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Review Article

POTENTIAL OF HERBAL MEDICINE IN ASIA FOR ORAL CANDIDIASIS THERAPY: A SYSTEMATIC REVIEW

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ABSTRACT

The objective of this review was to provide antifungal recommendations for Oral Candidiasis (OC) derived from herbal medicine based on the research results of the last 5 y. This systematic review was conducted according to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines using the PubMed and Science Direct databases with studies published between 2016 and 2021. The review was conducted on 13 studies, *in vitro* and clinical trial. A total of 41 species of plants have studied its antifungal effects on *Candida albicans*. The Minimum Inhibitory Concentration (MIC) and Minimum Fungicidal Concentration (MFC) varied in the range of 0.098 µl/ml to 125 µl/ml for different types of plants and *Candida* samples, while the mean inhibition zone (ZOI) was 11 mm. The most recommended herbal medicine for the development of antifungal drugs for oral candidiasis therapy were *Nigella sativa, Lawsonia inermis*, and *Zingiber officinale*.

Keywords: Herbal medicine, Antifungal, Oral candidiasis, *Candida albicans*

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INTRODUCTION

Oral candidiasis (OC), commonly referred to as "thrush" includes infections of the tongue and other oral mucosal sites and is characterized by fungal overgrowth that invades the superficial tissues. *C. albicans* is the main causative agent of OC, accounting for up to 95% of cases. The tongue dorsum is the initiation point of infection for the majority of the clinical forms of OC. Predisposing factors for candidiasis are the use of broad-spectrum antibiotics, immunosuppressive agents, installation of medical devices and Nasogastric tube (NGT), as well as decreased immunity related to human immunodeficiency virus (HIV) infection [1].

The pharmacological treatment of candidiasis can be distinguished between topical or systemic antifungal [2]. Antifungal agents comprise three main classes: polyenes, azoles, and echinocandins [1]. More than 200 polyene antifungals have been discovered, some of which are most commonly used in antifungal therapy, such as amphotericin B, nystatin, and natamycin. Polyenes were the first broad-spectrum antifungal drugs on the market and still used to treat a variety of fungal infections after 70 y [3]. The side effects of polyene antifungals are high toxicity, including fever, nausea and vomiting, nephrotoxicity, liver toxicity, and interactions with co-administered drugs. Another crucial problem is the increasing drug resistance that invalidates the clinical treatments [4].

Some of the side effects of existing antifungal agents and the need for cost-effective treatments to manage oral candidiasis have prompted the search for new alternatives in this field. Natural agents have emerged as sources of bioactive molecules with potential therapeutic applications in the medical and dental fields in recent years. Among them, plant extracts are considered a group of natural compounds that are highly desirable in the prevention and treatment of oral candidiasis [5]. Many studies have shown that plant extracts such as *Coriandrum sativum* [5], *Hypericum hircinum* [4], *Chrysobalanus icaco* [6], *Ononis spinosa* [7], *Ricinus communis* [8], and *Gymnema sylvestre* [9] have the potential as antifungal and inhibit the growth of *Candida albicans*. Medicinal plant extracts and selected active fractions have been investigated and have low cytotoxicity in human cells [5].

The large number of plant species that tested for antifungal activity in previous studies make it difficult to obtain an overview of the subject and their interpretation. In this context, the authors aimed to perform a systematic review of the literature on *in vitro* studies and clinical trials of medicinal plants that have anti-*Candida* potential, based on the research conducted in the last 5 y. Clinically, this systematic review aims to provide antifungal recommendations for OC derived from herbal medicine.

Method

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [10]. The themes in this study were arranged according to Population, Intervention, Comparison, and Outcome (PICO) [11] with the following details: Population is an articles discussing *Candida albicans* or Oral Candidiasis; Intervention are medicinal plants or herbs; a Comparison is a control group, and Outcomes is the Minimum Inhibition Concentration (MIC) or Minimum Fungicidal Concentration (MFC) or Zone of Inhibition (ZOI) of *Candida albicans* for *in vitro* studies or observation on lesion healing for clinical trial studies.

