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Article

Endophytic Fungi: A Natural Source of Bioactive Compounds and Biotechnological Applications

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ABSTRACT

Endophytic fungi are microorganisms that live inside plants and are a promising source of bioactive molecules. These fungi have aroused a growing interest in research due to their ability to produce a variety of substances. Thus, this study aims to emphasize the relevance of endophytic fungi present in plants as a source of bioactive compounds, which have several applications in biotechnology. For this, scientometrics was used as a methodology, based on a search in the ScienceDirect database using the terms "endophytic fungi", "plants", "metabolites" and "biotechnological application" in a time frame between 2015 and 2022. These fungi have aroused a growing interest in research due to their ability to produce a variety of bioactive compounds. The interaction between endophytic fungi and plants is crucial for plant survival, and many of the compounds produced by fungi have biotechnological potential. Scientometrics revealed an increase in the number of publications on the subject, with emphasis on research studies and reviews. The prospection of endophytic fungi has focused on families of plants with medicinal attributes. These complex interactions between fungi and plants play an important role in plant health and development. Research in this area continues to grow, with many compounds identified as potential bioactive products in diverse biotechnological applications.
Keywords: natural compounds; scientometrics; metabolites**.**

RESUMO

Fungos endofíticos são microrganismos que vivem dentro das plantas e são uma fonte promissora de moléculas bioativas. Esses fungos têm despertado um crescente interesse na pesquisa, devido à sua capacidade de produzir uma variedade de substâncias. Deste modo, este estudo tem como objetivo enfatizar a relevância dos fungos endofíticos presentes nas plantas como fonte de compostos bioativos, os quais têm diversas aplicações na biotecnologia. Para isso, utilizou-se a cienciometria como metodologia, a partir de uma busca na base de dados *ScienceDirect* utilizando os termos "*endophytic fungi*", "*plants*", "*metabolites*" e "*biotechnological application*" em um recorte temporal entre 2015 a 2022. Esses fungos têm despertado um crescente interesse na pesquisa, devido à sua capacidade de produzir uma variedade de compostos bioativos. A interação entre fungos endofíticos e plantas é crucial para a sobrevivência das plantas, e muitos dos compostos produzidos pelos fungos têm potencial biotecnológico. A cienciometria revelou um aumento no número de publicações sobre o tema, com destaque para estudos de pesquisa e revisões. A prospecção de fungos endofíticos tem se concentrado em famílias de plantas com atributos medicinais. Essas interações complexas entre fungos e plantas desempenham um papel importante na saúde e desenvolvimento das plantas. A pesquisa nessa área continua a crescer, com muitos compostos identificados como potenciais produtos bioativos em diversas aplicações biotecnológicas.
Palavras-chave: compostos naturais; cienciometria; metabólitos.

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1. Introduction

Natural products extracted from plants and microorganisms are rich in bioactive compounds that exhibit a wide variety of biological and pharmacological activities. The great diversity of bioactive compounds present in these products offers a wide range of possibilities for the research and development of different products that have a high potential for biotechnological applicability, such as new drugs. This high potential becomes more evident when the natural environmental conditions and their peculiar characteristics are considered (Costa-Coutinho et al. 2019). Such biodiversity of natural products has guided relevant research in the area of natural metabolites originating from plants or microorganisms, such as endophytic fungi (Antunes et al. 2021), which are microorganisms that inhabit the interior of plants without causing disease and are a promising source of bioactive compounds (Gupta et al. 2020).

The colonization of plants by endophytes can occur through natural openings, such as stomata and hydathodes, which are pores found on the edges and tips of leaves, through wounds caused by insects or phytopathogenic fungi, or even through seeds (Papik et al. 2020). The association between fungal endophytes and their host plant is mutualistic, as they help each other in several ways (Malicka et al. 2022). In addition, endophytic fungi are capable of producing relevant molecules that help their host to resist biotic (damage caused by pathogens) and abiotic (such as high salinity, temperature and drought) stresses through the production of bioactive metabolites (Harman et al. 2021; Lee et al. 2021). Although little explored, these fungi are capable of producing molecules with activities relevant to humanity.

