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BIOACTIVE COMPOUNDS OF FILAMENTOUS FUNGI WITH BIOLOGICAL ACTIVITY: A SYSTEMATIC REVIEW

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ABSTRACT

Filamentous fungi are a rich source of bioactive compounds, which make them a promising resource for the discovery of new drugs.

Objective: The objective of this study was to systematically review research data on bioactive compounds of filamentous fungi with biological activity.

Theoretical Frame: This study used, as a theoretical basis, the literature published in the Medline, Web of Science and Science Direct databases in the period from 2012 to 2021, with the main citations: Main Items for Reporting Systematic Reviews and Meta-analyses (PRISMA) and Meta-Analysis of Statistics Assessment and Review Instrument (MASTARI).

Method: A systematic electronic search was conducted in the Medline (PubMed), Web of Science (WoS) and Science Direct databases, using the descriptors "Filamentous fungi" AND "Bioactive compounds", in order to identify articles related to the selected topic. The articles were selected by three independent reviewers among those published in English in the last 10 years.

Results and Conclusions: The search resulted in 151 articles, of which 8 met the inclusion criteria and were eligible for bias risk assessment using six quality criteria. Filamentous fungi are a large and promising source of bioactive compounds due to various biological activities such as strong inhibition of phosphodiesterase 4B, cytotoxicity against cancer cells, and antimicrobial, immunosuppressive, antibacterial, antifungal, antiviral and anti-inflammatory activities. In view of the results, further efforts are hoped to discover new drugs from filamentous fungi. Currently, several studies are being developed with different strains of filamentous fungi collected in different environments, such as forests, sea, icy regions and soil. *Aspergillus* and *Penicillium* are among the most studied genera. These fungi produce several bioactive compounds, some already reported and others recently discovered. *In vitro* and *in silico* studies are being used to test the different biological activities provided by bioactive compounds; therefore, the results of these researches are very promising for the discovery of new drugs. Additionally, further studies are needed to test these activities in *in vivo* models. The results obtained are of great relevance for medicine and the pharmaceutical industry, as they bring an update of the main bioactive compounds and their biological activities from biodiversity, which can be used in the development of new drugs capable of fighting different diseases. Still, they can help the academic and scientific community about what has been studied and what remains to be researched. In the future, other species and strains of fungi can be studied,

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aiming to discover new bioactive compounds with biological activity; for this, fungi can be collected from different environments, such as forests, sea and soil microbiota, or isolated from plants, extreme and remote environments. In this way, it would be possible to make better use of the world's biodiversity, use molecular-based approaches and tools and produce resources capable of improving the quality of human life.

Implications of the research: This study is highly relevant for the purposes of the Programa de Pós-Graduação em Saúde e Desenvolvimento Socioambiental da Universidade de Pernambuco, *Campus* Garanhuns, as well as for the entire academic, scientific and pharmaceutical community interested in discovering new bioactive compounds with biological activity.

Originality and value: The study sought to present to the academic, scientific and pharmaceutical community what is currently being researched on bioactive compounds of filamentous fungi with biological activity, providing current information and main researchers, indicating what remains to be investigated and collaborating for the environmental and social management of the sector of health.

Keywords: Fungal Metabolites, Chemical Diversity, Potential Activity, Anticancer.

COMPOSTOS BIOATIVOS DE FUNGOS FILAMENTOSOS COM ATIVIDADE BIOLÓGICA: UMA REVISÃO SISTEMÁTICA

RESUMO

Os fungos filamentosos são uma fonte rica em compostos bioativos, tornando-se uma fonte de recursos promissores para a descoberta de novos medicamentos.

Objetivo: Assim, objetivou-se com este estudo sintetizar sistematicamente dados de pesquisas sobre compostos bioativos de fungos filamentosos com atividade biológica.

Referencial teórico: Este estudo utilizou como base teórica a literatura publicada nas bases de dados Medline, Web of Science e Science Direct referente ao período de 2012 a 2021, tendo como principais citações: Principais Itens para Relatar Revisões Sistemáticas e Meta-análises (PRISMA) e Meta-análise de Estatísticas na Avaliação e Revisão de Instrumento (MASTARI).

Método: Uma busca eletrônica sistemática foi conduzida nas bases de dados Medline (PubMed), Web of Science (WoS) e Science Direct, utilizando os descritores “Filamentous fungi” AND “Bioactive compounds”, visando identificar artigos relacionados a compostos bioativos de fungos filamentosos com atividade biológica. Os artigos foram selecionados por três revisores independentes, incluindo aqueles estudos dos últimos 10 anos publicados em inglês.

