

Exploring Antifungal Potential of Qusthul Hindi (*Saussurea lappa*) Root against *Candida albicans*: A Systematic Review

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Abstract

Candida albicans is a microflora fungal species that can be invasive in immunocompromised conditions. Challenges in its therapy include antifungal drug resistance, which encourages research to find natural ingredients to help treat fungal infections caused by *Candida albicans*. One of the natural ingredients empirically known to be useful as an antimicrobial is *Saussurea lappa*, as known as Qusthul Hindi. This study aims to review previous studies to find out the antifungal activity of this plant root extract against *Candida albicans*. The method used is a systematic review, by identifying, sorting, and reviewing scientific publications, particularly research articles in the specified database and time period. A few qualified scientific publications were then reviewed, and it was found that all these studies proved the antifungal activity of *Saussurea lappa* root extract in vitro. *Saussurea lappa* root provides potential to inhibit *Candida albicans* in vitro. However, scientific publications have not been found regarding the *Saussurea lappa* root extract in modulating immunity under conditions of fungal infection, nor has it been tested against *Candida albicans* in vivo. Therefore, further research is required to be able to utilize *Saussurea lappa* root in the treatment of human fungal infection.

Keywords: *Saussurea lappa*, Qusthul Hindi, *Candida albicans*, antifungal activity

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1 Introduction

Fungal infection is one of the most prevalent infections in human [1]. In Indonesia, approximately 7,7 million people are infected by various kind of pathogen fungi every year, wherein the total number of cases due to *Candida* sp. reach 5 million cases every year [2]. Infection by *Candida* sp. does not cause significant damage in healthy individuals, but in immunocompromised conditions, it can lead to superficial and systemic infections such as oropharyngeal candidiasis, vaginitis, and endophthalmitis [3], [4]. *Candida albicans* is fungal microflora that is commonly concentrated in human mucosal tissues. The species interacts with other normal flora and mutually influences growth [5]. However, in immunocompromised condition such as HIV patients, *Candida albicans* as well as other *Candida* species dominate the microflora population in oral mucosa and tend to be invasive [6]. One challenge in candidiasis therapy is antifungal drug resistance, a complex phenomenon that has not yet been fully understood. The resistance mechanism of *Candida* sp. is associated with biofilm formation including efflux pump potential and cell density escalation, matrix biofilm development, and increasing membrane sterol component [7].

The increasing number of drug-resistant fungi infections leads to prospective discoveries of antimicrobial activity agents from medicinal plants, both from isolated components or plant extract [8]. *Saussurea lappa* is a widely-known perennial plant come from India. Its roots are generally used as a traditional medicine to treat asthma, cough, cholera, skin diseases, and rheumatism [9]. It belongs to *Asteraceae* family, and known as other names such as *Aplotaxis lappa* Decne., *Aucklandia costus* Falc., *Aucklandia lappa* Decne., *Saussurea lappa* (Decne.) Sch.Bip., *Theodorea costus* Kuntze, as well as popularly known as Qusthul Hindi [10].

Recently, many studies investigate antimicrobial potency of *Saussurea lappa* root, including its antifungal activity against pathogen fungi. This article will examine the possibility to use *Saussurea lappa* root extract as an antifungal agent against *Candida albicans* through a systematic review.

2 Methods

This study used systematic review which was performed by searching for published scientific literatures in Scopus, Scienccdirect, and Clarivate Web of Science databases.

2.1 Eligibility criteria

The inclusion criteria were research articles published in 2018 to January 6th, 2023, written in English, full-text available, and using determined keywords to divide from the exclusions. Furthermore, articles were excluded if they met the following criteria: (a) written in non-English; (b) full-text unavailable; (c) they were duplicate articles, reviews, conference summaries and letters; and (d) the studies had unavailable data.

2.2 Search strategy

The keywords used in Scopus, Scienccdirect, and Clarivate Web of Science were “saussurea lappa or costus or aucklandia and antifungal or immunomodulator or candida albicans”; “saussurea lappa or costus and antifungal”; and “((((ALL=(saussurea lappa)) OR ALL=(costus)) OR ALL=(aucklandia)) AND ALL=(antifungal)) OR ALL=(immunomodulator)) AND ALL=(candida albicans)”, respectively.

