

Antifungal Activity of Natural Products and their Derivatives Using an Animal Model of Oral Candidiasis: A Systematic Review

Raimundo Euzébio da Costa Neto¹, Ana Karoline Vieira Melo², Felipe Queiroga Sarmiento
Guerra¹, Walicyranison Plinio da Silva-Rocha¹

¹Clinical Mycology Laboratory, Department of Pharmaceutical Sciences, Federal University of Paraíba, João Pessoa, PB, Brazil.

²Experimental Pharmacology and Cell Culture Laboratory, Department of Dentistry, Federal University of Paraíba, João Pessoa, PB, Brazil.

Corresponding author: Walicyranison Plinio da Silva-Rocha

E-mail: wps@academico.ufpb.br

Academic Editor: Alessandro Leite Cavalcanti

Received: May 17, 2024 / Review: December 07, 2024 / Accepted: December 09, 2024

How to cite: Costa Neto RE, Melo AKV, Guerra FQS, Silva-Rocha WP. Antifungal activity of natural products and their derivatives using an animal model of oral candidiasis: A systematic review. *Pesqui Bras Odontopediatria Clín Integr*. 2025; 25:e240090. <https://doi.org/10.1590/pboci.2025.112>

ABSTRACT

Objective: To conduct a systematic review of the literature to elucidate the effectiveness of natural products with antifungal properties in animal infection models, highlighting potential candidates for treating oral candidiasis. **Material and Methods:** The current study undertook a systematic review (registered in the open science framework — DOI10.17605/OSF.IO/8QB5V) using six databases (PubMed, Scopus, Web of Science, Embase, Scholar Google, OpenGrey) focusing on the antifungal potential of natural products and their derivatives, assessed through animal models of oral candidiasis. **Results:** A total of 22 articles were incorporated for data analysis. Purified compounds were the subject of the most extensive investigations, followed by compounds used in combination, crude and fractionated extracts, and essential oils. These compounds displayed diminished minimum inhibitory concentration (MIC) values and exhibited therapeutic efficacy within the context of the animal model. **Conclusion:** Among natural and derivative products, ellagic acid associated with 2-hydroxypropyl- β -cyclodextrin, phenethyl ester of caffeic acid, ethyl acetate fraction derived from *Eugenia uniflora* extract, crude extract of *Punica granatum*, and nano-encapsulated extract of *Erodium glaucophyllum* emerge as the most auspicious candidates for the treatment of oral candidiasis.

Keywords: Models, Animal; *Candida albicans*; Candidiasis, Oral; Biological Products.

■ Introduction

The oral cavity in humans comprises a heterogeneous community of microorganisms [1] existing in a multifarious and balanced milieu [2]. Bacteria, fungi, viruses, archaea, and protozoa collectively constitute the human oral microbiota [3], with yeasts prominently present in this anatomical niche's fungal cohort [4]. Concerning microbial diversity, it is noteworthy that only the colonic environment surpasses the oral cavity regarding microbial intricacy [5].

Candida species are commonly encountered within the oral cavity, with colonization rates in healthy adults ranging from 30% to 50% [6]. Under circumstances where the host's immunological integrity is compromised, coupled with yeast virulence attributes, the progression of oral candidiasis ensues, predominantly orchestrated by *C. albicans*, which stands as the most prevalent *Candida* species [4,7]. Despite *C. albicans* predominance in cases of oral candidiasis, recent years have witnessed a surge in the identification of non-*C. albicans Candida* species (NCAC), encompassing *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, and *C. krusei* [8].

Oral candidiasis is the predominant opportunistic infection afflicting the human oral cavity [9]. Recently, there has been a notable proliferation in strains exhibiting diminished susceptibility, and in some instances, outright resistance, to therapeutic interventions for oral candidiasis [10]. Numerous studies have been conducted globally demonstrating the resistance of *Candida* to azole and echinocandin antifungals. Additionally, there have been investigations into the molecular mechanisms underlying this resistance and potential therapeutic approaches in the context of antifungal resistance [11-13]. Consequently, this infection has garnered heightened recognition as an escalating public health concern, spurred by the dynamics of an aging demographic, alongside an augmented incidence of chronic ailments and immunosuppressive conditions among the patient cohort [14].

Given the limited accessibility to commercial antifungal agents and the escalating prevalence of strains exhibiting diminished susceptibility or outright resistance to these agents, the quest for therapeutic alternatives has become imperative [15]. Numerous investigations have been conducted over the years to assess the antifungal attributes intrinsic to natural products and their derivatives, with a salient focus on botanical entities, owing to their intricate metabolic diversity and pharmacological potency [16,17]. Nonetheless, a substantial proportion of these inquiries are confined to preliminary antifungal screening assays, with limited progression to subsequent stages, including the utilization of *in vivo* pharmacological evaluation models [18].

Numerous models have been postulated for the *in vivo* exploration of *Candida* pathogenic attributes, alongside assessing the antifungal potency inherent to compounds under scrutiny. Among these, invertebrate larval models, such as *Galleria mellonella* [19] and *Drosophila melanogaster* [20], have been advanced, as have rodent models employing rats and mice, which have proven efficacious in elucidating the intricacies of oral candidiasis, vulvovaginal candidiasis, and candidemia.

This study aims to systematically review the literature to elucidate the effectiveness of natural products possessing antifungal properties within animal infection models. This endeavor seeks to underscore potential contenders for addressing the therapeutic demands associated with oral candidiasis.

■ Material and Methods

Protocol

A comprehensive literature review was conducted to assess the efficacy of natural products for addressing oral candidiasis through animal infection models. The review adhered to the guidelines stipulated by

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [21] and was registered within the open science framework under the DOI 10.17605/OSF.IO/8QB5V.

Guiding Question, Eligibility and Exclusion Criteria

This review was crafted to address a precise inquiry framed in the PICO format: “Are natural products efficacious in animal model investigations targeting oral candidiasis?” Two autonomous evaluators conducted a methodical appraisal of the sources extracted from the search databases, employing predefined criteria for inclusion and exclusion as delineated in Table 1.

Search Mechanisms

Two reviewers systematically searched six databases (Table 1). Employing pertinent descriptors from platforms like Descriptors in Health Sciences (DeCS) and Medical Subject Headings (MeSH) and employing Boolean operators “AND” and “OR,” a comprehensive search strategy was meticulously formulated. The searches were conducted using terms that linked the use of natural products in animal models of oral candidiasis. These terms included oral candidiasis, oropharyngeal candidiasis, mice, murine oral candidiasis, biological products, plants, plant extracts, herbs, plant derivatives, natural antifungals, photochemical, and essential oils. All terms are detailed in Table 1. Publications up until May 11, 2024, were encompassed within the scope of inclusion. No limitations were imposed concerning publication years or languages. After the search, the studies retrieved were imported into the Rayyan software platform to facilitate the identification and elimination of duplicate entries.

Table 1. Databases, PICO approach, search strategy, and inclusion and exclusion criteria were addressed in the review.