Resultados e conclusão: A busca resultou em 151 artigos, dos quais 8 atenderam aos critérios de inclusão e foram elegíveis para avaliação do risco de viés utilizando seis critérios de qualidade. Os fungos filamentosos são um grande reservatório de compostos bioativos e têm se mostrado promissores em função das diversas atividades biológicas proporcionadas, como grande potencial para inibir a fosfodiesterase 4B, citotoxicidade contra células cancerosas, antimicrobiana, imunossupressora, anticancerígena, antibacteriana, antifúngica, antiviral e anti-inflamatória. Diante dos resultados, são notórios os esforços para a descoberta de novos medicamentos a partir de fungos filamentosos. Atualmente, vários estudos estão sendo desenvolvidos com diversas cepas de fungos filamentosos coletadas em diferentes ambientes, como florestas, mar, regiões geladas e solo. *Aspergillus* e *Penicillium* estão entre os gêneros mais estudados. Estes fungos produzem diversos compostos bioativos, alguns já relatados e outros descobertos recentemente. Estudos *in vitro* e *in silico* estão sendo feitos para testar as diferentes atividades biológicas proporcionadas pelos compostos bioativos; desta forma, os resultados destas pesquisas são muito promissores para a descoberta de novos medicamentos. Adicionalmente, fazem-se necessários mais estudos para testar estas atividades em modelos *in vivo*. Os resultados obtidos são de grande relevância para a medicina e indústria farmacêutica, pois trazem uma atualização dos principais compostos bioativos e suas atividades biológicas a partir da biodiversidade, que podem ser utilizadas no desenvolvimento de novos fármacos capazes de combater diferentes doenças. Ainda, podem auxiliar a comunidade acadêmica e científica sobre o que tem sido estudado e o que falta ser pesquisado. No futuro, outras espécies e cepas de fungos podem ser estudadas, visando descobrir novos compostos bioativos com atividade biológica; para isso, fungos poderão ser coletados de diferentes ambientes, como florestas, mar e microbiota do solo, ou isolados de plantas, ambientes extremos e

remotos. Desta forma, seria possível realizar um melhor aproveitamento da biodiversidade mundial, utilizar abordagens e ferramentas de base molecular e produzir recursos capazes de melhorar a qualidade da vida humana.

Implicações da pesquisa: Este estudo qualifica-se como de grande relevância para os propósitos do Programa de Pós-Graduação em Saúde e Desenvolvimento Socioambiental da Universidade de Pernambuco, *Campus* Garanhuns, assim como, para toda comunidade acadêmica, científica e farmacêutica interessada na descoberta de novos compostos bioativos com atividade biológica.

Originalidade/valor: O estudo buscou apresentar à comunidade acadêmica, cientifica e farmacêutica o que está sendo pesquisado atualmente sobre compostos bioativos de fungos filamentosos com atividade biológica, disponibilizando informações atuais e principais pesquisas, indicando o que falta ser investigado e colaborando para a gestão ambiental e social do setor de saúde.

Palavras-chave: Metabólitos Fúngicos, Diversidade Química, Atividade Potencial, Anticâncer.

1 INTRODUCTION

The relevance of intensifying studies using the great world biodiversity in a sustainable way, as well as microorganisms, is notorious and expressive, since, historically, the high demand for new antimicrobial and antitumor drugs has not been met by the discovery of new drugs (Conrado et al., 2022). In view of this, the study of fungal metabolites is of great importance, since, currently, among the known microbial metabolites, 45% come from fungi (Berdy, 2012).

Throughout human history fungi have played an essential role in the development of drugs, due to their ability to synthesize numerous secondary metabolites with great medicinal potential (Li et al., 2020; Zhang et al., 2021). Among fungi, the filamentous ones have the ability to develop in various environments, and can be found in water, soil and air (Egbuta et al., 2016). Filamentous fungi encompass many genera, with those belonging to the genera *Aspergillus*, *Penicillium*, *Fusarium*, *Alternaria* and *Cladosporium* being the most studied worldwide (Pitt & Hocking, 1997; Egbuta et al., 2016).

Filamentous fungi are especially abundant in natural products, which often show strong biological activity (Alberti et al., 2017). Depending on their chemical structures and biosynthetic pathways, bioactive compounds produced and isolated from fungi belong to different chemical classes such as polyketides, alkaloids, terpenes and non-ribosomal peptides (Nisa et al., 2015). Deshmukh et al. (2022) stated that fungi are also characterized by the diversity of secondary metabolites of various classes such as quinones, furanones, pyrones, benzopyranoids, xanthones, steroids and many acyclic compounds.

Fungal metabolites have shown significant biological activities, which indicate their potential as agents in the treatment of a gamma of different diseases (Zheng et al., 2021). Among them are antibiotics such as penicillins and statins for cholesterol reduction (Nielsen et al., 2017) as well as agents against fungal infections, cancer, parasitoses including malaria, autoimmune disorders, neurological and cardiovascular diseases (Newman & Cragg, 2016; Bills & Gloer, 2016).

Due to the recent increase in the resistance of fungal and bacterial pathogens to medicines, there is a growing need to search for new antifungal and antibacterial bioactive compounds (Xu et al., 2015; Reis et al., 2019). In this sense, Deshmukh et al. (2022) have recently highlighted the demand for new and more effective antiviral drugs due to the re-

emergence and development of resistance of viral strains. Drug resistance is a recurring problem, especially in bacteria (Bones et al., 2022). On the other hand, Mohammed et al. (2021) stressed the need for new anticancer drugs with greater efficacy and potential to reduce side effects. In view of this, there is a constant and urgent need for studies aimed at the development of new more effective drugs, for which the potential of bioactive compounds of filamentous fungi has been explored.