Articles search was conducted using the PubMed (Medline) and ScienceDirect databases, carried out between March to May 2021. The database filters used were: publications in the last 5 y (2016-2021) and articles in English. The articles type used were *in vitro*, *in vivo*, and clinical trials design studies, but the literature review or systematic review article was not used. The keywords used in the Medline via PubMed database was: ("candida"[All Fields] OR "candida albicans"[MeSH Terms] OR candida albicans [Text Word] AND "antifungal agents"[All Fields] OR "antifungal agents"[MeSH Terms] OR antifungal[Text Word] AND herbal[All Fields]), and keywords used in the Science Direct database was: (("oral candidiasis") AND ("herbal medicine" OR "plant medicine")). Another inclusion criteria was medicinal plants in Asia which were adapted from the purpose of this systematic review.

Articles were initially screened based on the title and abstract according to the scope. A manual hand-searching of the reference lists of relevant studies was also performed. The quality of the research methodology of the selected articles was assessed for risk of bias using "Risk of Bias Assessment of Non-randomized Studies (RoBANS)" tools [12]. RoBANS was chosen because it is most suitable for assessing the quality of non-randomized studies and observational studies. Furthermore, all articles that are judged to be of good quality are reviewed with thematic analysis, which is grouped by theme according to the purpose of writing. In terms of

writing this review, namely: country, species and parts of medicinal plants, active compounds, sample, outcomes (MFC/MIC or ZOI), and conclusions or recommendations.

RESULTS

Fig. 1 shows a complete process flowchart of article identification, screening, and eligibility assessment according to the inclusion criteria that have been determined. A total of 568 articles were obtained from the database Medline via PubMed and 412 articles from the database Science Direct. A total of 555 articles from Medline via PubMed and 410 articles from ScienceDirect were excluded because they did not meet the inclusion criteria using the filters in the database system. One of the 13 articles is known to be a duplication so that it is removed and remains 12 articles. Then we obtained another 1 article with manual hand searching, so the total articles that will be reviewed qualitatively are 13 articles.

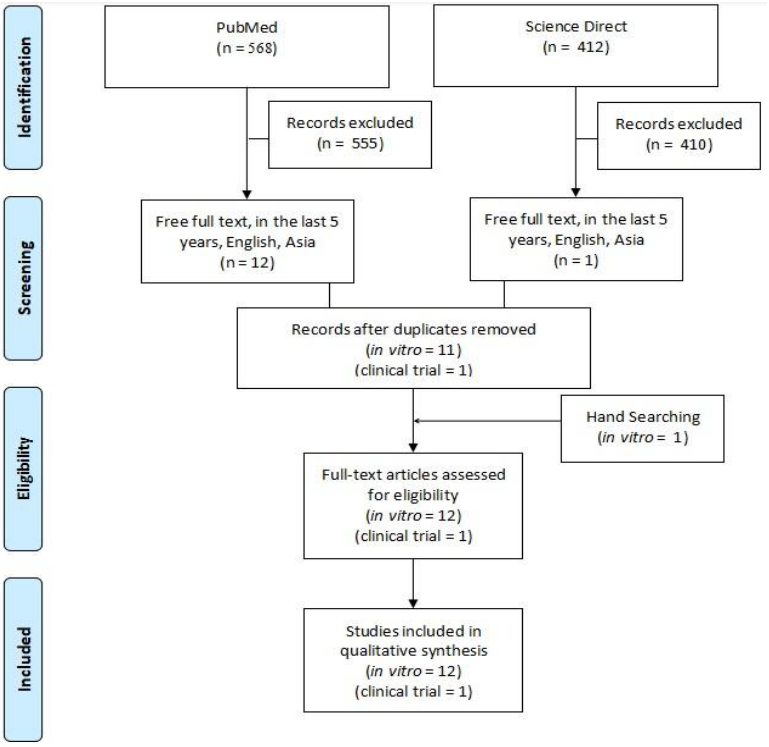

Fig. 1: Flowchart of the systematic article search process with PRISMA guidelines [10]

Assessment of the risk of bias for selected articles was performed using RoBANS. There are 6 assessment points as shown in table 1. The risk of bias assessment shows that all of these articles have a low risk of bias or have a high quality, so they can be reviewed systematically.

