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Fungi and their medicinal properties: a scientometric study

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ABSTRACT. Fungi are eukaryotic, heterotrophic, unicellular or multicellular organisms that feed by absorption. Some of their attributes stand out in the medicinal and pharmaceutical sector since several genera of fungi have metabolic properties and compounds related to the manufacture of numerous medicines. In this context, the objective of this study was to carry out a scientometric analysis to verify the application and properties of medicinal fungi as well as their contributions to the knowledge of medicinal fungi. A survey of applied literature, which included the word "Medicinal fungi", was carried out based on the articles indexed in the Thomson Reuters base (www.isiwebofknowledge.com), considering the period from 2003 to 2021. One hundred and thirty-nine scientific articles were used for the scientometric analysis, and these were divided into six time intervals (2003-2006, 2007-2009, 2010-2012, 2013-2015, 2016-2018, 2019-2021). An increase was noted in the scientific production on medicinal fungi from 2007 onwards, mostly presenting publications with an experimental approach. The phylum Basidiomycota, followed by Ascomycota, presented the highest number of records in the study, mainly with applications aimed at antitumor and antibacterial activity. Therefore, the importance of studies that aim to expand the knowledge of the properties of medicinal fungi is highlighted, providing effective results for various diseases, since their cultivation and development can positively generate equitable economic growth, with regional and national impacts.

Keywords: medicinal fungi; antitumor; antioxidants; natural treatments; illnesses.

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Introduction

Natural products have been used by human beings since their beginnings for various purposes, such as seasonings in food preparation, religious rituals, drinks, household cleaning and as an alternative way of treating diseases, so they are considered therapeutic elements. Due to their low side effects and efficiency, one of the most used forms of natural products is related to the production of drugs as the main therapeutic resource in the prevention, treatment and cure of disorders, dysfunctions or diseases in humans and animals (Toledo, Hirata, Buffon, Miguel, & Miguel, 2003; Turolla & Nascimento, 2006; Fortes & Novaes, 2010).

The discovery of the medicinal properties of plants occurred spontaneously, through the observation of animals, which sought the cure for their diseases among herbs. When they suffered from poor digestion, for example, they looked for resources within their natural habitat, ingesting them to reverse the situation, a very common method used by cats (Argenta, Argenta, Giacomelli, & Cezarotto, 2011). From these observations, human beings began to perceive the effectiveness of natural products and their consequent return (Ferreira, 2013). Since then, studies aimed at understanding the mechanisms of action and active principles of natural elements from plants have aroused wide interest from researchers for numerous taxonomic groups, such as fungi, organisms that are extremely important for the environment and society (Kruppa & Russomanno, 2008).

Fungi are eukaryotic, heterotrophic, unicellular or multicellular beings that feed by absorption (Evert & Eichhorn, 2014). It is estimated that there are between 2.2 and 3.8 million species of fungi in nature (Hawksworth & Lücking, 2017). However, other works point out that there are about 8.25 million estimated fungal species (Arnold, Maynard, Gilbert, Coley, & Kursar, 2000). Fortes and Novaes (2010) state that only 100,000 fungal species are described and identified in scientific studies, which may represent less than 8% of their estimated diversity.

Since the beginning of human civilization, fungi have had a wide applicability, such as in religious rituals and in the production of alcoholic beverages and drugs (Fortes & Novaes, 2010; Mussi-Dias, Araújo, Silveira, Rocabado, & Araújo, 2012). In recent years, fungi considered as medicinal have been intensively investigated by the scientific community due to their in vitro and in vivo effects, and many new substances, resulting from their secondary metabolism, are being identified and put to use (Shao et al., 2019; Wang et al., 2022). Such substances are used as antibiotics (Sangdee, Buranrat, Jaihan, Thongchai, & Sangdee, 2018), antioxidants (Lee et al., 2010), and anti-inflammatories (Puthusseri, Smina, Janardhanan, & Manimohan, 2010), among others.

Numerous genera or even species of fungi can be used in the production of drugs (Puthsseri et al., 2010; Kuo, Huang, & Chen, 2015). Among these, *Tolypocladium niveum* (O. Rostr.) Bissett stands out, which is a species used to mitigate the rejection of transplanted organs by the immune system, through the substance cyclosporine, and also in cancer cells, since its metabolites act to inhibit the growth of these cells after specific treatments (Hayakawa et al., 2008). Fungi of the *Penicillium* link genus have been used since the 1920s, and were responsible for the accidental discovery of penicillin by Alexander Fleming (Mussi-Dias et al., 2012). Penicillin has been classified as one of the main and most relevant classes of antibiotics since its discovery, and several bacterial diseases, which used to be inevitably fatal, can currently be treated with it (Mussi-Dias et al., 2012).

