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Fungal biocompounds as strategy to control infection associated with urinary catheter

Biocompostos fúngicos como estratégia de controle de infecção associada ao cateter urinário

Biocompuestos fúngicos como estratégia para el control de infecciones associadas a sonda urinaria

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Abstract
Catheter-associated urinary tract infections continue to be of concern, given the growth of epidemiological data, costs, bacterial resistance, and complications and morbidity. Bioprospection of plants as a strategy to control pathogenic microorganisms has gained space in the literature, due to the wide diversity existing in the Brazilian flora, which allows the exploration of endophytic fungi and various compounds, to be used in planktonic cells or to inhibit the formation of biofilms. This review aims to address the formation of biofilm in bladder catheters and perspectives with endophytic fungi, secondary metabolites and bioactive compounds against pathogenic microorganisms. The present data demonstrate a favorable use of endophytic fungi in the control of gram-positive and gram-negative microorganisms. The metabolites extracted from endophytic fungi with antibacterial action can be categorized especially among the class of phenolic compounds. In addition, they can be used to control the formation of biofilms in medical devices, such as indwelling bladder catheters, which are very susceptible to microbial colonization, being responsible for severe and persistent infections.
Keywords: Biofilms; Bioprospecting; Endophytes; Urinary tract infections; Anti-infective agents.

Resumo
As infecções do trato urinário associadas a cateteres continuam sendo motivo de preocupação, dado o crescimento de dados epidemiológicos, custos, resistência bacteriana, complicações e morbidade. A bioprospecção de plantas como estratégia de controle de microrganismos patogênicos tem ganhado espaço na literatura, devido à grande diversidade existente na flora brasileira, que permite a exploração de fungos endofíticos e diversos compostos, para serem utilizados em células planctônicas ou para inibir a formação de biofilmes. A presente revisão tem como objetivo abordar a formação de biofilme em cateteres vesicais e perspectivas com fungos endofíticos, metabólitos secundários e compostos bioativos contra microrganismos patogênicos. Os presentes dados demonstram um uso favorável de fungos endofíticos no controle de microrganismos gram-positivos e gram-negativos. Os metabólitos extraídos de fungos endofíticos com ação antibacteriana podem ser categorizados principalmente na classe dos compostos fenólicos. Além disso, podem ser usados para controlar a formação de biofilmes em dispositivos médicos, como sondas vesicais de demora, que são muito susceptíveis à colonização microbiana, sendo responsáveis por infecções graves e persistentes.
Palavras-chave: Biofilmes; Bioprospecção; Endófitos; Infecções do trato urinário; Anti-Infecciosos.

Resumen
Las infecciones del tracto urinario asociadas al catéter continúan siendo motivo de preocupación, dado el aumento de los datos epidemiológicos, los costos, la resistencia bacteriana y las complicaciones y la morbilidad. La bioprospección de plantas como estrategia para el control de microorganismos patógenos ha ganado espacio en la literatura, debido a la amplia diversidad existente en la flora brasileña, lo que permite la exploración de hongos endófitos y diversos compuestos, para ser utilizados en células planctónicas o para inhibir la formación de biopelículas. Esta revisión tiene como objetivo abordar la formación de biopelículas en sondas vesicales y perspectivas con hongos endófitos, metabolitos secundarios y compuestos bioactivos frente a microorganismos

patógenos.Los presentes datos demuestran un uso favorable de los hongos endófitos en el control de microorganismos grampositivos y gramnegativos. Los metabolitos extraídos de hongos endófitos con acción antibacteriana se pueden categorizar especialmente dentro de la clase de compuestos fenólicos. Además, pueden usarse para controlar la formación de biopelículas en dispositivos médicos, como sondas vesicales permanentes, que son muy susceptibles a la colonización microbiana, siendo responsables de infecciones graves y persistentes.

Palabras clave: Biopelículas; Bioprospección; Endófitos; Infecciones del tracto urinario; Agentes antiinfecciosos.

