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Antibiofilm Potential of Neem (*Azadirachta indica*) Against *Candida* Species: A Narrative Literature Review

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ABSTRACT

Candida species are opportunistic fungal pathogens capable of forming biofilms that contribute to persistent infections and reduced susceptibility to antifungal agents. The structural complexity of mature biofilms and their associated antifungal tolerance pose challenges for effective treatment, highlighting the need to investigate alternative antifungal agents. Neem (*Azadirachta indica*) contains bioactive compounds with potential antifungal properties. This narrative literature review aims to evaluate the available evidence regarding the potential of neem-derived preparations to inhibit *Candida* biofilm formation and reduce established biofilms. A structured literature search was conducted in Google Scholar, PubMed, and Scopus, covering publications from 2006 to 2025. Across the six studies reviewed, neem leaf extracts reduced biofilm formation by fluconazole-resistant clinical isolates of *C. albicans* and reduced the biomass or viable counts of established biofilms. A study found that ethanolic extracts demonstrated greater effectiveness than aqueous extracts, although their effects varied depending on extract concentration and experimental conditions. Neem was less effective than propolis and sodium hypochlorite in two studies, while no significant difference was observed between neem, propolis, and 2% chlorhexidine in a dentinal tubule model. Additionally, a study reported that an ethanolic neem leaf extract reduced *C. albicans* adhesion and viable cell counts on pretreated denture acrylic resin surfaces, although viable cells remained in the azole-resistant strain. However, the available evidence is limited by the small number of studies, lack of extract standardization, narrow species coverage, limited mechanistic and toxicity data, and absence of comparisons with antifungal agents known to exhibit antibiofilm activity.

Keywords: *Azadirachta indica*; neem; *Candida*; biofilm; antibiofilm; antifungal

INTRODUCTION

Fungal infections caused by *Candida* species remain a significant clinical concern, particularly among immunocompromised individuals and patients with medical devices or other predisposing conditions [1]. These opportunistic pathogens can cause a wide spectrum of infections, ranging from oral and vaginal candidiasis to invasive bloodstream infections [2]. Although *Candida* albicans remains the most frequently isolated species, non-albicans species, including C. tropicalis, C. glabrata, and C. parapsilosis, account for a substantial proportion of infections [2,3]. Their prevalence has also increased in certain clinical settings, and differences in virulence and antifungal susceptibility among these species present additional challenges for treatment [3].

An important factor contributing to the persistence of *Candida* infections is the ability to form biofilms on host tissues and on abiotic surfaces such as dentures, catheters, and implants [1,4]. A biofilm is a structured microbial community embedded in an extracellular matrix and attached to a biotic or abiotic surface [5]. The development of *Candida* biofilms generally involves several stages, including initial adhesion, cellular proliferation, maturation, and dispersal [6]. Once established, these biofilms pose significant treatment challenges because biofilm-associated infections are often difficult to treat and prone to recurrence, as cells within the biofilm are far less susceptible to antifungals than planktonic cells [5,7].

Conventional antifungal agents, particularly azoles, often perform poorly against established *Candida* biofilms [8]. In contrast, amphotericin B generally exhibits greater activity against biofilms than azoles [4]. Nevertheless, its clinical application is limited by a narrow therapeutic window and significant toxicity, particularly nephrotoxicity [9]. The concentrations required to substantially reduce biofilm-associated fungal cells may exceed safe therapeutic levels [4].

Furthermore, amphotericin B treatment may not completely eliminate biofilms on medical devices, allowing them to regrow after treatment discontinuation [4].

Echinocandins have emerged as alternative antifungal agents because of their antibiofilm activity and generally favorable safety profile compared with azoles and polyenes [10,11]. They are generally well tolerated but may cause adverse reactions, including hypersensitivity reactions [12]. Despite these advantages, their clinical application may be limited by the need for intravenous administration, high costs, and the absence of oral formulations [12]. Furthermore, a study analyzing 313 C. glabrata isolates from 293 episodes of bloodstream infection reported an increase in echinocandin resistance from 4.9% to 12.3% between 2001 and 2010 [13]. Taken together, these clinical limitations and the emergence of antifungal resistance highlight the need to explore alternative approaches, including medicinal plants, as potential sources of novel antibiofilm agents against *Candida* species.