Therefore, due to the potential of filamentous fungi in the production of secondary metabolites, it is necessary and justifiable to systematically synthesize research data on bioactive compounds from filamentous fungi with biological activity. In this context, the following question arises: what is currently being researched about bioactive compounds of filamentous fungi with biological activity, what environments are fungi being collected from, what are the most studied species, bioactive compounds, study methods and activities most promising biologics for the discovery of new drugs?

Given the relevance of the theme, the objective of this review was to systematically analyze research data from the last 10 years on bioactive compounds of filamentous fungi with biological activity in order to fill a gap in the literature.

2 MATERIALS AND METHODS

2.1 Strategic Search

In order to study relevant articles, this paper was restricted to articles written in English and published in the last 10 years, i.e., from January 2012 to December 2021. Bibliographic searches were performed in the electronic databases Medline (PubMed), Web of Science (WoS) and Science Direct, using the descriptors selected from the Descriptors in Health Sciences (DeCS) and combined with the boolean operator (AND), thus: "Filamentous fungi" AND "Bioactive compounds". In bibliometric studies and academic research, databases such as the Web of Science are widely used (Baracho & Scalize, 2023).

This review was done following to the Main Items for Reporting Systematic Reviews and Meta-analyses (PRISMA), according to the flowchart illustrated in Figure 1 that summarizes the flow of information during the different phases of articles selection.

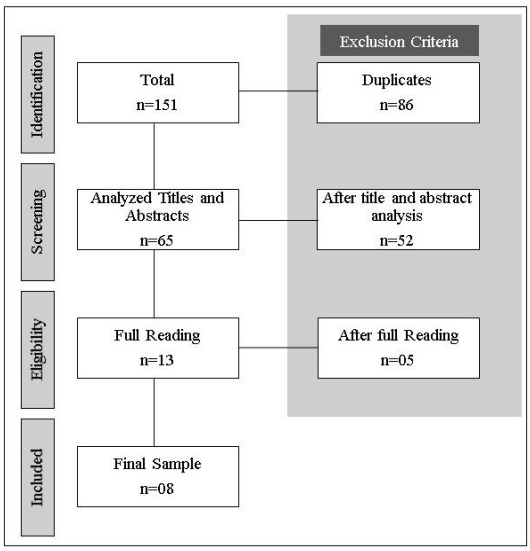

Figure 1. Flow chart of the articles selection process according to the Main Items for Reporting Systematic Reviews and Meta-analyses (PRISMA).
Source: Adapted from Page et al. (2021).

2.2 Eligibility Criteria

The articles located in the bibliographic searches were consulted in order to identify the possible eligible ones. Original research articles in English that used extracts or compounds isolated from filamentous fungi with biological activity were included. Instead, duplicate articles, book chapters, reviews, congress articles, non-original articles and studies with data that showed discrepancies in the information were excluded. After consulting the titles and abstracts of the articles, those not consistent with the inclusion criteria were excluded.

2.3 Selection of Articles

After selecting the articles consistent with the inclusion criteria, three independent reviewers selected among the authors carefully examined the full texts for eligibility, therefore disagreements were discussed and resolved in consensus. Three reviewers were used so that, if there was disagreement between the inclusion or exclusion criteria, a third opinion would have been possible to conciliate and reach a consensus.

2.4 Data Extraction

Data were extracted regarding place of origin, species (strain), extraction solvent, isolation method, bioactive compound, study model, biological activity, concentration (dose), treatment time and reference.

2.5 Assessment of the Risk of Bias

The risk of bias was evaluated using the following six questions as quality criteria adapted from the Meta-Analysis of Statistics Assessment and Review Instrument (MASTARI, 2014) protocol: 1 - Does the study report the method used to obtain bioactive compounds?; 2 - Did the study use any characterization method to identify the bioactive compounds existing in the sample?; 3 - Does the study mention any active principle involved in biological activity?; 4 - Did the study perform complementary tests to validate biological activity ?; 5 - Does the study mention possible mechanisms of action of bioactive compounds?; and 6 - Does the study describe the results in a clear way, enabling a complete evaluation of the data?

These criteria were evaluated in each of the included studies, such as: yes, no, unclear or not applicable. To assess the risk of bias in the included studies, the frequency of positive responses (yes) to each of the criteria used was obtained. The included study was classified as low risk of bias when the frequency of positive responses was greater than 70%, whereas frequency between 50 and 69% was classified as moderate risk of bias, and frequency less than 50% as high risk of bias (Peinado et al., 2020; Moura et al., 2021).

3 RESULTS

3.1 Bibliographic Search

The bibliographic search resulted in the selection of 151 articles, 49 of which were obtained from Medline (PubMed), 85 from Web of Science and 17 from Science Direct. Of these, 86 were excluded, 57 for being duplicated and 29 not original, and 52 excluded by the reviewers after reading titles and abstracts. Among the remaining 13 articles selected for full reading, 8 met the eligibility criteria and were included for qualitative analysis in this systematic review, according to the above PRISMA flowchart (Figure 1).

3.2 General Characteristics of Selected Studies

A general overview of the main methodological issues and results of the 8 studies published in English from 2012 to 2021 and included in this systematic review can be found in Table 1.

