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Extracts and Fractions with antifungal potential for the treatment of hair disorders

Extratos e Frações com potencial antifúngico para tratamento de desordens capilares

Extractos y Fracciones con potencial antifúngico para el tratamiento de trastornos capilares

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Abstract
Medicinal plants are used with several therapeutic applications, with hair disorders. Among the symptoms caused by these diseases, it is pertinent to emphasize the psychic damages such as loss of self-esteem and physical symptoms such as itching and burning. The present study aims to highlight the beneficial effect of medicinal plants against the symptoms caused by hair disorders. This is an integrative literature review using the Pubmed, Science direct and Google Scholar platforms and as descriptors “phytochemical”, “animal”, “seborrheic dermatitis”, “plant”, “anti-inflammatory extracts”, “antifungal” in English, crossed using the Boolean operators “AND” or “OR”. The selection of works took place after reading the title and abstract, with publication date between the years 2012-2022, excluding review studies, duplicate articles and thematic leakage. After extracting the data, 23 studies were selected that proved the effectiveness of plants on hair disorders, performing antifungal action (especially on fungi of the *Malassezia* spp. and *Trichophyton* spp.) and antioxidant due to the presence of phytochemical components such as flavonoids, phenolics, tannins, terpenoids, among others. It is noteworthy that most of these plants are processed using the maceration technique to obtain their extracts. Therefore, the bioactive compounds of these plants can be used for the development of pharmaceutical products with the purpose of expanding the therapeutic options on the market and optimizing the quality of life of patients, making it essential to encourage scientific research that discusses safety, efficacy and toxicity from the use of these metabolites.
Keywords: Plants; Medicinal; Hair preparations; Therapeutic uses; Hair diseases.

Resumo
As plantas medicinais são empregadas com diversas aplicações terapêuticas, como distúrbios capilares. Dentre os sintomas ocasionados por estas doenças é pertinente enfatizar os prejuízos psíquicos como perda da autoestima e os sintomas físicos como coceira e queimação. O presente estudo tem o intuito de destacar o efeito benéfico de plantas medicinais frente aos sintomas causados por distúrbios capilares. Trata-se de uma revisão integrativa da literatura em

que foram utilizadas as plataformas Pubmed, Science direct e Google Acadêmico e como descritores “phytochemical”, “animal”, “seborrheic dermatitis”, “plant”, “extracts anti-inflammatory”, *“antifungal”* em inglês, cruzados através dos operadores boleanos “AND” ou “OR”. A seleção das obras ocorreu após leitura do título e resumo, com data de publicação entre os anos de 2012-2022, excluindo estudos de revisão, artigos duplicados e com fuga temática. Após a extração dos dados foram selecionados 23 estudos que comprovaram a eficácia das plantas sobre os distúrbios capilares, desempenhando ação antifúngica (especialmente sobre os fungos do gênero *Malassezia* spp. e *Trichophyton* spp.) e antioxidante devido a presença de componentes fitoquímicos como flavonoides, compostos fenólicos, taninos, terpenoides, entre outros. Ressalta-se que grande parte dessas plantas são processadas utilizando a técnica de maceração para obtenção dos seus extratos. Portanto, os compostos bioativos desses vegetais podem ser empregados para o desenvolvimento de produtos farmacêuticos com o propósito de ampliar as opções terapêuticas no mercado e otimizar a qualidade de vida dos pacientes tornando-se fundamental o fomento às pesquisas científicas que discorram sobre a segurança, eficácia e toxicidade do uso desses metabólitos.
Palavras-chave: Plantas medicinais; Preparações para cabelo; Usos terapêuticos; Doenças do cabelo.

Resumen
Las plantas medicinales se han utilizado con varias aplicaciones terapéuticas, como, trastornos del cabello. Entre los síntomas que provocan estas enfermedades, es pertinente destacar los daños psíquicos como la pérdida de autoestima y los síntomas físicos como picazón y ardor. El presente estudio tiene como objetivo resaltar el efecto beneficioso de las plantas medicinales frente a los síntomas causados por los trastornos del cabello. Esta es una revisión integrativa de la literatura utilizando las plataformas Pubmed, Science direct y Google Scholar y como descriptores “fitoquímico”, “animal”, “dermatitis seborreica”, “planta”, “antiinflamatorio extracts”, “antifúngico” en inglés, cruzados usando los operadores booleanos “AND” u “OR”. La selección de trabajos se realizó después de la lectura del título y resumen, con fecha de publicación entre los años 2012-2022, excluyendo estudios de revisión, artículos duplicados y fugas temáticas. Tras la extracción de los datos, se seleccionaron 23 estudios que demostraron la eficacia de las plantas sobre los trastornos capilares, ejerciendo acción antifúngica (especialmente sobre hongos de las especies Malassezia spp. y Trichophyton spp.) y antioxidante debido a la presencia de componentes fitoquímicos como flavonoides, fenoles, taninos, terpenoides, entre otros. Cabe destacar que la mayoría de estas plantas se procesan mediante la técnica de maceración para obtener sus extractos. Por lo tanto, los compuestos bioactivos de estas plantas pueden ser utilizados para el desarrollo de productos farmacéuticos con el fin de ampliar las opciones terapéuticas del mercado y optimizar la calidad de vida de los pacientes, por lo que es fundamental fomentar la investigación científica que discuta la seguridad, la eficacia y la toxicidad por el uso de estos metabolitos.
Palabras clave: Plantas medicinales; Preparaciones para el cabello; Usos terapéuticos; Enfermedades del cabello.

1. Introduction

Medicinal plants represent a potential source for extracting active metabolites for the production of herbal medicines worldwide. In Brazil, within the scope of the national pharmaceutical assistance policy of the Unified Health System (SUS), the program of live pharmacies was created, which encompasses the stages involving the cultivation, collection, production and dispensing of magistral and officinal formulations of medicinal herbs. and herbal medicines. This program includes popular and scientific knowledge about Brazilian biodiversity with medicinal application, with the objective of preserving local vegetation and disseminating its traditional use in various pharmaceutical forms such as capsules or even the consumption of tinctures in natura. (Carmona & Pereira, 2022).

Therefore, herbal formulations have a vast composition of active metabolites that are able to act in various regions of the body, performing pharmacological action with minimal side effects, compared to synthetic drugs. Products extracted from plants as extracts can be incorporated into pharmaceutical forms to treat various diseases, for example hair disorders. The most common formulations for this therapeutic approach are: hair tonic, gel, mask and cream; these products provide an optimization of the skin texture, increase the amount of collagen, provide softness, shine and strength to the hair, which is why they are used in the treatment of problems such as alopecia (Kaur et al.,2020).

