently reported class; several articles highlighted their importance against both yeasts and filamentous fungi (Hasan et al. 2011; Alsabri et al. 2013b, a; Gamal and Atraiki 2015; El-Hawary et al. 2016; El-tawaty et al. 2018; Duletić-Laušević et al. 2018; Elgubbi et al. 2019; Elmarimi et al. 2019; Bengleil et al. 2020; Alamami et al. 2021; Mohammed et al. 2022; Dakhil et al. 2023; Adem and Auzi 2024; Fouad et al. 2024; Alkabou et al. 2024); (Hasan et al. 2024). These studies confirmed the presence of flavonoids as key compounds linked to antifungal activity. Although the specific mechanism of action was not explicitly elucidated within the included studies, the observed antifungal activity of flavonoids, particularly catechin remains significant. For instance, Alamami et al. (Alamami et al. 2021) identified catechin as a major active compound in *C. salviifolius* extract, which exerted strong inhibitory activity against *A. fumigatus* and *A. niger*. In addition to catechin, within the same study isolated gallic acid as one of the main active constituents. Gallic acid or (3,4,5-trihydroxybenzoic acid) is a well-known phenolic acid that has antioxidant, anti-inflammatory and antimicrobial properties. Previously reported mechanisms indicate that catechin can induce oxidative stress through the generation of reactive oxygen species (ROS), damaging essential cellular components (Bernatoniene and Kopustinskiene 2018), whereas the proposed mechanism of action for gallic acid is by binding to membrane ergosterol, leading to fungal membrane disruption and loss of intracellular content (Carvalho et al. 2018). Consequently, potent inhibitory effect of *C. salviifolius* could be attributed to synergistic the presence of both catechin and gallic acid.

In addition to flavonoids, tannins were found to be present and have shown antifungal activity in nine of the reviewed studies (Hasan et al. 2011; Alsabri et al. 2013b, a; Berfad et al. 2015; Gamal and Atraiki 2015; El-tawaty et al. 2018; Elmarimi et al. 2019; Alkabou et al. 2024); (Hasan et al. 2024). Based on previous research, the suggested mechanisms the presence of these compounds can act synergistically by providing a source of stable free radicals and also forms complex with nucleophilic amino acids in protein leading to the inactivation of the protein and loss of function (Suurbaar et al. 2017).

Thymol or 2-isopropyl-5-methylphenol and 5-methyl-2-isopropylphenol, is classified as a monoterpenoid phenol, that has antiseptic, anti-inflammatory, antioxidant, antifungal, antibacterial and healing properties (Escobar et al. 2020). It was found a major compounds of the essential oil with isomeric carvacrol in *T. capitatus* L., and *S, thymbra*, both of which exhibited strong activities against *C. albicans, A. niger* (El-Jalel et al. 2018; Khalil et al. 2020). Previous studies have reported that thymol can significantly reduce the viability *C. albicans* cells and decrease biofilm mass by up to 82%. It acts at the plasma membrane level by inhibition of ergosterol biosynthesis, promotes increased membrane permeability and cause the depletion of components essential for fungal cell vitality (De Castro et al. 2015).

Saponins are phytochemicals widespread in higher plants. In this review, some studies demonstrated antifungal activity in the presence of saponins (Alsabri et al. 2013b; Berfad et al. 2015; Elmarimi et al. 2019; Adem and Auzi 2024; Hasan et al. 2024). The proposed mechanism suggests the formation of a complex between saponin aglycone and the sterols within fungal cell membrane, leading to membrane permeabilization and pore formation (Shakeel et al. 2025)

Plants produce several terpenoids (also called isoterpenoids) as secondary metabolites, in this review, a number of studies demonstrated that plant extracts such as *D. syrticus, P. oceanica, A. pavarii, F. communis* and *C. coccineum* L., contained terpenoids in chemical profiles, remarkably antifungal activities against *A. flavus, A. niger, C. albicans, C. neoformans* and *C. glabrata* (Abd-Alla et al. 2013; Berfad et al. 2015; Gamal and Atraiki 2015; Elmarimi et al. 2019; Adem and Auzi 2024). Particularly, significant concentration of sesquiterpenes like caryophyllene in *B. andreuzziana*, germacrene-D in *T. zanonii* and 1-octen-3-ol in *V. tenuisecta* were linked to potent inhibition against *C. albicans* (Abdelshafeek et al. 2010). Other active constituents have been identified such as γ-terpinene p-cymene in *S. thymbra* (Giweli et al. 2012); β-asarone in *D. syrticus* (Abd-Alla et al. 2013); 1,8-cineole in *S. fruticosa* (Giweli et al. 2013); sabinene, β-pinene, β-cis-ocimene, bornyl acetate and β-eudesmol in *Artemisia monosperma* Del. (El Zalabani et al. 2017); α-pinene, thunbergol, aromadendrene oxide, limonene, β-Caryophyllene in *P. halepensis* L and *P. pinea* Mill. (Elkady et al. 2021); phenol,3-pentadecyl, benzene,1-(1,1-dimethylpropoxy)-4 methyl, isobutyl-3-methylpyrazine, 1,2,3-benzenetriol, benzoic acid,3-hydroxy and quinic acid in *P. lentiscus* L. (El-tawaty et al. 2023); δ-3-carene, bornyl acetate and limonene aldehyde in *H. tuberculatum* (Elshibani et al. 2024). Further studies are required to fully explore mechanisms of action of these compounds, as they have not yet been well investigated.