The relationship between endophytic fungi and plants is quite complex and may vary according to the host. Several species of endophytic fungi can inhabit the same plant, but it is known that this relationship is mutualistic, that is, both benefit (Yan et al. 2019; Mattoo & Nonzom 2021). Endophytic fungi co-evolved with their host plants, while providing nutrients and protection for the plant, in return, the plant receives useful chemical compounds such as enzymes, alkaloids and antibiotics (Lu et al. 2021; Baron & Rigobelo 2022; Wen et al. 2022).

Recently, the definition of endophytic microorganisms was expanded, dividing them into two types: Type I and Type II. Type I refers to microorganisms that colonize the interior of plants without causing any apparent change in their morphology or physiology. Type II refers to microorganisms that promote changes in plant growth and development through the production of hormones, enzymes and other compounds that stimulate root growth and increase resistance to biotic and abiotic stresses (Hagh-Doust et al. 2022). This new classification expands the possibilities of interaction between endophytes and plants, allowing a better understanding of the mechanisms involved in this relationship.

Understanding these interactions is crucial for the development of new natural products, since endophytic fungi are an important source of active biomolecules with a unique structure. The search for bioactive molecules derived from endophytic fungi can lead to the development of new products that contribute to improving the quality of life of the population, collaborating with economic development and promoting the circular economy (Plakantonaki et al. 2023). Because of the ability of these microorganisms to produce chemical substances with therapeutic and pharmacological properties, they have aroused great interest in the pharmaceutical industry, agriculture and biotechnology (Rana et al. 2019).

An example of a secondary metabolite generated by an endophytic fungus is podophyllotoxin, a molecule with natural anticancer properties, widely used in the pharmaceutical industry. This substance is identified in several species of endophytic fungi, as well as in their host plants (Biswas et al. 2020). Additionally, there are studies that show the synthesis of substantial amounts of phenolic compounds and flavonoids in fungal extracts. Such compounds have a remarkable value in industrial applications, especially in pharmaceuticals (Hassane et

al. 2022). Furthermore, to their beneficial applications, the phytopathogenic potencial of these fungi is also observed. In a study mentioned by Abdel-Motaal et al. 2022, the production of volatile and non-volatile compounds was investigated as a means of controlling okra rot. This approach stands out not only for lower cost but also for lower environmental impact.

Endophytic fungi can be used as tools in the biological control of insect pests in agriculture, as highlighted by Saad et al. (2019). Because they occupy the same niche as phytopathogens, these fungi are capable of producing chemical compounds such as alkaloids and enzymes that have action against herbivores, plant parasitic nematodes and phytopathogenic microorganisms, considering that gene transposition between plants and fungi may occur endophytes, it being possible that the fungus produces the same chemical substances as the plant that hosts it, opening new perspectives for the bioprospecting of biologically active molecules and with promising possibilities of application (Fontana et al. 2021; Caruso et al. 2022).

Thus, the mechanism of action of endophytic fungi in biological control can be associated with the production of metabolites or toxins. In addition, endophytic fungi are also responsible for the production of enzymes of industrial interest, such as cellulases, xylanases, pectinases and amylases (Hawar, 2022), which are important for the growth and maintenance of the organism, as well as for the degradation of cell walls and obtaining nutrients (Gow & Lenardon 2023). Research in this area has grown in recent decades, due to the need to find more sustainable and efficient alternatives for the production of food and medicine. Endophytic microorganisms represent an important source of bioactive compounds, which can be used to control pests and diseases, promote plant growth and treat various diseases. Thus, this study aims to highlight the importance of endophytic fungi as a source of bioactive compounds and their biotechnological applications.

2.Material and Methods

2.1 The nature of the research

The research was carried out along the lines of scientometrics, which consists of a research model used in bibliometrics and is based on the qualitative and quantitative assessment of scientific production within a given area of study (Wang & Schneider 2020). This methodology makes use of technology, mainly related to information and analyzes them through mathematics and statistics (Mao et al. 2018). According to Ávila-Robinson & Sengoku (2017), this methodology allows mapping the scientific literature using metrics, visual analyzes and indicators that outline relevant patterns and trends, being able, through the construction of bibliographic data networks, to assess the impact and interdisciplinarity of a given object or phenomenon.