Table 1: Assessment of the risk of bias

S. No.	Author	Assessment item						Total point	Risk of bias	Quality
		Item 1	Item 2	Item 3	Item 4	Item 5	Item 6			
1	Sajjadi *et al.*, 2016 [13]	1	1	1	1	1	1	6	Low	High Quality
2	Hovijitra *et al.*, 2016 [14]	1	1	1	1	1	1	6	Low	High Quality
3	Aghazadeh *et al.*, 2016 [15]	1	1	1	1	1	1	6	Low	High Quality
4	Sharma, Hunny *et al.* [16]	1	1	1	1	1	1	6	Low	High Quality
5	Soliman *et al.*, 2017 [17]	1	1	1	1	1	1	6	Low	High Quality
6	Al-Thobity *et al.*, 2017 [18]	1	1	1	1	1	1	6	Low	High Quality
7	Naeini *et al.*, 2017 [19]	1	1	1	0	1	1	5	Low	High Quality
8	Bhat *et al.*, 2018 [20]	1	1	1	1	1	1	6	Low	High Quality
9	Samadi *et al.*, 2019 [21]	1	1	1	1	1	1	6	Low	High Quality
10	Nosratzehi *et al.*, 2019 [22]	1	1	1	1	1	1	6	Low	High Quality
11	Ariamanesh *et al.*, 2019 [23]	1	1	1	1	1	1	6	Low	High Quality
12	Zainal *et al.*, 2020 [24]	1	1	1	1	1	1	6	Low	High Quality
13	Ghorbani *et al.*, 2018 [25]	1	1	1	1	1	1	6	Low	High Quality
Domain assessment (%)		100	100	100	87.5	100	100			

Item 1 = Selection of material studies; Item 2 = Confounding variables; Item 3 = Intervention (exposure) measurement; Item 4 = Blinding of outcome assessment; Item 5 = Incomplete outcome data; Item 6 = selective outcome reporting; 1 = Yes; 2 = No; Total point 0-2 = high; Total point 3–5 = low.

Selected articles were published from 2016-2021. From a total of 13 articles, 12 articles are *in vitro* studies and 1 article is a clinical trial study. The number of plants studied was 41 species from all studies. A resume from a systematic review of articles on the potential of medicinal plants as an anti-fungal for the development of oral candidiasis therapy, as listed in table 2.

Table 2: The potential of medicinal plants as anti-fungal for the development of oral candidiasis therapy