2.3 Selection process

After completing the searching process, duplicate articles were then removed. The titles and abstracts of articles were reviewed, and irrelevant articles were removed. The full text of

related articles was reviewed, and unrelated items were removed. Two authors independently performed the selection of articles. Disagreements were also investigated and resolved by the third author. The collected articles were then identified and screened according to PRISMA 2020 Flow Diagram for New Systematic Reviews.

2.4 Data extraction

The data extraction for all included studies was done by using a spreadsheet software. The information from all included studies was extracted as follows: publication title, author name, year of publication, origin, and concentration of plant extract, *Candida albicans* strains, antifungal susceptibility testing method, minimum inhibitory concentration (MIC), and zone of inhibition (ZOI). Potential antifungal components provided by the studies were also noticed for additional observation.

3 Results and Discussions

3.1 Study Characteristics and Search Results

The total amount of articles collected from the databases until January 6th, 2023 was 117 articles. The articles found were then identified for duplication and eligibility as we activated the limitation feature on each database for publication year, article type, and whether the full-text was open-accessed. The number of duplicated articles was 6 articles, while the number of other ineligible articles from the three databases was 89 articles. At the next stage, 23 articles were collected, and by screening their titles and abstracts, we excluded 15 articles which do not contain the specified keywords as *Saussurea*, *lappa*, *costus*, *aucklandia*, and *Candida albicans*, and 2 articles which were restricted to generate the full text version. Finally, the entire number selected in this review was 6 articles [9], [11]–[15]. The process of identification, screening, and selection is shown in Figure 1. Four studies used ethanol 70% as a solvent to extract the crude roots, while only one study used dichloromethane solvent to extract essential oil form of the roots, and the other study used methanol 95% diluted with a different type of solvents such as n-hexane, n-butanol, dichloromethane, and ethyl acetate.

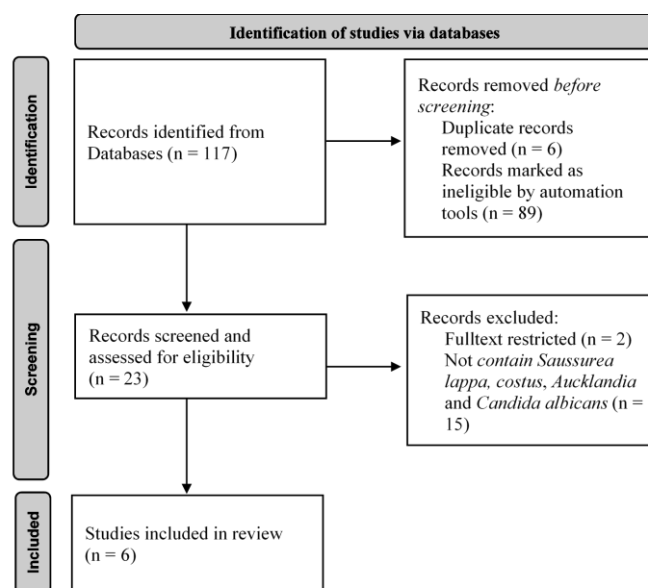


Figure 1. Process Diagram of Articles Identification and Screening

The antifungal testing methods used included disc diffusion, agar well diffusion, microdilution, and specific method like stainer-uptake assay, and MICs were obtained. As many as four studies tested standardized fungal strains, while two studies also included isolated strains from humans. All studies were conducted in vitro. All of which are antifungal activity studies, and none of which are studies on immunomodulatory effects.

3.2 Possible Antifungal Mechanism of *Saussurea lappa*

The summary of antifungal activity of *Saussurea lappa* against *Candida albicans* is shown in **Table 2**. All of the studies used root extract, whether in crude or essential oil form, which the most common solvent was ethanol 70%. The extracts were then examined for antifungal activity using different testing methods, such as disc diffusion, microdilution, and other specific methods. We can see that all forms of extract provided antifungal activity against various strains of *Candida albicans*, both standardized strains and patient isolates, as well as drug-resistant and sensitive strains. The resulting MICs were varied and highly dependent on some factors affecting the studies. Among all the studies reviewed, the dichloromethane extract of root essential oil

showed the smallest MIC of 6.25 µg/ml, while the largest ZOI was found in the root extract diluted with n-hexane, reaching 18 mm [9], [11]. Meanwhile, a study specifically examined the effects of ethanol extract to fungal cell wall and

cell membrane used a stainer-uptake assay interestingly showed that it needs different concentrations to affect fungal cell wall and bilayer membrane [12], [13].