Cephalosporin, another substance extracted from fungi, has a bactericidal action developed by *Cephalosporium acremonium* Corda, similar to penicillin due to the inhibition of the growth of gram-positive bacteria; Griseofulvin has antifungal action, and is produced by *Penicillium griseofulvum* Dierckx in the fight against superficial mycoses and onychomycoses, which affect nails (Kruppa & Russomanno, 2008). The fungus *Cordyceps sinensis* (Berk.) Sac. has bioactive components such as cordycepin, cordyceptic acid and ergosterol (Kuo et al., 2015), which stimulate the immune system and provide physical resistance for the body. It is mainly used among athletes, as it acts on fatigue and respiratory problems.

Psilocybe cubensis (Earle) Cantora is a species of mushroom that can act gradually in people suffering from depression. When ingested in natura, these fungi demonstrated positive effects in relation to mood and behavior, acting directly on serotonin (Faria, Monteiro, Auer, & Ângelo, 2017). The species *Ganoderma lucidum* (Curtis) P. Karst. improves the immune system and acts in the treatment of liver diseases; some studies have shown the anticancer action of its bioactive compounds (Taofiq et al., 2017). *Agaricus blazei* Murrill, popularly known as sun mushroom, has bioactive properties in the compound of immune-stimulating drugs, cholesterol control and treatment of type C hepatitis (Melo, Teles, & Júnior, 2020).

Understanding and listing the substances with medicinal properties that can be extracted from fungi is of paramount importance for scientific and technological advancement in the pharmacological and medical field. In this context, the present study aimed to analyze the work carried out regarding the medicinal applications of fungi, based on scientometric analysis, in order to summarize the knowledge in this area, evaluating trends, gaps and contributions on the subject.

Material and methods

A scientometric analysis was performed based on research articles indexed in the Thomson Reuters database (www.isiwebofknowledge.com) in January 2022, aiming to gather articles that had the keywords 'Medicinal fungi', published until December 31, 2021. For this, cataloged scientific productions were used as an indicator of results.

The selected articles were categorized according to i) temporal trend of publication; ii) design used in the studies: descriptive (comparative studies), predictive (ecological predictive models), experimental (studies carried out in the field or laboratory with controlled conditions), and review (literary reviews); iii) Phylum; iv) gender and v) medicinal application.

A total of 1,003 articles were found in the Thompson Reuters database; however, of these, only 139 articles were included for the scientometric analysis, as the others did not fall within the scope of the study (supplementary material 01). Years of publications were grouped into three-year intervals starting in 2003 (first publication included in the analysis) and ending in December 2021, with the exception of the first interval, which lasted four years. In this way, the results were categorized into six time intervals, which were 2003-2006, 2007-2009, 2010-2012, 2013-2015, 2016-2018, 2019-2021.

Finally, a Regression Tree (MRT) (De'Ath & Fabricius, 2002) was carried out with the help of R software (R Development Core Team, 2018) in order to verify in which year the effective change in the situation of publications on medicinal fungi was observed.

Regarding scientific nomenclature, all scientific names were reviewed in the Mycobank database (Robert et al., 2013).

Results

The results showed an increase in scientific production on medicinal fungi in 2006, as suggested by MRT. The threshold was observed in 2007 and, from that year onwards, there was an increase in the number of publications over time, with a peak in the 2016-2018 interval (n=43) (Figure 1).