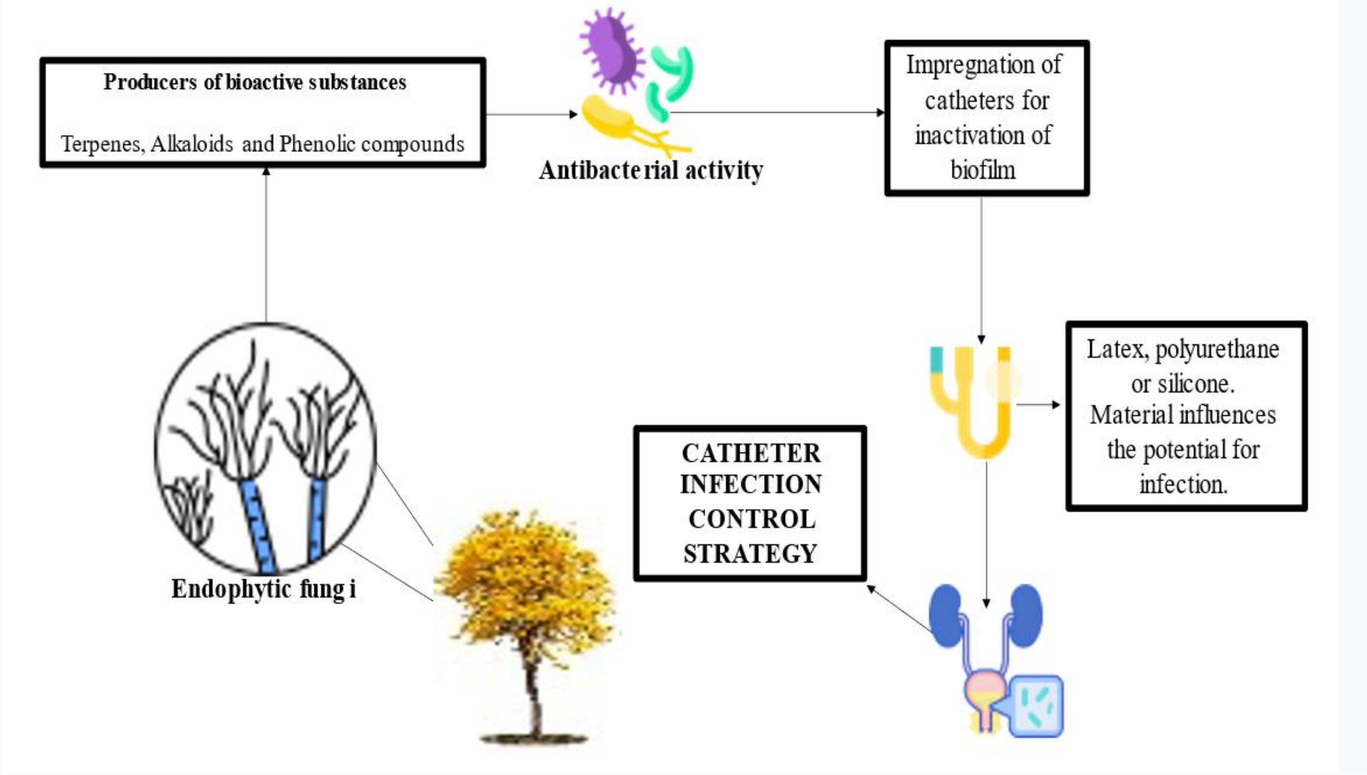
1. Introduction

Catheter-Associated Urinary Tract Infection (CAUTI) is one of the most frequent nosocomial infections in clinical practice, involving medical devices. Epidemiological data reveal that Urinary Tract Infection (UTI) accounts for 45% of these infections, with an incidence of 3.1-7.4/1,000 catheters/day (Anvisa 2017). According to a study by Vallejo-Torres et al. (2018), the average cost of hospitalization per patient is 5,700 euros in complicated UTIs. One of the factors associated with complicated UTI is bacterial resistance (Vaz et al. 2018a). Pathologies resulting from resistance cause about 700,000 deaths per year worldwide, and approximately 2.4 million people could die between 2015 and 2050, even in the most developed countries, if there are no sustained efforts to contain the problem of microbial resistance (WHO 2019).

Among the mechanisms that generate microbial resistance are gene mutations and recombinations, which favor the development of environmental factors of adaptation, such as the formation of biofilms. Biofilms consist of a matrix of exopolysaccharides (EPS), proteins and microorganisms that attach to surfaces such as catheters (Rabin et al. 2015). Biofilm infections associated with medical devices comprise a current topic of research, as they are the predominant reason for persistent infections (Mulla et al. 2016), with the financial impact of damage caused by biofilms estimated at billions of dollars each year (Cattó et al. 2018). Eradicating biofilms is arguably more work than eliminating cells in planktonic form (González-Vera and Shukla 2020; Jenks et al. 2020), especially when attached to devices (Mitchell et al. 2016), as they become about 5 to 4000 times less susceptible to the action of an antimicrobial (Sasani et al. 2021).

Thus, the use of antimicrobial compounds in urinary devices is promising, especially among those that are able to meet the essential characteristics, such as tensile strength, softness, flexibility, biocompatibility and that meet the requirements of urinary flow (Singha et al. 2017). To the best of our knowledge, few studies have reviewed publications on this topic. Strategies using natural compounds have been widely explored to control microorganisms. This review gathers information to improve the understanding of the topic of urinary catheter-associated infections, the materials and their influence on biofilm infections, as well as the perspectives of compounds arising from endophytic fungi. To compose an alternative applicable to medical devices, it is essential to understand these factors involved that can bring new insights to the control of infections in catheters by biofilms, as can be seen in figure 01.

Figure 1 - Graphical abstract of study including endophytic fungi, bioactive compounds, antibacterial activity, catheter impregnation, catheter material and urinary catheter infection control.



Source: Authors.

This review aims to address the formation of biofilm in bladder catheters and perspectives with endophytic fungi, secondary metabolites and bioactive compounds against pathogenic microorganisms.

2. Methodology

This is a narrative review of the literature, in which the search for articles was carried out in the databases BDENF (Nursing Database), LILACS (Latin American and Caribbean Literature in Health Sciences), SCIELO (Scientific Electronic Library Online), Google Scholar, Web of Sciences and PubMed, with descriptors available in DeCS (Descriptors in Health Sciences): Bioprospecting, Endophytes and Urinary Tract Infections, using the Boolean AND operator.