Table 1 Summarize of Antifungal Activity of *Saussurea lappa* against *Candida albicans*

Type of Root Extract	Plant/Root Origin	Concentration of Extract	Antifungal Testing Method	Activity	<i>Candida albicans</i> Strain	Minimum Inhibitory Concentration (MIC), Zone of Inhibition (ZOI)	References
Ethanol 70% Extract, chitosan-nanoconjugated	Saudi Arabia	1% w/v	Inhibition Zones technique/Paper disc diffusion	(ZOI) disc	<i>Candida albicans</i> ATCC 10,261 (Ca - S); <i>Candida albicans</i> -Resistant isolated from patient urine samples (Ca - R)	MIC: Extract to Ca-S: 2.5; extract to Ca-R: 4.25; extract-nano to Ca-S: 1.75; extract-nano to Ca-R: 2.50 mg/ml ZOI: Extract to Ca-S: 11.4±0.6 mm; extract to Ca-R: 7.2±0.3 mm; extract-nano to Ca-S: 13.8±0.7 mm; extract-nano to Ca-R: 12.5±0.7 mm	[15]
Dichloromethane-Essential Oil Root Extract	Jazan, Saudi Arabia	266.67% w/v	Paper disc diffusion		<i>Candida albicans</i> ATCC7596	MIC: 6.25 µg/mL ZOI: 12±1.7–15±1.1 mm	[11]
Ethanol 70% Extract	Korea	10% w/v	Standard microdilution M27-A3 protocol with slight modification	broth CLSI	<i>Candida albicans</i> SC5314	MIC: 0.78 mg/mL to decrease (1,3)-b-D-glucan synthase activity; 8x MIC to interfere sorbitol protection assay	[13]
Ethanol 70% Extract	Korea	10% w/v	Calcofluor white-staining, ethidium bromide (EtBr)-Uptake Assay, Spectrofluorometric	white-iodide dual	<i>Candida albicans</i> SC5314	MIC: 0.39 mg/mL to affect cell membrane integrity	[12]
Ethanol 70% Extract	Pakistan	10% w/v	Disc diffusion and microdilution		<i>Candida albicans</i> ATCC90029	MIC: 125 µg/mL ZOI: 16.0±0.2 mm	[14]
Methanol 95% diluted with n-hexane (nH), n-butanol (nB), dichloromethane (Dc), ethyl acetate (Et)	Egypt	61.67% w/v	Agar well diffusion		<i>Candida albicans</i> ATCC 10231 (Ca-S), <i>Candida albicans</i> isolated from patient urine samples (Ca-U)	MIC: nH extract: to Ca-S: 1 mg/mL; to Ca-U: 0.2 mg/mL. Dc extract: Ca-S: 3 mg/mL; Ca-U: 3 mg/mL. ZOI: nH extract: to Ca-S: 13±2 mm; to Ca-U: 11±1–18±2 mm. Dc extract: Ca-S: 10±1 mm; Ca-U: 0.8±1–12±2 mm. nB and Et extract showed no inhibitory effect	[9]

Fungal cell wall surrounding cell membrane provides rigidity and protection against osmotic pressure, dehydration, and temperature extremes. The cell wall is also important for attachment to host cell as it contains adhesin. The inner layer of *Candida albicans* cell wall is rich in chitin and polysaccharide matrix, while the outer layer is rich in mannoproteins. The polysaccharide matrix that builds inner layer structure consists of (1,3)-β-D-glucan and (1,6)-β-D-glucan, of

which the proportion of (1,3)-β-D-glucan fills 40%, and chitin as much as 20% of total cell wall biomass. *Candida albicans* can grow in conditions where other fungi cannot, such as at high temperatures, and under certain environmental osmotic pressure conditions [13].

Ethanol extract of *Saussurea lappa* root was discovered to perform antifungal activity against *Candida albicans* by inhibiting synthesis of chitin and (1-3)-β-D-glucan in the cell wall.

