Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/kevg0x97

THE ROLE OF FUNGI IN THE PATHOGENESIS OF PERIODONTITIS: A SYSTEMATIC REVIEW

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ABSTRACT

Background: The association between periodontitis and specific bacterial pathogens are well established. However, Fungal organisms, particularly Candida species, have been frequently detected in periodontal pockets, with Candida albicans being the most commonly isolated species.

Aim: The aim of the present study is to evaluate the role of fungi in pathogenesis of periodontitis through a systematic review.

Material and method: Literature search was performed in various electronic databases for articles published upto December 31 2024. Two reviews independently reviewed the articles. Five studies were selected based on the inclusion criteria. The Joanna Briggs Institute Critical Appraisal Checklist for Quasi-Experimental Studies was used to evaluate the risk of bias in the included studies.

Results: Five studies (cross sectional Study -4, and case control -1) were selected based on the inclusion and exclusion criteria. The findings of this Systematic review suggests that there is a strong association between the presence of Candida species and periodontal diseases.

Conclusion:

Fungal organisms, particularly Candida species, are found to be associated with periodontal pockets. Therefore, periodontitis that is resistant to conventional treatment may require additional broad spectrum antibiotics for coverage of fungal organisms also.

KEYWORDS: Fungi, Candida, Periodontitis, Candida albicans, Systematic review, Meta Analysis

INTRODUCTION

Traditionally, the pathogenesis of periodontitis has been attributed to bacterial dysbiosis, with well-established periodontal pathogens such as Porphyromonas gingivalis, Tannerella forsythia, and Aggregatibacter actinomycetemcomitans playing crucial roles in disease initiation and progression.[1,2] .Periodontitis is a chronic inflammatory disease affecting the supporting structures

of teeth, leading to progressive destruction of periodontal tissues, alveolar bone loss, and ultimately, tooth loss.

However, recent studies have expanded this microbial paradigm by highlighting the role of fungal species in periodontal infections, suggesting a polymicrobial etiology that involves interkingdom interactions.[3,4]

Fungal organisms, particularly Candida species, have been frequently detected in periodontal pockets, with Candida albicans being the most commonly isolated species. [5] The presence of fungi in subgingival biofilms indicates that periodontitis is not solely a bacterial-driven condition but rather a multifaceted microbial disease. Fungi contribute to disease pathogenesis by modulating host immune responses and interacting synergistically with periodontal bacteria. [6]

Candida spp. have been shown to exacerbate periodontal inflammation by promoting the production of pro-inflammatory cytokines, facilitating tissue invasion, and enhancing the virulence of periodontal bacteria.[7] These interkingdom interactions can lead to an amplified inflammatory response, accelerating periodontal tissue destruction.

Addressing the fungal component in periodontal infections could lead to more effective therapeutic approaches, ultimately improving both oral and overall health outcomes. The aim of the present study is to evaluate the role of fungi in pathogenesis of periodontitis through a systematic review. This systematic review aims to critically assess the role of fungi in the pathogenesis of periodontitis. By synthesizing existing literature, we seek to elucidate the interactions between fungal pathogens and the host immune system in periodontal disease.

MATERIAL AND METHODS

Protocol:

This systematic review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, ensuring transparent reporting of the review process. Additionally, the systematic review protocol was registered on the PROSPERO platform, enhancing transparency and accountability in the research process (Registration number: CRD420251053713)

Focused Question:

“What is the role of fungi in the pathogenesis of periodontitis?”.
The question for the current systematic review was formulated based on the PECOS criteria: (Table 1)

Table 1; PECOS criteria

P (Population/Problem)	Individuals with periodontitis
E (exposure)	Presence of fungal infections or dysbiosis in periodontitis
C (Comparison)	-
O (Outcome)	Association of both

Information sources and Search strategy:

Data search was mainly carried out through an electronic search in several renowned databases, which mainly included the PubMed, Google Scholar, Scopus, Embase, EBSCO, Web of Science, Clinical Trials Registry India, The Cochrane Oral Health Group's Trials Register, The Cochrane Central Register of Controlled Trials (CENTRAL), The PROSPERO International prospective register of systematic review, and the National Institutes of Health Trials Register. The literature search will be limited to articles published between January 1, 2000, and December 31, 2024, ensuring that the literature gathered provided a comprehensive picture of the role of fungi in progression of

periodontitis and its link to cardiovascular diseases. Published articles in English or those which have a detailed summary in English will be included. All references of the studies included and excluded will be searched for additional relevant reports.