The inclusion criteria defined for the selection of articles were: articles published in Portuguese and English, which portrayed the theme of the study and indexed in the aforementioned databases from 1999 to 2022. Initially, 327 articles were found, and later, through the criteria of exclusion (duplicity, non-compliance with the objective of this review and escape from the theme) selected 130 articles that met the eligibility criteria described.

The reading of the titles was used as a strategy for selection and, according to these, the analysis of the summaries of the total sample, taking into account the inclusion and exclusion criteria, subsequently, the content and sequence analysis was carried out, the synthesis of bibliographic data in a descriptive way, grouped by themes relevant to the subject studied to facilitate the organization of each theme.

3. Urinary Catheters and Associated Infections

The urinary system has the purpose of excreting waste produced by the body, ensuring homeostasis through substance concentration regulations (Tortora and Derrickson 2017). Urination, that is, the release of urine, is a voluntary reflex of the autonomic nervous system, triggered by contraction of the bladder muscle (parasympathetic nervous system) and relaxation of the urethral sphincter (sympathetic nervous system) (Guyton and Hall 2017).

However, there are clinical conditions such as impaired spontaneous urination, need to monitor urinary output, clinical cases of intensive care, postoperative and chronic diseases in which it is necessary to use an invasive device that performs the function of urine elimination (Anvisa 2017).

Urinary Catheter or Indwelling Bladder Catheter (IDC) is an invasive device in the form of a tube made of latex, polyurethane or silicone material, inserted through the orifice of the urethra extending to the bladder. The presence of the catheter causes damage to the urinary system, resulting in an inflammatory response, which can potentially become infectious (Walker et al. 2017).

Although they benefit the patient in the sense of performing part of the function of the urinary system, on the other hand, the presence of the medical device causes infections that can be fatal, since it causes mechanical stress, histological, immunological changes, edema, exfoliation, epithelial irritation and injury (Francolini et al. 2017; Andersen and Flores-Mireles 2020).

The permanence of pathogenic microorganisms in the urinary tract results in numerous complications and pathologies that may be limited to the bladder, called cystitis, extend to the kidneys, causing pyelonephritis, or may even project to other systems (sepsis) and become more persistent (Levinson 2011).

The use of medical devices such as urinary catheters are associated with CAUTI (Anjos et al. 2020), often linked to the female gender, due to the anatomical characteristics that facilitate the ascension of microorganisms and the colonization of the vagina by members of the fecal microbiota (Conover et al. 2019; Malinovski & Estorillo 2021), with the duration of catheterization being a determining risk factor for infection (Kranz et al. 2020; Batista et al. 2018).

The duration of catheter use differs according to clinical conditions and may be 14 days or less (short-term catheterization), or extend for approximately 30 days or more (long-term catheterization) (Geng et al. 2012). In a documentary study carried out in a Brazilian state, a higher prevalence of CAUTI was observed in patients whose length of stay was equal to or greater than 15 days and the use of IDC was equal to or greater than 10 days, with the outcome being death in 11,7% (Barbosa et al. 2019).

Belfield et al (2019) report that CAUTI has effects on quality of life, mental health and financial costs, being the most common origin among nosocomial infections (Hosseini et al. 2018). It is important to note that the choice of material for the urinary catheter influences the potential for infection. Latex catheters are highly prone to biofilm formation, due to the favorable composition of irregular hydrophobic and hydrophilic surfaces that allow attachment and colonization by various microorganisms (Stickler 2014).

Polyurethane catheters are considered more biocompatible, due to their properties, such as tenacity, which ensure greater strength and durability (Verma et al. 2016). Lee and colleagues (2017) concluded that silicone-based catheter materials are smooth and can reduce microbial biofilm formation, especially silver-alloy coated silicone, representing one of the most studied nanomaterials in biomedical applications (Anjum, et al., 2016). Silicone is a polymer that contains the chemical element silica along with hydrogen, oxygen and carbon, present in various medical devices, including urinary catheters, long-term vascular access and equipment for parenteral nutrition (Marino 2015).

Biofilm-forming uropathogens were seen more in patients with silicone-coated latex catheter compared to pure silicone catheter, with the difference being significant between them (Kumar & Bose 2020). Corroborating this, Lawrence and

Turner (2005) state that the silicone material is preferred for the urethra due to its mechanical strength, elasticity, greater rigidity and relatively thin wall, which reduces incrustation and blockage. Although they emphasize that this does not confer superiority when it comes to delaying the onset of infection and encrustation, in addition, they state that the more rigid nature of the catheter can compromise patient comfort.

However, the Foley catheter, introduced in the mid-1930s, composed of water, dry rubber content, hydrates, proteins, lipids, sugars and others (Zhang 1999; Synaflex 2000), it is still the most used device, as it is easily processed and molded, minimizing production costs, allied to the physical characteristics of good resistance and relatively high tensile forces (Wiley 2004).

In general, a material that offers total inhibition of the growth of bacteria and fungi has not been developed, however, strategies have been raised to modify the surface and interior of the catheter, in order to reduce infections related to these devices and assistance to the patient. health (Anjum et al. 2017). There are those that coat only externally (first generation) or those that coat both externally and internally (second generation) (Abad and Sufdar 2011).