From this perspective, other diseases also affect the scalp with dermatitis, dandruff, folliculitis and scalp tinea, which can also be treated with herbal medicines. One of the most frequent symptoms related to these is microbial proliferation due to the presence of sweating pores, high humidity and certain darkness in this body area due to the coverage promoted through the hairs. Medicinal plants are a treatment bias for these diseases because they contain bioactive compounds with antimicrobial and antifungal action, representing an alternative to conventional drugs that exhibit a high rate of resistance due to their indiscriminate use by the population (Rajput & Kumar, 2020; Domingues, et al., 2020).

Hair disorders represent congenital or acquired changes that involve the hair follicle, congenital changes are abnormalities that influence capillary strength and cause hair loss and breakage, being largely associated with genetic factors. Acquired diseases are related to involvement by exogenous agents such as exposure to mechanical factors (trauma), chemical (use of harmful beauty products), biological (proliferation of microorganisms) and physical (thermal damage related to the use of dryers). An example of a disease caused by external physical agents is trichorrhexis nodosa, which manifests itself through the appearance of white nodules along the strands, causing capillary breakage (Miteva & Tosti, 2013; Hoffmann, et al., 2021).

Hair is a human characteristic that demonstrates intrinsic particularities to personal identity, representing cultural, religious, social traits, being associated with each person's beauty and youth. The main consequences of hair diseases are related to the loss of self-image, which impacts the quality of life causing psychological damage such as loss of self-confidence, low self-esteem, affects sexuality causing less desire to relate to another individual, causes irritation, anxiety and concern, these psychic symptoms are common in patients who have alopecia, for example. As for the most common physical manifestations in hair diseases, the itching accompanied by local redness and burning is highlighted, which are often reported by individuals who suffer from hair damage caused by dandruff (Gonul et al., 2018; Sanclemente et al., 2017).

With this perspective, in recent decades the hair cosmetics industry has undergone transformations incorporating actives from the national flora with a focus on cleaning, restoration, antioxidant action and hair growth, aiming to meet all types of hair and consumer needs, launching more natural alternatives with less harmful impact on individuals and the environment (Madnani; Khan, 2013). Thus, associated with these market requirements, companies that work with herbal products for hair use in Brazil (whether manipulated or industrialized) must also comply with the rules of the Agência Nacional de Vigilância Sanitária (ANVISA-BRASIL), which controls the steps from manufacturing to end-user marketing (Manfio; Junior, 2017; Hoang, et al., 2021).

In view of the above, the present work aims to carry out an integrative review of the literature based on the use of medicinal plants and /or phytochemicals, essential oil, extract or formulation that includes them for the treatment of hair disorders caused by fungi. Based on the description of the pharmacological activities of plant species by folk medicine and proven by scientific studies through in vitro, in vivo or ex vivo tests that prove the benefits of applying these herbal medicines on the scalp in order to minimize the physical and emotional impact that the disorders capillaries cause through the dissemination of this scientific information.

2. Methodology

The study design was carried out from an integrative bibliographic research of the literature, demonstrating an analysis of the descriptive content, allowing to observe and classify the data in order to gather the knowledge (Sousa et el., 2010; Lubbe, et al, 2020), in electronic databases such as PubMed, Science Direct and Google Scholar. The research involves the analysis of studies that use plants and/or phytochemicals, essential oil, extract or formulation that contain these agents, for the treatment of hair disorders such as hair loss, seborrheic dermatitis, dandruff and psoriasis, identifying antifungal actions. All descriptors were searched in English and with variation in key word combinations, which were: “anti-inflammatory”, “phytochemical”, “antioxidants”, “animal”, “seborrheic dermatitis”, “plant”, “extracts anti-inflammatory”, “antifungal” using boolean operators “AND” or “OR” to combine the search terms, demonstrating articles that contain all the words described or at least one of the words, to expand the results. The research used articles published from 2012 to 2022, separated by title and abstract. In this study, articles were included that proved the efficacy of phytochemicals or plant extracts, in vitro and/or in vivo and/or ex vivo, as well as randomized clinical trials for the treatment of hair disorders caused by fungi. The study excluded review articles,

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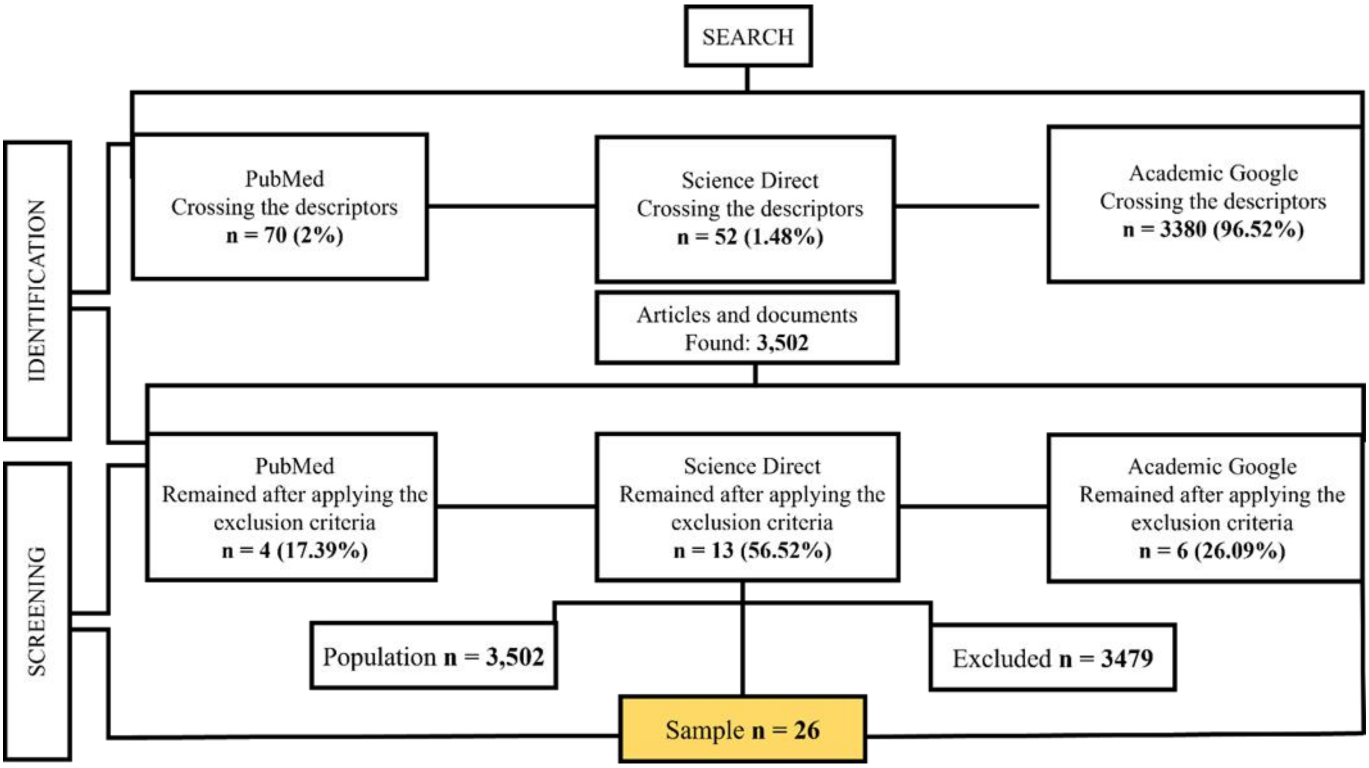
articles that only addressed chemical characterizations, studies without performing clinical tests or in vitro or in vivo or randomized studies, duplicate articles, articles that portrayed social issues of plant use or demographic aspects or articles that they did not use studies to treat the disorders mentioned above.