The presence of different active components in the plants enhances their medicinal properties. In spite of this, some of these compounds can have harmful impact depending on the dosage or concentration. Therefore, critical parameter in validating prospective is establishing their safety profiles alongside therapeutic efficacy.

In this review, a methodological evaluation revealed that only 16 out of the

45 included studies incorporated toxicological screening, cytotoxicity assays, as summarised in (Table 3). Regarding *in vivo* Acute Toxicity, the methanolic extract of *H. lippii,* and essential oil of *H. tuberculatum* exhibited wide safety margins, their median lethal doses (LD_{50}) exceeding 15,000 mg/kg and 10 g/kg body weight, respectively, showed no signs of toxicity (Alsabri et al. 2013a; Sabry et al. 2016). Similarly, the LD_{50} of *A. monosperma* Del. oil was determined to be greater than 0.05 ml/kg body weight, indicating that oil is relatively safe at affective doses against pathogenic fungi (El Zalabani et al. 2017). According to the American National Cancer Institute (USA) criteria of cytotoxic activity for the crude extract, is an IC_{50} value under 30 µg/mL (Mongalo et al. 2018). Based on these criteria *P. halepensis* (Sidi Alhamry region) extract exhibited remarkable cytotoxicity against breast and colon cell lines with IC_{50} values of 0.8 µg/mL and 1.60 µg/mL, respectively (Fathallah et al. 2022). Furthermore, *S. thymbra* essential oil, tested using sulforhodamine B assay on MCF-7 and HCT-116 cell lines, showed potent activity particularly against HCT-116 with $IC_{50} = 2.45 \pm 0.21$ µg/mL (Khalil et al. 2020). Similarly, *H. tuberculatum* essential oil showed cytotoxic against human cancer cell lines (HEPG2, MCF-7, HEP2, HCT116), with values IC_{50} ranging 5.91 to 8.91 µg/mL (Elshibani et al. 2024). Other extracts showed moderate or low cytotoxicity. For instance, the extract of *Ephedra alata* showed cytotoxicity on MCF7 cells (IC_{50} = 38,7 µg/mL), while *S. fruticosa* ethanolic extract exhibited moderate cytotoxicity against HCT-116 with (IC_{50} =375.96 µg/mL) (Duletić-Laušević et al. 2018; Alshalmania et al. 2020). Conversely, *Jasonia glutinosa* extract showed minimal haemolytic or cytotoxic effects (Mohammed et al. 2022). Part-specificity was clearly highlighted in *D. maritima* leaves demonstrated moderate toxicity on human red blood cells (52 % hemolysis), while tubers were completely safe (Abushiba et al. 2023). Despite, *in vitro* cell line study evaluate provide valuable preliminary screening, but lack the physiology complexity of the living organism. Therefore, is a need to explore the toxicity of these crude extracts using *in vivo* models to definitive safety margins.

A quality assessment was performed using the modified Quality Assessment Tool For *In Vitro* Studies (QUIN) to evaluate *in vitro* studies, aiming to categorize the level of evidence provided by the included studies and to augment the transparency and applicability of antifungal research. This assessment revealed that the methodological quality of most included studies was acceptable. Nearly all included studies adequately described the extraction procedures, antifungal assays and use of controls, which showed the highest rate of compliance for the assessed criteria. In contrast, statistical analysis, randomisation and conflicts-of-interest declarations showed the lowest compliance rate. These findings highlight the value of the QUIN tool in assessing *in vitro* research.

To our knowledge, this is the first systematic review providing a comprehensive overview across a wide range of Libyan medicinal plants and their antifungal activity against human pathogenic fungi adhering to PRISMA guidelines to identify as many relevant studies as possible. However, the variability in plant species, antifungal testing protocols and methodologies used by the reported studies were not of a standardised nature and which made a quantitative synthesis (meta- analysis) unfeasible. A major limitation of this review is that most of the included studies focused on evaluating the activity of crude plant extracts, without investigating the specific bioactive compounds responsible for these effects, their mechanisms of action, or their safety profile. Despite these limitation, the finding of this review provide the way toward a potential more standardized and methodologically researches in the future.

This systematic review summarizes the available evidence on the *in vitro* antifungal properties of Libyan medicinal plants against clinically relevant fungal pathogens, based on literature assessments published from 1 January 2010 to 26 August 2025. A total of 45 studies were included, covering 51 plant species. However, only a limited number of studies demonstrated strong inhibitory antifungal activity, whereas most of the studies reported weak -to- moderate inhibitory effect. These findings may reflect variability in plant species, extraction solvents, and experimental methodologies. Despite these inconsistencies, the findings highlight the potential therapeutic value of Libyan plants as a source of bioactive compounds. However, Libyan medicinal plants and their natural products remain largely untapped as sources of antifungal compounds. Based on these findings, this review recommends more innovative and standardised in *vitro* and *in vivo* studies on several medicinal plants as well as the isolation of active compounds and investigation of their antifungal activities, their mechanism of action and cytotoxicity.

Conflicts of interest

The authors declare no conflicts of interests in this study.

Authors' Contributions

Both authors contributed equally to the study and manuscript preparation.

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