Among the microorganisms that cause CAUTI are the bacteria *Escherichia coli*, *Enterococcus* sp., *Proteus mirabilis*, *Pseudomonas aeruginos*a and the yeast *Candida albicans* (Stickler 2014). Salzani et al (2019) highlighted *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Staphylococcus* spp. and *Proteus* spp.

4. Biofilms in Urinary Catheters

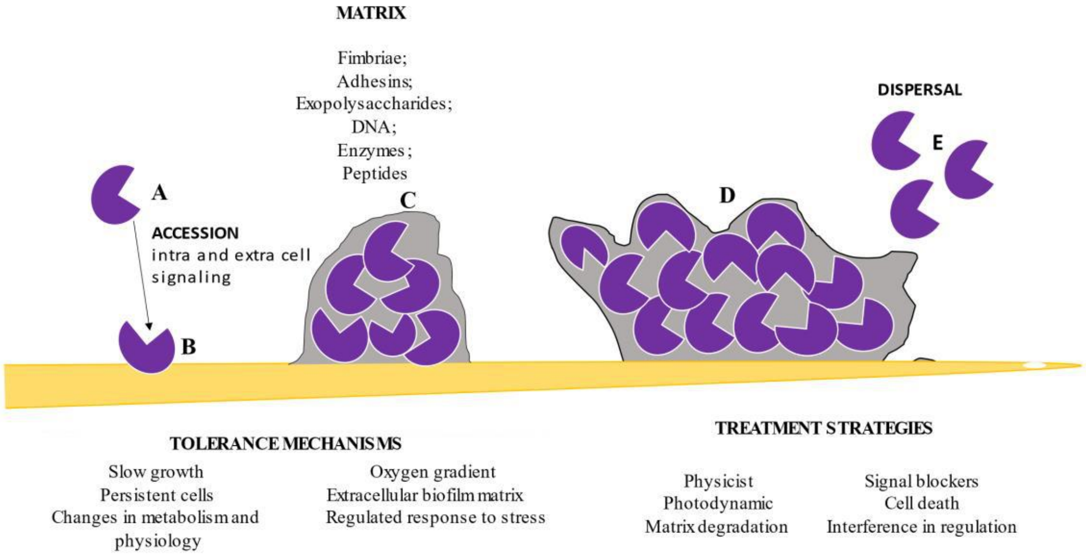
According to Singh et al. (2017) biofilms comprise a community of microorganisms that agglomerate, attach to surfaces, associated with a matrix of exopolysaccharides (EPS). They constitute a defense mechanism of bacteria, in which growth depends on many biotic and abiotic factors (Tasneem et al. 2018).

The process of biofilm formation begins with the adhesion of planktonic bacteria, which approach the surface by Brownian motion or by means of flagella. When the microorganism and the surface reach a critical point of proximity (in the range of ≈1 nm), their adhesion depends on attractive and repulsive forces, where physicochemical interactions occur, and under favorable conditions, bacterial proliferation increases and begins to EPS production (Vaz et al. 2018b).

The EPS are high molecular weight polymers composed of sugar residues, serving as a support for the adhesion of other carbohydrates, proteins, nucleic acids and lipids. When seen under electron microscopy, they appear with long ribbons that are fixed to the cell surfaces and extended to form large networks, the biofilms (Rabin et al. 2015).

Although biofilm formation was first observed in 1708, when Antonie Van Leeuwenhoek investigated tissue colonized by microbes with his new microscope, research into biofilm constitution only began to make significant and exponential advances in the last 15-20 years (Winter et al. 2019). The biofilm formation cycle occurs in seven stages, as illustrated in Figure 2.

Figure 2 - Constitution, training process and treatment strategies for biofilms. In (a): free-swimming cell. (b): reversible surface fixation. (c) irreversible attachment to the surface, formation of microcolonies through cell division and production of extracellular matrix. (d) formation of a mature three-dimensional biofilm architecture; (e) cells can actively disintegrate from the biofilm.



Source Adapted from Romling and Balsalobre (2012).

Biofilm formation is also associated with expression of virulence genes (Gunardi et al. 2021) and expression of proteins (Romling & Balsalobre 2012; Romling et al. 2014), such as cytochrome bd, essential for uropathogen homeostasis (Beebout et al. 2017). Because the bladder is an iron-limited organ, pathogens use siderophores to capture iron (Flores-Mireles et al. 2019), employing methods to contain the host's immune system response (Green & Mecsas 2016).

Thus, antibiofilm treatments must address the pathogen-host interactions, local microbiota and strategies to contain the diversity of infections, however, there is complexity in the eradication of biofilms (Silva et al. 2021; Trindade et al. 2020). The fouling and colonization of catheters remains independent of the creation of new coatings and drugs (Machul et al. 2018), which becomes a challenge to the scientific field.

The surface of the urinary catheter can be colonized by microorganisms (Tarabal et al. 2021) and become a starting point for the formation of biofilms (Sampaio 2018), which consequently, once installed, create barriers for antibacterial agents, camouflaging themselves (Gayani et al. 2021) and requiring greater amounts of antibiotics to combat it (Mulla et al. 2016).

