OBJN
Online Brazilian Journal of Nursing
ISSN: 1676 - 4285 | www.objnursing.uff.br

Submission: 09-Sep-2024
Approved: 07-May-2025

ANTIMICROBIAL AND ANTIFUNGAL ACTIVITY OF *ALLIUM SATIVUM L.* (GARLIC): SCOPING REVIEW PROTOCOL

ATIVIDADE ANTIMICROBIANA E ANTIFÚNGICA DO *ALLIUM SATIVUM L.* (ALHO): PROTOCOLO DE REVISÃO DE ESCOPO

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How to cite: Leão AAS, Drigo RTSC, Caroci-Becker A, Araújo NM, Sahin S, Caroci L, et al. Antimicrobial and antifungal activity of *Allium sativum L.* (garlic): scoping review protocol. Online Braz J Nurs. 2025;24(Suppl 1):e20256828. https://doi.org/10.17665/1676-4285.20256828

RESUMO

Objetivo: Mapear os diferentes tipos de estudos e métodos usados para investigar a atividade antimicrobiana e antifúngica do *Allium sativum L.* (alho). **Método:** Seguindo a metodologia do JBI, será realizada uma análise de escopo que considerará estudos que envolvam tanto animais quanto seres humanos, abrangendo contextos geográficos e culturais. Serão incluídos estudos, como os experimentais, quasiexperimentais, observacionais e descritivos, bem como literatura cinzenta, sem restrição de idioma. Para a busca dos estudos, serão utilizadas bases de dados como Web of Science, PubMed, Scopus, ScienceDirect, Epistemonikos, Embase, Cochrane Library, CINAHL, Biblioteca Digital Brasileira de Teses e Dissertações, bem como as referências de estudos relevantes. Serão incluídos estudos publicados e não publicados dos últimos anos. Dois revisores independentes serão responsáveis pela seleção dos títulos e resumos, pela leitura completa dos textos e pela extração dos dados, empregando uma ferramenta baseada no protocolo previamente publicado intitulado "*Wound-healing properties of Stryphnodendron adstringens (barbatimão) in skin and mucosa injuries: a scoping review protocol*". Caso seja necessário, um terceiro revisor poderá ser adicionado ao processo. Para melhor visualização e interpretação dos resultados, estes serão exibidos em forma de mapa, diagrama ou tabela.

Descritores: Alho; Compostos Fitoquímicos; Fitoterapia; Produtos Biológicos; Candidíase Vulvovaginal.

ABSTRACT

Objective: To map the different types of studies and methods used to investigate the antimicrobial and antifungal activity of *Allium sativum L.* (garlic). **Method:** Following the JBI methodology, a scoping analysis will be carried out that will consider studies involving both animals and humans, covering geographical and cultural contexts. Studies will be included, such as experimental, quasi-experimental, observational and descriptive, as well as gray literature, with no language restrictions. To search for studies, databases such as Web of Science, PubMed, Scopus, ScienceDirect, Epistemonikos, Embase, Cochrane Library, CINAHL, Brazilian Digital Library of Theses and Dissertations will be used, as well as the references of relevant studies. Published and unpublished studies from recent years will be included. Two independent reviewers will be responsible for selecting the titles and abstracts, reading the texts in full and extracting the data, using a tool based on the previously published protocol entitled "*Wound-healing properties of Stryphnodendron adstringens (barbatimão) in skin and mucosa injuries: a scoping review protocol*". If necessary, a third reviewer can be added to the process. For better visualization and interpretation of the results, they will be displayed in the form of a map, diagram or table.

Descriptors: Garlic; Phytochemical compounds; Phytotherapy; Biological products; Vulvovaginal candidiasis.

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INTRODUCTION

Allium sativum L. (garlic) has been recognized for its medicinal properties for millennia[1], with modern evidence highlighting its potential as an antimicrobial and antifungal agent of clinical relevance[2]. *In vitro* studies show that allicin, its main active compound, inhibits *Staphylococcus aureus*, *Escherichia coli* and *Bacillus subtilis* at concentrations ranging from 25 to 200 µg/ml, as well as having a synergistic action with conventional antifungals[3-11]. Against *Candida albicans*, garlic essential oil has a Minimum Inhibitory Concentration (MIC) of 0.35 g/ml, structurally damaging the fungal cell membrane and inducing cell death[12].

Experimental research aimed at evaluating the antifungal action of garlic "*in vitro*" on *Candida albicans* samples, using agar diffusion techniques and morphological evaluation, tested the effect of garlic in three versions: chopped, macerated extract and aqueous extract. It was concluded that the macerated garlic extract surpassed the efficacy of Nystatin® in controlling Candida colonies, with 85% inhibition of growth in morphological tests[13] while combinations with Amphotericin B reduced the MIC values in all the strains tested[14].