One plant of interest is neem (*Azadirachta indica*), a member of the Meliaceae family native to the Indian subcontinent [14–16]. Neem has been widely used in traditional medicinal practices, including Ayurveda and Unani, particularly for the treatment of skin diseases, infections, inflammatory disorders, and dental problems [16,17]. Various parts of the plant, including its leaves, flowers, fruits, seeds, roots, bark, and oil, contain numerous phytochemicals associated with a wide range of biological and pharmacological activities, including antibacterial, antifungal, antiviral, anti-inflammatory, anticarcinogenic, and antioxidant properties [16–18]. Given these properties, neem may represent a promising source of natural compounds with potential antibiofilm activity. This review evaluates the potential of neem to inhibit *Candida* biofilm formation and reduce established biofilms.

METHODS

This study is a narrative literature review and does not follow the PRISMA 2020 reporting guidelines. Nevertheless, a structured literature search was performed to improve methodological transparency and reduce the potential for selection bias. Relevant studies were retrieved from Google Scholar, PubMed, and Scopus using search terms related to the antibiofilm potential of neem (*Azadirachta indica*) against *Candida* species.

Search Strategy

The search was limited to English-language publications published between 2006 and 2025. Keywords included "neem," "*Azadirachta indica*," "*Candida*," "biofilm," "biofilm formation," "biofilm inhibition," "biofilm eradication," "biofilm reduction," "antifungal activity," and "antibiofilm activity." These terms were combined using Boolean operators to identify relevant publications. As Google Scholar may have limitations in processing complex Boolean search queries, three separate, simplified search strings were used to identify additional relevant publications. The final literature searches across all databases were conducted on 31 October 2026.

Eligibility Criteria

Eligible studies included original experimental research investigating the antibiofilm activity of A. indica against *Candida* species, particularly studies examining biofilm formation, biofilm inhibition, or reduction of established biofilms. Review articles were also consulted to provide background information on *Candida* biofilms, antifungal resistance, and the potential antibiofilm properties of neem. However, only original experimental studies were included in the main evidence synthesis.

Articles were excluded if they were conference abstracts, study protocols, or case reports; if they reported only planktonic growth without a biofilm outcome; if they tested neem only in a mixture that did not allow its individual effect to be determined; or if their results were insufficiently reported.

Screening and Data Extraction

Records from the three sources were combined, and duplicates were removed. Titles and abstracts were screened against the eligibility criteria, and the full text of every potentially eligible record was assessed. From each included study, the following were extracted into a standardized form: first author, year, study title, sample and biofilm model, neem preparation, outcome measurement, and main findings.

RESULTS AND DISCUSSION

Six experimental studies investigating the antibiofilm activity of *Azadirachta indica* against *Candida* species were included in this review. These studies examined different neem preparations and experimental biofilm models, focusing on the inhibition of biofilm formation and the reduction of established biofilms. The characteristics and main findings of the selected studies are summarized in Table 1.

TABLE 1: Summary of Studies Included in the Literature Review.