Adhesion to the catheter surface is one of the most important and fundamental points for biofilm formation, being influenced by material properties, catheter surface morphology, polar interactions, hydrophobicity and hydrophilicity (Cattó et al. 2018).

Antimicrobial resistance and biofilm formation hinder infection control strategies (Moura 2020; Ramírez-Castillo et al. 2018; Tiago et al. 2020), making it a challenge for global health (Scott et al. 2019; Who 2019). The triad of virulence factors, biofilm formation and host-pathogen interaction interfere with infection prevention and control (Vipin et al. 2019). But it is notable that simple modifications to the hydrodynamic characteristics of the catheter can have a significant impact on bacterial colonization (Ionescu et al. 2021).

5. Natural Perspectives with Endophytic Fungi

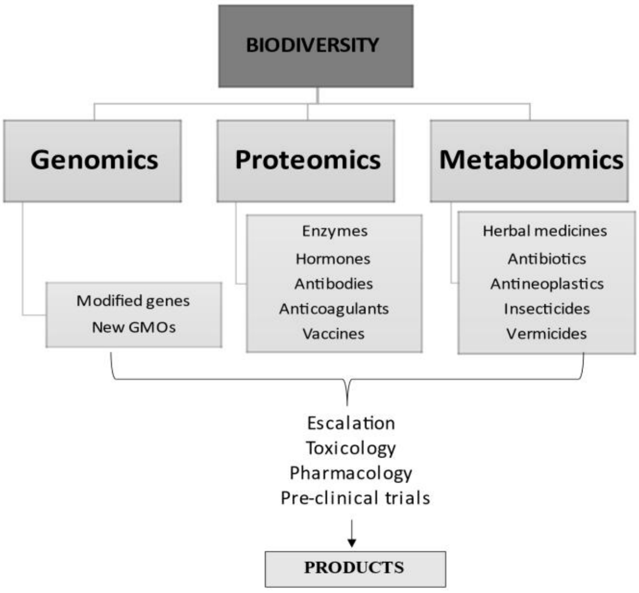
Brazil encompasses six biomes with distinct characteristics, each one harboring its own specific fauna and flora. The diversity of a biome with unique characteristics favors the discovery of new bioactive compounds and the search for product innovations, capable of controlling many diseases and illnesses, as well as solving therapeutic problems (Florindo 2019).

Despite recent interest, the use of natural products through medicinal plants is distant, dating back to 2400 BC (David et al. 2015), or even when pathologies were treated with herbs based on traditional knowledge linked to nature (Lócio 2019). Added to this, the issues of long-term resistance of microorganisms, increased consumption of antibiotics and limitation of therapeutic possibilities, require the prospection of natural bioactive compounds (Boecke et al. 2014; Chen et al. 2016; Adeleke and Babalola 2021).

Thus, biodiversity can be explored for the discovery of new compounds, products, drugs and herbal medicines. Natural antimicrobials are extracted and produced from natural sources, being safer, and may even be substitutes for synthetic drugs (Anjum et al. 2017) and subsequently optimized to increase production and inhibition of bacterial growth (Moreno et al. 2018; Sousa et al. 2019).

Biotechnological bioprospecting is a strategy for using biodiversity, in which the products found can be replicated, synthesized or produced in laboratories in a more sustainable way (Figure 3) (Astolfi Filho et al. 2014; Saccaro and Nilo 2011; Brasil 2015).

Figure 3 - Schematic representation of possible ways of obtaining products with biological activity from biodiversity.



Source Adapted from Astolfi Filho et al. (2014).

Prospecting consists of searching for organisms, genes, enzymes and compounds that may have biological activities and potential for product development (Wani et al. 2015; Freitas et al. 2020). Among these, endophytes stand out, a term first introduced in 1866 by Bary, which refers to organisms found in plant tissues (Hughes 2016), inhabiting intracellular spaces, without causing damage to the host plant (Nair & Padmavathy 2014; Wani et al. 2015; Pamphile et al. 2017).

Microbial endophytes are present in all known plant species, but it is still unexplained how many produce host metabolites, in addition there is no database for endophytic microorganisms and their metabolites, which brings greater difficulties in characterization (Khare et al. 2018). In this way, there is a great need to study endophytic fungi, catalog their prospection and register patents, because in Brazil, research on this topic is small compared to the existing unexplored biodiversity (Oliveira et al. 2021). Endophytes enter plants through natural openings, such as hydathos, stomata and lenticels, wounds caused by abrasion with soil particles, formation of lateral roots and micropores (Lata et al. 2018), varying according to the phase (age) of the plants, tissue type and environmental conditions (Jia et al. 2016).

Nair and Padmavathy (2014), Schulz et al. (2015), Wani et al. (2015) and Pamphile et al. (2017), list the numerous functionalities of fungal endophytes: they help in the growth and development of the plant, with phytostimulation, the absorption of essential elements such as carbon, oxygen, hydrogen, nitrogen; produce various growth hormones; protect the host plant from unfavorable environmental conditions (abiotic and biotic stress); produce pigments for industrial applicability; secrete enzymes such as pectinases, cellulases, xylanases and proteases; produce and secrete secondary metabolites and are a source of bioactive compounds with distinct biological activities.