No	Author	Country	Plant		Active compound	Sample/ control	Outcome		Conclusion
			Spesies	Part			MIC/MFC	ZOI	
1	Sajjadi *et al.*, 2016 [13]	Iran	*Cyclamen coum*	tuber	Saponin, Triterpenoid	Sample: *C. albicans* ATCC 10231 Control (+): Ketoconazole	MIC: 5 µg/ml	(-)	*Cyclamen coum* tuber extract is rich in triterpenoid saponins and has anti-Candida effect (*in vitro* study)
2	Hovijitra *et al.*, 2016 [14]	Thailand	*Cinnamomum zealanicum*	bark	Phenolic	Sample: *C. albicans* ATCC 10231 Control (+): Clotrimazole	0.098 µl/ml	13±4.63 mm	Cinnamon essential oil (*Cinnamomum zealanicum*) and basil leaf herbal oil (*Ocimum basilicum*) can be the most effective anti-Candida options based on the comparison of MFC and ZOI (*in vitro* study)
			Ocimum basilicum	leaves	Phenolic		0.391 µl/ml	11±1.47 mm	
			Foeniculum vulgare	leaves	Not mentioned		6.25 µl/ml	8±0.55 mm	
			Citrus limon	peel	Not mentioned		125 µl/ml	8±1.47 mm	
			Citrus aurantifolia	peel	Not mentioned		0	0	
			Citrus hystrix	leaves, peel	Not mentioned		1.563 µl/ml	7±1.47 mm	
			Citrus sinensis	peel	Not mentioned		1.563 µl/ml	9±0.98 mm	
			Alpinia galanga	rhizome	Not mentioned		0	0	
			Allium sativum	clove	Not mentioned		0	0	
			Curcuma longa	rhizome	Not mentioned		0	0	
			Cocos nucifera	milk	Not mentioned		0	0	
			Mentha spicata	leaves	Not mentioned		3.125 µl/ml	9±1.51 mm	
			Mentha piperita	leaves	Not mentioned		0	0	
3	Aghazadeh *et al.*, 2016 [15]	Iran	*Zingiber officinale*	rhizome	Not mentioned	Sample: *C. albicans* ATCC 10231 Control (+): 70% ethanol	MIC: 0.625 ml/ml	(-)	*Zingiber officinale* extract has potential as an anti-Candida (*in vitro* study)
4	Sharma *et al.*, 2016 [16]	India	*Glycyrrhiza glabra*	bark	Not mentioned	Sample: C. albicans ATCC 66027 Control (+): clotrimazole, fluconazole	(-)	19.8±0.83 mm	*G. glabra* extract was the most effective as an anti-Candida with the largest inhibition zone (*in vitro* study)
			Ficus religiosa	stem	Not mentioned		(-)	11.4±0.54 mm	
			Plantago major	husk	Not mentioned		(-)	10.6±0.89 mm	
5	Soliman *et al.*, 2017 [17]	United Arab Emirates	*Avicennia marina*	leaves	Not mentioned	Sample: C. albicans SC 5314 Control (+): Ketoconazole	0	0	*L. inermis* and *P. oleracea* extracts had the most effective anti-Candida activity based on the comparison of MIC and ZOI (*in vitro* study)
			Fagonia indica	leaves	Not mentioned		0	0	
			Lawsonia inermis	leaves	Not mentioned		10±1.3µg /ml	15±0.5 mm	
			Portulaca oleracea	leaves	Not mentioned		10±0.2µg /ml	11±1 mm	
			Salvadora persica	leaves	Not mentioned		25±0.5µg /ml	10±0.2 mm	
			Ziziphus spina-Christi	leaves	Not mentioned		0	0	
			Asphodelus tenuifolius	leaves	Not mentioned		50±0.4 µg/ml	9±0.1 mm	
6	Al-Thobity *et al.*, 2017 [18]	Saudi Arabia	*Nigella sativa*	seeds	Monoterpenoid	Sample: C. albicans ATCC 10231 Control (-): Concentration 0%	MIC: 2.5%	(-)	The use of thymoquinone isolate in *Nigella sativa* was effective in preventing the adhesion of *C. albicans* (*in vitro* study)
7	Naeini *et al.*, 2017 [19]	Iran	*Nigella sativa*	seeds	Monoterpenoid	Sample: C. albicans from oral mukosa Control: -	(-)	8 mm	*N. sativa* and *F. vulgare* extracts are good anti-Candida agents (*in vitro* studies)
			Foeniculum vulgare	seeds	Phenolic		(-)	5.8 mm	
			Camellia sinensis	leaves	Phenolic		(-)	0	
8	Bhat *et al.*, 2018	India	*Origanum vulgare*	leaves	Phenolic	Sample: C. albicans from	MIC: 0.024%	30±3 mm	*O. vulgare* extract has anti-Candida activity