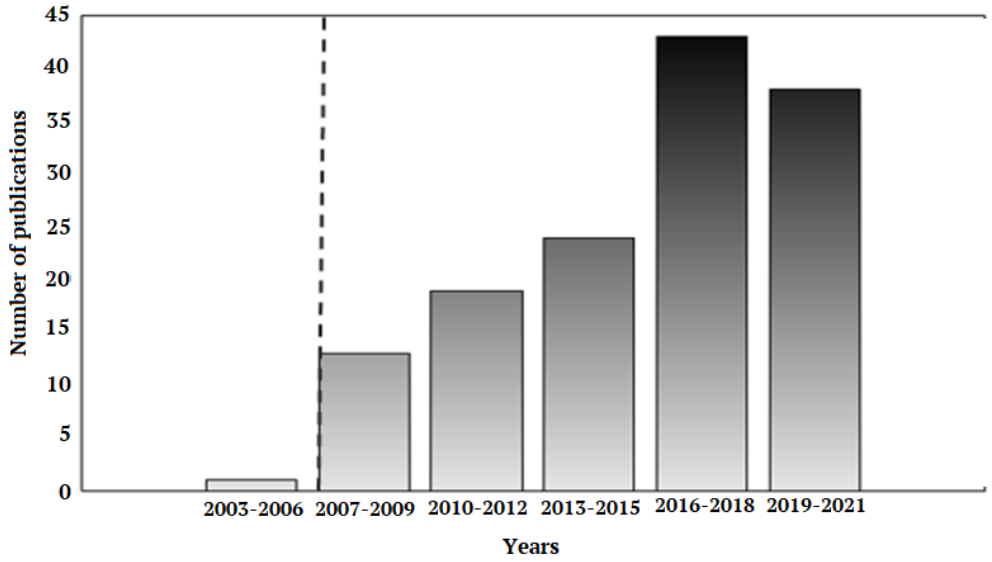

Figure 1. Time trend in the number of publications on medicinal fungi indexed in the Thomson Reuters database.

As for the design used in the studies retained for scientometric analyses, the experimental ones represented the majority of publications (n=115) and were present at all time intervals, with the highest number recorded in 2016-2018. The other articles with review design (n=19), predictive (n=15) and descriptive (n=12) presented low representation in terms of the number of publications over time intervals (Figure 2).

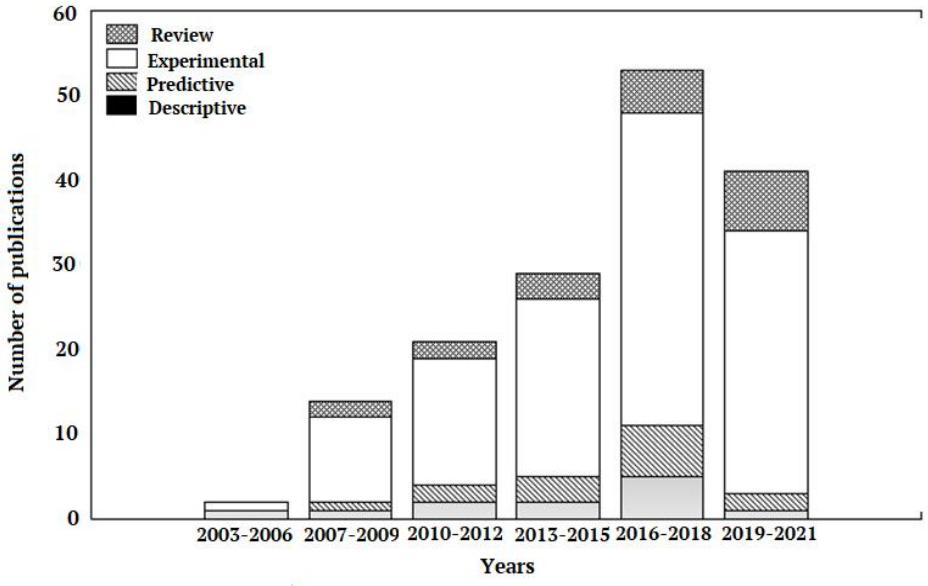

Figure 2. Number of publications classified according to the design in the scientometric survey.

From the selected articles, the phylum Basidiomycota had the highest number of records (n=53), followed by Ascomycota (n=51), both found in all time intervals, with their peak in 2016-2018. The phyla Glomeromycota and Chytridiomycota did not present records in any of the time intervals. The 2003-2006 interval registered the lowest number of publications. In sequence, all time intervals presented articles that did not specify the groups studied (Figure 3).