Endophytic fungi are considered promising for new biotechnological discoveries, as they constitute a source of potential and active metabolites, being inspected for biomolecules with antibacterial activity (Rajamanikyam et al. 2017; Moura 2020), due to microbial resistance issues that have caused concerns in global scale (Schulz et al. 2015).

The possibility of being major producers of bioactive substances classifies them as organisms of interest, combined with the advantages of low production cost and ease of handling (Specian et al. 2014). The pharmacological importance of these fungi is promising for prospecting bioactive compounds in agricultural, pharmaceutical and medicinal areas, being able to produce antimicrobial substances and other products of biotechnological interest (Hughes 2016; Adeleke and Babalola 2021).

For Strobel (2018) frequently isolated fungal genera include *Fusarium* sp., *Colletotrichum* sp., *Phoma* sp., *Pestalotiopsis* sp., *Xylaria* sp., *Curvularia* sp. and *Cladosporium* sp. Hardoim et al. (2015) carried out a survey of endophytic fungi and their respective phyla in a database containing 8,439 eukaryotic sequences recovered from the National Center for Biotechnology Information (NCBI), as of August 2014, in which they were listed among the belonging to the class of Glomeromycota (40%), Ascomycota (31%), Basidiomycota (20%), unidentified phyla (8%) and, to a lesser extent, Zygomycota (0.1%).

Gonçalves et al. (2017) mapped the patents of the European Patent Office (EPO), National Institute of Industrial Property (INPI) of Brazil and World Intellectual Property Organization (WIPO), in order to verify the frequency of deposits on the use of endophytic fungi and their applications in the pharmaceutical industry. Of the 36 patents registered between 2003 and 2015, only five listed at the INPI were related to endophytic fungi and pharmaceutical applications. China in general has been found to be the largest depositor of patents on endophytic fungi, being one of the powerhouses in biotechnology. In relation to the ranking of patents, the United States of America, Japan and China lead, with Brazil occupying the last places.

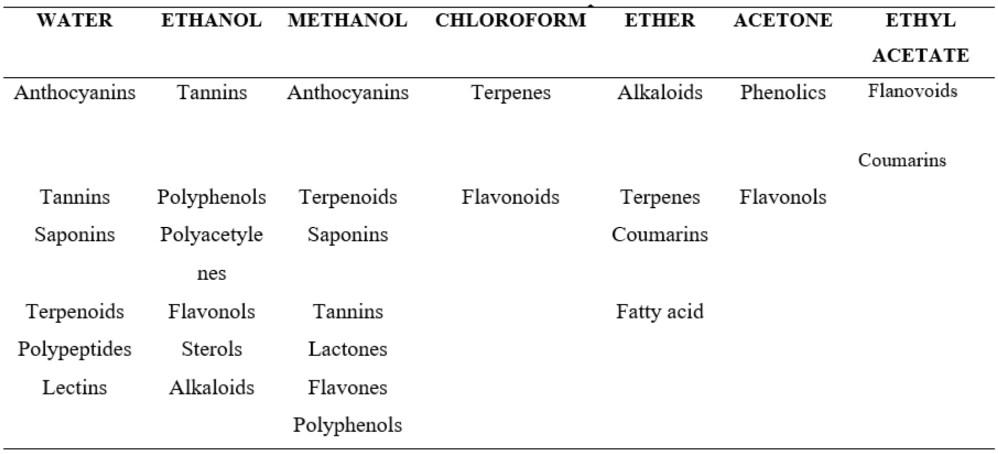
6. Secondary Metabolites and Bioactive Compounds

Secondary metabolites are defined by small, organic molecules, produced by endophytic fungi together with enzymes (Scharf et al. 2014), depending on the environmental conditions of insertion (Card et al. 2015). Fundamental in the metabolic interactions between the fungus and the host plant, they are associated with the process of signaling, regulation and defense (Bhardwaj and Agrawal 2014). A relevant reference in the use of fungal metabolites was the discovery of Penicillin, a substance synthesized by the fungus *Penicillium chrysogenun*, described in 1928 by Alexander Fleming (Pereira and Pita 2005).

There are several methods of obtaining extracts of secondary metabolites from endophytes, including maceration, percolation, infusion, decoction and aqueous-alcoholic extraction by fermentation (Pandey and Tripathi 2014). For the concentration of extracts, it is essential that drying processes are carried out, such as spray-dryer, lyophilization or evaporation (Rodrigues et al. 2016).

When it comes to the solvent for extraction, it must be as selective as possible and, through its polarity, the desired substances will be extracted. Table 01 shows examples of extraction solvents and the main compounds obtained in each.

Table 1 - Solvents used in the extraction of active compounds.



WATER	ETHANOL	METHANOL	CHLOROFORM	ETHER	ACETONE	ETHYL ACETATE
Anthocyanins	Tannins	Anthocyanins	Terpenes	Alkaloids	Phenolics	Flanovoids
						Coumarins
Tannins	Polyphenols	Terpenoids	Flavonoids	Terpenes	Flavonols	
Saponins	Polyacetylenes	Saponins		Coumarins		
Terpenoids	Flavonols	Tannins		Fatty acid		
Polypeptides	Sterols	Lactones				
Lectins	Alkaloids	Flavones				
		Polyphenols				

Source Adapted from Choze (2004) and Pandey and Tripathi (2014).