Guiding question	Are natural products effective in animal model studies against oral candidiasis?
PICO approach	Population – P: Oral candidiasis and murine models Intervention – I: Natural products
Databases	Search strategy
PubMed (http://www.ncbi.nlm.nih.gov/pubmed)	((("candidiasis oral") OR ("candidiasis oral"[MeSH Terms]) OR ("oral candidiasis")) OR ("Oropharyngeal candidiasis")) AND (((("mice"[MeSH Terms]) OR (mice)) OR ("murine oral candidiasis")) OR ("murine model")) OR (murine)) AND (((((((((((("Biological Products") OR ("Biological Products"[MeSH Terms]) OR ("plants, medicinal"[MeSH Terms]) OR ("plants, medicinal") OR ("Plant Extracts") OR ("Plant Extracts"[MeSH Terms]) OR ("Plant Extracts") OR ("natural product") OR (herbs)) OR (phytochemically)) OR ("essential oil")) OR (plant)) OR ("plant derivatives")) OR ("natural antifungal"))
Scopus (http://www.scopus.com/)	TITLE-ABS-KEY ("candidiasis oral" OR "oral candidiasis" OR "Oropharyngeal candidiasis") AND TITLE-ABS-KEY (mice OR "murine oral candidiasis" OR "murine model" OR murine) AND TITLE-ABS-KEY ("Biological Products" OR "plants, medicinal" OR "Plant Extracts" OR "natural product" OR herbs OR photochemically OR "essential oil" OR plant OR "plant derivatives" OR "natural antifungal"
Web of Science (http://apps.webofknowledge.com/)	((ALL=("candidiasis oral" OR "oral candidiasis" OR "Oropharyngeal candidiasis")) AND ALL=(mice OR "murine oral candidiasis" OR "murine model" OR murine)) AND ALL=("Biological Products" OR "plants, medicinal" OR "Plant Extracts" OR "natural product" OR herbs OR photochemically OR "essential oil" OR plant OR "plant derivatives" OR "natural antifungal")
Embase (https://www.embase.com/)	('candidiasis oral':ab,ti OR 'oral candidiasis':ab,ti OR 'oropharyngeal candidiasis':ab,ti) AND (mice:ab,ti OR 'murine oral candidiasis':ab,ti OR 'murine model':ab,ti OR murine:ab,ti) AND ('Biological Products':ab,ti OR 'plants, medicinal':ab,ti OR 'Plant Extracts':ab,ti OR 'natural product':ab,ti OR herbs:ab,ti OR photochemically:ab,ti OR 'essential oil':ab,ti OR plant:ab,ti OR 'plant derivatives':ab,ti OR 'natural antifungal':ab,ti)
Google Scholar (https://scholar.google.com)	("oral candidiasis " OR "Oropharyngeal candidiasis") AND (mice OR "murine oral candidiasis" OR "murine model" OR murine) AND ("essential oil" OR "plants, medicinal" OR "Plant Extracts" OR "natural product")
OpenGrey (https://opengrey.eu/)	(*candidiasis oral" OR "oral candidiasis" OR "Oropharyngeal candidiasis") AND ('mice' OR "murine oral candidiasis" OR "murine model" OR "murine") AND ("Biological Products" OR "plants, medicinal" OR "Plant Extracts" OR "natural product" OR "herbs"

	OR "photochemically" OR "essential oil" OR "plant" OR "plant derivatives" OR "natural antifungal")
Inclusion Criteria	Studies that evaluated the antifungal activity of natural products and their derivatives in the treatment of oral candidiasis using animal models of infection; Studies that used natural products such as essential oil, crude extracts, fractions of extracts, isolated compounds, associated compounds, and complex compounds; Studies that evaluated the antifungal efficacy of natural products and their derivatives using histological analyses, clinical aspects of lesions, or colony-forming units counting
Exclusion Criteria	Letter to the editor; Literature reviews; Congress summary; Only studies <i>in vitro</i> ; Studies dealing with synthetic antifungals only; Plants with no or little antifungal activity; Studies with artificial tissue model and cell culture to evaluate the antifungal action.

Selection of Studies

As a component of the calibration process, the assessors engaged in discussions regarding the eligibility criteria. Subsequently, they applied these criteria to a subset comprising 20% of the retrieved references to ascertain concordance among the evaluators. Given the attainment of a substantial level of agreement ($Kappa \geq 0.80$), the evaluators proceeded to review all identified studies. This phase encompassed a bifurcation into two sequential steps. During the initial phase (Phase 1), both reviewers perused the titles and abstracts of the studies. Those studies exhibiting titles and abstracts congruent with the thematic focus of this systematic review were earmarked for progression to Phase 2. The subsequent step (Phase 2) entailed a comprehensive analysis of the full-text content of the selected studies. Additionally, the reference lists of the incorporated studies were assessed to identify pertinent research contributions. All studies deemed ineligible were meticulously documented, along with the respective rationales for their exclusion. In instances of discordance between the two evaluators, a third reviewer was consulted to facilitate a final consensus.

Data Extraction

Two assessors autonomously executed the data extraction procedures. Each evaluator utilized a designated spreadsheet meticulously devised to facilitate the extraction of requisite information (as delineated in Table 2). A third reviewer was additionally engaged in this process, serving as an arbiter in situations where disparities emerged between the primary evaluators.

Risk of Bias

The potential for bias within the eligible studies was evaluated using the tools provided by the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) [22]. The SYRCLE tool recommends that the risk of bias be assessed by two researchers independently. All selected articles were read in detail, and the presence of items related to guiding questions indicated by the SYRCLE tool was reported. The observed items were noted by both reviewers and analyzed in consensus. The terms suggested by the SYRCLE tool corresponded to 10 questions, which were categorized under the following themes: selection bias, performance bias, risk, attrition bias, reporting bias, and the examination of potential alternative biases. The investigated questions were: 1) Has the allocation sequence been appropriately generated and executed? 2) Were the groups comparable at the outset, or were they adjusted for confounding variables during analysis? 3) Has the allocation to diverse groups been effectively concealed during the study? 4) Were the animals subject to random housing throughout the experimentation phase? 5) Were the caretakers and/or investigators blinded to the interventions administered to each animal during the study? 6) Were the animals randomly selected for outcome evaluation? 7) Was the evaluator of outcomes blinded? 8) Have incomplete data pertaining to results been managed appropriately? 9) Do the study reports demonstrate an absence of selective outcomes reporting?

10) Did the study appear devoid of other potential issues that might lead to a heightened risk of bias? A high risk of bias was considered when the study achieved $\leq 49\%$ of “yes” responses. The percentage of “yes” responses ranged from 50% to 69% for moderate risk of bias, whereas for low risk of bias, these responses reached $\geq 70\%$.

■ Results

Search Mechanisms

Using the established search criteria and specific descriptors about the topic, the bibliographic search was carried out in 6 databases described in Table 1. In total, 370 references were obtained, and after the removal of duplicate references, 330 remained. After the screening process, 19 articles were considered eligible and in addition to these, three articles were included after additional search in the references of the included articles, totaling 22 studies that met the eligibility criteria. The flowchart of the screening and selection process of the articles included in the final review is represented in Figure 1.