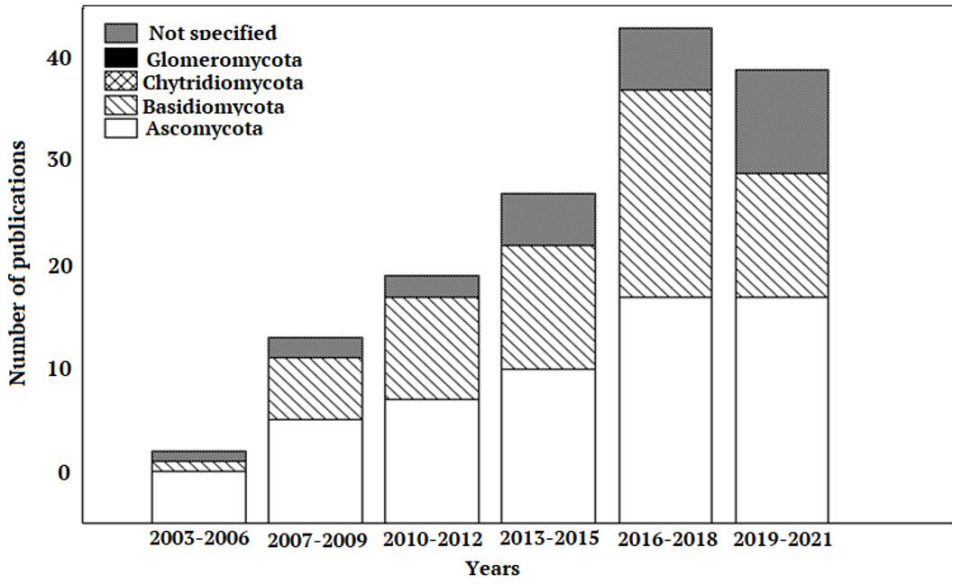

Figure 3. Number of publications classified according to Phylum.

Regarding the genus, it was possible to verify that *Cordyceps* Pe. presented the highest number of publications (n=23), present in all intervals, especially in 2013-2015. *Ganoderma* P. Karst. also presented a large number of publications (n=20) in all intervals, with its peak in 2010-2012. The other genera found showed a low level of records over the time intervals. On the other hand, all intervals presented articles that did not specify the genus of the study in question (Figure 4).

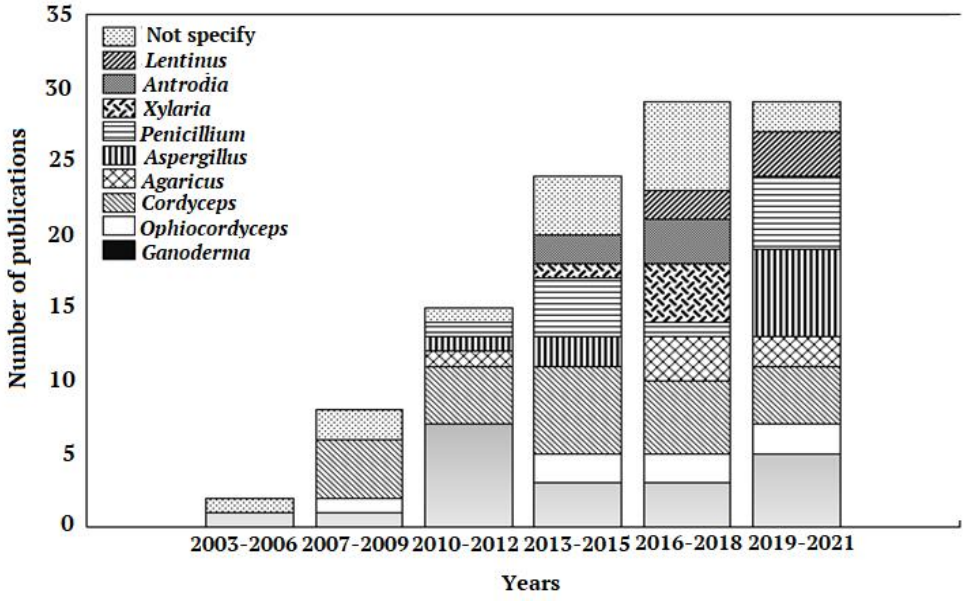

Figure 4. Number of publications selected from the grouping of genera.

As for medicinal application, the application of these organisms in relation to antitumor activity showed the highest record in the literature (n=39), especially in the 2016-2018 interval. Next came antibacterial activity (n=39), with emphasis on the 2019-2021 range. The other medicinal applications showed relatively increasing rates from the 2010-2012 interval. In all periods, the category 'other applications' (n=19) was present, except in 2003-2006 (Figure 5).

Discussion

It is widely reported in the literature that fungi are organisms that have important medicinal properties (Zhou et al., 2016; Agrawal, Adholeya, Barrow, & Deshmukh, 2018; Kupcova et al., 2018). The study showed

that numerous compounds can be extracted from these organisms and used as raw material for the production of drugs, as they have antioxidant properties, stimulate the immune system, fight cancer cells, and help in the treatment of hepatitis C, among others. It can also be observed that their use has been expanding and becoming well known in the pharmaceutical sector.