Author, year	Title	Sample and Biofilm Model	Neem Preparation	Outcome Measurement	Main findings
Tyagi et al., 2013 [19]	Comparison of antimicrobial efficacy of propolis, *Morinda citrifolia*, *Azadirachta indica* (neem) and 5% sodium hypochlorite on *Candida albicans* biofilm formed on tooth substrate: An *in vitro* study	*C. albicans* ATCC 10231; 2-day biofilm formed on extracted human mandibular premolar teeth	Ethanolic neem leaf extract	Viable fungal count (CFU)	Neem extract reduced viable *C. albicans* counts in established biofilms compared with saline, although its activity was lower than that of propolis and 5% sodium hypochlorite.
Sinha et al., 2015 [20]	Comparison of antimicrobial efficacy of propolis, *Azadirachta indica* (neem), *Melaleuca alternifolia* (tea tree oil), *Curcuma longa* (turmeric) and 5% sodium hypochlorite on *Candida albicans* biofilm formed on tooth substrate: An *in vitro* study	*C. albicans* MTCC 3017; 2-day biofilm formed on extracted human mandibular premolar teeth	Ethanolic neem leaf extract	Viable fungal count (CFU)	Neem extract reduced viable fungal counts in established biofilms compared with saline but showed lower antimicrobial efficacy than several of the other tested agents.
Sinha et al., 2015 [21]	Dentinal tubule disinfection with propolis & two extracts of *Azadirachta indica* against *Candida albicans* biofilm formed on tooth substrate	*C. albicans* ATCC 10231; 2-day biofilm in dentinal tubules of infected human mandibular premolar teeth	Ethanolic and aqueous neem leaf extracts	Viable fungal count (CFU)	Ethanolic neem extract demonstrated greater antifungal activity than the aqueous extract, reducing viable fungal growth within dentinal tubules. Its activity was not significantly different from that of propolis and 2% chlorhexidine gel.
Neglo et al., 2022 [22]	Antibiofilm activity of *Azadirachta indica* and *Catharanthus roseus* and their synergistic effects in combination with antimicrobial agents against fluconazole-resistant *Candida albicans* strains and MRSA	Four fluconazole-resistant *C. albicans* isolates; biofilm formed *in vitro*	Ethanolic neem leaf extract	Crystal violet assay (biofilm biomass)	Neem extracts inhibited *C. albicans* biofilm formation, with inhibition ranging from 10.1% to 83.4% among the tested isolates.
Bhattacharya et al., 2024 [23]	Investigating the antimicrobial activity of neem and clove extract on biofilm-producing oral microflora	Oral *Candida* sp. isolate OS4B; biofilms formed *in vitro*	Alcoholic neem leaf extract and its dilutions	Crystal violet assay with spectrophotometric measurements (biofilm biomass); phase-contrast microscopy	Neem extract reduced the biomass of preformed biofilms. The 1/6 dilution produced the greatest reduction, approximately 54% after 24 hours and 56% after 48 hours of exposure.
Philip et al., 2025 [24]	Antifungal efficacy of *Azadirachta indica* and *Ficus benghalensis* extracts against azole resistant *Candida albicans* on denture resin	Azole-resistant, azole-susceptible, and standard (MTCC 3018) *C. albicans* strains; adhesion at 3 and 36 hours and subsequent 24-hour biofilm development on denture acrylic resin discs pretreated with extract	Ethanolic neem leaf extract	Fungal adhesion assessed by microscopic cell count after 3 and 36 hours; viable fungal count (CFU) after 24 hours of biofilm development	Pretreatment with ethanolic neem extract reduced adhesion after 3 and 36 hours by 72% and 76.7% in the azole-resistant strain, 98.2% and 77.8% in the azole-susceptible strain, and 35.7% and 32.9% in the standard strain, respectively. After 24 hours of biofilm development, no viable cells of the azole-susceptible or standard strains were detected, and the azole-resistant strain showed a 71% reduction in viable counts compared with saline. Viability of the azole-resistant strain was not significantly different from that with 0.2% chlorhexidine.

CFU = colony-forming unit.