In general, the filamentous fungal strains mentioned in these studies were isolated from different environmental niches such as the sea, woody debris from forest and soil as well as different climatic regions of the planet.

Table 1. Characteristics of bioactive compounds from filamentous fungi with biological activity.

Place of origin	Species / Strain	Extraction solvent	Isolation method	Bioactive compound	Study model	Biological activity	Volume or concentration	Treatment time	Reference
Highly decomposed woody debris from a tropical forest	*Chaetothyriales* (MSX 47445)	1:1 $CHCl_3$:MeOH	Flash chromatography; HPLC	Betulinan A	*In vitro*; *In silico*	Phosphodiesterase 4B inhibitor	20 µg/ml	- - -	El-Elimat et al. (2013)
				Betulinan C		Phosphodiesterase 4B inhibitor Cytotoxicity Antimicrobial			
				BTH-II0204-207:A		Phosphodiesterase 4B inhibitor Cytotoxicity Antimicrobial			
North Sea water sample	*Penicillium bialowiezense* (IBT 28294)	Ethyl acetate containing 1% formic acid	UHPLC-DAD-QTOFMS; MS/HRMS Library	Mycophenolic acid	*In vitro*; *In silico*	Immunosuppressant	- - -	- - -	Kildgaard et al. (2014)
Sea water sample collected near Greenland	*Aspergillus insuetus* (IBT 28443)			Isomers of asperphenamate 6-epi-Ophiobolin K Ophiobolin H Ophiobolin K Ophiobolin C		Anticancer			
Sea water sample from the coast of the Danish island Fanoe	*Emericellopsis* sp. (IBT 28361)			Helvolic acid		Antimicrobial			
Soil sample collected in Buyeo city, Chungcheongnam-do, Korea	*Aspergillus fumisynnematus* F746	Acetone 80%	TLC; HPLC; LC/MS	Cyclopiazonic acid	*In vitro*	Antibacterial	20 µl	16 – 20 h	Hong et al. (2015)
Environmental samples collected in four climatic regions	Co-culture CF-118005 with *Botrytis cinerea*	Acetone	LC-HRMS	SNF 4794-7	*In vitro*	Antifungal	10 µl	24 h	Serrano et al. (2017)
	Co-culture CF-187233			Cordyol C; (C15H16O4)					

	with *Botrytis cinerea*								
	Co-culture CF-189741 with *Botrytis cinerea*			Mycorrhizin A and Chlorinated C14H15ClO4					
	Co-culture CF-246868 with *Botrytis cinerea*			Palmarumycins C7 and C15					
	Co-culture CF-268787 with *Botrytis cinerea*			Penicillic acid					
Coranroo, West Coast of Ireland	*Eurotium chevalieri* MUT 2316	EtOAc:CH_2Cl_2 and MeOH:CH_2Cl_2	Flash chromatography; HPLC	Physcion	*In vitro*	Antiviral; Antibacterial	6.25 - 50.0 µg/mL	18 - 48 h	Bovio et al. (2019)
				Dihydroauroglaucin		Antibacterial			
				Isodihydroauroglaucin		Antibacterial			
				Neoechinulin D		Antiviral; Antibacterial			
				Asperflavin		Antibacterial			
				Cinnalutein					
Soil samples collected in Kalubia, Egypt	*Aspergillus* sp. DHE 4	Ethyl acetate	Column chromatography on silica gel	R(−)-mevalonolactone	*In vitro*	Antimicrobial	40 mg/mL	24 h bacteria and yeasts; 72 h fungi	Abdel-Razek et al. (2020)
				Poly-hydroxysterol					
				Kojic acid					
				α-/β-glucoside mixture					
Centrient Pharmaceuticals	*Penicillium rubens* DS68530	Acetone; Methanol	LC-MS	Macrophorin A	*In vitro; In silico*	Antimicrobial	100 µl	24 h	Mózsik et al. (2021)
				Macrophorin D					
				4'-Oxomacrophorin D					
University of Iowa (USA) and Bioresources Collection and Research Center (Taiwan)	*Cunninghamella bainieri* ATCC 9244	EtOAc:Butanol (9:1)	Column chromatography with Kieselgel silica; HPLC; TLC	*ent*-13,15β-dihydroxy-kaur-16-en-19-oic acid	*In vitro; In silico*	Anti-inflammatory	10 µM	24 h	Chang et al. (2021)
	Mortierella isabellina ATCC 38063			*ent*-3α,13-dihydroxy-kaur-15-en-19-oic acid					
				ent-13,17-dihydroxy-kaur-15-en-19-oic acid					

Source: Authors (present article).

3.2.1 Filamentous fungal species

Strains of several species of filamentous fungi were used in these studies, namely *Penicillium bialowiezense* IBT 28294, *Aspergillus insuetus* IBT 28443, *Emericellopsis* sp. IBT 28361, *Chaetothyriales* MSX 47445, fungal strains of the wild type: CF-118005, CF-187233, CF-189741, CF-246868, CF-090071 and CF-268787, *Penicillium rubens* DS68530, *Eurotium chevalieri* MUT 2316, *Aspergillus fumisynnematus*, *Aspergillus* sp. DHE 4, *Cunninghamella bainieri* ATCC 9244 and *Mortierella isabellina* ATCC 38063. It can be seen that most strains belong to species of the genera *Aspergillus* and *Penicillium*.