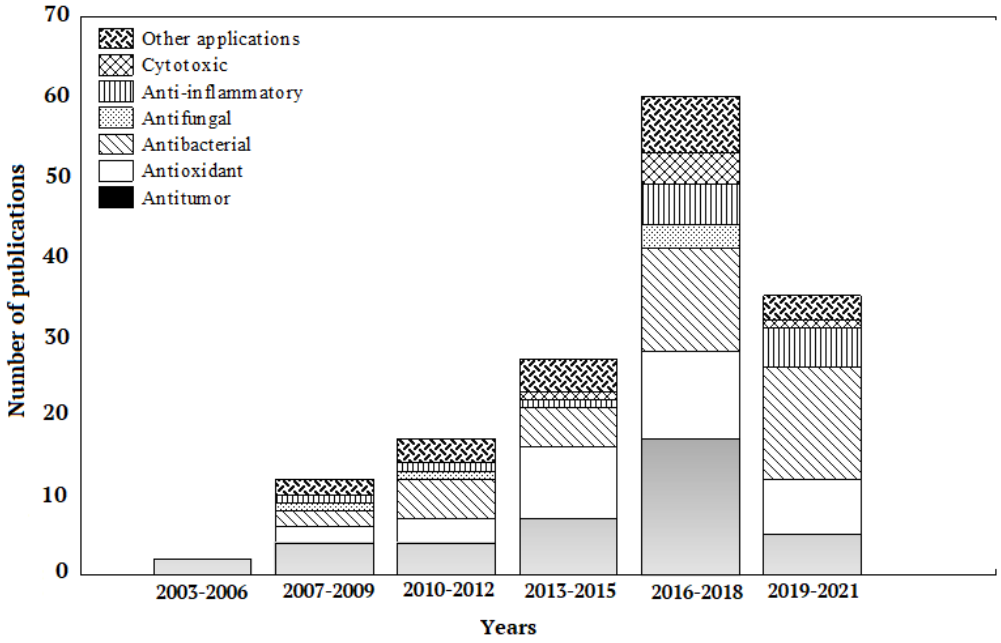

Figure 5. Selected publications regarding medicinal application.

The growing number of publications related to the medicinal properties of fungi over the years may be an indication of the advancement of science and the growing interest in alternatives in the treatment of various diseases. Additionally, the greater interest in substances extracted from nature and their benefits for humans is due to the search for a healthier lifestyle, which may also indicate this increase.

The first interval of studies showed that, initially, the research presented a descriptive and experimental design. Descriptive studies are closely related to the search for basic knowledge, that is, knowledge that allows the researcher to make observations and, consequently, make inferences that may indicate probable casual routes for later experiments to be carried out or for review studies (Bomfim et al., 2016; Mantovano et al., 2018). Experimental studies have possibly presented the greatest record over the years, due to the growing interest in the medicinal properties of these organisms (such as antitumor, antibacterial and antioxidants). This design is performed to verify that a new drug, procedure, or treatment is safe and effective. Initially, tests are carried out on animals so that, later, a substance can be tested on humans.

The phylum Basidiomycota had the highest number of records, followed by Ascomycota, probably because it is the best known and most studied (in taxonomic, physiological, genetic, molecular research, etc.), including popularly known representatives such as mushrooms (Lee et al., 2010). Currently, more than 376 genera of Basidiomycota are registered in Brazil, many of which are widely known in other countries for their medicinal application as antitumor, cytotoxic, antibacterial and anticoagulant therapies (Cavalcanti, Barros, Lopes, & Sousa, 2021). The phylum Ascomycota is the most numerous group among fungi (Evert & Eichhorn, 2014), so it is also very present in research (as is the case of the well-known Cordyceps, a medicinal fungus widely used in many Asian countries) (Wu, Chen, & Siu, 2014; Chen, Agrawal, Wang, Chen, & Tsay, 2014). The medicinal properties that range across this phylum include antitumor, anti-inflammatory and antioxidant action (Kuo et al., 2015).

The high representation of *Cordyceps* and *Ganoderma* genera in research may be related to the fact that both have been used for many years in traditional Chinese medicine (Cavalcanti et al., 2021). The accumulated knowledge of these genera may have facilitated the discovery of different properties and uses, as well as giving them enough popularity to generate interest in their substances (Cavalcanti et al., 2021). *Cordyceps* is a genus of fungi from which numerous substances have recently been isolated, such as glycopeptide (Cs-GP1) (Wu et al., 2014), exopolysaccharide (EPS) (Chen et al., 2014), and poly-N- acetylhexosamine (Chen et al., 2014),

intended for the production of antioxidants. Additionally, Cordyceps is used in the compounds of the most common medicines consumed by the Chinese, and its medicinal applications extend from the treatment of kidney to lung diseases (Dong, Guo, Wang, & Liu, 2015). Due to its high applicability, the exploitation of Cordyceps is increasing significantly, which has aroused concern among researchers, since this genus is endemic to the Chinese region and its cultivation, both on small and large scales, is difficult to control and replicate (Shao et al., 2019). As a result, the price of these drugs is increasing gradually. On the other hand, this whole process has benefited the region's farmers and herders, providing investment in these regions (Dong et al., 2015).