Effects of Neem on Established *Candida* Biofilms

Four studies investigated the effects of neem on established biofilms. Tyagi et al. [19] evaluated the antimicrobial efficacy of neem (*A. indica*) against *C. albicans* biofilms formed on tooth substrates. The study compared ethanolic neem extract with ethanolic propolis extract, *Morinda citrifolia* juice, and 5% sodium hypochlorite. In this study, biofilms were grown for two days on extracted human teeth before treatment. The samples were irrigated for 10 minutes with 3 mL of ethanolic neem extract, resulting in a mean colony count of 3.8, compared to 133.2 in the saline control group. These findings indicate that the neem treatment resulted in a lower microbial count than the saline control. Neem also demonstrated greater antimicrobial efficacy than *Morinda citrifolia* juice. However, its antimicrobial effect was lower than that observed with propolis and sodium hypochlorite, both of which achieved complete elimination of detectable viable *C. albicans* cells within the established biofilms in 8 out of 10 samples, whereas no complete elimination was observed in the neem groups, in which the lowest recorded colony count was 3. Overall, these findings suggest that neem extract possesses activity against established *C. albicans* biofilms, although its effectiveness was lower than that of propolis and sodium hypochlorite.

Similarly, Sinha et al. [20] investigated the antimicrobial activity of neem extract against *C. albicans* biofilms formed on tooth substrates. However, Sinha et al. [20] used a different neem-to-solvent ratio (10 g of neem leaf powder in 100 mL of ethanol) compared with that used by Tyagi et al. [19] (25 g of neem leaf powder in 50 mL of ethanol). The biofilms were allowed to develop for two days before being exposed to different antimicrobial agents. Neem treatment resulted in a mean count of 51.7, compared to 106.85 in the saline control group. Nevertheless, its activity was lower than that of several other tested agents, including propolis, *Melaleuca alternifolia* (tea tree oil), *Curcuma longa* (turmeric), and 5% sodium hypochlorite. This study provides additional experimental evidence that neem extract can reduce viable cells within established *C. albicans* biofilms.

Another study by Sinha et al. [21] investigated the use of aqueous and ethanolic neem extracts against *C. albicans* biofilms formed within dentinal tubules. The ethanolic extract was prepared using 25 g of neem leaf powder in 50 mL of absolute ethanol, whereas the aqueous extract was prepared by mixing 25 g of neem leaf powder with 100 mL of sterile distilled water. The study also included propolis, 2% chlorhexidine, calcium hydroxide, and absolute ethanol, with sterile saline as the negative control. The study reported that the ethanolic neem extract was more effective than the aqueous extract. However, this difference may be influenced by both the extraction solvent and the neem-to-solvent ratio used in preparing each extract. Therefore, the observed difference in antimicrobial activity cannot be attributed solely to the type of solvent. The ethanolic neem extract did not differ significantly from propolis or from 2% chlorhexidine, and it was far more effective than calcium hydroxide, a standard intracanal medicament, as reflected by the lower colony counts observed with ethanolic neem (1.6–17.4) compared with calcium hydroxide (28.4–87.4). These findings are consistent with previous reports of the resistance of *Candida* species to calcium hydroxide [25].

Bhattacharya et al. [23] also investigated the effects of neem extract on preformed biofilms of an oral *Candida* isolate. Results were assessed using crystal violet staining and spectrophotometric measurements. Biofilms were allowed to develop for 24 and 48 hours before exposure to crude neem extract and its different dilutions. A 20 mL extract was prepared from fresh neem leaves using absolute alcohol, and the working dilution was made by diluting the extract to 1/2, 1/4, and 1/6 of its original concentration using absolute alcohol. The crude neem extract produced a 15% reduction in biofilm biomass at both time points. Different reductions were observed with the diluted preparations, with the 1/2 dilution producing reductions of 23% and 20% after 24 and 48 hours, respectively. The 1/4 dilution resulted in reductions of 49% and 47%, whereas the 1/6 dilution achieved reductions of 54% and 56% at the corresponding time points. These findings indicate that diluted neem preparations, particularly the 1/6 dilution, produced greater reductions in preformed biofilm biomass than the crude extract. This study also compared neem extract with clove extract. Although both extracts showed their greatest activity at the 1/6 dilution, neem produced a numerically greater reduction in biofilm biomass than clove under these conditions.

Although these studies support the potential activity of neem against established *Candida* biofilms, the experimental models were primarily related to dental applications, and the outcomes were largely based on viable fungal counts and spectrophotometric measurements. Therefore, the results cannot automatically be generalized to other biofilm environments or interpreted as evidence of complete biofilm eradication.