3.2.2 Solvents and methods of isolation of bioactive compounds

In the included studies, different solvents were used to extract bioactive compounds, mainly acetone and ethyl acetate, but also $CHCl_3$:MeOH, EtOAc:CH_2Cl_2, MeOH:CH_2Cl_2, and EtOAc:Butanol.

The isolation methods used were ultra-high performance liquid chromatography (UHPLC), automatic high-resolution mass spectrometry (MS/HRMS), flash chromatography, high performance liquid chromatography (HPLC); high resolution liquid chromatography-mass spectrometry (LC-HRMS), liquid chromatography with mass spectrometry (LC-MS), thin layer chromatography (TLC), column chromatography with silica gel, and column chromatography with Kieselgel silica.

3.2.3 Techniques for testing biological activities

The techniques used in the selected studies to test the biological activities of bioactive compounds comprised pre-clinical *in vitro* and *in silico* trials.

3.2.4 Concentration or volume and treatment time

The highest concentration or volume used in the *in vitro* tests reported in the selected studies was 40 mg/mL or 100 µl, while the lowest one 6.25 µg/mL or 10 µl, respectively, whereas the longest treatment time was 72 hours and the shortest one 16 hours.

3.2.5 Bioactive compounds and biological activities

A total of 34 bioactive compounds from filamentous fungi were identified in the selected studies, which, when submitted to *in vitro* and *in silico* tests, showed 9 different biological activities, i.e., phosphodiesterase 4B inhibitor, cytotoxic, antimicrobial, antibacterial, immunosuppressive, anticancer, antifungal, antiviral and anti-inflammatory activities (Table 1).

The analyses have also shown that some biological activities were provided by more than one bioactive compound, as well as, some of the compounds had more than one bioactivity. The results of the selected studies are discussed below in more detail.

When studying anticancer activity, El-Elimat et al. (2013) found that Betulinan C, with half maximal inhibitory concentration (IC_{50}) of 26.1, 19.5 and 32.8 µM, and Terphenyl, with IC_{50} of 39.0, 21.8 and 38.8 µM, were moderately cytotoxic against three cancer cell lines, namely MCF-7, H460 and SF268, in addition to having antimicrobial activity against *Staphylococcus aureus*, with minimum inhibitory concentration (MIC) of 25 µg/mL. They also found that Betulinan C (Benzoquinone) was the compound with the most potent phosphodiesterase (PDE4B2) inhibiting activity (IC_{50} of 17 µM), followed by Terphenyl BTH-II0204-207:A (IC_{50} of 31 µM) and Betulinan A (Benzoquinone) (IC_{50} of 44 µM); however, all of them were less potent than Rolipram used as a positive control.

In the study conducted by Kildgaard et al. (2014), the dereplication of marine fungal metabolites was performed using chromatography and spectrometry to investigate the extracts of the strains. Comparison with a library of 1300 compounds allowed to identify already known compounds as well as new bioactive compounds, including Mycophenolic acid, a compound with immunosuppressive activity used in transplant medicine, the isomers of asperphenamate 6-epi-Ophiobolin K, Ophiobolin H, Ophiobolin K and Ophiobolin C with anticancer activity, and the compound Helvolic acid with antimicrobial activity.

In order to identify new bioactive compounds, Hong et al. (2015) performed an overexpression of the *laeA* gene to activate the clusters of secondary metabolite genes in

Aspergillus fumisynnematus F746. This effort resulted in the production of new bioactive compounds, one of which, identified as Cyclopiazonic acid, was expressed in high level and displayed antibacterial activity against Gram-positive bacteria with MIC of 10-50 μg mL^{-1}. According to these researchers, overexpression of the *laeA* gene can be used as a tool for the synthesis of essential bioactive compounds.

In order to induce chemical diversity and produce therapeutic agents, Serrano et al. (2017) studied the co-cultivation of the fungal strains CF-118005, CF-187233, CF-189741, CF-246868 and CF-268787 with the fungus *Botrytis cinerea*, whose interactions resulted in the presence of the following compounds in the extracts SNF 4794-7, Cordyol C (C15H16O4), Mycorrhizin A and Chlorinated $C_{14}H_{15}ClO_4$, Palmarumycins C7 and C15, and Penicillic acid. So, the co-cultivation led to the release of compounds with antifungal activity against human fungal pathogens like *Candida albicans* and *Aspergillus fumigatus*, in addition to the identification of new secondary metabolites.

Among the marine fungi isolated from the Atlantic sponge *Grantia compressa* by Bovio et al. (2019) using the OSMAC approach, *Eurotium chevalieri* MUT 2316 demonstrated to possess a diversity of metabolites. Among them, the compounds Physcion, Dihydroauroglaucin, Isodihydroauroglaucin, Neoechinulin D, Asperflavin and Cinnalutein showed significant antiviral activities against herpes and influenza viruses as well as antibacterial activity against Gram-positive bacteria.