One of the main advantages of scientometric research is that it encourages critical reflection and new insights can be released, thereby identifying unexplored issues or gaps in the scientific literature, which can lead to new research and discoveries (Mao et al. 2018; Do Carmo et al. 2023). Another advantage of scientometric research is that it can be used to plan public policies in the area of science, technology and innovation. By identifying research areas with greater potential for impact and development, it is possible to direct resources to these areas, promoting the country's scientific and technological development (Jeong et al. 2021; Capari et al. 2022).

2.2 Search strategies and information sources

The search was conducted using the terms "endophytic fungi", “plants”, “metabolites” and “biotechnological application”, in the ScienceDirect database. According to Manes-Rossi et al. (2020), this method helps in the composition and development of knowledge, as it provides critical reflection and new insights into the research object or phenomenon.

2.3 Inclusion criteria and selection of studies

The initial search returned a significant number of articles. In this sense, some criteria were adopted to delimit the articles providing the research, initially a search for scientific articles was carried out to compose the review database, and some criteria were promptly determined, in order to guarantee that the articles met the research objectives (Bisogno et al. 2018). A screening was performed on the articles, adopting the inclusion and exclusion criteria (Table 1).

Table 1. Inclusion and exclusion criteria

Inclusion	Exclusion
Period from 2015 to 2022	PDF documents
Open access	Dissertations and theses
Reports the biotechnological application	
Relevance of the study	

Source: Prepared by the authors.

The inclusion and exclusion criteria are established based on the objectives of the review and must be clearly defined and documented to provide a study of relevance to the area of knowledge (Peters et al. 2020). They are also related to aspects relevant to the research, in a way the adoption of criteria allows for a more objective conduction of the research (Patino & Ferreira 2018).

2.4 Data collection and compilation process

Data were collected from selected articles and treated with Excel 2019 software.

3. Results and Discussion

Based on data analysis, it was found that the articles selected for evaluation published in the period from 2015 to 2022 were mostly focused on research studies, making up 75% of the articles published (Figure 1A). Regarding the review articles, it was found that there were variations in publications over time, but they still remained a relevant source of information in the area in question, especially in the years 2021 and 2022 (Figure 1B). A similar situation was observed for publications of research articles in the same period (Figure 1C). The results indicate a trend in the number of articles published over the evaluated period, showing that there was an increase in the total number of articles published, especially in the years 2020, 2021 and 2022 (Figure 1D). Showing a strong growth trend and interest in studies related to endophytic fungi present in plants.

This profile in publications may be related to new discoveries about natural products and metabolites produced by endophytic fungi. A good example is the production of taxol obtained from the fungus *Taxomyces andreanae*, which later led to research on the pharmacological potential of endophyte metabolites (Tiwari & Bae 2022).

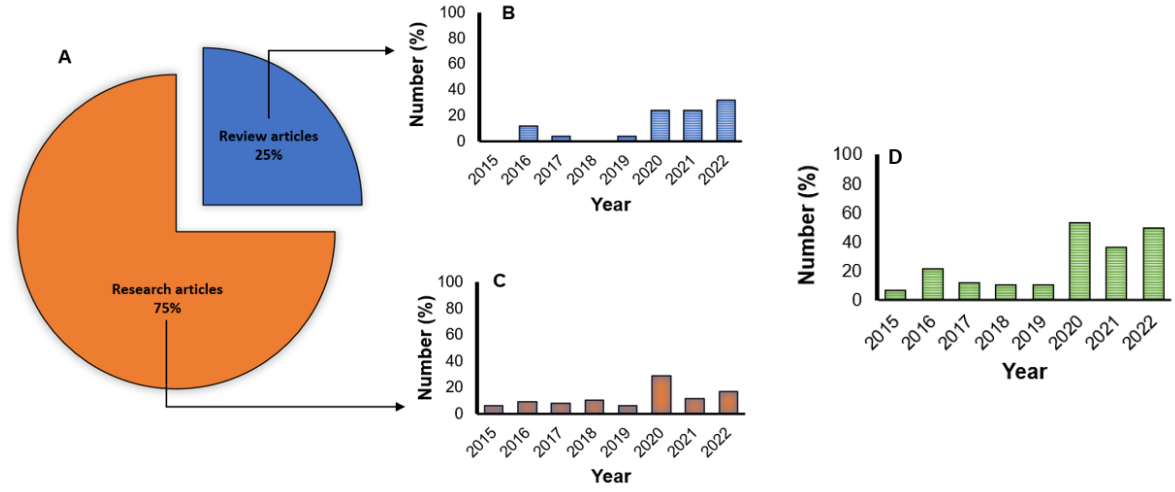

Figure 1. Analysis of review and research articles on endophytic fungi from plants from 2015 to 2022. Source: Elaborated by the authors with the research data, being the total number of articles in the period (A); review articles published from 2015 to 2022 (B); research articles published from 2015 to 2022 (C) and total articles published per year within the period (D).