Inhibition of *Candida* Biofilm Formation

In addition to targeting established biofilms, neem extracts have also been investigated for their ability to prevent or inhibit biofilm formation. This approach differs from biofilm eradication because the extract is present during, or applied before, the development of the biofilm rather than being applied after a mature biofilm has formed.

Neglo et al. [22] evaluated the antibiofilm activity of ethanolic neem leaf extract against four fluconazole-resistant *C. albicans* isolates obtained from pregnant women with vulvovaginal candidiasis. The extract was prepared by cold maceration of 40 g of neem leaves in 200 mL of 70% ethanol. The study demonstrated that neem extract inhibited biofilm formation across all four *C. albicans* isolates at concentrations ranging from 1 to 32 mg/mL. The degree of inhibition varied among the isolates, ranging

from 10.1% to 83.4%. The variation in activity suggests that the response to neem extract may differ among fungal isolates.

Bhattacharya et al. [23] also examined the effects of neem extract on biofilm formation in an oral *Candida* isolate. Biofilm development was assessed using crystal violet staining, spectrophotometric measurements, and phase-contrast microscopy. Compared with the untreated control, neem extract produced reductions in biofilm formation of 12%, 31.5%, 41.6%, and 46.7% at the crude, 1/2, 1/4, and 1/6 dilutions, respectively. This study also examined the effects of clove extract on biofilm formation, with reductions of 0%, 11%, 37%, and 36% at the corresponding preparations. Thus, neem extract produced numerically greater reductions in biofilm formation at all four preparations, with the greatest reduction observed at the 1/6 dilution. These findings indicate that neem preparations could reduce or inhibit biofilm formation, in addition to reducing the biomass of preformed biofilms. This suggests that neem may exert antibiofilm activity at different stages of biofilm development.

Philip et al. [24] investigated the antifungal efficacy of ethanolic neem leaf extract against azole-resistant, azole-susceptible, and standard strains of *C. albicans* on denture acrylic resin surfaces. The neem leaf extract was prepared by cold maceration using ethanol, and the resin discs were pretreated for 30 minutes with the extract at a concentration of 300 µg/mL before exposure to yeast suspensions. The study evaluated fungal adhesion at 3 and 36 hours, as well as viability following 24 hours of biofilm development. Pretreatment with ethanolic neem extract reduced adhesion in all three *C. albicans* strains tested. In the azole-resistant strain, adhesion was reduced by 72% after 3 hours and 76.7% after 36 hours. The corresponding reductions were 98.2% and 77.8% in the azole-susceptible strain and 35.7% and 32.9% in the standard strain, respectively. Compared with ethanolic *Ficus benghalensis* extract at the same concentration, neem demonstrated greater reductions in adhesion against the azole-resistant strain at both 3 and 36 hours (72% and 76.7%, respectively, compared with 44.6% and 34.5% for *F. benghalensis*). In contrast, *F. benghalensis* produced greater reductions against the standard strain (91.5% and 65.8% versus 35.7% and 32.9% for neem). The results also varied across time points in the azole-susceptible strain, with neem showing a greater reduction at 3 hours (98.2% for neem versus 90.2% for *F. benghalensis*), whereas *F. benghalensis* showed a greater reduction at 36 hours (89.75% for *F. benghalensis* versus 77.8% for neem).

In the same study [24], 0.2% chlorhexidine served as the positive control and generally produced greater reductions in adhesion than neem across the tested strains. However, neem showed a slightly greater reduction than chlorhexidine against the azole-susceptible strain at 3 hours (98.2% versus 97.2%). After 24 hours of biofilm development, no viable cells of the azole-susceptible or standard strains were detected on either neem- or chlorhexidine-treated discs. For the azole-resistant strain, neem pretreatment resulted in significantly lower viable cell counts than *F. benghalensis* and the saline control, with no significant difference compared with chlorhexidine. These findings suggest that ethanolic neem extract may have potential as a preventive surface treatment against *C. albicans* adhesion and early biofilm development on denture-resin surfaces.