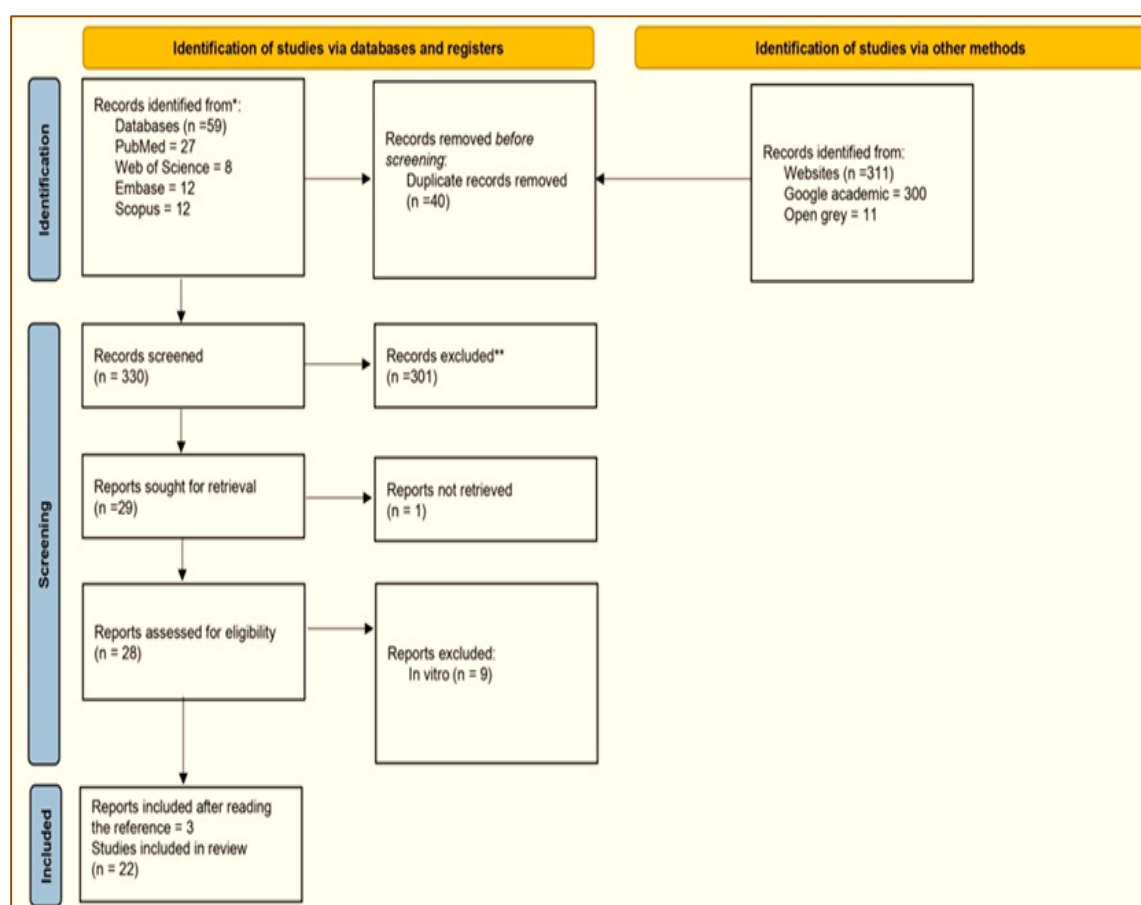


Figure 1. Flowchart of the selection process of articles investigated in the review, according to PRISMA guidelines.

Risk of Bias

According to the recommendations of the PRISMA tool, the risk of bias was evaluated, and the methodological characteristics observed in the studies obtained in the research are shown in Chart 1 [23-44]. After the individual analysis of each selected study, based on recommendations obtained in the SYRCLE tool, it was observed that 17 studies were considered to be at low risk of bias [23,24,26-40], three studies were considered to be at moderate risk of bias [25,41,42], and two were considered to be at high risk of bias [43,44].

Chart 1. Methodological quality was assessed using the SYRCLE tool (Systematic Review Center for Laboratory Animal Experimentation).

Author	Selection Bias			Performance Bias		Detection Bias		Attrition Bias	Reporting Bias	Other
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
[23]	Yellow	Blue	Rose	Blue	Rose	Yellow	Blue	Blue	Blue	Blue
[24]	Rose	Blue	Rose	Blue	Blue	Blue	Blue	Blue	Blue	Blue
[25]	Yellow	Blue	Rose	Blue	Blue	Yellow	Blue	Blue	Blue	Blue
[26]	Rose	Blue	Rose	Blue	Rose	Blue	Blue	Blue	Blue	Blue
[27]	Rose	Blue	Rose	Rose	Rose	Yellow	Blue	Yellow	Blue	Blue
[28]	Rose	Blue	Rose	Rose	Rose	Yellow	Blue	Blue	Blue	Blue
[29]	Yellow	Blue	Rose	Blue	Blue	Yellow	Blue	Blue	Blue	Blue
[30]	Rose	Blue	Rose	Yellow	Yellow	Yellow	Yellow	Yellow	Blue	Blue
[31]	Rose	Blue	Rose	Blue	Yellow	Blue	Blue	Blue	Blue	Blue
[32]	Rose	Blue	Rose	Blue	Blue	Blue	Blue	Yellow	Blue	Blue
[33]	Rose	Blue	Rose	Blue	Blue	Blue	Blue	Yellow	Blue	Blue
[34]	Rose	Blue	Rose	Blue	Rose	Blue	Blue	Blue	Blue	Blue
[35]	Rose	Blue	Rose	Blue	Rose	Blue	Blue	Blue	Blue	Blue
[36]	Rose	Blue	Rose	Blue	Rose	Blue	Blue	Blue	Blue	Blue
[37]	Rose	Blue	Rose	Blue	Blue	Blue	Blue	Blue	Blue	Blue
[38]	Rose	Blue	Rose	Blue	Rose	Blue	Blue	Blue	Blue	Blue
[39]	Rose	Blue	Rose	Blue	Rose	Blue	Blue	Blue	Blue	Blue
[40]	Rose	Blue	Rose	Blue	Yellow	Blue	Blue	Blue	Blue	Blue
[41]	Yellow	Blue	Rose	Blue	Blue	Yellow	Blue	Blue	Blue	Blue
[42]	Rose	Blue	Rose	Blue	Rose	Blue	Blue	Blue	Blue	Blue
[43]	Rose	Blue	Rose	Rose	Yellow	Blue	Blue	Blue	Blue	Blue
[44]	Rose	Blue	Rose	Blue	Rose	Blue	Blue	Blue	Blue	Blue

Blue = Yes; Rose = No; Yellow = Incerte answer.

Natural Products and their Derivatives Obtained in the Search

The use of isolated compounds was the most observed among the studies (13 articles, 50%), followed by isolated compounds in associations (5 articles, 19 %) and crude extracts (4 articles, 15%). The use of fractionated extracts and essential oils in evaluating antifungal action in a model of oral candidiasis was observed in 2 (8%) and 2 (8%) articles, respectively.

In Vitro Antifungal Activity

During the qualitative synthesis of the retrieved articles, a broad spectrum of action of *in vitro* antifungal activity was observed among the compounds studied. Among the 22 selected studies, data from the *in vitro* antifungal activity against *C. albicans* isolates were reported in 18 (81.7%) cases. In relation to the isolated compounds, the MICs obtained ranged from 16 µg/mL obtained from the Caffeic acid phenethyl ester [26] to 20,000 µg/mL obtained in terpinen-4-ol [40]. The analysis of MIC values in studies involving isolated

compounds in combinations was performed and a MIC of 25 µg/mL was reported in the evaluation of ellagic acid combined with 2-hydroxypropyl-β-cyclodextrin [25].

The *in vitro* antifungal activity of crude extracts was evaluated and a variation was observed between 50 µg/mL obtained with *Erodium glaucophyllum* leaves extract [24] and 2040 µg/mL when *Syzygium aromaticum* cloves crude extract was evaluated [44]. Among the studies carried out with fractionated extracts, a previous study carried out by Assunção Ferreira et al. [45] reported an MIC of 62.5 µg/mL to the ethyl acetate fraction of *Eugenia uniflora* extract.