These data gain urgency in the context of public health, where antimicrobial resistance (AMR) affects 35% of global bacterial infections, according to the World Health Organization (WHO), and invasive fungal infections have a mortality rate of up to 40%. Garlic is emerging as a complementary therapeutic alternative, especially against multi-resistant pathogens such as *Helicobacter pylori* and *Candida spp.*[9-11,15-17]. The National Health Surveillance Agency (ANVISA) already recognizes its use for respiratory conditions and the prevention of comorbidities[18], in line with integrative practices that seek to reduce dependence on synthetic drugs and their side effects.

Despite these advances, 98% of the available evidence is limited to "*in vitro*" studies and narrative reviews[4,19-20] with critical gaps in clinical trials that validate the translationality of these findings. This scoping review protocol proposes mapping the different types of studies and methods used to investigate the antimicrobial and antifungal activity of *Allium sativum L.* (garlic), to guide future research and clinical applications underpinned by quantitative evidence. Such an approach is vital to consolidate garlic's role as a safe and affordable therapeutic resource, particularly in regions with limited access to state-of-the-art antibiotics.

Review questions

1. What types of studies have been carried out on the antimicrobial and antifungal activity of *Allium sativum L.* (garlic), including animals, humans and *in vitro*?
2. What forms of presentation, application and dosage of *Allium sativum L.* (garlic) were used in these studies?
3. What are the profiles of the participants and the contexts of these studies?

Inclusion criteria

The review will include studies with any type of animal, as well as *in vitro* and *in vivo* models. It was decided to expand the review to include non-human participants, since the number of studies with human beings seems to be limited. Furthermore, there will be no restrictions on comorbidities, age, skin color, race or gender. Studies involving compounds associated with *Allium Sativum L.* will also be included, which will be analyzed separately from the traditional forms, taking into account the specificities of each variation. Similarly, human, animal and *in vitro* studies will be analyzed separately, given the methodological and experimental differences, allowing for a more precise comparison among the results obtained in each model. To guarantee the studies relevance and timeliness, a time frame of five years will be established.

Concept

This review will include studies that explore the antimicrobial and antifungal activities of *Allium sativum L.* in different dosages, duration and preparation methods (such as chopped, macerated, crushed, oil extract, among others). Sources indicating geographical locations where evidence of garlic use has been observed will also be considered, along with the characteristics of services or communities that use garlic for its antimicrobial and antifungal properties.

Context

This review will consider studies carried out in any context, including laboratories, clinics, hospitals or in community settings, in various geographical and cultural locations.

Types of evidence sources

The scoping review will include all experimental studies, quasi-experimental studies, randomized controlled clinical trials, non-randomized controlled clinical trials, observational before-and-after studies and time series studies. Analytical observational studies, retrospective and prospective cohort studies, case-control studies, cross-sectional analytical studies, as well as descriptive observational studies, case series and cross-sectional observational studies will also be included. *In vitro* and *in vivo* studies will be included, along with systematic reviews, scoping reviews, qualitative methods, mixed studies and gray literature studies.

METHODS

The scoping analysis will follow the JBI methodology[21] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping reviews (PRISMA-ScR)[22]. It is worth mentioning that this review protocol is registered with the Open Science Framework (osf.io/a8rfj/).

Search strategy

The search strategy will aim to locate published studies and grey literature in the following databases: Web of Science, CINAHL (EBSCOhost), PubMed (NCBI), Scopus, Embase, Cochrane Library, LILACS, SciELO, ScienceDirect, Google Scholar and Epistemonikos. Grey literature sources will also be explored, including conference proceedings and clinical trials registered on the ClinicalTrials.gov *website* and the International Clinical Trials Registry Plat-

form (https://trialsearch.who.int). Dissertations and theses will also be included through the "Brazilian Digital Library of Theses and Dissertations (BDTD) and the CAPES Catalog of Theses and Dissertations".

A preliminary search was conducted in PubMed (NCBI), LILACS (VHL), EMBASE and Scopus, as illustrated in Figure 1. The keywords extracted from the titles and abstracts of the relevant articles, together with the descriptors, were used to create a complete search strategy for PubMed. This first search approach, which encompasses all the keywords and descriptors, will be adjusted according to each database and information source used in the scoping analysis. In addition, the bibliographic references of the articles chosen for analysis will be examined to detect possible additional research. Due to the large volume of research and to prevent variations in the results of the initial research on the subject, the study will prioritize studies published in the last five years to capture the most recent progress and findings in the field. Studies in all languages will be incorporated to ensure comprehensive coverage of the relevant literature and reduce publication bias.