No	Author	Country	Plant		Active compound	Sample/ control	Outcome		Conclusion
			Spesies	Part			MIC/MFC	ZOI	
	[20]					denture Control (+): Nystatin	MFC: 0.097%		against clinical isolates from oral Candida (*in vitro* study)
9	Samadi *et al.*, 2019 [21]	India	*Lawsonia inermis*	leaves	Not mentioned	Sample: C. albicans from oral mukosa Control (+): Clotrimazole, Fluconazole	MIC: 5 mg/ml	17±0.22 mm	The herbal extracts of *Lawsonia inermis, Withania somnifer, Cymbopogon citrates* and *Zingiber officinale* gave the best inhibitory effect and had the potential to control the growth of *Candida albicans* with an inhibition zone above 12 mm and statistical analysis p>0.05 (*in vitro* study)
			Withania somnifera	leaves	Not mentioned			16±0.16 mm	
			Zingiber officinale	leaves	Not mentioned			13±0.12 mm	
			Curcuma longa	leaves	Not mentioned			15±0.06 mm	
			Cymbopogon citrates	leaves	Not mentioned			11±0.21 mm	
			Tamarindus indica	leaves	Not mentioned			10±0.36 mm	
			Limonia acidissima	leaves	Not mentioned			07±0.04 mm	
			Psidium guajana	leaves	Not mentioned			10±0.17 mm	
			Annona reticulata	leaves	Not mentioned			08±0.17 mm	
			Swertia chirata	leaves	Not mentioned			10±0.43 mm	
			Euphorbia hirta	leaves	Not mentioned			24±0.15 mm	
			Pogostemon parviflorus	leaves	Not mentioned			15±0.06 mm	
			Adenocalyma alliacum	leaves	Not mentioned			14±0.23 mm	
			Echinophora platybola	leaves	Not mentioned			20±0.20 mm	
			Cuminum cyminum	leaves	Not mentioned			07±0.17 mm	
10	Nosratzehi *et al.*, 2019 [22]	Iran	*Curcuma longa*	rhizome	Phenolic	Sample: C. albicans from oral mukosa Control (+): Nystatin	(-)	1.36±0.89 mm	*Curcuma longa* extract has no inhibitory effect on *Candida albicans* (*in vitro* study)
11	Ariamanesh *et al.*, 2019 [23]	Iran	*Nigella sativa*	seeds	Monoterpenoid	Sample: C. albicans ATCC 10231 Control (+): Nystatin	MIC: 20 mg/ml	(-)	High concentration of *N. sativa* extract has anti-Candida effect (*in vitro* study)
12	Zainal *et al.*, 2020 [24]	Malaysia	*Allium sativum*	clove	Organosulfur	Sample: C. albicans ATCC 14053 Control (+): Nystatin	MFC: 16 mg/ml	(-)	*Allium sativum* extract has anti-Candida effect (*in vitro* study)
13	Ghorbani *et al.*,2018 [25]	Iran	*Camellia sinensis*	leaves	Phenolic, flavonoid	Sample: 22 denture stomatitis patients (11 Control+)	The mean length and width of the lesions shown in the green tea (*Camellia sinensis*) test group decreased with treatment duration		Mouthwash from green tea leaves extract (*Camellia sinensis*) exhibits anti-Candida activity comparable to nystatin (clinical trial)

DISCUSSION

Based on this review from 13 articles, 41 types of plants were known to be tested for anti-Candida activity, namely: *Cyclamen coum* [13], *Cinnamomum zealanicum* [14], *Ocimum basilicum* [14], *Foeniculum vulgare* [19], *Citrus limon* [14], *Citrus aurantifolia* [14], *Citrus hystrix* [14], *Citrus sinensis* [14], *Alpinia galanga* [14], *Allium sativum* [15, 24], *Curcuma longa* [21, 22], *Cocos nucifera* [14], *Mentha spicata* [14], *Mentha piperita* [14], *Zingiber officinale* [15, 21], *Glycyrrhiza glabra* [16], *Ficus religiosa* [16], *Plantago major* [16], *Avicennia marina* [17], *Fagonia indica* [17], *Lawsonia inermis* [17, 21], *Portulaca oleracea* [17], *Salvadora persica* [17], *Ziziphus spina-Christi* [17], *Asphodelus tenuifolius* [17], *Nigella sativa* [18, 19, 23], *Camellia sinensis* [19, 25], *Origanum vulgare* [20], *Withania somnifera* [21], *Cymbopogon citrates* [21], *Tamarindus indica* [21], *Limonia acidissima* [21], *Psidium guajana* [21], *Annona reticulata* [21], *Swertia chirata* [21], *Euphorbia hirta* [21], *Pogostemon parviflorus* [21], *Adenocalymma alliacum* [21], *Echinophora platybola* [21], and *Cuminum cyminum* [21]. There are several plants that after being tested did not have anti-Candida activity, including *Alpinia galanga* [14], *Allium sativum* [15, 24], *Cocos nucifera* [14], *Mentha piperita* [14], *Avicennia marina* [17], *Fagonia indica* [17], and *Ziziphus spina-Christi* [17].