3. Results and Discussion

3.1 Data extraction

After applying the inclusion criteria, the files were evaluated based on absolute and relative frequency using Microsoft Excel® software. A total of 3,502 articles were found, of which 70 were located in the PubMed database, 52 in Science direct and 3,380 in Google Scholar, after screening, the final sample consisted of 23 articles (Figure 1).

Figure 1 - Flowchart of the search and selection of articles for the integrative review.



Source: Authors (2022).

All data were extracted and studied by researchers who initially identified abstract information from the articles, including the name of the plant, the effective dose, the category of phytochemicals and the treatment results that include antifungal activity, to address the hair disorders involved. This information was categorized in Chart 1. In the second stage, the articles were read in full and described according to the scope of this study.

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Table 1 - Summary of selected publications that include the study outline.

Medicinal plant (scientific name) / Author	**Effective dose / Extract or part / Formulated**	**Models / Type of study**	**Outline and action of agents**
Asparagus racemosus (Onlom et al.,2014)	0.20 and 0.40 mg/mL of extract	*In vitro*	The extract showed antifungal activity against Malassezia furfur and Malassezia globosa microorganisms associated with dandruff and dermatitis.
Azardirachta indica (Gebremedhin et al., 2020)	100% extract	*In vitro*	The extract at 100% concentration of nem has anti-dandruff activity and showed inhibition against *Malassezia* species.
Emblica officinalis (Rasika et al., 2016)	100% extract	Randomized (dandruff patients)	The *E. officinalis* extract demonstrated antifungal activity against *Malassezia sp.*
Cocos nucifera (Khalid Thebo et al., 2016)	-	*In vitro*	They showed a high percentage of antioxidant and antifungal activity against dermal mycoses.
Cibotium barometz (Heng et al.,2020)	0.02-0.31 mg/mL of extract	*In vitro*	It showed good antifungal activity (*Trichophyton rubrum* and *Trichophyton mentagrophytes*).
Lawsonia inermis (Abirami et al., 2021)	MFC 50-800 µg/mL	*In vitro*	Good antifungal activity against *Trichophyton spp*.
Allium sativum (Abirami et al., 2021)	MFC 50-100 µg/mL	*In vitro*	High antifungal activity against *Trichophyton spp*.
Citrus limon (Abirami et al., 2021)	MFC 50-800 µg/mL	*In vitro*	Good antifungal activity against *Trichophyton spp*.
Solanum surattense (Narayanan et al., 2021)	5-25% of the methanolic extract	*In vitro*	It has antifungal activity against *Trichophyton rubrum*.
Hypoxis hemerocallidea (Mwinga et al., 2019)	50% of the extract with a minimum inhibitory concentration (MIC) of less than 1 mg/ml .	*In vitro*	High antifungal activity against *Trichophyton tonsurans*.
Ranunculus sceleratus (Sharma et al., 2012)	MIC 1,25 a 10,00 mg/mL do extrato	*In vitro*	It has high antifungal activity against *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, *Microsporum gypseum*, *Microsporum fulvum*.
Pongamia pinnata (Sharma et al., 2012)	MIC 1.25 to 10.00 mg/mL of extract	*In vitro*	It has high antifungal activity against *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, *Microsporum gypseum* and *Microsporum fulvum*.
Salvia fruticosa e S. lanígera (Duletić-Lauŝević et al., 2018)	MFC of 8 mg/mL	*In vitro*	It has antifungal activity against *Trichophyton mentagrophytes.*
Thymus capitatos (Benoutman et al., 2022)	MIC on average 0.69–2.36 µL/mL	*In vitro*	It has antifungal activity against *Trichophyton rubrum*, *Microsporum canis* .
Psoralea corylifolia L. (Baig, 2022)	MIC 100 µg/ml to 200 µg/ml of the extract	*In vitro*	Shows antifungal activity against *Trichophyton rubrum* .
Coriandrum sativum	MIC of 3.1 and 25 µg/mL	*In vitro*	It shows activity against *Malassezia furfur*.