The newly discovered terrestrial fungus *Aspergillus* sp. DHE 4 was the subject of a study by Abdel-Razek et al. (2020), who identified four bioactive compounds, namely R(−)-mevalonolactone, Poly-hydroxysterol, kojic acid and α-/β-glucoside mixture, with strong antimicrobial biological activity mainly against Gram-positive bacteria and yeasts, suggesting this fungus as a potential source for obtaining new drugs.

Studying transcriptional activation in silent genes of the filamentous fungus *Penicillium rubens*, Mózsik et al. (2021) found that the strain DS68530 produced the compounds Macrophorin A, Macrophorin D and 4'-Oxomacrophorin D, resulting in antimicrobial activity against *Micrococcus luteus*. According to these researchers, this methodology can help in identifying new bioactive compounds with biological activities.

Also, in one of the studies the microbial transformation of 15-ene steviol derived from stevioside was used to produce the new compounds *ent*-13,15β-dihydroxy-kaur-16-en-19-oic acid (by the fungus *Cunninghamella bainieri* ATCC 9244), *ent*-3α,13-dihydroxy-kaur-15-en-19-oic acid and *ent*-13,17-dihydroxy-kaur-15-en-19-oic acid (by *Mortierella isabellina* ATCC 38063), which resulted, compared to control (dexamethasone), in a similarly better inhibiting effect on induced secretion by expressed and secreted normal T-cell lipopolysaccharides - RANTES (Chang et al., 2021).

3.3 Risk of Bias of the Included Studies

Figure 2 shows the result of the assessment of the risk of bias of the included studies, according to the quality criteria used, aiming to show unbiased results.

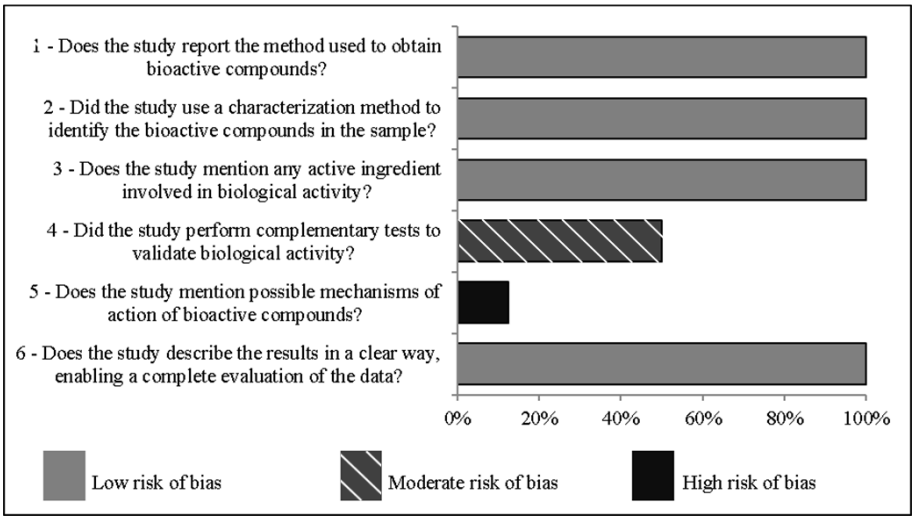

Figure 2. Risk of bias of all studies included presented as percentages.
Source: Authors (present article).

The assessment of the risk of bias of the included studies resulted in most quality criteria classified as low risk of bias (high quality of studies). Only criterion 4 was categorized as moderate risk of bias, because complementary tests to validate biological activity were performed only in 50% of the studies, and only criterion 5 was classified as a high risk of bias, because only 12.5% of the studies mentioned possible mechanisms of action of bioactive compounds. Since the quality of the included studies was based on the criteria of exclusive quality of the review itself, some of them may have not responded positively to the criteria, and then were classified as moderate or high risk of bias, as they may have had other objectives not considered in this evaluation (Moura et al., 2021). This information may justify the classification as high or moderate risk of bias of some studies included in the present review.

4 DISCUSSION

The therapeutic applications of filamentous fungi have been studied due to the production of a great diversity of bioactive compounds, which have several biological activities. In view of this, the studies included in this review follow this idea.

The antimicrobial activity of filamentous fungi was identified in four of the included studies (El-Elimat et al., 2013; Kildgaard et al., 2014; Abdel-Razek et al., 2020; Mózsik et al., 2021), and the production of substances by filamentous fungi resulted in the development of new antimicrobial agents (Svahn et al., 2012). Due to the emergence of microorganisms resistant to antimicrobial drugs available on the market, these recent studies have sought to identify new compounds with potential to be used as antimicrobial agents. The continuation of the bacterial cell cycle is mainly regulated by DNA gyrase and topoisomerase IV. Fungal extract containing helvolic acid showed potential to interact with these two enzymes, and this effect was detected through the inhibitory activity of *S. aureus*. Furthermore, an anchorage simulation revealed the compound clearly aggregated in the active pocket of DNA gyrase and topoisomerase IV. The packaging inside the ATP binding cavity of the two enzymes was favored by the existence of the carboxylic group in the compound. The increase in inhibitory activity was confirmed by the progression of significant H-binding relationships (Hussein et al., 2022). This set of information demonstrates how bioactive compounds exert their antimicrobial mechanism.