A set of keyword combinations; (("periodontitis"[Mesh])) OR ("periodontal disease" [Title/Abstract])) AND ("pathogenesis"[Mesh])) AND ("fungi"[Mesh]))) OR (“fungal organisms” [Title/Abstract])) OR (“Fungal species” [Title/Abstract])) AND ((“Candida" [Title/Abstract])) AND ("candida species" [Title/Abstract])) OR ("link" [Title/Abstract])) OR ("Association" [Title/Abstract])) AND (“oral microbiome” [Title/Abstract])) AND (“interkingdom interactions” [Title/Abstract])) were used to search the literature in all the databases to ensure that all relevant articles were screened.

Eligibility Criteria

Studies were included based on the following criteria:

- Original research articles
- Full-text, English-language studies
- Studies investigating the role of fungal species, particularly *Candida* spp., in the pathogenesis of periodontitis.
- Studies examining interkingdom interactions between fungi and periodontal bacteria.
- Research exploring the potential link between fungal infections in periodontitis.
- Studies in human subjects were included.
- Both prospective and retrospective studies were included.
- Randomized and non-randomized, interventional studies, or cohort studies were included.

Exclusion criteria:

- Systematic reviews with or without meta-analysis, case reports, case series, and expert opinions were excluded.
- Articles are available in languages other than English
- Animal research or in vitro studies.
- Only abstracts or articles where full-text versions were not available
- Studies focusing solely on bacterial pathogens without fungal analysis.
- Research involving immunocompromised patients with systemic fungal infections.

Study selection:

The study selection process consisted of two stages. Initially, two reviewers independently evaluated the chosen articles based on their titles and abstracts. Using predefined selection criteria, the studies were categorized as either relevant or irrelevant. Subsequently, the full texts of the relevant studies underwent a second and final analysis, again applying the same criteria for labeling. And irrelevant articles were excluded. If needed, the third author was called in.

Data collection process:

From the finalized papers, the following information was retrieved: 1) Study characteristics, such as the authors, country, publication year; 2) study design; 3) total sample size and sample groups; 4) exposure; 5) follow up; 6) outcomes,7) conclusion.

Risk of bias and quality of assessment:

The study quality and presence of biases were determined using the Joanna Briggs Institute Critical Appraisal Checklist for Quasi-Experimental Studies. The tool consisted of nine questions regarding the study design, with the option to answer ‘yes’, indicating higher quality; ‘no’, indicating poor quality; or ‘unclear’. The bias risk percentage calculation is done by the amount of “Y” that has been selected in the checklist. When “NA” was selected, this question was not considered in the calculation,

according to the guidelines of the Joanna Briggs Institute. Up to 49% was considered a high risk of bias. From 50% to 70% was moderate risk and above 70% was low risk of bias.

Data synthesis:
A narrative synthesis of the findings were provided from the included studies, structured around the type of intervention, target population characteristics, type of outcome, and intervention content.

RESULT

Synthesis Of Results:
A narrative synthesis was provided for the findings from the included studies, focusing on intervention details, characteristics of participants (age, gender), inclusion criteria, exclusion criteria, study designs, outcome, and summaries of intervention effects for studies were provided by calculating mean and standardized mean difference (for continuous outcomes).

Literature search:
The kappa value was 0.98; therefore, an agreement amongst the 3 investigators was acceptable. Through searches from electronic databases and other gray literature, 1492 articles were identified. After the duplicate removal process, 754 articles remained. The titles and abstracts of the 754 records were examined on the basis of predefined eligibility criteria. Consequently, 700 articles were excluded because they were off topic. The full text of the remaining 44 articles was carefully read by 2 reviewers for potential inclusion. Two articles were excluded as they did not report the outcome and 39 articles did not meet the inclusion criteria. The articles were narrowed down to 5 articles. Thus 5 studies were selected to draw the results of the systematic review and meta-analysis. The process of study selection is documented in the PRISMA flowchart in Figure 1.