(Sathishkumar et al., 2016)			
Cinnamomum verum J. (Mariapan et al., 2013)	MIC of 0.75 mg/ml	*In vitro*	It shows activity against *Malassezia globosa*, *Malassezia sympodialis*, and *Malassezia furfur*.
Dittrichia viscosa L. (Rhimi et al., 2017)	Better activity of the methanolic extract at a concentration of 1mg/mL	*In vitro*	It demonstrates antifungal activity against *Malassezia furfur* and *Microsporum canis*.
Dittrichia viscosa L. (Rhimi et al., 2018)	MIC of 5 mg/mL in extract concentrations of 50 and 100mg/mL	*In vitro*	The lipid extract demonstrates activity against *Malassezia furfur*.
Zingiber officinale, *Alpinia galanga*, *Curcuma longa* e *Zingiber cassumunar* (Laokor & Juntachai, 2021)	The best antifungal activity was for the species Alpinia galanga presenting MIC and MFC, respectively, of (0.04–0.08 mg/mL) and (0.04–0.16 mg/mL) for the crude extract and (0.313 –2.5%-v/v) and (0.625–2.5%-v/v) for portion V	*In vitro*	The extract of A. galanga has inhibitory activity against *Malassezia furfur*.
Ilex guayusa (Cadena-Carrera et al., 2019)	For the *Trichophyton rubrum* strain the MIC is 0.25 mg/mL and for *Trichophyton mentagrophytes*, *Microsporum gypseum* and *Microsporum canis* the MIC is 0.25 mg/mL.	*In vitro*	The ethanolic extract of the leaves of Ilex guayusa has inhibitory activity against several fungal species responsible for causing hair diseases such as tinea of the scalp.
Artemis indica (DahaL et al., 2021)	MIC of methanolic extract of 300 mg/mL	*In vitro*	The methanolic extract has activity against *Malassezia furfur*, the species that causes dandruff.
Trigonellafoenum-graecum L. (Kulkarni et al., 2020)	Extract at a concentration of 30%	*In vivo and in vitro*	The gel maintained anti-dandruff activity during the storage period of three months under accelerated conditions, in vitro tests showed activity of the extract against *Malassezia furfur* strains.
Embelia ribes (Sivasankar et al., 2017)	MIC of 400 µg/ml extracts	*In vitro*	Antifungal activity evidenced against *Malassezia spp.* by the extract's ability to inactivate lipases, causing the inhibition of fungal growth.
Emblica officinalis (Hossain et al., 2012)	MIC for the ethanol extract ranged from 8.5-12.7mg/disk, while for the acetone extract it ranged from 9.5-11.0 mg/disc. The MFC for the ethanol extract ranged from 9.5-11.0 mg/disk and for the acetone extract from 9.5-10.0 mg/disc.	*In vitro*	Antibacterial and antifungal action evidenced from the extracts of the Amla fruit.
Cocos nucifera L. (Uy et al., 2019)	Extract at a concentration of 0.17g/mL .	*In vitro*	Antimicrobial action against strains of *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Candida albicans*.

Source: Authors (2022).

In view of the selected publications that make up Table 1, it is worth noting that several medicinal plants have metabolites capable of assisting in the treatment of hair disorders, especially by performing antifungal action.. The studies portrayed which effective dose evidenced from the parameters of MIC and CFM were able to inhibit the species in question and portrayed in which state the plant was being manipulated, being massively in the form of extract. The pharmacological activities were confirmed by in vitro and randomized studies that determined main inhibition against fungi of the genus *Malassezia* and *Trichophyton*.

3.2 Assessment of antifungal activity

In the study developed by Heng et al. (2020) extracts from the rhizome hairs of *Cibotium barometz* (L.) were evaluated for their phytochemical content and antimicrobial capacity. The extract was obtained through the maceration technique using different solvents, such as chloroform, methanol, ethanol, ethyl acetate, hexane and water. The antifungal activity of which was tested for the strains *Trichophyton rubrum* and *Trichophyton interdigitale*, obtaining an effective dose for these microorganisms of 0.02-0.31 mg/mL. The qualitative evaluation of the phytochemicals present in the extract indicated a change in the phytochemical content according to the solvent used and its polarity, in which in the more polar extracts (ethyl acetate, ethanol, methanol and water) higher concentrations of total phenolic compounds were found. , and the presence of polyphenols, flavonoids, phenolic compounds and tannins was observed in all samples studied. As for the antimicrobial character, ethyl acetate has the highest activity, but the most present metabolites in this sample are not the only ones responsible for the antimicrobial activity.

In addition, another species with pharmacological activity is *Thymus capitatos*, in which its essential oil, its acetone and methanolic extract act against the dermatophyte *Microsporum caniso*. The preparation of acetone and methanolic extracts was carried out using the filtration method, while the essential oil was obtained using the Clevenger apparatus. The methanolic extract showed a higher amount of flavonoids and phenolic compounds, being later quantified by UV-visible spectrophotometry, but the acetone extract showed a higher yield. All extracts obtained high antifungal activity against all studied fungal strains, with *M. canis* being the most sensitive. The essential oil showed minimum inhibitory concentration (MIC) of 0.73–2.5 µL/mL and minimum fungicidal concentration (MFC) of 0.84–6.66 µL/mL. In addition, the methanolic extract presented MIC values of 0.52–1.25 mg/mL and MFC values of 0.63–2.08 mg/mL and the acetone extract MIC 0.73–2.5 mg/mL and MFC 1.10–9.17 mg/mL. Therefore, it is assumed that the presence of compounds such as carvacrol, o-cymene and α-paraben, as they are the most frequent, are responsible for the activity against *M. canis* (Benoutman et al., 2022).

In this perspective, an investigation was also carried out on the *in vitro* antifungal activity of extracts from two plants characteristic of India. Using different solvents such as chloroform, methanol and water, extracts of *Ranunculus sceleratus* (R. sceleratus) and *Pongamia pinnata* (P. pinnata) were obtained and their fungicidal properties were evaluated against *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, *Microsporum gypseum* and *Microsporum fulvum*, all are dermatophyte fungi and are associated with harmful scalp infections (Bronson et al., 1983; Nagabhushan & Shrisha, 2013; Aruna, Ramalingappa, 2022). The extracts were prepared following the filtration method and then placed in desiccators until the solvents were completely removed. The percentages of inhibition of fungi by *R. sceleratus* and *P pinnata* were 25.6% and 24.4%, respectively, for the chloroform extract against *T. mentagrophytes*, which was the extract with the highest activity, followed by the methanolic extract. , where the minimum inhibitory concentration ranged from 1.25 to 10.00 mg/mL in these extracts. There was no evaluation of the phytochemical profile of the extracts, which makes the understanding of the antifungal process difficult, but does not cancel the importance of the study and exalts the need to apply more studies in order to verify with greater robustness the medicinal application of these plants (Sharma, Kotoky & Barthakur, 2012).