Studies by Hong et al. (2015) and Bovio et al. (2019) showed antibacterial activity against Gram-positive bacteria when using bioactive compounds extracted from filamentous

fungi. Keeler et al. (2021) corroborated these results by verifying the antibacterial activity of seven isolates of filamentous fungi against the two human pathogens *S. aureus* ATCC-35556 and *Escherichia coli* ATCC-25922. Lagashetti et al. (2022) also identified antibacterial activity of the fungus *Gonatophragmium triuniae* against the bacteria *Bacillus subtilis*, *S. aureus* and *M. luteus*. These results demonstrate the potential of filamentous fungi as a source of bioactive compounds against a diversity of Gram-positive and Gram-negative bacteria. Antibacterial compounds can play their mechanisms of action by chemically intervening in the synthesis or activity of essential constituents of bacterial cell and/or are able to circumvent the mechanisms of bacterial resistance. In addition, they have the potential to achieve multiple bacterial targets, such as protein or cell wall biosynthesis, DNA replication and restoration, metabolic pathway inhibition, or bacterial cell membrane destruction (Khameneh et al., 2019).

The study by Serrano et al. (2017), using interactions between different fungal strains to induce chemical diversity, resulted in increased production and new metabolites with antifungal activity. Fungal strains of the genus *Aspergillus*, when compared to those belonging to other genera, stood out as producers of new antifungal compounds, which suggests their further investigation in order to discover new compounds with antifungal activity (Xu et al., 2015). Reis et al. (2019) found that the extract of the fungus *Diaporthe schini* has antifungal activity against *Candida krusei*, a budding yeast deeply resistant to some drugs (Gong et al., 2021). These studies show the potential of bioactive compounds of fungi of different genera as promising sources for obtaining new drugs with an inhibiting effect against drug-resistant pathogens already used in antifungal therapy. The compounds reported in the study by Serrano et al. (2017) included in this review displayed broad-spectrum antifungal activities against human fungal pathogens. New antifungal agents that are close to having clinical use, such as the new triazoles, also have an extremely broad antifungal spectrum, while the new classes of echinocandins and sordarins have new mechanisms of action that prevent the syntheses of fungal cell wall polysaccharides and proteins, respectively (Odds et al., 2003). Furthermore, according to these authors, regardless of the mechanism of action, new antifungal agents should have a wider spectrum as possible of susceptible fungal species.

Antiviral activity was observed for Physcion and Neoechinulin D isolated from the fungus *E. chevalieri*, which showed, for the first time, total inhibition (100%) of human herpes simplex virus - type 1 (HSV-1). So, a thorough investigation on the mechanism of action of these compounds against HSV-1 is underway (Bovio et al., 2019). Other studies corroborate this result, such as that by Liang et al. (2018), in which compounds extracted from *Aspergillus ruber* also demonstrated expressive antiviral activity against this virus. The compound Neoechinulin B from the fungus *Aspergillus amstelodami* showed anti-HCV (chronic hepatitis C virus) activity, thanks to its ability to reduce the rate of RNA replication. Furthermore, by targeting the cellular liver X receptor (LXR), Neoechinulin B may decrease the infection rate of the HCV virus (Nakajima et al., 2016; Mitra et al., 2022). These outcomes demonstrate the great potential of Neoechinulins as antiviral agents.

Compounds isolated from the fungi *C. bainieri* and *M. isabellina* resulted in anti-inflammatory activity, with *ent*-13,15β-dihydroxy-kaur-16-en-19-oic acid and *ent*-13,17-dihydroxy-kaur-15-en-19-oic acid being able to reduce the expression of interleukin-6 (IL-6), while *ent*-13,15β-dihydroxy-kaur-16-en-19-oic acid, *ent*-3α,13-dihydroxy-kaur-15-en-19-oic acid and *ent*-13,17-dihydroxy-kaur-15-en-19-oic acid exerting an inhibiting effect on lipopolysaccharide-induced secretion of expressed and secreted normal T cells (RANTES) (Chang et al., 2021). Also, according to the authors, these bioactive compounds may perform anti-inflammatory activity downstream of the TRL4 pathway associated with the membrane and MyD88 molecules. Xu et al. (2019) reported that compounds of the chemical classes of polyketides and terpenoids derived from marine fungi have great potential to develop new drugs

against inflammation. In this context, it is evident the great significance of bioactive compounds and biological activities provided by filamentous fungi.

The bioactive compounds extracted from a fungus of the order Chaetothyriales (MSX 47445) were shown to inhibit phosphodiesterase 4B2 (PDE4B2), although less powerfully than the type 4 phosphodiesterase (PDE4) inhibitor Rolipram used as a positive control (El-Elimat et al., 2013). De Franceschi et al. (2008) found that Rolipram can act through two mechanisms of action, the former directly via inhibition of cell degradation of cyclic adenosine monophosphate (cAMP), and/or the latter indirectly by decreasing the magnitude of vasoconstriction to reduction of inflammatory response. In the case of airway inflammation, PDE4 inhibitors reduce this response through a mechanism that prevents cAMP breakdown (Taylor and Abdel-Rahman, 2009). According to Houslay et al. (2005), PDE4B is especially linked to inflammation, since this isoform is predominantly present in monocytes and human neutrophils. Therefore, PDE4B2 is relevant due to the role it plays over several inflammatory stimuli, such as lipopolysaccharide stimulation and interleukin inhibition (Wang et al., 1999; Ghosh, et al., 2012; Shepherd et al., 2004; Tibbo & Baillie, 2020). In view of this set of information, the inhibition of human PDE4B2 becomes an alternative target for the discovery of new anti-inflammatory drugs from filamentous fungi.