Regarding studies using essential oils, the species obtained in the search was *Melaleuca alternifolia*, which a MIC of 1950 µg/mL was reported by de Campos Rasteiro et al. [37] and in a study carried out by Ninomiya et al. [40], also with *M. alternifolia*, the MICs varied between 5000 and 20000 µg/mL. The MIC values obtained for natural and derived products are described in Table 2.

Cytotoxic Effect of Selected Compounds

The ability of natural and derivative products to cause cell damage was evaluated in a few studies only, with a total of 5 among the 22 selected. Caffeic acid phenethyl ester showed no toxic effect at the concentrations evaluated, from 5 to 20 mg/kg [26]. The ellagic acid associated with 2-hydroxypropyl-β-cyclodextrin cytotoxic activity was evaluated, and it was observed 63% of cell viability at 250 µg/ml [25].

Regarding the crude extracts and fractions, *Punica granatum* crude extract [33] did not show cytotoxic activity at evaluated concentrations, unlike *E. glaucophyllum* extract, which showed toxic effects at concentrations above 150 µg/ml [24]. The *E. uniflora* ethyl acetate fraction showed no toxic action, even at concentrations of up to 8000 µg/mL [35]. The cytotoxic effects obtained for natural products and derivatives are described in Table 2.

Studies with *in Vivo* Models of Antifungal Action against Oral Candidiasis

All natural compounds obtained in the present search, whether isolated, combined, crude extracts or fractions, as well as essential oils, had their antifungal activity evaluated in animal model of oral candidiasis.

Among isolated and complex compounds, at a concentration of 100 µg/mL of artemisinin, a reduction in oral lesions appearance was not present in the mice model, and it was not possible to observe a reduction in the tissue invasion in histopathological analysis, as well as the colony forming units (UFC) count decrease. However, when associated with amphotericin B, there was synergism with the antifungal action of this drug [27]. Another compound that did not have *in vivo* action when tested alone, but in association, obtained good results was curcumin. When evaluated at 260 µM, it was not possible to observe antifungal action in mice; however, in a nanoencapsulated formulation in association with photodynamic therapy, an improvement in the evolution of the infection was observed [32].

Cinnamaldehyde was evaluated on its own at 9500 µg/mL and was associated with 1% methylcellulose and it was reported that with this combination, the healing response of oral lesions, as well as a decrease in tissue infiltrate and CFU reduction, was more pronounced [41]. All other isolated compounds showed a reduction in the oral lesions appearance, as well as a decrease in tissue infiltrate and a decrease in CFU count, according to the evaluations performed by the authors (Table 2). In relation to extracts, fractions and essential oils, all showed antifungal activity in oral candidiasis models, either through lesions reduction, tissue invasion reduction or decrease of CFU counts.

Table 2. Antifungal properties of natural products and derivatives obtained after refining the search strategy.

Study	Animal Model	Compound Origin	Type of Compound	Material Used	MIC	Assessed Concentration (OC)	Cytotoxic Effect	Macroscopic Analysis	Histological Evaluation and CFU Count
[23]	Mice	<i>Curcuma longa</i>	Isolated compound	Curcumin	Not assessed	128 µg/ml	Not assessed	Reduction of oral lesions	Not assessed
				Nanocurcumin		64 µg/ml		Reduction of oral lesions**	
[24]	Mice	<i>Erodium glaucophyllum</i>	Nano encapsulated extract with silver nanoparticles	Leaves	50 µg/mL	50 µg/mL	Toxic effect above 150 µg/mL	Reduction of oral lesions	Reduction of tissue invasion
[25]	Mice	Various species of plants	Complexed compound	Ellagic acid + HP-β-CD***	25 µg/mL	250 µg/mL	63% cell viability at 250 µg/mL	Not assessed	Reduction of tissue invasion
[26]	Mice	Propolis	Isolated compound	Caffeic acid phenethyl ester	16 to 64 µg/mL	15 mg/kg	No toxic effect 5 - 20 mg/kg	Reduction of oral lesions	Reduction of tissue invasion
[27]	Mice	<i>Artemisia annua</i>	Isolated compound	Artemisinin	>200 µg/mL	100 µg/mL	Not assessed	There was no reduction in oral lesions	There was no reduction in tissue invasion and no reduction in CFU
			Associated compound	Artemisinin + Amphotericin B		0.5 µg/mL + 0.100 µg/mL		Reduction of oral lesions	Reduced both tissue invasion and CFU counting
[28]	Mice	Rutaceae	Isolated compound	Nerol	0.77 µL/mL	10.8 mg/kg	Not assessed	Reduction of oral lesions	Reduction of tissue invasion
[29]	Mice	<i>Perilla frutescence</i>	Isolated compound	Perillaldehyde	760 µg/mL	380 µg/mL 570 µg/mL 760 µg/mL**	Not assessed	Reduction of oral lesions	Reduced both tissue invasion and CFU counting
[30]	Mice	<i>Mollugo pentaphylla</i>	Isolated compound	Stigmasterol	25 µg/mL	100 µg/mL	Not assessed	Not assessed	Reduction of tissue invasion
[31]	Mice	<i>Cinnamomum cassia</i>	Isolated compound	Cinnamaldehyde	130 mg/mL	1.3 mg/kg 2.6 mg/kg 3.9 mg/kg**	Not assessed	Reduction of oral lesions	Reduced both tissue invasion and CFU counting
[32]	Mice	Isolated compound	Isolated compound	Curcumin	Not assessed	260 µM	Not assessed	Not assessed	There was no reduction in tissue invasion and no reduction in CFU
			Associated nanoencapsulated isolated compound	Nanoencapsulated curcumin** + Photodynamic therapy		260 µM			Reduced both tissue invasion and CFU counting**
[33]	Rat	<i>Punica granatum</i>	Crude extract	Peel	125 to 250 µg/mL	125 µg/mL 250 µg/mL 500 µg/mL**	No toxic effect	Reduction of oral lesions	Reduction of tissue invasion
[34]	Mice	<i>Cocos nucifera</i>	Isolated compound	Monolaurin	0.125 mmol/L	12.5 mmol/L	Not assessed	Reduction of oral lesions	Reduced both tissue invasion and CFU counting
[35]	Mice	<i>Eugenia uniflora</i>	Ethyl acetate fraction	Leaves	62.5 µg/mL†	1.000 µg/mL	No toxic effect 18 - 8000 µg/mL	Reduction of oral lesions	Reduced both tissue invasion and CFU counting