In addition, another research also evaluated the in vitro antifungal activity of common medicinal plants in India against pathogens that cause dermal infections. One of the fungal species studied was *Trichophyton spp*. The plants studied were *Acalypha indica*, *Lawsonia inermis*, *Allium sativum* and *Citrus limon*, using acetone as solvent. The acetone extract was obtained through the dynamic maceration method, in which the solvent remained in contact with the plant samples for 72 hours at room temperature. Acalypha indica showed no activity against the Trichophyton spp. strain, while Lawsonia inermis and Citrus limon showed good antifungal activity with an effective dose of 50-800 μg/mL for both. The Allium sativum extract showed the greatest effectiveness in the treatment of fungi, with an effective dose of 50-100 μg/mL. This activity of *A. sativum* may be associated with the presence of allicin, the most incident and effective bioactive of the extracts of this plant. All extracts obtained in this study showed antifungal activity to a greater or lesser degree for different strains, which suggests that the use of these extracts for the treatment of fungal infections should be better studied and consequently applied (Abirami et al., 2021).

Thus, another study also verified the antifungal activity of plant extracts of *Solanum surattense* against the species *Trichophyton rubrum* using different solvents and evaluated the phytochemical profile of the extracts. The extraction took place through the Soxhlet apparatus, using acetone, methanol, ethyl acetate and chloroform as solvents. The analysis of the phytochemical profile showed that the methanol solvent was responsible for the greater extraction of metabolites, highlighting flavonoids, steroids, terpenoids, phenols and quinones, therefore, it showed greater effectiveness in the treatment of the strains studied, with 5-25 % of extract. These compounds enter fungal cell constituents through cytosine permease, cause structural damage to fungal DNA and inhibit enzymes responsible for maintaining the fungal cell membrane structure. These mechanisms are directly related to cell destruction or inhibition of mycelial growth, thus leading to loss of fungal activity (Narayanan et al., 2021).

Fungi of the genus *Trichophyton* are responsible for causing several hair problems, so they are widely studied in the scientific literature. Thus, the plant species of African origin *Hypoxis hemerocallidea* was tested against the strains of *Trichophyton tonsurans* and *Trichophyton rubrum*. The plant bulbs were dried, ground and subjected to contact with two different solvents, methanol and petroleum ether, being vortified, sonicated and finally filtered through filter paper. The antifungal activity was observed only in Trichophyton tonsurans where the minimum inhibitory concentration (MIC) was <1 mg/ml, and the extract with 50% methanol concentration had the highest antifungal activity with a MIC of 0.39 mg/ml, while the petroleum ether extract had a MIC of 0.78 mg/ml. Na avaliação do perfil fitoquímico, foram encontrados flavonoides e fenólicos totais. Phenolic compounds act on the cell membrane of microorganisms, causing its rupture and consequently causing cell destruction. Despite the high activity against these fungi, studies of the selectivity index showed that both extracts have low selectivity against *Trichophyton tonsurans*, which suggests a greater toxicity of the extracts to the host organism than to the pathogen (Mwinga et al., 2019).

In this bias, other species that demonstrate antimicrobial and antioxidant activity are *Salvia fruticosa* and *Salvia lanígera*, which are plants originating in Libya. Its extracts were obtained through maceration, using different solvents such as dichloromethane, ethyl acetate, methanol, ethanol and hot distilled water, but only the aqueous and ethanolic extract that were applied in the studies against fungi. The antifungal assay showed low activity when correlated with the activity of ketoconazole, which has a minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) of 0.0078–0.0156 mg/mL, respectively, being used as a control in the study. The only extract that showed activity against the fungus *Trichophyton mentagrophytes* was the aqueous extract of both species, with MIC and MFC anging from 8 mg/mL to 32 mg/mL. Alcoholic extracts showed the highest yields, while ethyl acetate had the lowest yields. In addition, the dichloromethane extract revealed the highest amount of total phenolics and flavonoids. Therefore, the extract of *S. fruticosa* has more activity against bacteria, while *S. lanígera* has more antifungal action, which was effected by the inhibition of fungal tyrosinase (Duletić-Laušević et al., 2018).

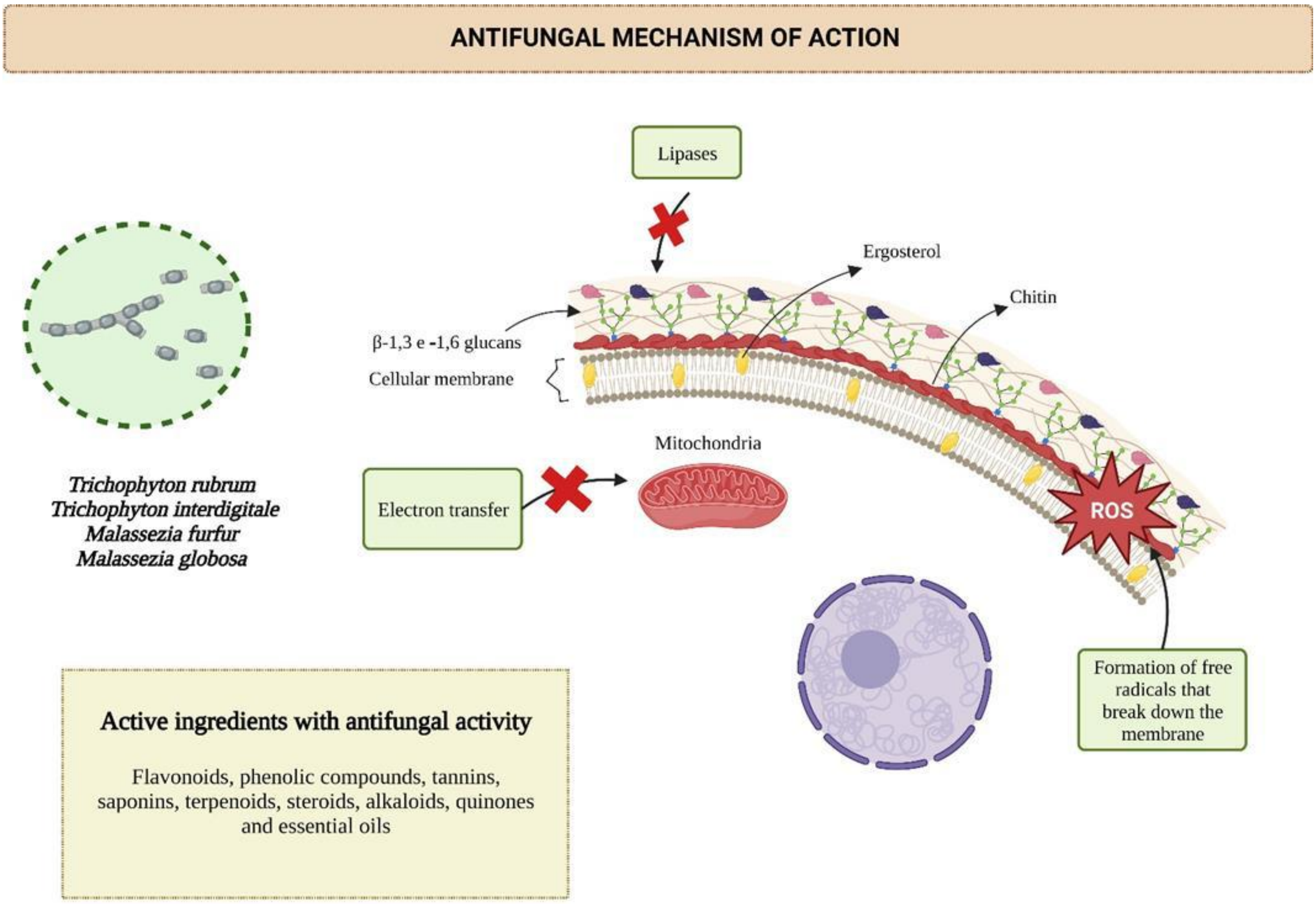
Another species that performs antimicrobial activity is *Psoralea corylifolia L.*, especially its seeds. The extract was obtained by keeping the seeds in contact with ethanol, in which the presence of 11 bioactives was verified, highlighting psoralen, isopsoralen, bavaquin, corillin, psoralidine, bavaquinin, bavachalcone, bavacromene, corylyfol, neobavaisoflavone and isobavachalcone. The antifungal activity was performed against the pathogen *Trichophyton rubrum*, a dermatophyte fungus associated with scalp infections, using MIC, MFC and IC_{50} as parameters. The bioactive that showed the highest IC_{50} value was isobavachalcone, being 152.52±2.77µg/ml, in addition to the highest MFC of 275µg/ml. The crude extract of *Psoralea corylifolia* L. had a lower IC_{50} than all the bioactives used separately, corresponding to 78.52±2.77 µg/ml, MFC of 200µg/ml and MIC of 150µg/ml. Thus, both the isolated bioactive compounds and the crude extract of medicinal plants, such as the one addressed in the study, must be well evaluated for the development of new therapies (Baig, 2022).