The cytotoxic activity of benzoquinone and terphenyl produced by MSX 47445 was also successful in the inhibition of the proliferation of human cancer cells MCF-7 (breast cancer cells), H460 (large lung cells) and SF268 (human astrocytoma) (El-Elimat et al., 2013), thus confirming the results of other studies carried out on the cytotoxic activity of the organic extract of filamentous fungi of the family Bionectriaceae against the same human cell lines (Kinghorn et al., 2009; Orjala et al., 2012; Figueroa et al., 2012). Benzoquinones have cytotoxicity mechanisms associated with intercalation and alkylation of cellular nucleophiles and oxidative stress (Bolton et al., 2000). Cellular damage can occur through the direct intercalation of benzoquinone to DNA and alkylation of essential proteins and nucleic acids (Brunmark and Cadenas, 1989; Asche, 2005) as well as the production of reactive oxygen species (ROS) released by reductase-catalyzed reactions, which act on DNA, lipids, telomerase proteins and shock protein 90 (Monks et al., 1992). On the other hand, the mechanism of terphenyl compounds through the formation of ROS can induce cell cycle cessation and apoptosis, with subsequent fragmentation of double DNA tape (Liu et al., 2012; Zhang et al., 2018).

Filamentous fungi are mainly known as producers of secondary metabolites such as anticancer polypeptides (Bladt et al., 2013). Kildgaard et al. (2014) identified in the fungi *P. bialowiezense* and *A. insuetus* the petide asperphenamate and the sesterterpenoid ophiobolin, both with anticancer activity. According to Subko et al. (2021), asperphenamate received great relevance due to its antitumor activity; however, other studies with this compound have also demonstrated potential neuroinflammatory activity (Zhou et al., 2017), anti-HIV properties (Bunteang et al., 2018) and cytotoxicity against cancer cell lines (Kozluovski et al., 2004). On the other hand, ophiobolins have anticancer activity against various cancer cells and antifungal activity against various fungi (Bladt et al., 2013). Compounds derived from asperphenamate were shown to inhibit the growth of MCF-7 cells, through a mechanism induced by autophagy rather than apoptosis or cell cycle arrest (Yuan et al., 2012; Liu et al., 2016). Also, a significant activity against apoptosis-resistant glioblastoma cells was identified for ophiobolin A, a fungal secondary metabolite that induced non-apoptotic cell death (Dasari et al., 2015).

Mycophenolic acid, a compound with immunosuppressive activity, was detected in the fungus *P. bialowiezense* (Kildgaard et al., 2014). This acid acts as an inhibitor of inosine monophosphate dehydrogenase (IMPDH), a fundamental enzyme for the new synthesis of guanosine nucleotides. Since T and B lymphocytes are more dependent on this pathway than other cell types, mycophenolic acid displayed a more powerful cytostatic effect on them (Allison and Eugui, 200). Mycophenolic acid belongs to the immunosuppressive drug group

but also has anticancer, antiviral, antifungal and antibacterial activities (Siebert et al., 2017). According to Bressan et al. (2010), immunosuppressants act in cell division and have anti-inflammatory properties. Immunosuppressive agents are generally used in transplants, in the treatment of autoimmune and immunomediated diseases, in addition to other inflammatory conditions (Wiseman, 2016; Sobotková and Bartůňková, 2019). These studies as a whole highlight the potential of mycophenolic acid as a therapeutic agent.

5 CONCLUSION

Filamentous fungi are a large and promising reservoir of bioactive compounds due to various biological activities such as strong inhibition of phosphodiesterase 4B, cytotoxicity against cancer cells, and antimicrobial, immunosuppressive, antibacterial, antifungal, antiviral and anti-inflammatory activities.

In view of the results, further efforts are hoped to discover new drugs from filamentous fungi.

Currently, several studies are being developed with different strains of filamentous fungi collected in different environments, such as forests, sea, icy regions and soil. *Aspergillus* and *Penicillium* are among the most studied genera. These fungi produce several bioactive compounds, some already reported and others recently discovered. *In vitro* and *in silico* studies are being used to test the different biological activities provided by bioactive compounds; therefore, the results of these researches are very promising for the discovery of new drugs. Additionally, further studies are needed to test these activities in *in vivo* models.

The results obtained are of great relevance for medicine and the pharmaceutical industry, as they bring an update of the main bioactive compounds and their biological activities from biodiversity, which can be used in the development of new drugs capable of fighting diseases. Still, they can help the academic and scientific community about what has been studied and what remains to be researched.

In the future, other species and strains of fungi can be studied, aiming to discover new bioactive compounds with biological activity; for this, fungi can be collected from different environments, such as forests, sea and soil microbiota, or isolated from plants, extreme and remote environments. In this way, it would be possible to make better use of the world's biodiversity, use molecular-based approaches and tools and produce resources capable of improving the quality of human life.

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