Candida albicans were used in the *in vitro* studies using ATCC 10231 in 5 studies, whilst ATCC 66027, SC 5314, and ATCC 14053 each in 1 study. ATCC and SC cell cultures are easy to control as desired by environmental physicochemistry and inexpensive [26]. In addition, there are 4 *in vitro* studies using cell cultures taken from the oral mucosa and removable dentures of patients with oral candidiasis. This clinical trial study was followed by 22 patients with a diagnosis of denture stomatitis and 11 patients given conventional therapy as positive controls.

In the *in vitro* test, the negative control comparators were ethanol and 0% concentration of plant extracts. All reviewed studies used established antifungal drugs as positive controls, such as ketoconazole, clotrimazole, fluconazole, itraconazole, and nystatin. Parameters from the *in vitro* studies were evaluated by determining at the Minimum Inhibitory Concentration (MIC) or Minimum Fungicidal Concentration (MFC), and/or Zone of Inhibition (ZOI). The culture media used in the *in vitro* studies were Sabouraud Dextrose Agar (SDA).

Nigella sativa is the most tested plant, which is commonly found in South and Southwest Asia. The part of the plant used is the seeds which are commonly called black cumin seeds. The extract has been explored and had antifungal properties. *Thymoquinone* is the main ingredient in *N. sativa,* which is a monoterpenoid [18, 19, 23]. The mechanism of action of monoterpenoids on *N. sativa* inhibit calcineurin signaling, affect cell surface integrity (cell walls and cell membranes), yeast to hyphae transition, biofilm formation, cell cycle arrest in S phase and mitochondrial dysfunction [27].

Other active plant compounds are phenolic compounds contained in *Lawsonia inermis* [17, 21], and *Zingiber officinale* [15, 21]. Phenolic compounds act by damaging cell walls, inhibiting the isocitrate lyase enzyme activity, disrupting plasma membrane dimorphism inhibition, *in vitro* immunoregulatory, effect on monocytes against *C. albicans* and against biofilms [28]. The mechanism of action of these polyphenol compounds and monoterpenoids is similar to the mechanism of action of Nystatin which has been established in the treatment of Oral candidiasis. Nystatin induces membrane permeability by forming complexes with ergosterol located in fungal membranes, leading to intracellular leakage and cell death [3].

Of all the articles reviewed, there were several plants that were of concern to the author. There were 3 articles that explored the potential of the *Nigella sativa* plant. The *in vitro* study of *Nigella sativa* plants showed that it can prevent the adhesion of *Candida albicans* and have a good antifungal potency [18, 19, 23]. In addition, there are also two studies conducted on *Lawsonia inermis* (henna nail) plant. The inhibition of *L. inermis* against *C. albicans* was very good with ZOI of 15±0.5 mm and 10±0.22 mm [17, 21]. Finally, there were also two articles that discussed the antifungal potential of *Zingiber officinale* (ginger). It also said it has good inhibition and anti-biofilm formation activities against *C. albicans* with the MIC of 0.625 ml/ml and ZOI of 16±0.12 mm [2, 21]. Apart to these three plants, each of the other plants was only carried out once, or did not have good antifungal activity. The secondary metabolites that play a role in the antifungal activity of these plants are monoterpenoids and/or polyphenolic/phenolic compounds. So that these three plants, *Nigella sativa, Lawsonia inermis,* and *Zingiber officinale,* are recommended to be researched by using clinical trial design as an antifungal alternative for oral candidiasis therapy.

CONCLUSION

The most recommended herbal medicine for the development of antifungal drugs for Oral candidiasis therapy were *Nigella sativa, Lawsonia inermis,* and *Zingiber officinale*.

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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