[36]	Mice	<i>Glycyrrhiza inflata</i>	Isolated compound	Lichochalcone A	50 to 150 µM	7.5 mM	Not assessed	Reduction of oral lesions	Reduced both tissue invasion and CFU counting
[37]	Mice	<i>Melaleuca alternifolia</i>	Essential oil	Leaves	1950 µg/mL	12500 µg/mL	Not assessed	Reduction of oral lesions	Reduced both tissue invasion and CFU counting
[38]	Mice	<i>Melaleuca alternifolia</i>	Isolated compound	Terpinen-4-ol	5000 µg/mL	10000 to 40000 µg/mL	Not assessed	Not assessed	Reduction of tissue invasion
[39]	Mice	<i>Curcuma longa</i>	Associated compound	Curcumin + Photodynamic therapy	Not assessed	7.4 µg/mL + FS ^{††} 14.7 µg/mL + FS 29.5 µg/mL + FS ^{**}	Not assessed	Not assessed	Reduced both tissue invasion and CFU counting
[40]	Mice	<i>Melaleuca alternifolia</i>	Essential oil	Leaves	5000 to 20000 µg/mL	10000 to 40000 µg/mL	Not assessed	Reduction of oral lesions	Reduced both tissue invasion and CFU counting
			Isolated compound	Terpinen-4-ol	1250 to 20000 µg/mL	10000 to 40000 µg/mL		Reduction of oral lesions	Reduced both tissue invasion and CFU counting
[41]	Mice	<i>Cinnamomum cassia</i>	Isolated compound	Cinnamaldehyde	19500 µg/mL	9500 µg/mL	Not assessed	Reduction of oral lesions	Reduced both tissue invasion and CFU counting
			Associated compound	Cinnamaldehyde + Methylcellulose	Cinnamaldehyde	Cinnamaldehyde 9500 µg/mL Cinnamaldehyde + 1% Methylcellulose		Reduction of oral lesions ^{**}	Reduced both tissue invasion and CFU counting ^{**}
[42]	Mice	<i>Cinnamomum cassia</i>	Crude extract	Peel	1% to 5 %*	100%	Not assessed	Reduction of oral lesions	Reduced both tissue invasion and CFU counting
[43]	Rat	<i>Acorus calamus</i>	Fractions F1 and F2 of the crude extract	Rhizomes	Not assessed	Not assessed	Not assessed	Not assessed	Reduced both tissue invasion and CFU counting
[44]	Mice	<i>Syzygium aromaticum</i>	Crude extract	Clove	415 to 2040 µg/mL	10380 µg/mL	Not assessed	Reduction of oral lesions	Reduction of tissue invasion

^{**}Most expressive result; ^{***}2-hydroxypropyl-beta-cyclodextrin; [†]Assunção Ferreira et al. [45]; ^{††}Photodynamic therapy.

Discussion

The available data in the scientific literature about in vitro studies of the antifungal activity of natural products is vast. However, although these data are widely available, there are limited investigations that have advanced to stages of studies using in vivo models. It is necessary for these studies to advance from the screening stage and in vitro evidence, given the reduced current scenario of antifungals available on the market and the increasing reports of the emergence of conventional treatment-resistant strains. This context points to real demand for the development of new compounds aimed at the treatment of fungal infections [46]. The findings of the present study make this more evident, as it was observed that only 22 articles were included in the final review [23-44]. These evaluated isolated compounds, associated compounds, extracts, and essential oils using in vivo models of oral candidiasis.

The use of natural compounds to treat diseases in the population has been registered for many years, however, the number of studies progressing in research and reaching the level of active molecules within these compounds is limited. A study by Newman and Cragg [47] highlighted that between 1981 and 2014 the Food and Drug Administration (FDA) approved 1,562 drugs, of which 64 (4%) were unaltered natural products, 141 (9.1%) were botanicals (mixtures), 320 (21%) were derived from natural products and 61 (4%) were synthetic drugs, but with a pharmacophore of natural products. Regarding the use of natural compounds intended for oral candidiasis treatment, this trend was observed in the present study, where the number of natural products evaluated in animal models was very small, which reflects little progress in this field of research.

An interesting finding observed in the present study is that although there is a high number of publications evaluating the extracts and essential oils antifungal action by *in vitro* methodologies when *in vivo* models are used, it was observed that most studies were carried out with isolated compounds, such as curcumin [23], ellagic acid [25], artemisinin [27], nerol [28], stigmasterol [30], cinnamaldehyde [41] and monolaurin [34]. These data may be related to the fact that, after the screening stages of the *in vitro* antifungal actions of extracts and essential oils, the main constituents are selected for evaluation in animal models, since this is a later step in the investigation process. Furthermore, in recent years, scientific journals publishing in the field of natural products are becoming increasingly demanding, prioritizing in their editions the works performed with isolated compounds [48,49].

With regard to studies carried out with *in vitro* assays, 18 articles selected in the present study highlighted the antifungal potential of natural compounds using methodologies such as broth microdilution. The most promising compounds against *C. albicans* showed low MIC values, such as caffeic acid phenethyl ester, whose MIC was 16 µg/mL [26] and stigmasterol [30], which was obtained 25 µg MIC /mL. These results are quite promising, as they confirm the trend that isolated compounds are more effective than extracts. These, in turn, showed much higher MICs, such as the *Syzygium aromaticum* extract, whose MIC was 2040 µg/mL [44]. It is important to note that most studies performed the minimum inhibitory concentration assessment only in *C. albicans* [24,34,37]. The ethyl acetate fraction of *E. uniflora* extract, used in the study carried out by Silva-Rocha et. al. [35], was tested against other *Candida* species, such as *C. dubliniensis*, *C. glabrata* and *C. krusei*, with MICs ranging from 15.62 µg/mL against *C. krusei* and 31.25 µg/mL against *C. dubliniensis* [45]. Although *C. albicans* is the most frequent species in cases of oral candidiasis, in recent years the number of infections associated with CNCA has been increasing. In a study carried out by Erfaninejad et al. [50] in HIV patients from southwestern Iran, the species distribution in cases of oral candidiasis was evaluated and it was observed that 26.5% of the patients had their oral cavity colonized by *C. glabrata* and 19.5% by *C. dubliniensis*. Thus, it is important to highlight the importance of performing the assessments of the minimum inhibitory concentration also in CNCA species.

Promising results are expected for natural compounds since they are compounds that present high structural diversity. In assessing the pharmacological action of natural products, there is a potential tendency for them to be used as therapeutic agents, either in their native form or as semi-synthetic derivatives [51]. However, it is necessary that these compounds have low or no toxicity. It is noteworthy that although the assessment of cellular toxicity is a very important step in advancing the pharmacological properties investigation of a compound, only five studies included this information in their results [24,26,33,35]. In the case of isolated compounds, only caffeic acid phenethyl ester was tested against cytotoxic action and no toxic effect was observed at concentrations between 5 and 20 mg/kg [26]. Regarding the extracts, the *E. glaucophyllum* extract,

nanoencapsulated with silver nanoparticles, had significant antifungal action with a MIC of 50 µg/mL; however, it started to present a toxic effect when evaluated at concentrations above 150 µg/mL, only three times above the MIC value [24]. The ethyl acetate fraction of *E. uniflora* extract showed no toxic action even at a concentration of 8000 µg/mL [35]. These findings are relevant because although a compound presents excellent pharmacological results, further research in therapeutic products may not be possible, since it presents toxic results for human cells. In addition, in order to reduce the toxic action, the attempt to structurally modify the compounds may not be feasible.

The use of animal models to understand the health-disease process, as well as to understand the action of new drugs is fundamental in the pharmacology field. Jemel et al. [19] assert that the use of *in vivo* models is needed to test antifungal treatments prior to their use in humans. Several aspects, such as saliva, pH, antibodies, local molecules, and microbiota are typical of *in vivo* models, and these variants are conducive to obtaining a study model closer to the reality of humans conditions. As complex as the *in vitro* study is, it cannot reproduce all these characteristics observed *in vivo* [52]. Regarding the study of candidiasis, *in vivo* models allow the observation of the colonization and infection process, highlighting, for example, the ability to observe tissue invasion caused by the genus *Candida*, mainly *C. albicans* [53]. All natural products mentioned in the present study were evaluated in a model of oral candidiasis in rats or mice. These models made it possible to observe the formation of macroscopical lesions, as well as their reduction after the treatments, and microscopically, the decrease in tissue invasion. In addition, the local fungal burden was evaluated by colony forming units counting. Thus, these models provide a complete study of the clinical potential of natural products.