With the increase of new studies on the discovery of natural products from biological species, endophytes are being increasingly explored as platforms for the production of bioactive metabolites with different chemical structures (Gupta et al. 2021). Furthermore, studies have established that endophytes mimic host metabolism and can produce, induce and modify chemical compounds and their concentrations within the host (Taghinasab & Jabaji 2020). Medicinal plants are a good example and may contain endophytes that can produce their active ingredients in greater quantities.

In developing countries, the use of medicinal plants as a source of medicine represents a viable and accessible alternative for the population, especially in regions where access to chemical medicines is limited. In addition, the use of medicinal plants can contribute to the preservation of biodiversity and to the appreciation of traditional knowledge related to the use of plants for medicinal purposes. Some countries stand out as pioneers in the development of studies with plants and for the use of their phytochemicals in biotechnological applications. In this sense, countries which carry out research with endophytic microorganisms can express the production of these phytochemicals, the main countries that carry out these studies are China for presenting a vast technological field and Brazil, for being a country that has an enormous biological biodiversity still little explored, with great potential for the investigation of endophytes of native plants (Figure 2). The search for new bioactive molecules takes place all over the world, aiming to contribute to the expansion of therapeutic options and employability in various segments of society.

There are approximately 300,000 species of plants on the planet, and only about a sixth of them have compounds with therapeutic potential for the treatment of diseases. These plants have the ability to synthesize several bioactive compounds in special indoor environments, different from the common environment, such as the soil, thus providing exclusive niches for microorganisms, as mentioned by Nisa et al. (2015). Among these microorganisms, endophytic fungi are especially numerous, reaching up to 1 million different species, most of which have not yet been described. These endophytic fungi represent a highly promising source for the discovery of new natural substances and according to Caruso et al. (2020), these microorganisms need to receive more attention in scientific research, as they offer a vast potential for the discovery of promising natural products.

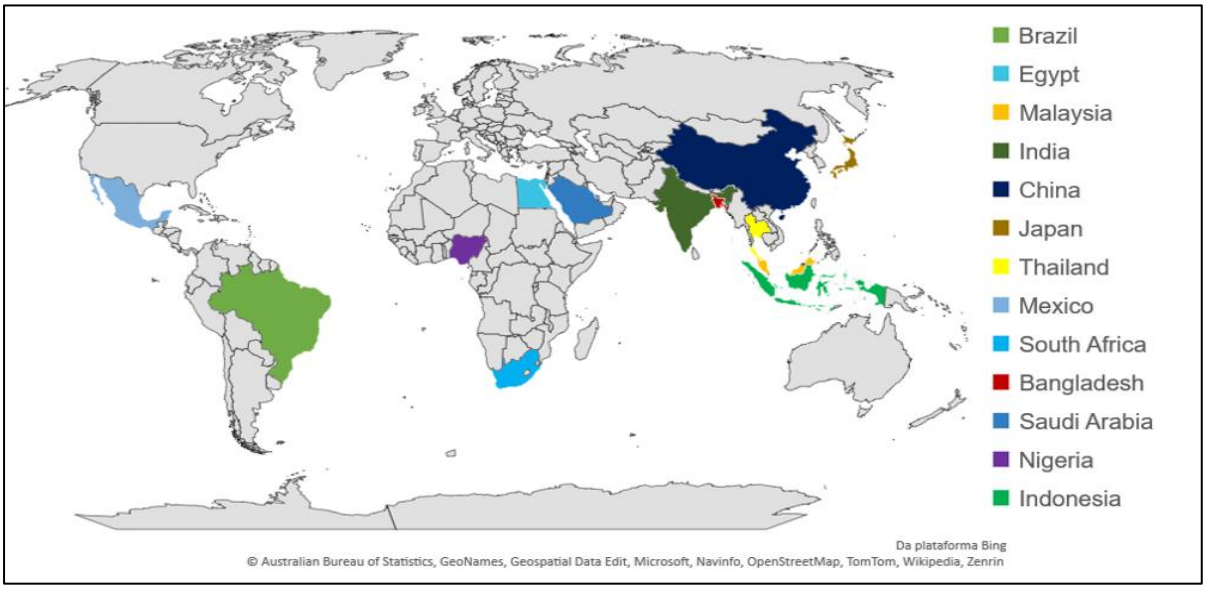

Figure 2. Countries that carry out studies aimed at the production of metabolites by endophytic fungi of plants in the period from 2015 to 2022.Source: Prepared by the authors based on research data.