Treatment of the extract against these pathogenic fungi under extreme conditions, namely at 45°C for 4 hours, as well as in sorbitol which supports the fungal cells to survive without cell walls, showed that the effect of inhibiting cell wall components synthesis and cell lysis still occurs [13]. In a subsequent study, treatment with the same extract was shown to induce functional changes in cell membrane, thereby increasing their permeability. In addition, the application of the extract also damaged DNA and protein in *Candida albicans* cells. The anticandidal effect was increased at 40°C compared to 35°C [12]. Other study comparing antimicrobial activity of various plant extracts found that the ethanol extract of *Saussurea lappa* showed activity in inhibiting growth of all types of fungi, including *Candida albicans* [14].

Methanol extract of *Saussurea lappa* root diluted with n-hexane showed stronger inhibitory effect on *Candida albicans* than dichloromethane-diluted extract, while n-butanol and ethyl acetate-diluted ones showed no inhibitory effect. In n-hexane-diluted extract, a greater proportion of sesquiterpene lactone was obtained. This study also showed that polarity of sesquiterpene lactone is ideal for penetrating fungal cell wall and supported data from other studies which stated that dehydrocostus lactone selectively inhibits fungal growth. In general, the mechanism of antifungal activity of these plant derivatives against *Candida albicans* is damaging membrane and cell wall. Several processes were thought to occur, namely inhibition of synthesis and destruction of structural components of cell wall, as well as formation of pores and channels in bilayer membrane which causes release of cytoplasmic components [9]. Other study using dichloromethane essential oil extract of *Saussurea lappa* root also provided inhibition on *Candida albicans* growth, where the main component extracted was costunolide [11].

Ethanol extract of *Saussurea lappa* root formulated with chitosan-nanoparticle system showed increased antifungal activity against *Candida albicans*, both in sensitive and drug-resistant strains. Chitosan and sodium tripolyphosphate as carriers in this delivery system also have antifungal activity, which made their formulation with *Saussurea lappa* synergizes to provide stronger inhibition. The

mechanism to increase the antifungal activity was initiated by attachment of chitosan nanoparticles into fungal cells, which led to inhibition of cell wall synthesis and increased membrane porosity as the *Saussurea lappa* extract could easily enter the cells to provide a fungicidal effect [15].

By all the studies reviewed, it was found that antifungal activity of *Saussurea lappa* root can produce different MIC possibly depending on the solvent and extraction method, delivery system, as well as the *Candida albicans* strains. Other factors that also need to be considered as they may affect are the condition and origin of the plant.

The assessment was carried out by author 1 and clarified by authors 2 and 3, on all articles reviewed including analysis methods in antifungal activity testing against *Candida albicans*, comprehensiveness of results and discussions, as well as supporting prospective researches. Based on the methods, five articles are well-presented but one article not well-presented. In the five articles, three of them used disc-diffusion and microdilution testing methods either traditionally or with modifications to generate ZOI and MIC, one used the disc diffusion method only, and the other one was a follow-up study from the same author using cell stainer and fluorometry assay methods [9], [11]–[13], [15]. One other article by Abdelwahab *et al.*, also examined toxicity of the extract in addition to its effectiveness [11]. The five well-presented articles were complemented with scanning microscopy and other advanced testing methods to observe morphological changes of the fungal cells [9], [11]–[13], [15]. One article, in our perspective, was less explored due to the limited traditional but established testing methods only, without other advanced examination or characterization of phytochemical compounds [14]. All six articles used appropriate statistical analysis methods [9], [11]–[15].

The results of the studies were mostly explained and discussed comprehensively, except one article. Five articles explained that *Saussurea lappa* root extracts inhibit *Candida albicans* depending on the concentration, and the discussion includes predicted potential antifungal components of the extracts [9], [11]–[13], [15]. Two of them even characterized the compounds of the extract [9], [11]. While one of

them proved the increase in the antifungal effect of *Saussurea lappa* in chitosan-nanoparticle formulation [15]. On the contrary, one article presented less-comprehensive discussion of phytochemical compounds and possible antifungal mechanisms, which was in line with insufficient testing methods [14].

Since all studies were conducted in vitro, it is certainly required in vivo testing in the future to prove effectiveness and toxicity of the extracts in inhibiting the growth of *Candida albicans*. Until then, the optimal concentration and exposure time of each type of extract are essential to be determined. In silico testing also supports research development towards the characterization and isolation of *Saussurea lappa* root components. However, the six articles reviewed provide interesting insights into the utilization of *Saussurea lappa* as a potential natural antifungal agent.