The association between the *in vitro* effects and their application in *in vivo* models is observed in the curcumin evaluation studies. This compound is widely studied and has several pharmacological activities, such as anti-inflammatory, antioxidant and beneficial action in neurological, cardiovascular and anti-cancer studies [54]. However, curcumin is practically insoluble in water and is sensitive to degradation, especially at alkaline pH. These characteristics confer low bioavailability to this compound [54]. In a study carried out by Sakima et al. [32], it was observed that curcumin alone was not able to reduce oral lesions in mice, however, once nanoencapsulated, improvement in infection was observed. This finding reinforces the idea that not always a great *in vitro* inhibitory action is observed *in vivo* and that this model allows a more detailed study of the pharmacological characteristics of natural products. Among the articles included in this review, only the study conducted by Ninomiya et al. [40] evaluated the immune response of mice to the compound. It was observed that oral administration of 50 µL of 40 mg/mL terpinen-4-ol, 3 hours *post-Candida* infection, significantly reduced the elevation of myeloperoxidase activity and macrophage inflammatory protein-2, highlighting the compound's anti-inflammatory action. *In vitro* studies demonstrated that 800 µg/mL of terpinen-4-ol markedly inhibited cytokine production in macrophages exposed to heat-killed *C. albicans* cells.

Murine models are widely used to study experimental oral *Candida* infections, as rodents present oral characteristics similar to those found in the human oral cavity. In addition, it is possible to insert a prosthetic device into the palate to carry out studies on *Candida* denture stomatitis, which is the most common form of oral candidiasis in the elderly population who use dental prostheses [55].

Analyzing the entire research context, among the natural products evaluated in the present study, the *E. glaucophyllum* nanoencapsulated extract [24], ellagic acid associated with 2-hydroxypropyl-β-cyclodextrin [25], the caffeic acid phenethyl ester [26], the *P. granatum* crude extract [33] and the ethyl acetate fraction of *Eugenia uniflora* extract [35] are the most prominent candidates for new therapeutic agents in the oral

candidiasis treatment, as they have low MIC values, low or no toxic effects, and have been proven capable of reducing oral lesions and tissue invasion process in murine models of oral candidiasis.

The present review underscores that while a plethora of studies within the literature have examined the antifungal efficacy of various naturally derived compounds against clinical isolates of oral candidiasis, only a limited subset have progressed to the phase involving animal models. Despite the impressive *in vitro* antifungal performance demonstrated by numerous compounds, a considerable portion of these substances lack a verified safety profile in toxicity models or suffer from an absence of pertinent toxicity data. A limitation of the present study is the lack of data regarding the analysis of the immune response in the animals, as well as the enzymatic biochemical profile and behavioral study of the animals, both following the administration of the bioactive compounds. These limitations may serve as a guide for other researchers to address this data deficiency, thereby making these studies more robust and consistent so that, in the future, these compounds can be made available as therapeutic agents for the treatment of oral candidiasis. In addition, variations in the protocols for using animal models can introduce an additional limitation. Differences in strains, ages, and conditions of the animals can hinder comparisons between studies. Furthermore, the diversity in methods of infection induction and immune responses among species limits the replicability and translational potential of the findings to humans. Addressing these limitations is essential for a critical and comprehensive evaluation of the literature. Among the compounds evaluated, ellagic acid in combination with 2-hydroxypropyl- β -cyclodextrin, caffeic acid phenethyl ester, the ethyl acetate fraction extracted from *E. uniflora*, the crude extract of *P. granatum*, and the nanoencapsulated extract of *E. glaucophyllum* stand out. This distinction arises from their robust antifungal activity alongside their confirmed safety in human cellular systems. The discussion could be significantly enhanced by identifying specific areas for future research. For instance, exploring the mechanisms of action of the most promising compounds would provide valuable insights into their efficacy and potential applications. Additionally, conducting clinical trials could help validate the findings from preclinical studies and facilitate the translation of these compounds into therapeutic options. By outlining these research directions, the manuscript would not only highlight existing gaps in knowledge but also encourage further investigation in critical areas that could advance the field.

■ Conclusion

This review demonstrates that while numerous studies have evaluated the antifungal action of various natural compounds against oral candidiasis clinical isolates, few have progressed to animal model testing. Although several compounds show intense *in vitro* antifungal activity, many lack safety data in toxicity models. Compounds such as ellagic acid combined with 2-hydroxypropyl- β -cyclodextrin, caffeic acid phenethyl ester, the ethyl acetate fraction of *E. uniflora* extract, the crude extract of *P. granatum*, and the nano-encapsulated extract of *E. glaucophyllum* exhibit effective antifungal activity and safety in human cells, making them excellent candidates for clinical studies. These findings underscore the importance of natural product research in infectious diseases and highlight the potential for developing novel antifungal agents for treating oral candidiasis in the future. These compounds, as evidenced by the presented data, highlight the significance of natural product research in the realm of infectious diseases, with promising prospects for developing novel antifungal agents for treating oral candidiasis in the years to come.

■ Authors' Contributions

REC N		https://orcid.org/0000-0002-4300-1201	Conceptualization, Methodology, Formal Analysis, Investigation, Data Curation and Writing - Review and Editing.
AKVM		https://orcid.org/0000-0001-8900-7193	Methodology and Investigation.
FQSG		https://orcid.org/0000-0003-2057-4821	Methodology, Investigation and Project Administration.
WPSR		https://orcid.org/0000-0003-0639-2781	Methodology, Data Curation, Writing - Review and Editing, Supervision and Project Administration.
All authors declare that they contributed to a critical review of intellectual content and approval of the final version to be published.			

■ Financial Support

None.

■ Conflict of Interest

The authors declare no conflicts of interest.

■ Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

■ References

- [1] Handsley-Davis M, Jamieson L, Kapellas K, Hedges J, Weyrich LS. The role of the oral microbiota in chronic non-communicable disease and its relevance to the Indigenous health gap in Australia. *BMC Oral Health* 2020; 20(1):327 <https://doi.org/10.1186/s12903-020-01308-y>
- [2] Gheorghe DC, Niculescu AG, Bircă AC, Grumezescu AM. Biomaterials for the prevention of oral candidiasis development. *Pharmaceutics* 2021; 13(6):803. <https://doi.org/10.3390/pharmaceutics13060803>
- [3] Peng X, Cheng L, You Y, Tang C, Ren B, Li Y, et al. Oral microbiota in human systematic diseases. *Int J Oral Sci* 2022; 14(1):14. <https://doi.org/10.1038/s41368-022-00163-7>
- [4] Patel M. Oral Cavity and *Candida albicans*: Colonisation to the development of infection. *Pathogens* 2022; 11(3):335. <https://doi.org/10.3390/pathogens11030335>
- [5] Kitamoto S, Nagao-Kitamoto H, Hein R, Schmidt TM, Kamada N. The bacterial connection between the oral cavity and the gut diseases. *J Dent Res* 2020; 99(9):1021-1029. <https://doi.org/10.1177/0022034520924633>
- [6] Hato H, Sakata K ichiro, Sato J, Hasebe A, Yamazaki Y, Kitagawa Y. Factor associated with oral candidiasis caused by co-infection of *Candida albicans* and *Candida glabrata*: A retrospective study. *J Dent Sci* 2022; 17(3):1458-1461. <https://doi.org/10.1016/j.jds.2021.10.020>
- [7] Bonifácio BV, Vila TVM, Masiero IF, da Silva PB, da Silva IC, de Oliveira Lopes É, et al. Antifungal activity of a hydroethanolic extract from *Astronium urundeuva* leaves against *Candida albicans* and *Candida glabrata*. *Front Microbiol* 2019; 10:2642. <https://doi.org/10.3389/fmicb.2019.02642>
- [8] Singh DP, Verma RK, Sarswat S, Saraswat S. Non- *Candida albicans* *Candida* species: Virulence factors and species identification in India. *Curr Med Mycol* 2021; 7(2):e8-13. <https://doi.org/10.18502/cmm.7.2.7032>
- [9] Hu L, He C, Zhao C, Chen X, Hua H, Yan Z. Characterization of oral candidiasis and the *Candida* species profile in patients with oral mucosal diseases. *Microb Pathog* 2019; 134:103575. <https://doi.org/10.1016/j.micpath.2019.103575>
- [10] Srivastava D, Yadav A, Naqvi S, Awasthi H, Fatima Z. Efficacy of flavonoids in combating fluconazole resistant oral candidiasis. *Curr Pharm Des* 2022; 28(21):1703-1713. <https://doi.org/10.2174/1381612828666220324140257>
- [11] Pristov KE, Ghannoum MA. Resistance of *Candida* to azoles and echinocandins worldwide. *Clin Microbiol Infect* 2019; 25(7):792-798. <https://doi.org/10.1016/j.cmi.2019.03.028>
- [12] Paiva JÁ, Pereira JM. Treatment of invasive candidiasis in the era of *Candida* resistance. *Curr Opin Crit Care* 2023; 29(5):457-462. <https://doi.org/10.1097/MCC.0000000000001077>
- [13] Czajka KM, Venkataraman K, Brabant-Kirwan D, Santi SA, Verschoor C, Appanna VD, et al. Molecular mechanisms associated with antifungal resistance in pathogenic *Candida* Species. *Cells* 2023; 12(22):2655. <https://doi.org/10.3390/cells12222655>
- [14] Mundula T, Ricci F, Barbetta B, Baccini M, Amedei A. Effect of probiotics on oral candidiasis: A systematic review and meta-analysis. *Nutrients* 2019; 11(10):2449. <https://doi.org/10.3390/nu11102449>
- [15] Jin Y, Yip HK, Samaranayake YH, Yau JY, Samaranayake LP. Biofilm-forming ability of *Candida albicans* is unlikely to contribute to high levels of oral yeast carriage in cases of human immunodeficiency virus infection. *J Clin Microbiol* 2003; 41(7):2961-2967. <https://doi.org/10.1128/JCM.41.7.2961-2967.2003>
- [16] Heard SC, Wu G, Winter JM. Antifungal natural products. *Curr Opin Biotechnol* 2021; 69:232-241. <https://doi.org/10.1016/j.copbio.2021.02.001>

- [17] Hsu H, Sheth CC, Veses V. Herbal extracts with antifungal activity against *Candida albicans*: A systematic review. *Mini Rev Med Chem* 2021; 21(1):90-117. <https://doi.org/10.2174/1389557520666200628032116>
- [18] Berkow EL, Lockhart SR, Ostrosky-Zeichner L. Antifungal susceptibility testing: Current approaches. *Clin Microbiol Rev* 2020; 33(3):e00069-19. <https://doi.org/10.1128/CMR.00069-19>
- [19] Jemel S, Guillot J, Kallel K, Botterel F, Dannaoui E. *Galleria mellonella* for the evaluation of antifungal efficacy against medically important Fungi: A narrative review. *Microorganisms* 2020; 8(3):390. <https://doi.org/10.3390/microorganisms8030390>
- [20] Sampaio ADG, Gontijo AVL, Araujo HM, Koga-Ito CY. In vivo efficacy of ellagic acid against *Candida albicans* in a *Drosophila melanogaster* infection model. *Antimicrob Agents Chemother* 2018; 62(12):e01716-18. <https://doi.org/10.1128/AAC.01716-18>
- [21] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *J Clin Epidemiol* 2009; 62(10):1006-1012. <https://doi.org/10.1016/j.jclinepi.2009.06.005>
- [22] Hooijmans CR, Rovers MM, De Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol* 2014; 14:43. <https://doi.org/10.1186/1471-2288-14-43>
- [23] Abd Elmonaem SN, Moussa E, Aboulela AG, Essawy MM, Anwar SK. Evaluation of topical application of nanocurcumin suspension in treatment of oral candidal infection (experimental study). *Alexandria Dent J* 2022; 47(1):e56-61.
- [24] Abdallah BM, Ali EM. Therapeutic effect of green synthesized silver nanoparticles using *Erodium glaucophyllum* extract against oral candidiasis: In vitro and in vivo study. *Molecules* 2022; 27(13):4221. <https://doi.org/10.3390/molecules27134221>
- [25] Sampaio AG, Gontijo AVL, Lima GMG, de Oliveira MAC, Lepesqueur LSS, Koga-Ito CY. Ellagic acid-cyclodextrin complexes for the treatment of oral candidiasis. *Molecules* 2021; 26(2):505. <https://doi.org/10.3390/molecules26020505>
- [26] de Barros PP, Rossoni RD, Garcia MT, Kaminski VL, Loures FV, Fuchs BB, et al. The anti-biofilm efficacy of Caffeic Acid Phenethyl Ester (CAPE) in vitro and a murine model of oral candidiasis. *Front Cell Infect Microbiol* 2021; 11:700305. <https://doi.org/10.3389/fcimb.2021.700305>
- [27] Zhu C, Liao B, Ye X, Zhou Y, Chen X, Liao M, et al. Artemisinin elevates ergosterol levels of *Candida albicans* to synergise with amphotericin B against oral candidiasis. *Int J Antimicrob Agents* 2021; 58(3):106394. <https://doi.org/10.1016/j.ijantimicag.2021.106394>
- [28] Wang Z, Yang K, Chen L, Yan R, Qu S, Li YX, et al. Activities of Nerol, a natural plant active ingredient, against *Candida albicans* in vitro and in vivo. *Appl Microbiol Biotechnol* 2020; 104(11):5039-5052. <https://doi.org/10.1007/s00253-020-10559-2>
- [29] Chen L, Qu S, Yang K, Liu M, Li YX, Keller NP, et al. Perillaldehyde: A promising antifungal agent to treat oropharyngeal candidiasis. *Biochem Pharmacol* 2020; 180:114201. <https://doi.org/10.1016/j.bcp.2020.114201>
- [30] Niyogi P, Pattnaik S, Maharana L, Mohapatra R, Kolet SP. An Epidemiological correlation of oral candidiasis mice model study of an isolate from *Mollugo pentaphylla* Linn. and in silico docking approach. *Iran J Sci Technol Trans A Sci* 2019; 43(3):785-799. <https://doi.org/10.1007/s40995-018-0619-4>
- [31] Chen L, Wang Z, Liu L, Qu S, Mao Y, Peng X, et al. Cinnamaldehyde inhibits *Candida albicans* growth by causing apoptosis and its treatment on vulvovaginal candidiasis and oropharyngeal candidiasis. *Appl Microbiol Biotechnol* 2019; 103(21-22):9037-9055. <https://doi.org/10.1007/s00253-019-10119-3>
- [32] Sakima VT, Barbugli PA, Cerri PS, Chorilli M, Carmello JC, Pavarina AC, et al. Antimicrobial photodynamic therapy mediated by curcumin-loaded polymeric nanoparticles in a murine model of oral candidiasis. *Molecules* 2018; 23(8):2075. <https://doi.org/10.3390/molecules23082075>
- [33] Bassiri-Jahromi S, Pourshafie MR, Ardakani EM, Ehsani AH, Doostkam A, Katirae F, et al. In vivo comparative evaluation of the Pomegranate (*Punica granatum*) peel extract as an alternative agent to Nystatin against oral candidiasis. *Iran J Med Sci* 2018; 43(3):296.
- [34] Seleem D, Freitas-Blanco VS, Noguti J, Zancope BR, Pardi V, Murata RM. In vivo antifungal activity of Monolaurin against *Candida albicans* biofilms. *Biol Pharm Bull* 2018; 41(8):1299-1302. <https://doi.org/10.1248/bpb.b18-00256>
- [35] Silva-Rocha WP, de Azevedo MF, Ferreira MRA, da Silva J de F, Svidzinski TIE, Milan EP, et al. Effect of the ethyl acetate fraction of *Eugenia uniflora* on proteins global expression during morphogenesis in *Candida albicans*. *Front Microbiol* 2017; 8:1788. <https://doi.org/10.3389/fmicb.2017.01788>
- [36] Seleem D, Benso B, Noguti J, Pardi V, Murata RM. In vitro and in vivo antifungal activity of Lichochalcone-A against *Candida albicans* biofilms. *PLoS One* 2016; 11(6):e0157188. <https://doi.org/10.1371/journal.pone.0157188>
- [37] de Campos Rasteiro MM, da Costa PCBP, Araújo FF, de Barros PP, Rossoni DD, Anbinder LL, et al. Essential oil of *Melaleuca alternifolia* for the treatment of oral candidiasis induced in an immunosuppressed mouse model. *BMC Complement Altern Med* 2014; 14:489. <https://doi.org/10.1186/1472-6882-14-489>
- [38] Ninomiya K, Hayama K, Ishijima SA, Maruyama N, Irie H, Kurihara J, et al. Suppression of inflammatory reactions by terpinen-4-ol, a main constituent of tea tree oil, in a murine model of oral candidiasis and its suppressive activity to cytokine production of macrophages in vitro. *Biol Pharm Bull* 2013; 36(5):e838-844. <https://doi.org/10.1248/bpb.b13-00033>