Likewise, another genus of fungi responsible for causing hair disorders is *Malassezia spp*. Therefore, the extract of *Cinnamomum verum* bark proves to be effective for the treatment of these diseases, so a research performed the extraction using the soxhlet apparatus, using methanol as a solvent and performing a redissolution after filtration to obtain the MIC and screening of phytoconstituents present in the extract. The methanolic extract presented MIC ranging from 0.5 to 2 mg/mL against all microorganisms studied (*M. furfur*, *M. globosa* and *M. sympodialis*), in which *M. globosa* presented the lowest MIC value, being 0.75 mg/ml. In addition, the extract showed less antifungal activity than the drug ketoconazole, with *M. furfur* being the most sensitive. Phenolic compounds, flavonoids, terpenoids and tannins were found. The action against fungi occurs due to several mechanisms, such as inhibition of the enzymatic activity of amino acids by aromatic aldehydes and interference in electron transfer in nitrogen-containing compounds by cinnamaldehyde (Mariappan et al., 2013).

Furthermore, antifungal activity of *Asparagus racemosus* against species of the genus Malassezia was also reported in the literature. With this, the extract of the roots of the species was developed by different methods in which they presented expressive levels of saponins, detected by ELISA technique. They were evaluated against strains of *M. furfur* and *M. globosa*, in which extracts with higher levels of saponins showed better antifungal activities, evaluated by disk diffusion methods (concentration of 1 mg per disk) and broth microdilution (MIC: 0.2 and 0.4 mg/mL), suggesting that such compounds are important for pharmacological activity. No synergism or antagonism was observed when the extract was associated with ketoconazole and zinc pyrithione. Considering the low toxicity and potent anti-inflammatory effect of the plant, the species has a promising action for the treatment of patients who have dandruff coexisting with inflammation of the scalp (Onlom et al., 2014).

It is worth noting that another species with antifungal activity against *Malassezia spp*. is *Trigonellafoenum-graecum L*., particularly its leaves. From them, a phytotherapic formulation was prepared using the aqueous and ethanolic extract that showed activity against a strain of *Malassezia furfur*, *Aspergillus niger* and *Candida albicans*. The qualitative and quantitative phytochemical evaluation of aqueous extract showed predominantly flavonoids, alkaloids, saponins, carbohydrates, phenols and proteins. The possible mechanism of action of these agents is described in Figure 2. The active principles can induce fungal cell apoptosis through the induction of free radicals that permeate the cell wall and plasma membrane; through interference in the transfer of electrons and, inactivation of the action of lipases, making the environment inappropriate for the development of fungi.

Figure 2 - Mechanism of action of antifungal activity.



Source: Authors (2022).

The *in vitro* tests showed that the aqueous extracts of the leaves of this plant had activity against the *Malassezia furfur* strain compatible with the 2% w/v ketoconazole solution (parameter used clinically for the treatment of dandruff), emphasizing the beneficial activity of the plant extract (Kulkarni et al., 2020).

Thus, a study carried out with 16 species investigated the use of several plant extracts for in vitro evaluation against *Malassezia spp*. In the preparation of extracts, as the materials of manufacture of the materials in contact with two different solvents, the ethyl acetate and the petroleum material separately. Among the species studied, the maximum degree of activity was observed in the extract of *Embelia ribes*, and the fungal inhibition with percentage dependent on the solvent used, where for the ethyl acetate extract it was 65% and the petroleum ether extract 77%. Based on this result, *E. ribes* was used for further studies in which extracts were prepared with other solvents (methanol and chloroform) and compared with previously tested extracts. All extracts showed maximum activity between 64-74% of the strains, except for methanol which did not show any activity. The minimum inhibitory concentration was calculated at 400 µg/ml with 79% activity. The *Malassezia spp*. are highly dependent on the performance of lipase to obtain fatty acids that are part of their cell wall and stimulate their growth, so the ability to inactivate lipases observed in *E. ribes* causes inhibition of the growth of this fungus, as evidenced by the lipase assay which showed a significant reduction in fungal lipase secretion ($p \leq 0.05$). With this, the authors suggest that *Embelia ribes* be used in drug therapy combined with fungicidal drugs (such as ketoconazole), since the activity of the extract only inhibits the proliferation and does not cause the death of the fungus (Sivasankar et al., 2017).