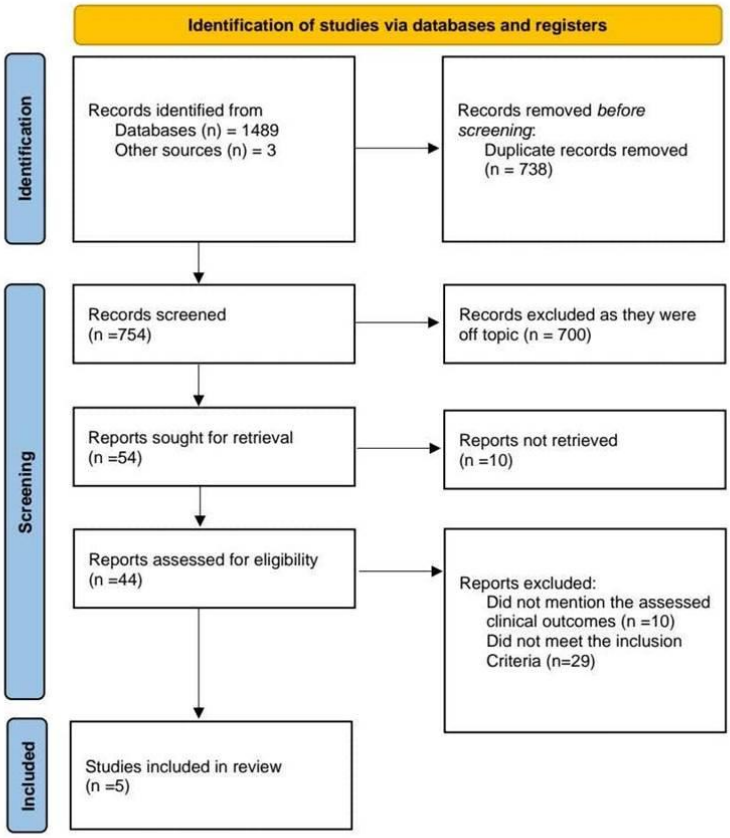

Figure 1; Flowchart representing the process of study selection

General characteristics of included studies:

A total of 5 studies were included in the review. Out of these 5 studies, 4 were cross-sectional studies and 1 was casecontrol study. The characteristics of all included studies are summarized in Table 2 and 3.

Table 2; Study characteristics of the included studies

Author	Design	SAMPLE	Site/Condition	Fungal Species Identified	Detection Method	Characteristic features
Nemmat A. Hussein [9]	Cross-sectional study	Total sample size – 60 Groups: Group 1- healthy (N=15) Group 2- Gingivitis (N=15) Group 3- Periodontitis (N=15) Group 4- Dental caries (N=15)	Oral cavity (Teeth & Mucosa)	*C. albicans*, *C. ciferrii*, *C. dubliniensis*, *C. glabrata*, *C. tropicalis*	Germ tube test, CHROMagar, SDA, CMA	Total fungal isolates: 210; Candida spp. - 147 isolates (70%); High fungal count in gingiva (59.15% in periodontitis), followed by saliva, tongue, tooth. Significant differences across groups
Nebras Nasir Al-Dabbagh [10]	Cross-sectional observational study	50 patients with chronic periodontitis	Periodontitis patients	*C. albicans*, *C. glabrata*, *C. kefyr*, *C. dubliniensis*, *C. parapsilosis*	PCR (26S rRNA gene sequencing)	Age Range of Positive Patients -18–65 years.*C. albicans* was the predominant species in periodontitis; other species showed lower frequencies, tooth loss range: 1-6 teeth lost; toothbrushing frequency: 1-3 times/day among positive cases.
Wael Khalil [11]	Cross sectional study	120 healthy adult patients	CP, AP, PI, PC, and saliva	*Candida spp.*, non-*Candida fungi* (not species-typed)	qPCR	**Adenovirus** (42.86%) and HPV-16 (14.28%) were most prevalent in periapical infections, with significant associations ($p = 0.004$ and $p = 0.027$). EBV was most common in healthy controls (29.33%) but not significant. Non-Candida fungi were highly prevalent in all infections (up to 85.71%) and saliva (89.87%), with significant levels in CP, PC, AP, and saliva. Candida peaked in peri-implantitis (37.14%) but showed no significant difference.
Frank Schwarz et al [12]	Cross sectional study	Total sample size- 29 patients Group 1- Peri-implantitis Group 2- Healthy	Peri-implantitis, healthy implants, periodontitis teeth	C. albicans, C. boidinii, C. dubliniensis, C. cladosporioides, Penicillium spp., Paelicomyces spp., Rhodotorula laryngis, Fusarium	Real-time PCR (SYBR Green), sequencing	Fungal organisms in 31.6% of peri-implantitis sites, mainly *C. albicans*. Significant negative correlations to *P. micra* and *T. forsythia*. Fungi in healthy implants

		implant sites with a history of periodontitis		solani, Saccharomycetes		correlated positively with *P. micra* and *T. forsythia*.
Brandilyn A. Peters et al [8]	Pilot observational case-control study	Total sample size- 30 adult subjects Group 1-15 patients with periodontal disease Group 2- 15 patients with good oral health	Periodontitis	Candida, Aspergillus, Schizophyllum, Rhodotorula, and Gibberella.	Oral wash samples, Mycobiome assay, Sequence read processing, α-diversity	Average age 67 ± 7.8 years, and 46.7% male. Candida and Aspergillus were found in 100% of participants. Candida was more abundant in the periodontal disease group (33.2%) compared to healthy individuals (2.2%), but this difference was not significant ($p = 0.52$). Specific Candida and Aspergillus niger OTUs were more frequent in periodontal disease (up to 53.3%), but none were significant after multiple comparisons. Overall fungal diversity was higher in the disease group, but not statistically significant ($p > 0.4$).