Overall, these studies suggest that neem may inhibit *Candida* biofilm development at different stages, including preventing initial fungal adhesion to surfaces and reducing biofilm formation. However, the findings were obtained using different experimental models, neem preparations, and *Candida* isolates, with outcomes ranging from biofilm biomass reduction to decreased fungal adhesion and viability. Furthermore, the evidence is limited to a small number of studies, predominantly involving *C. albicans*. Therefore, these findings should be interpreted cautiously and cannot yet be generalized to other Candida species or biofilm environments.

Overall Synthesis of Findings

Across the included studies, neem consistently demonstrated inhibitory effects on *Candida* biofilm-related outcomes, although the magnitude of its activity differed among experimental conditions. Several studies reported reductions in established biofilm biomass or viable fungal counts, while others demonstrated inhibition of biofilm formation or reduced fungal adhesion to surfaces. Comparisons with other antimicrobial agents also revealed that neem did not consistently outperform established treatments, although some preparations showed comparable activity to certain reference agents. These findings suggest that the antibiofilm potential of neem is not limited to a single stage of biofilm development, although its observed effectiveness depends on the preparation and experimental conditions used.

Research Gaps and Future Perspectives

Although the available experimental findings suggest promising antibiofilm activity, several limitations should be considered when interpreting the evidence.

All of the identified studies investigated *C. albicans* or an unidentified *Candida* species. Although *C. albicans* is an important cause of candidiasis, non-*albicans Candida* species may also contribute to clinically relevant infections [2,3]. The limited representation of non-*albicans Candida* species restricts the generalizability of the current findings. Further studies should therefore investigate a broader range of clinically relevant species, including *C. tropicalis*, *C. glabrata*, and *C. parapsilosis*, to determine whether the observed antibiofilm effects extend beyond *C. albicans*.

Furthermore, substantial differences exist in the preparation of neem extracts, which may contain different concentrations and compositions of bioactive compounds. Differences in extraction methods and plant materials may influence the observed antifungal

and antibiofilm effects. Standardized extraction procedures and phytochemical characterization are therefore necessary to improve reproducibility and facilitate comparisons between studies.

The experimental models and outcome measurements also varied considerably. Some studies evaluated viable fungal cells using CFU counts, whereas others measured biofilm biomass using crystal violet staining or assessed fungal adhesion through microscopic examination. These measurements represent different aspects of biofilm development and activity. Therefore, they should not be considered directly interchangeable. Future studies should employ standardized biofilm models and complementary assessment methods to provide a more comprehensive evaluation of antibiofilm activity.

All of the available evidence is derived from *in vitro* experiments. Although these studies provide preliminary information regarding the potential activity of neem extracts, they do not establish clinical efficacy or safety. Further investigations involving cytotoxicity assessment, formulation development, and appropriate *in vivo* models are required before neem-based preparations can be considered for clinical application.

CONCLUSIONS

Neem (*Azadirachta indica*) has shown promising *in vitro* antibiofilm activity against *Candida* species in laboratory models. However, the available evidence is predominantly derived from studies on *C. albicans*, with limited evidence involving other *Candida* species and a small number of oral isolates. Experimental findings suggest that neem extracts may reduce the viability or biomass of established biofilms and inhibit biofilm formation [19–23]. Additionally, neem pretreatment has been shown to reduce *Candida* adhesion and subsequent biofilm-associated viability on denture-resin surfaces [24]. The extent of these effects varies depending on the neem preparation, fungal isolate, experimental model, and outcome measurement.

Nevertheless, the available evidence remains limited by the small number of studies, lack of extract standardization, narrow species coverage, limited mechanistic and toxicity data, and limited comparisons with clinically established antifungal agents with recognized antibiofilm activity. Further research involving a broader range of *Candida* species, standardized extraction methods, mechanistic investigations, toxicity assessments, and clinically relevant biofilm models is needed to better characterize neem's antibiofilm activity and evaluate its potential therapeutic applications.

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