In this sense, another investigation was carried out using the crude extract of the leaves of *Dittrichia viscosa* L. against the strains of *Malassezia furfur* and *Microsporum canis*. The extracts were obtained using methanol, ethanol and butanol as solvents through the maceration method. The phytochemical evaluation resulted in high levels of phenolics, flavonoids and tannins. Methanolic extraction showed higher activity against *Malassezia furfur*, which may be associated with higher phytochemical extraction due to the high polarity observed in this solvent. In addition to this strain, the extracts were able to inhibit the germination, sporulation and growth of *Microsporum canis* at concentrations above 1 mg/mL, with the best activity also being observed in the methanolic extract. The antifungal activity derives from the potential of phenolic compounds and flavonoids to cause lipid disorders that interfere with and disrupt the fungal cell membrane (Rhimi et al., 2017).

To corroborate this study, another research was developed that also analyzed the extract of *Dittrichia viscosa* L leaves, but focused on the lipid fraction. The extract was obtained through the Soxhlet apparatus using hexane as a solvent, and used to test antifungal activity against *Malassezia furfur*. The predominant fatty acids in the extract were linoleic acid and linolenic acid, in addition most of the fatty acids were of the unsaturated type, tocopherols were also found in high concentration, especially α-tocopherol and δ-tocopherol. The evaluation of the inhibitory activity was evaluated at concentrations of 50 mg/mL and 100 mg/mL against *Malassezia spp.*, demonstrating greater activity than the drug fluconazole, with the value of the minimum inhibitory concentration of 5 mg/mL. The low sensitivity to azole drugs (such as fluconazole) and the ability to promote resistance to them favors the use of the lipid extract of *D. viscosa* to obtain a new drug that circumvents this problem due to its anti-elastase activity (Rhimi et al., 2018).

It is important to highlight another plant family with antifungal action that has been used in Brazil since the time of colonization: the Zingiberaceae. A research evaluated the antifungal potential against *Malassezia furfur* strains of 4 plants belonging to this family, *Zingiber officinale*, *Alpinia galanga*, *Curcuma longa* and *Zingiber cassumunar*. The extracts were obtained using ethanol, methanol and n-hexane as solvents. The extract of *A. galanga* exhibited a significantly more relevant activity than the others, being the extract obtained with n-hexane the one that showed greater efficacy in the antifungal treatment. Purification of the *A. galanga* extract by thin layer chromatography (TLC) resulted in a portion (called the V portion) that was shown to be responsible for the antifungal activity. Both the crude extract and the V portion showed strong antifungal action, exhibiting MIC and MFC of 0.04–0.08 mg/mL and 0.04–0.16 mg/mL (for the crude extract) and 0.313–2.5 % (v/v) and 0.625–2.5% (v/v) (for portion V). The mechanism of activity against Malassezia furfur consists of modifying the cell structure and inhibiting the transition from yeast to mycelium, as illustrated in Figure 2 (Laokor; Juntachai, 2021).

In this way, another study analyzed the extracts from the leaves of Ilex guayusa, a typically Amazonian plant, and contacted its biological activities and main constituents. The extracts were obtained with the use of ethanol as solvent and co-solvent, in addition to the application of supercritical CO_2 in the Soxhlet apparatus, later they were tested against the fungal strains *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Microsporum gypseum* and *Microsporum canis*. The biological activity of the extracts was totally dependent on the solvent and the extraction method, with the use of supercritical CO_2 being harmful to the process, while the use of ethanol as a co-solvent improved the extraction of phytochemicals such as caffeine. In addition to caffeine, squalene and α-amyrin were also extracted, which were found in high amounts. The *T. rubum* strain showed greater sensitivity to the extract obtained by Soxhlet who used ethyl acetate and ethanol as solvents with a MIC of 0.25 mg/mL. The other strains showed moderate antifungal activity with a MIC of 0.50 mg/mL (Cadena-Carrera et al., 2019).

Following the traditional use of plant species, *Artemis indica* has potential application for the treatment of various conditions, from abdominal discomfort to hair disorders such as dandruff. To obtain the extracts of this plant, a cold method was used, using methanol, ethanol and water separately as solvents. Phenolic compounds, flavonoids and proanthocyanidin were identified in the extracts as constituents in greater quantity, with the methanolic extract being the type that presented the highest concentration of these metabolites. To verify the anti-dandruff action of the methanolic extract, the *Malassezia furfur* strain was used due to its relationship with scalp infections that cause dandruff, with a MIC of 300 mg/mL (Dahal, Bista & Dahal, 2021).

Furthermore, a research developed with plant extracts used the bark of the plant known as Neem, which also have anti-dandruff activity and represent an alternative to conventional synthetic drugs, since many of them face the problem of increasing fungal resistance. For this, an extract containing 100 g of Neem bark was developed using a Soxhlet in which the samples were extracted with different solvents with yield of: ethanolic extract (5.25 g), water (3.84 g), ethyl acetate (3 g), chloroform (2.37 g) and diethyl ether (1.13 g). The phytochemical analysis showed the presence of alkaloids, flavonoids, tannins, phenols, terpenoids, steroids, carbohydrates, amino acids and proteins. The evaluation of anti-dandruff efficacy was obtained *in vitro* for strains of *Malassezia globosa* and *Malassezia stricta*, from the agar diffusion method that showed a greater zone of inhibition for the ethanol extract (14 mm), aqueous extract (12 mm), ethyl acetate extract (11 mm), chloroform extract (10 mm) and diethyl ether (9 mm), while the positive control with ketoconazole revealed (17 mm), this lower number for the zone of inhibition compared to the positive control group may be linked to the difficulty in extracting active metabolites from the hard parts of the vegetable (peel). Regarding the evaluation of the MIC, the ethanolic extract showed efficacy of 39.4% while ketoconazole 40.5% and the aqueous extract showed efficacy of 39.1% while ketoconazole 41.1%, highlighting greater activity against the Malassezia species tested, compared to the other extracts analyzed (Gebremedhin et al., 2020).