Table 3: Outcome Measures

Study	Prevalence	Correlations / Notes
Nemmat A. Hussein [9]	Not quantified per condition	Characteristic colony color and morphology used for differentiation
Nebras Nasir Al-Dabbagh [10	Most frequent: *C. albicans* (12/23)	Linked with poor hygiene and higher tooth loss
Wael Khalil [11]	Fungi in 71–86% of lesions; *Candida* in 21–37%	Non-*Candida* fungi RQ ↑ in CP, AP, PC; *Candida* not significant
Frank Schwarz[12]	Fungi in: 32% peri-implantitis, 40% healthy implants, teeth	Fungi correlated with *P. micra*, *T. forsythia* (significant); broad species diversity
Brandilyn A. Peters [8]	Candida (21%) and Aspergillus (44%) were also the most highly abundant genera in the samples	Observed trends of higher Candida abundance in participants with periodontal disease, and participants with greater tooth loss.

Risk of Bias and Quality assessment of the included studies

The study quality and presence of biases were determined using the Joanna Briggs Institute Critical Appraisal Checklist for Quasi-Experimental Studies. All five studies, Nemmat A. Hussein et al.[9] , Nebras Nasir Al-Dabbagh et al.[10], Wael Khalil et al.[11], Frank Schwarz et al.[12], and Brandilyn A. Peters et al.[8] had clearly defined inclusion criteria, well-described study populations and settings, and used valid, reliable methods for measuring exposures and outcomes. However, a notable limitation across most studies was the lack of identification and management of potential confounding factors, except in Frank Schwarz's study [12], which addressed both. This strengthens the internal validity of Schwarz's findings and contributes to its overall low risk of bias.

In contrast, the other four studies, despite strong methodological approaches, did not explicitly acknowledge or manage confounding factors, which could influence the reliability of their conclusions. Additionally, Nebras Nasir Al-Dabbagh et al[10]. had an unclear use of statistical analysis, slightly weakening the robustness of its findings. As a result, Nemmat A. Hussein [9], Nebras Nasir Al-Dabbagh [10], Wael Khalil [11], and Brandilyn A. Peters [8] were all assigned an overall moderate risk of bias, indicating generally sound methodology with room for improvement in addressing confounding variables and statistical rigor.(Table 4)

Table 4; Risk of bias assessment: JBI critical appraisal checklist for Quasi-Experimental Studies

JBI Criteria	Nemmat A. Hussein et al.[9]	Nebras Nasir Al-Dabbagh[10]	Wael Khalil [11]	Frank Schwarz [12]	Brandilyn A. Peters [8]
1. Were the criteria for inclusion in the sample clearly defined?	Yes	Yes	Yes	Yes	Yes
2. Were the study subjects and the setting described in detail?	Yes	Yes	Yes	Yes	Yes
3. Was the exposure measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes
4. Were objective, standard criteria used for measurement of the condition?	Yes	Yes	Yes	Yes	Yes
5. Were confounding factors identified?	No	No	No	Yes	No
6. Were strategies to deal with confounding factors stated?	No	No	No	Yes	No
7. Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes
8. Was appropriate statistical analysis used?	Yes	Unclear	Yes	Yes	Yes
Overall	Moderate	Moderate	Moderate	Low	Moderate

DISCUSSION

The role of fungi, especially Candida species, is very minimally investigated in the literature. The present study aimed to evaluate the role of fungi in pathogenesis of periodontitis. In the present study, a total of five articles were included in the review.

The human oral cavity harbours more than 1500 different species of microorganisms and a dysbiotic deviation from subgingival gram-positive bacteria to gram-negative bacteria in the periodontal pocket flora leads to Periodontitis, a multifactorial disease.[13,14] Candida species are commensal yeasts in healthy humans and may cause systemic infection under immunocompromised situations. [15] Candida albicans is considered the most common and well known fungi in candida species that is the main causative organism of candidiasis. [20] Nonetheless, candidiasis caused by non-albicans Candida species, such as C. tropicalis, C. parapsilosis, C. krusei, C. glabrata, and C. dubliniensis, are also becoming common among certain groups of patients. [21] There are supporting studies in literature in that associate severe periodontitis with the isolation of Candida species from periodontal lesions.[16,17]

Peters et al [8] in their study found that Genus Candida was isolated from almost all the participants both in periodontitis cases and healthy volunteers control but quantitative analysis showed that was candida isolated abundantly in participants with periodontal disease compared to participants with oral health (33.2% Vs 2.2%), and the difference was not statistically significant.