It is relevant to elucidate that plants produce two different metabolites, the primary ones (structural function, growth and development) and the secondary ones divided into three chemically distinct groups, presented below.

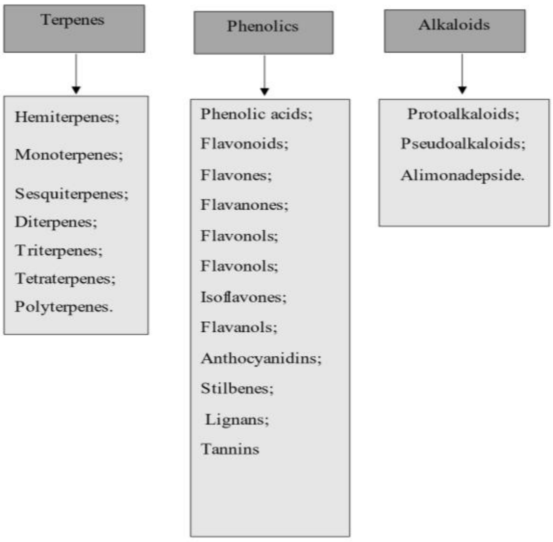
Terpenes present a great structural diversity, with more than 35 thousand substances identified. They are theoretical derivatives of isopentenylpyrophosphate, a five-carbon structure reaching up to 40 carbons. Although they present structural differences, all terpenes are essentially structured in five-carbon blocks (Felipe & Bicas 2017).

Alkaloids are grouped together because they have an alkaline character, conferred by the presence of nitrogen-rich organic substances within one or more heterocyclic rings. It is estimated that of the 27,000 known alkaloids at the moment, 21,000 are of plant origin. Within this group are chemical compounds such as nicotine and caffeine (Reyes-Silva et al. 2020).

Phenolic compounds are part of one of the most abundant groups, characterized by the presence of a functional hydroxyl attached to an aromatic ring and biosynthesized in plants via shikimic acid and acetate-malonate. They stand out for their application importance, variety in the chemical structure and biological activity of polyphenols, with reports of antioxidant, antimicrobial, anticancer activities, among others (Martin 2018).

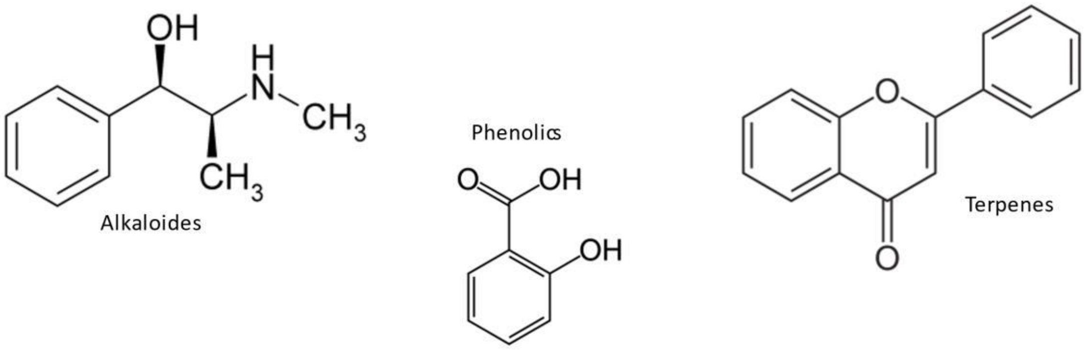
The types of compounds belonging to each group are represented in Figure 4 and the basic structure of some classes of secondary metabolites in Figura 5.

Figure 4 - Main categories of compounds obtained from the secondary metabolism of endophytic fungi.



Source Vizzotto, Krolow and Weber (2010).

Figure 5 - Basic structure of some classes of secondary metabolites: Alkaloids, terpenes and phenolics.



Source Costa (2009), Moderno (2009) Moreira (2013), Souza (2014).

Flavonoids are the most representative of the group, having as their basic structure two benzene rings connected through a pyrone, derived from aromatic amino acids. They are mostly based on a fundamental structure that has a skeleton formed by 15 carbon atoms consisting of two benzene rings, linked through a three-carbon chain between them and an oxygen as a heteroatom (Santos & Rodrigues 2017).

Its subgroups vary according to the pattern of hydroxylation, glycosylation, esterification and amidation, capable of modulating the polarity, toxicity and intracellular targeting of these compounds (Huber & Rodriguez-Amaya 2008; Arnoso et al. 2019).

Endophytic fungi produce metabolic compounds such as pestacin, taxol, camptothecin, ergoflavin, podophyllotoxin, benzopyran, isopestacin, phloroglucinol, tetrahydroxy-1-methylxanthone, salhydride, borneol, dibenzofuran, methyl peniphenone, lipopeptide, and peniphenone (Adeleke & Babalola 2021). Specian et al (2014) cite mainly alkaloids, steroids, terpenoids, isocoumarins, quinones, phenylpropanoids, lignins, phenols and phenolic acids, aliphatic metabolites, lactones, cytocatalasins, flavonoids, peptides and xanthones.