In human *Candida albicans* infection, the immune response regulation depends on IL-17 cytokine, and the main effector to eliminate fungal pathogen was phagocytic cells that produce antimicrobial peptides such as defensins [16]. The other key defense against the extracellular pathogenic fungi was Th17 cell [17]. Currently, we found no studies that prove the effectiveness of *Saussurea lappa* immunomodulating effect in candidiasis infection. Research on immunomodulating effect of *Saussurea lappa* combined with honey and *Nigella sativa* was carried out against SARS-COV-2 virus, and found that the combination increased components of immune system which also have a role against fungal pathogens, namely Th17, IL -17A, and β -defensins [18]. Therefore, this may also have to be considered as other potential mechanism of *Saussurea lappa* root extract in modulating immune system against *Candida albicans*.

3.3 Possible Antifungal Components in *Saussurea lappa* Root

Saussurea lappa root contains about 13.25% and 79.80% of monoterpenoids and sesquiterpenoids respectively. The main types of sesquiterpenes are dehydrocostus lactone (C₁₅H₁₈O₂) or 3,6,9-trimethylidene-dodecahydroazuleno[4,5-*b*]furan-2-one, and costunolide (C₁₅H₂₀O₂) or eudesma-5,11(13)-dien-8,12-olide [10].

The highest concentration of dehydrocostus lactone and costunolide can be found in *Saussurea lappa* root essential oil, which was 46% and 10% respectively of total sesquiterpenoids [19]. Whereas in the root extract form, the two main active components were found to be the most abundant in n-hexane extract, namely 22.5% and 5.38% respectively [9]. In other study using essential oil root extract diluted in dichloromethane, the highest content was found to be costunolide, which was as much as 52.01% [11]. Ethanol extract of the same simplicia which was formulated in lyophilized nanoparticle delivery system showed an increased inhibition against *Candida albicans*, although the concentration of potential antifungal components was not tested in this study [15].

While the other study also proposed that components of *Saussurea lappa* which are useful as antifungals against *Candida albicans* are costunolide and dehydrocostus lactone [13]. Other components such as flavonoids and glycosides from the roots also showed antifungal activity [11], [15].

According to the reviewed articles that discussed possible antifungal components, costunolides and dehydrocostus lactones are thought to be *Saussurea lappa* roots' main components that are responsible for antifungal activity [9], [11]-[13], [15]. This is confirmed by the characterization conducted by Soliman *et al.*, and Abdelwahab *et al.*, who found the two components as major components in the extract used in the studies [9], [11]. The other articles that discussed predicted active compounds concurred on this, but it does not rule out the possibility that other components also have antifungal activity [12], [13], [15]. From our perspective, the results and discussions on potential active compounds are encouraging, but need further exploration both in silico, in vitro, and in vivo. The continuation of this research can be the basis for developing antifungal phytopharmaceutical dosage form in the future.

4 Kesimpulan

Saussurea lappa root extract is capable to inhibit *Candida albicans* growth in in-vitro studies. The inhibitory activity and concentration of *Saussurea lappa* against

Candida albicans are vary and highly dependent on various factors affecting the studies. The antifungal activity of *Saussurea lappa* roots could be various, depending on the solvent and extraction method, fungal strain, delivery system, as well as the variation of plant characteristics. Active components in *Saussurea lappa* that possibly provide antifungal activity are dehydrocostus lactone and costunolide, both of which are found in large proportions in the root extract. Other types of sesquiterpene components, as well as components of the glycoside and flavonoid groups from *Saussurea lappa* may support the antifungal activity. Currently, we found no recent studies regarding the antifungal and immunomodulating activity of *Saussurea lappa* against *Candida albicans* infection in vivo. Therefore, further exploration is required regarding the effectiveness of *Saussurea lappa* to support its use in pathogenic fungal infection treatment.

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6 Pernyataan

6.1 Kontribusi Penulis

The contribution of the three authors in preparing the manuscript is equal, where the first and second author played a role in conceptualization, designing and developing methodology, as well as writing the original draft. While the third author had a role in validating the data obtained, managing data display, curating the original draft, and mediating opinion differences between the first and second author.

6.2 Penyandang Dana

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6.3 Konflik Kepentingan

No conflict of interest involved in this review article.

7 Daftar Pustaka

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