Database	Search	Search strategies	Identified records
PubMed (NCBI)	#1	"Garlic"[Mesh] OR "garlic"[Title/Abstract] OR "allium sativum"[Title/Abstract]	2,240
Embase	#1	'garlic':ab,kw,ti OR 'garlic extract':ab,kw,ti OR 'allium sativum':ab,kw,ti	1,964
	#2	'antifungal agent':ab,ti,kw OR 'antifungal activity':ab,kw,ti OR 'antifungal':ab,kw,ti OR 'antiinfective agent':ab,kw,ti OR 'antimicrobial therapy':ab,kw,ti OR 'antibacterial activity':ab,kw,ti	40,330
	#3	#1 AND #2	124
Scopus	#1	TITLE-ABS-KEY (allium AND sativum) OR TITLE-ABS-KEY (garlic)	6,654
	#2	TITLE-ABS-KEY (antifungal AND activity) OR TITLE-ABS-KEY (antifungal AND agents) OR TITLE-ABS-KEY (antifungal) OR TITLE-ABS-KEY (antimicrobial AND activity) OR TITLE-ABS-KEY (antimicrobial AND agents) OR TITLE-ABS-KEY (antiinfective AND agents) OR TITLE-ABS-KEY (antiinfective) OR TITLE-ABS-KEY (anti-infective AND agents) OR TITLE-ABS-KEY (anti-infective) OR TITLE-ABS-KEY (antibacterial AND agents) OR TITLE-ABS-KEY (antibacterial AND activity) OR TITLE-ABS-KEY (antibacterial)	272.638
	#3	#1 AND #2	964
Note: Limited to 5 years.			

Figure 1 - Preliminary search strategy in the PubMed, LILACS, Embase and Scopus databases. São Paulo, SP, Brazil, 2024

Study/source of evidence selection

After the search, all the records found will be gathered and uploaded to Endnote 21 (Clarivate Analytics) and duplicates will be eliminated.

Studies will be screened in two stages: in the first, two independent reviewers will assess the titles and abstracts for inclusion criteria, and the references considered potentially eligible will be imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia)[23]; in the second stage, the independent reviewers will read the full text of the studies selected in the previous stage and assess whether they meet the inclusion criteria. Articles that do not meet the inclusion criteria will be eliminated, and the reasons for exclusion will be recorded in the scoping review.

Any disagreement between the two reviewers will initially be discussed between them. If the disagreement persists, a third reviewer will be consulted to decide whether the study should or not be included in the review.

The stages of the study search and selection process will be detailed in the scoping review and represented visually using a PRISMA flowchart[24].

Data extraction

Data will be collected from the articles by two independent *reviewers*, using a tool based on the published protocol "*Wound-healing properties of Stryphnodendron adstringens* (barbatim) *in skin and mucosa injuries: a scoping review protocol*"[25]. Two independent reviewers will evaluate the instrument in three randomly selected studies, which may be adjusted and refined as necessary during the data collection stage, with all changes duly documented in the final scoping review. Any disagreements between the evaluators will be resolved through dialog or with the intervention of a third evaluator. If necessary, the authors of the articles may be contacted up to two times to request any additional or missing information.

Data analysis and presentation

The results will be displayed in the form of a map, diagram or table, as well as a narrative, making it easier to understand and analyze the data. Using maps, diagrams and tables, the results will be organized in such a way as to highlight the main conclusions and patterns identified. The nar-

rative accompanying these graphical representations will be key to connecting the findings to the review central aim and the research questions, providing a richer and more detailed context.

Data will be categorized and stratified according to the implications of the study based on relevant criteria such as study design, year of publication, context, species examined, type of microorganism affected by *Allium sativum L.*, frequency and/or duration of intervention, dosages, method of formulation *of Allium sativum L.*, comparison groups and any other relevant categories that arise during data extraction.

The practical developments of this scoping protocol could include the construction of therapeutic protocols that integrate the use of *Allium sativum L.* in antifungal and antimicrobial treatments, as well as contributing to the formulation of public policies that promote the use of herbal medicines. Clinical recommendations could also be drawn up, guiding health professionals on the safe and effective use of *Allium sativum L.* to fight infections. Thus, this study will not only enrich academic knowledge but could also benefit clinical practice and public health policies.

CONFLICT OF INTERESTS

The authors have declared that there is no conflict of interests.

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Data analysis and interpretation: Leão AS
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Final approval of the version to be published: Leão AS, Drigo RTSC, Becker AC, Araújo NM, Sahin S, Caroci L, Nick JM
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