In addition, another species with anti-dandruff activity is the fruit of Amla (Emblica officinalis). Thus, ethanol, aqueous and juice extracts were prepared from the fruit, at different concentrations (50, 75 and 100%), which were tested against strains of *M. furfur* and *M. globosa* in disk diffusion assays in agar. These strains were isolated from 25 women complaining of hair loss and dandruff and were identified by microscopy, catalase test, esculin/urease hydrolysis analysis and tween utilization test. Only 2 samples were positive for these species and the extracts showed relevant antifungal activity against the inoculums, being more pronounced in the concentration of 100%. The fresh juice of the *E. officinalis* fruit was considered more effective than the extracts with the highest inhibition zone diameter, being respectively 22 mm for *M. furfur* and 20 mm for *M. globosa*. The Amla fruit contains inhibitory metabolites of the dandruff-causing fungi, the activity of its extract is influenced by the solvents used and their concentrations (Rasika et al., 2016).

It is worth mentioning another study that confirms the antifungal action of the fruit of Amla, the methodology was performed from the extraction of the fruit with ethanol and acetone, using a cold technique. An *in vitro* antibacterial and antifungal test of the extracts was carried out using ten species of gram-positive and gram-negative bacteria and ten species of fungi by the agar disk diffusion method, using as standard, respectively, 0.1 mg amoxicillin per disc and 0.1 mg griseofulvin to compare test samples. The results of bacterial activity demonstrated efficacy against five of the microorganisms and greater susceptibility of the ethanol extract and acetone to *Staphylococcus aureus* (10.6/10.0), *Bacillus subtilis* (11.0/10.7), *Shigella dysenteriae* (12.7/11.0) while the standard of amoxicillin for the same species (28.0/ 33.0/ 28.0). The evaluation of antifungal activity showed action of ethanol/acetone extracts only for two species, *Fusarium equiseti* (9.5/10) and *Candida albicans* (11.0/9.5) while the standard griseofulvin (11.0/11.5). These results enable the application of Amla fruits to create medicinal formulations that aim to inhibit microorganisms (Hossain et al., 2012).

Therefore, another study evaluated the antimycotic potential of coconut husks (*Cocos nucifera*), usually discarded as agricultural waste. The methanolic extract of the bark was prepared by the Soxhlet method, which presented a total phenolic content of 5.33 ± 0.02 mg/g and 28 fatty acids, quantified by gas chromatography. Regarding the pharmacological activity of the extract, an antioxidant effect ranging from 92.32% to 94.20% was verified in the DPPH elimination assays. Furthermore, different fractions of the extract were tested for their antifungal potential against clinical strains of *Aspergillus niger*, *Microsporum canis*, *Microsporum gypseum*, *Aspergillus flavus*, *Trichophyton rubrum*, *Aspergillus fumigatus*, *Trichophyton vercossum* and *Tinea corporis*. The inhibition effect was greater in the methanolic extract (93 and 91% against *A. niger* and *A.*

fumigatus, respectively) and chloroform extract (72.5% against *M. gypseum* and *A. flavus*). The crude extract, in turn, was highly effective against all strains tested with MIC ranging from 62 mm to 90 mm, these data demonstrate the antioxidant and antifungal potential of this species (Khalid Thebo et al., 2016).

To confirm these data, a study with the roots of *Cocos nucifera* L. was also selected to obtain an ethanolic extract. To determine the antimicrobial activity of this extract, the agar diffusion test was used against gram-negative bacteria *Klebsiella pneumoniae*, *Salmonella typhimurium* and gram-positive bacteria *Bacillus subtilis*, *Staphylococcus aureus* and against fungal isolates of *Candida albicans* and *Aspergillus niger*. The results showed that the greatest inhibitory action was observed against *Klebsiella pneumoniae*, followed by *Staphylococcus aureus* and *Candida albicans*, with a lower effectiveness than standard antimicrobials, being attributed to the thickness of the cell wall of bacteria and fungi that hinder the penetration of the extract, in addition, no inhibitory activity was observed against *Salmonella typhimurium* and *Aspergillus niger*. The phytochemical screening showed the presence of alkaloids, flavonoids, saponins, steroids and tannins. To analyze the antioxidant activity, the extract (IC_{50} = 1.74 ppm) was compared with vitamin C (IC_{50} 24.25 ppm), which is fourteen times more effective than the latter, which can be attributed to the dilution of the extract that reduces the antioxidant action. Qualitative evaluation of the presence of constituents in the extract by gas chromatography and by mass spectrometry delineated the presence of twenty-one antimicrobial bioactive compounds (n-decane, n-tridecane, n-hexadecane; antifungal, 2,4-di-tert-butylphenol, n-eicosane, hexadecanoic acid, ethyl ester, 3,7,11,15-tetramethyl-2-hexadecen-1-ol) and antioxidants (2,3,3-trimethyloctane, n-hexadecane, n-eicosane, hexadecanoic acid ethyl linoleolate). These compounds, respectively, act by facilitating the penetration of bioactive constituents into the membranes of fungi and can reprogram the ability of auto-oxidation, a fact that prevents the formation of free radicals and interrupts their proliferation, breaking the auto-oxidative chain (Uy et al., 2019).

4. Conclusion

It can be concluded that plants, because they present metabolites such as flavonoids, phenolic compounds, tannins, saponins, terpenoids, steroids, alkaloids, quinones and essential oils, are able to act by inhibiting fungal proliferations and with antioxidant action on hair diseases, serving as a basis for obtaining of new pharmaceutical products that will offer an optimization to existing therapies and will act in a way that provides direct benefits to the quality of life of patients. Thus, for the incorporation of new therapeutic tools in the market, it is necessary to develop strategies to standardize the herbal constituent to be incorporated (such as the type of extract), as well as methods for antifungal testing with the objective of standardizing therapeutic doses, toxic doses and the long-term follow-up of possible adverse effects related to the administration of these pharmaceutical products. Finally, based on these criteria, it is also essential to recommend physical-chemical control tools, regulate the incorporation of pharmacotechnical adjuvants and lend itself to the evaluation of techniques for obtaining formulations that can guarantee obtaining products with greater safety and stability.

From this perspective, in order to constitute formulations of high therapeutic quality, it is necessary to include accelerated and prolonged stability studies, since, although ANVISA determines that these studies be carried out for the registration of herbal pharmaceutical products, this industrial information is protected and is not transferred to scientific literature, preventing the obtainment of more robust data to guide the creation of other herbal formulations. It is worth mentioning that as limiting criteria of this review, the lack of research that demonstrates in depth criteria related to ethnopharmacology, for example, demonstrating the side effects, the determination of efficacy in the clinical context and the design of the safe use of plant metabolites in question, signaling the need to develop new studies based on these principles that corroborate the construction of pharmaceutical products with high technological rigor.

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