Ganoderma is a large and complex genus of wood ear fungi, characterized by the presence of pores under the caps (or 'hats', as they are popularly known). *Ganoderma* species are one of the most used fungal elements in the medical field. Additionally, they are also referred to as a health tonic as they are known to cure a wide range of ailments (Ekandjo & Chimwamurombe, 2012). Among the species of this genus, the popular 'Reishi' stand out, fungi that grow on trees, and which are identified as *Ganoderma lucidum* or *Ganoderma sinense*. This genus has long been used in medicine in East Asia for the purpose of increasing longevity, preventing cellular aging and increasing energy (Wang, Cao, Zhao, & Feng, 2017). It is currently used to stimulate the immune system of cancer patients receiving chemotherapy or radiotherapy (Souza, Pfenning, Moura, Salgado, & Takahashi, 2013). Among the best known examples, there are *G. lucidum*, with its antioxidant properties and allies of the immune system; *Cordyceps sinensis*, which acts mainly in the immune system and in some cases, in the treatment of hepatitis C, among others (Liu & Shen, 2003).

The antitumor and antibacterial medicinal properties were the ones with the highest number of records in scientometrics. Some species of fungi are known to affect the immune system and help stop or slow the growth of tumors, or even fight tumor cells (Shiao, 2013). Chemical compounds such as polysaccharides (beta-glucans) extracted from the fungus *Trametes versicolor* (turkey tail) are examples of such substances, as they strengthen the immune system and consequently help fight cancer. Another component extracted from fungi that have similar effects is polysaccharide-K (PSK). PSK acts on the immune system, including immune cells called natural killer cells, and is widely used to treat patients with stomach cancer, breast cancer, colorectal cancer and lung cancer. PSK has been used as an adjuvant cancer therapy in patients lately. In Japan, it has been used safely for a long time, with few reported side effects (Tripathi & Monica, 2010).

It is clear that the search for new antimicrobial potential is increasing, since organisms that produce substances with such properties have selective toxicity, that is, they are toxic to bacteria, but not to the host cell, from their secondary metabolites extracted from fungi. The methanolic and chloroform extracts extracted, respectively, from *Ganoderma applanatum* and *G. lucidum*, have potential antibacterial agents, preventing the proliferation of bacteria, and they are the most used and known in this field (Karaman, Jovin, Malbaša, Matavuly, & Popović, 2010).

Traditional Chinese medicine has already described cures for infections using plants with properties similar to antibiotics, but it was only after the discovery of penicillin by Alexander Fleming that antibiotics began to be widely used, having a great impact on the practice of medicine and the cure of infectious diseases around the world. According to Mamede et al. (2012) antimicrobial properties result in several mechanisms of action of antibiotics, of which the main ones are the inhibition of bacterial chromosome duplication, as well as enzymatic inhibition through the imitation of bacterial metabolites, the modification of the permeability of the plasma membrane bacteria and inhibition of bacterial protein synthesis. Antibiotics are most used in the treatment of bacterial diseases.

Conclusion

The predominance of studies with fungi was noted, especially those referring to the phyla Ascomycota and Basidiomycota, since they have numerous antibacterial and antitumor medicinal applications. The high number of studies that emphasize the application of secondary compounds of fungi as antibacterials showed greater evidence, since super-resistant bacteria are being selected, and with that, studies related to the production of these drugs are necessary. Additionally, fungi with antitumor properties are notable, since many people still die of cancer, because there are no medicines that guarantee a cure. In this context, it is of the utmost importance that research continues to discover effective results in both subjects.

Literature reviews help to understand the "state of the art" of research and its development over the years. This understanding, in turn, serves as a guideline for planning and conducting further research. This work

helped to profile the latest research on medicinal fungi carried out in the world, and thus serves as a basis for new ones to come. With regard to medicinal fungi, little is known about the subject in Brazil. It is therefore essential that there are incentives, funding, structure and human resources to carry out research with these organisms, given their already proven importance not only in the environment, but also in human health.

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