- [39] Dovigo LN, Carmello JC, De Souza Costa CA, Vergani CE, Brunetti IL, Bagnato VS, et al. Curcumin-mediated photodynamic inactivation of *Candida albicans* in a murine model of oral candidiasis. *Med Mycol* 2013; 51(3):243-251. <https://doi.org/10.3109/13693786.2012.714081>
- [40] Ninomiya K, Hayama K, Ishijima SA, Maruyama N, Irie H, Kurihara J, et al. Suppression of inflammatory reactions by terpinen-4-ol, a main constituent of tea tree oil, in a murine model of oral candidiasis and its suppressive activity to cytokine production of macrophages in vitro. *Biol Pharm Bull* 2013; 36(5):838-844. <https://doi.org/10.1248/bpb.b13-00033>
- [41] Taguchi Y, Hayama K, Okada M, Sagawa T, Arai R, Abe S. Therapeutic effects of cinnamaldehyde and potentiation of its efficacy in combination with methylcellulose on murine oral candidiasis. *Med Mycol J* 2011; 52(2):145-152. <https://doi.org/10.3314/jjmm.52.145>
- [42] Taguchi Y, Takizawa T, Ishibashi H, Sagawa T, Arai R, Inoue S, et al. Therapeutic effects on murine oral candidiasis by oral administration of cassia (*Cinnamomum cassia*) preparation. *Nihon Ishinkin Gakkai Zasshi*. 2010; 51(1):13-21. <https://doi.org/10.3314/jjmm.51.13>
- [43] Subha T, Gnanamani A. Combating oral candidiasis in albino rats using bioactive fraction of *Acorus calamus*. *J Appl Biosc* 2009; 21:1265-1276.
- [44] Taguchi Y, Ishibashi H, Takizawa T, Inoue S, Yamaguchi H, Abe S. Protection of oral or intestinal candidiasis in mice by oral or intragastric administration of herbal food, clove (*Syzygium aromaticum*). *Nihon Ishinkin Gakkai Zasshi* 2005; 46(1):27-33. <https://doi.org/10.3314/jjmm.46.27>
- [45] Ferreira MRA, Santiago RR, Langassner SMZ, Mello JCP, Svidzinski TIE, Soares LAL. Antifungal activity of medicinal plants from Northeastern Brazil. *J Med Plants Res* 2013; 7(40):3008-3013. <https://doi.org/10.5897/JMPR2013.5035>
- [46] Ferreira EDS, Rosalen PL, Benso B, de Cássia Orlandi Sardi J, Denny C, Alves de Sousa S, et al. The use of essential oils and their isolated compounds for the treatment of oral candidiasis: A literature review. *Evid Based Complement Alternat Med* 2021; 2021:1059274. <https://doi.org/10.1155/2021/1059274>
- [47] Newman DJ, Cragg GM. Natural products as sources of new drugs from 1981 to 2014. *J Nat Prod* 2016; 79(3):629-661. <https://doi.org/10.1021/acs.jnatprod.5b01055>
- [48] Calixto JB. The role of natural products in modern drug discovery. *An Acad Bras Cienc* 2019; 91(Suppl. 3):e20190105. <https://doi.org/10.1590/0001-3765201920190105>
- [49] Atanasov AG, Zotchev SB, Dirsch VM, International Natural Product Sciences Taskforce, Supuran CT. Natural products in drug discovery: advances and opportunities. *Nat Rev Drug Discov* 2021; 20(3):200-216. <https://doi.org/10.1038/s41573-020-00114-z>
- [50] Erfaninejad M, Zarei Mahmoudabadi A, Maraghi E, Hashemzadeh M, Fatahinia M Epidemiology, prevalence, and associated factors of oral candidiasis in HIV patients from southwest Iran in post-highly active antiretroviral therapy era. *Front Microbiol* 2022; 13:983348. <https://doi.org/10.3389/fmicb.2022.983348>
- [51] Aldholmi M, Marchand P, Ourliac-Garnier I, Le Pape P, Ganesan A. A decade of antifungal leads from natural products: 2010-2019. *Pharmaceuticals* 2019; 12(4):182. <https://doi.org/10.3390/ph12040182>
- [52] Vila T, Sultan AS, Montelongo-Jauregui D, Jabra-Rizk MA. Oral candidiasis: A disease of opportunity. *J Fungi* 2020; 6(1):15. <https://doi.org/10.3390/jof6010015>
- [53] Rodríguez-Cerdeira C, Martínez-Herrera E, Carnero-Gregorio M, López-Barcenas A, Fabbrocini G, Fida M, et al. Pathogenesis and clinical relevance of *Candida* biofilms in vulvovaginal candidiasis. *Front Microbiol* 2020; 11:544480. <https://doi.org/10.3389/fmicb.2020.544480>
- [54] Chung H, Yoon SH, Cho JY, Yeo HK, Shin D, Park JY. Comparative pharmacokinetics of Theracurmin, a highly bioavailable curcumin, in healthy adult subjects. *Int J Clin Pharmacol Ther* 2021; 59(10):684-690. <https://doi.org/10.5414/CP204058>
- [55] Costa ACBP, Pereira CA, Junqueira JC, Jorge AOC. Recent mouse and rat methods for the study of experimental oral candidiasis. *Virulence* 2013; 4(5):391-399. <https://doi.org/10.4161/viru.25199>