Endophytic fungi have a long association with plants, dating back more than 400 million years, and have been extensively studied in diverse geographic and climatic zones (Yadav et al. 2022). Studies conducted by Schön et al. (2018) demonstrate that altitude and plant age have a major impact on fungal diversity and composition.

Due to population growth and the need for new bioactive molecules from natural sources, which can be applied in areas such as industry, pharmacology and food, compounds produced by endophytic fungi are in evidence as an alternative for biotechnological exploration (Yan et al. 2018). These endophytic fungi represent a valuable source of new products with significant potential for agriculture, industry and medicine. The search for bioactive molecules through the bioprospecting of these microorganisms is an excellent strategy for the discovery of new pharmaceutical products with potent properties, such as anticancer, antifungal, antimicrobial and antioxidant activity (Rana et al.2019).

Plants are an integral part of the ecosystem, which interact with various groups maintaining biodiversity and ecosystem stability. The interaction between plants and endophytic microorganisms can be seen as a network of complex relationships, where different species of microorganisms' act on different parts of the plant, such as fungi that can be found from the roots to the leaves and fruits (Figure 3).

Plants have a great diversity of microorganisms in different parts of the plant, cohabiting in beneficial symbiosis that can improve survival, biodiversity and ecosystem function (Sasse et al. 2017). Endophytic interactions are important for plant fitness, since microorganisms can produce bioactive compounds that protect the plant against pathogens and pests, in addition to improving nutrient absorption. Studies have shown that endophytic microorganisms can enhance plant growth, improve resistance to stress such as drought, and even increase the production of bioactive compounds in plants (Singh & Dubey 2018). Some compounds produced by these microorganisms are reported in the literature and identified as secondary metabolites belonging to different structural groups such as alkaloids, terpenoids, flavonoids, phenolics, coumarins, glycosides, among others (Harshitha et al. 2023).

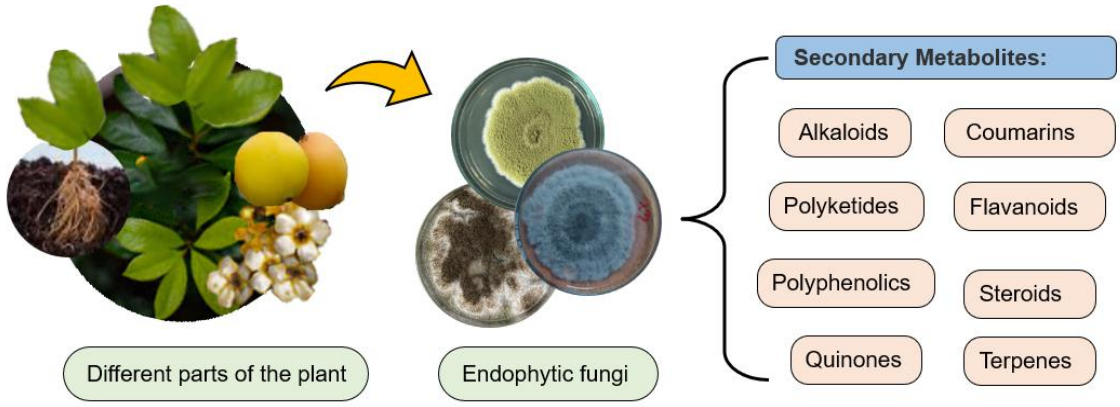

Figure 3. Plant parts and the diversity of endophyte fungi associated with the production of secondary bioactive compounds. Source: Elaborated by the authors