Schwarz et al [12] in their study noted a high prevalence of fungal organisms in submucosal plaque samples obtained at both peri-implantitis (31.6%) and healthy (40%) implant sites. On the other hand Al-Dabbagh et al [10] reported that candida albicans showed a prevalence of 26%, while other species such as C. Parapsilosis, C. glabrata, C. Kefyr and C. dubliniensis showed comparatively lesser prevalence. Nemmat A. Hussein et al.[9] reported that the Periodontitis cases had the highest percentage of total count (34.65 %) compared with the control group. Similarly, De la Toree et al.,[23] reported that chronic periodontitis patients have a higher Candida colonization rate than those without chronic periodontitis.

Urzua et al [29] found that colonies of C.albicans and C. dubliniensis may present in periodontal pockets particularly in patients with chronic periodontitis. Another study found that in diabetic patients, 57% C.albicans, 75% C.dubliniensis, 16% C. tropicalis and 5% C. glabrata seems to be present in the periodontal pockets of the patients. [30]

Jarvensivu et al [31] in their study found that there was presence of hyphae into the periodontal tissues through immunohistochemistry. Also, another study reported that presence of fungi in the subgingival tissues not only causes periodontal diseases, but also results in Candidiasis, particularly in immunocompromised patients. Candida is also associated with periodontal pathogens such as A.A. comitans, P.gingivalis , T.forsythia etc.. to cause periodontal destruction. [32]

In contrast to these studies, Khalil et al [11] reported that the presence of fungi was significantly associated with dental infection, however candida species was an exception. Popova et al. [25] study found no Candida species in patients with chronic periodontitis.

A recent meta-analysis reported that Candida spp. may increase the chance of chronic periodontitis development by 1.76 times. And Candida spp. were found higher in patients with chronic periodontitis than in periodontally healthy patients. [26]

The exact pathogenic mechanism by which Candida species contribute to the progression of periodontal disease is not still known. The fungal organisms especially Candida species. have virulence factors such as adhesion, dimorphism, invasion, and biofilm formation that facilitate colonization and proliferation in the oral mucosa and, possibly, in periodontal pockets. In periodontal pockets the fungal organisms can co-aggregate with anaerobic bacteria in periodontal pockets. [25,27]

The fungi may act directly, in conjunction with subgingival bacterial pathogens, or as a cofactor by inducing the production of pro-inflammatory cytokines, invading gingival conjunctive tissue, causing microbial colonization and periodontal attachment loss that subsequently contributes to progression of oral diseases. [18,22]

In addition to these properties, Candida spp. also produces enzymes, such as the collagenases and proteinases that degrade extracellular matrix proteins, and immunoglobulin. [19] Another group of virulence factors considered includes secreted aspartic proteases (Sap) and other secreted hydrolytic enzymes. The specific structure of the candida cell wall, dynamically changing during morphological transitions of the fungus that favor the biofilm formation. [28]

The results of the present systematic review suggests that there is a strong association between the presence of Candida species and periodontal diseases.Therefore, periodontitis that is resistant to conventional treatment may require additional broad spectrum antibiotics for coverage of fungal organisms also.

LIMITATIONS

The present study has several limitations. Only five studies were included in the review. Four of the included studies were of Cross Sectional design and one was case control study. There is a wide heterogeneity among the study participants, sample collection, methodology, isolation and identification of pathogen organisms. Majority of studies have evaluated Candida species on the whole or Candida albicans and have not evaluated other candida species such as C.dubliniensis, C. tropicalis, C. glabrata, etc. Non candidal fungal was assessed only in one study. The data from the included studies were not eligible for quantification hence meta analysis could not be done.

Also, considering that candida species are commensal organisms, there are several chances of contamination of the specimens by normal oral flora.

CONCLUSION

Candida species are commensal organisms of the oral cavity. The present systematic review points that there is a strong association between the presence of Candida species and periodontal diseases. However, considering the above mentioned limitations of the present study, generalisability has got limitations.

Further research should be undertaken in this field/area to establish the exact pathogenic mechanism of this opportunistic fungus in periodontal diseases and also confirm the results using a long-term follow-up by evaluating the effect of periodontal treatment on this opportunistic fungus.

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