7. Potential of Endophytics and Compounds

The follow-up of impregnation of catheters using natural products has been promising, associated with direct functionalization of the surface with antimicrobial molecules, use of nanoparticles, capable of better penetrating the dense matrix of biofilms (González-Vera & Shukla 2020) and antifouling strategies aiming prevention of bacterial adhesion and colonization of catheter surfaces (Faustino et al. 2020).

Nanoscale materials provide ideal means to retain the antimicrobial activities of secondary metabolites (Al-Jumaili et al. 2018; Rahman et al. 2019) and can be used for coatings due to their excellent interaction with bacterial and fungal cell membranes (Karimi et al. 2018).

Medical devices can be impregnated in the prevention and inactivation of biofilm with antimicrobials such as chlorhexidine, silver (Bayramov & AnnNeff 2017), chitosan polymers, alone or associated with enhanced films of plant extracts (Ramos et al. 2018) and/or with phytochemicals (Kot et al. 2015).

Phytochemicals act to reduce metabolic activity, disrupt cell membranes and reduce biomass production (Porto 2016). The mechanism of activity appears to be involved in the hydrophobic nature of metabolites and their ability to act on the membrane, causing failure of chemiosmotic control (Al-Jumaili et al. 2018), but has not been fully clarified and, in some cases, has not been fully understood the identity of the molecule is still unknown (Pompilio et al. 2022).

Previous research concluded that the use of natural products in urinary catheters significantly reduced colonization (Jordan et al. 2015) and bacterial adhesion (Adesina et al. 2015), showing an antibiofilm effect (Cai et al. 2014; Namasivayam & Roy 2013; Akhlaghi-Ardekani et al. 2021), with more promising results than standard antibiotics (Ezeonu et al. 2009).

Lócio (2019) isolated endophytic fungi of Anadenanthera macrocarpa (Angico Vermelho), in which 70.8% of the extracts of secondary metabolites of the endophytic fungi showed antibacterial activity and 39.28% of the isolated endophytic fungi showed to be producers of antibiotic molecules against *S. aureus* and *E. coli* bacteria.

Nascimento et al. (2014) evaluated the effect of 44 filamentous fungi from the caatinga on antimicrobial activity, in which 86.36% of the fungi showed activity against *E. coli* and *S. aureus*, producing halos up to 33 mm in diameter for *E. coli*, this measure being superior to the positive control with amoxicillin, which obtained a halo of 30 mm.

Chagas et al. (2017) tested the antimicrobial action of 116 endophytic fungi isolated from *Hancornia speciosa* bark, in which 33.6% of the fungi showed antimicrobial activity against gram-positive bacteria, gram-negative bacteria and pathogenic yeasts. The results of Silva et al. (2018) also confirmed that endophytic fungi isolated from plants in the semi-arid region of Alagoas have potential against *E. coli*, *S. aureus* and *P. aeruginosa*.

Another study evaluated metabolites of endophytic species of *Trichoderma* isolated from the Vinca plant, found in Iran, obtaining a positive result in the bioactivity of the ethyl acetate extract, in comparison with the bioactivity of the methanol extract against pathogenic bacteria S. *aureus* and *E. coli* (Leylaie & Zafari 2018).

The alkaloid Aziridine, 1-(2-aminoethyl)- isolated from endophytic fungus exhibited antibacterial, antibiofilm, and antilarval potency, including multidrug-resistant strains (Santra et al. 2022). The coumarin metabolite was able to inhibit *P. aeruginosa* biofilm formation by up to 78% and reduce sessile colony counts (Urquhart et al. 2020). Corroborating this, phenolic compounds such as p-coumaric acid, ellagic acid and Kaempferol showed antibiofilm properties greater than 70% (Nassima et al. 2019).

Secondary metabolites also showed good results against biofilm formation in urinary catheters and deterioration of biofilm architecture in *Proteus mirabilis*, with promising anti-quorum sensing properties, as well as a visible reduction in the number of microcolonies (Younis et al. 2016). Another study determined an antimicrobial effect against uropathogenic strains of *E. coli* by the presence of polyphenols, tannins, flavonoids, rutin and quercetin (Vamanu et al. 2021).

However, the existing research was not enough to contain the problem, the manufacture of coatings faces challenges, mainly due to the formation of crystalline biofilms in urinary catheters (Coad et al. 2016) and colonization of catheter lumen (Werneburg et al. 2020).

In general, studies demonstrate the potential of compounds produced by endophytic fungus for the control of pathogenic microorganisms, emphasizing the biological antibacterial activity, however, few studies address the application of secondary metabolites in catheters and medical devices.

8. Final Considerations

Strategies using natural compounds obtained from endophytic fungi to control infections have shown promising results, and can be explored for use in medical devices, such as u6rinary catheters. In addition, they may make a valuable contribution to the control of antibiotic-resistant bacterial infections.

The literature contains several studies describing endophytic fungi extracted from plants as well as bioactive compounds with diverse biological activities, especially antimicrobial in microorganisms, but lacks on their use in medical devices, such as catheters. In the midst of Brazilian biodiversity, future research suggests the application of compounds derived from endophytic fungi in measured devices and, consequently, the development of biotechnological products.

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