The variety of bioactive compounds produced by endophytes is largely influenced by the metabolic profile of the host plant. Plant-produced volatiles, transported underground, exert a strong influence on the composition of the microbial community in the rhizosphere, thus affecting soil microstructure and edaphic factors (Gouda et al. 2016). Some characteristics make these microorganisms promising sources for metabolites. According to Singh and Dubey (2018), the main characteristics of endophytic fungi are: excellent producers of new metabolites; high capacity to produce the same metabolites produced by the host plant; potential for biosynthesis of the same secondary metabolite by endophytes of different genera. Biotechnology with the use of genomics, metabolism and proteomics promote high yields of compounds, ensuring the maintenance of new bioactive molecules, from renewable sources such as endophytic fungi (Constantin et al. 2022; Shakour & Farag 2022).

Some fungal endophytes are able to colonize a wide range of plant species, while others are more specific and only occur within a restricted number of plants. In addition, specificity may also be present in relation to the portion of the plant that is colonized (Grabka et al. 2022), it can be inferred that there is a complex symbiotic relationship between biotic and abiotic factors, the plant and the microbial communities, and the variation of one or more of these factors can significantly influence the composition and functioning of the microbial communities associated with plants (Agler et al. 2016).

The host-endophyte relationship can be considered as a flexible and dynamic interaction, in which endophytes change their gene expression or produce different metabolites based on small changes in host plant growth and vice versa (Ek-Ramos et al. 2019). This association is maintained by a dynamic regulation that comprises the phenotype and metabolism of the host, fundamental for the survival of endophytic fungi and to provide benefits to plants (Vorholt et al. 2017). Endophytic fungi produce bioactive metabolites that can protect plants against pathogens and pests, in addition to providing better nutrient absorption (Qin et al. 2023). These benefits are possible thanks to dynamic regulation that allows fungi to survive without causing symptoms and provide advantages to plants.

The biological diversity of endophytic fungi represents a great potential for the production of biologically active compounds such as vitamins, polysaccharides, steroids and other compounds such as plant hormones (Alamgir & Alamgir 2018). These compounds are produced by different biosynthetic pathways and belong to different structural groups. Such compounds possess extremely high medicinal value being from natural sources and therefore are attracting great attention. This is due to the fact that endophytic fungi have the ability to produce compounds similar to the plants in which they are present.

However, environmental conditions, such as temperature, humidity and soil nutrition levels, were important factors in determining the types and amounts of secondary metabolites in host plants, which would indirectly affect the population structure of endophytic fungi (Jia et al. 2016). A good example is in tropical plants, which have little variation in secondary metabolites in their different parts, however, there is variation between different species that inhabit the same place (Sedio et al. 2017). Studies developed by Chowdhury et al. (2017), reported that the composition of the endophyte community differs between distinct geographic areas. These authors infer those environmental characteristics, such as different biomes, act as ecological filters that result in the selection of endophytes.

Some plants have a great diversity of endophytes, having great potential as a source of new endophytic microorganisms with high potential for the production of metabolites. Endophytic fungi can be found on plants such as trees, grasses, algae, and herbaceous plants and medicinal plants (Nisa et al. 2015). The data show that among plant families, the number of studies that used the Zingiberaceae and Orchidaceae it is superior to the studies using the other families for the prospection of endophytic fungi (Figure 4).

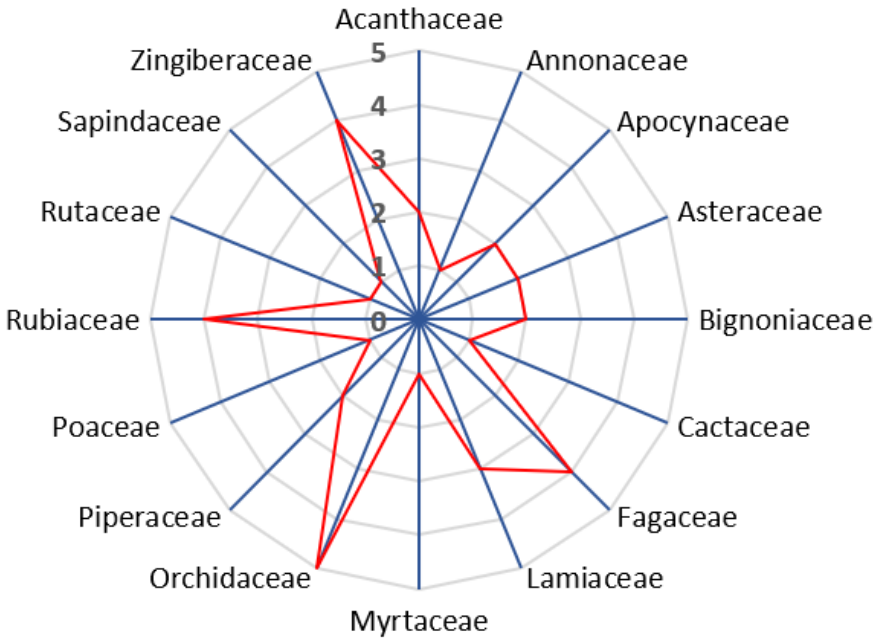

Figure 4. Plant families with potential for prospecting endophytic fungi. Source: Elaborated by the authors

The Zingiberaceae family is composed of approximately 52 genera distributed in several countries. This family includes aromatic herbs that have horizontal or tuberous creeping rhizomes, and many species have great economic importance as ornamental plants, spices or for use in folk medicine. In addition, the Zingiberaceae family is also home to vital groups of medicinal plants that contain high quality volatile essential oils and oleoresins for export (Chakrabartty & Rangan 2022). These authors describe that the endophytic fungi present in these plants are responsible for the production of secondary metabolites that have great potential for biotechnological use, mainly because such compounds have a series of properties beneficial to health, such as antimicrobial, antiarthritic, antioxidant, anticancer, anti -inflammatory and antidiabetic (Hartanto et al. 2019; Satheesan & Sabu, 2020). Zingiberaceae species have a high potential for the presence of endophytic microorganisms that can synthesize different metabolites with different bioactivities.

The other family Orchidaceae constitutes one of the largest and most important families of medicinal plants, it has more than 28,000 species identified in approximately 763 genera (Christenhusz & Byng 2016; Zhang et al. 2018). Due to the large number and variety of orchids, they have long been investigated for their biology and associations with various endophytic fungi. Recent studies have isolated endophytic fungi from two genera of Orchidaceae and observed that the endophytes have a symbiosis that enables better plant growth, increases resistance to disease-triggering pathogens, reduces the incidence of weeds and improves tolerance to biotic stresses and abiotic (Salazar et al. 2020; Wang et al. 2021).

In addition to these advantages, the endophytes of these plants produce vast secondary metabolites that can be used in various industrial processes (Mishra et al. 2021; Nawrot-Chorabik et al. 2022). Given their resistance to a wide range of pathogens, these metabolites produced by endophytes may have antimicrobial properties in addition to having other functionalities depending on the active phytochemicals biosynthesized by these microorganisms. Endophytic fungi have unique complex biosynthetic machinery capable of producing numerous bioactive compounds, and when well exploited they can become true biofactories for the production of new molecules, to be used in the most diverse areas of knowledge and optimizing green chemistry, as well as conserving the promising source of natural sources and ensuring environmental sustainability.

4. Final considerations

From data analysis, it is possible to see the growing interest in research on endophytic fungi present in plants, as a sustainable and efficient alternative for the production of bioactive compounds in different biotechnological applications. Both research and review articles have been relevant sources of information in this area, indicating an increase in the number of publications over the years. This highlights the continued importance of investments in research and development in this field, in order to explore the full potential of these microorganisms and their applications in production in different areas of knowledge.

Some countries stand out as pioneers in the development of studies with plants and for the use of their phytochemicals in biotechnological applications. Endophytic fungi can colonize many plant species and their respective parts, while others are more specific. What this niche has in common is that they are capable of synthesizing a huge number of bioactive molecules. Of the analyzed plant families, the most studied were Zingiberaceae and Orchidaceae in relation to the other families in the prospection of endophytic fungi, as they have medicinal attributes and have a wide geographic distribution and have important bioactive compounds in their composition.

In addition, endophytic interactions between plants and microorganisms have been shown to be complex and important for plant survival and fitness. Endophytic microorganisms have the potential to produce bioactive compounds that can protect the plant against pathogens and pests, improve nutrient uptake and even increase the production of bioactive compounds in plants. Research in this area has grown and many compounds produced by endophytic microorganisms have already been identified as secondary metabolites with potential use in various biotechnological applications.

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