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Original Article

Antifungal activity of terpenes isolated from the Brazilian Caatinga: a review

Atividade antifúngica de terpenos isolados da caatinga: uma revisão

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Abstract

Terpenoids, also named terpenes or isoprenoids, are a family of natural products found in all living organisms. Many plants produce terpenoids as secondary metabolites, and these make up a large part of essential oils. One of most important characteristic is that the compounds are volatile, have odor and can be used in a variety of applications in different industrial segments and traditional medicine. Brazil has a rich and diverse flora that can be used as a source of research for obtaining new molecules. Within the Brazilian flora, it is worth mentioning the Caatinga as an exclusively Brazilian biome where plants adapt to a specific series of weather conditions and therefore become a great storehouse of the terpenoid compounds to be described herein. Fungal infections have become increasingly common, and a great demand for new agents with low toxicity and side effects has thus emerged. Scientists must search for new molecules exhibiting antifungal activity to develop new drugs. This review aims to analyze scientific data from the principal published studies describing the use of terpenes and their biological applications as antifungals.

Keywords: terpenoids, antifungal activity, Brazil, Northeast, essential oils.

Resumo

Os terpenóides, também chamados terpenos ou isoprenóides, são uma família de produtos naturais encontrados em todos os organismos vivos. Muitas plantas são produtoras destes metabolitos secundários, que constituem uma grande parte dos óleos essenciais. Uma das características mais importantes é que os compostos são voláteis, têm odor e podem ser utilizados numa variedade de aplicações em diferentes segmentos industriais ou na medicina tradicional. O Brasil tem uma flora rica e diversificada que pode ser utilizada como fonte de pesquisa para a obtenção de novas moléculas. Dentro desta flora, vale a pena mencionar a Caatinga como um bioma exclusivamente brasileiro que possui plantas adaptadas a uma série de condições climáticas e, portanto, um armazém de compostos a serem descritos. As infecções fúngicas são doenças cada vez mais comuns, devido a isso existe uma grande procura de novos agentes com baixa toxicidade e efeitos secundários. Os cientistas devem procurar novas moléculas que exibam atividade antifúngica para o desenvolvimento de novos medicamentos contra as infecções fúngicas. Esta revisão visa analisar dados científicos dos principais estudos publicados que descrevem o uso de terpenóides e as suas aplicações biológicas como antifúngicos.

Palavras-chave: terpenóides, atividade antifúngica, Brasil, Nordeste, óleos essenciais.

1. Introduction

The Caatinga's phytogeographic domains are primarily in Brazil's northeast and contain a significant number of native flora species. Plants from the Caatinga, present a considerable variety of secondary metabolites, phytoconstituents, and essential oils, and have thus stood out in the pharmaceutical industry (Moura et al., 2020).

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These compounds are produced by plants in defense against disease, and can be classified into primary and secondary metabolites. Primary metabolites involve sugars, amino acids, proteins, and chlorophyll among others, while secondary metabolites involve alkaloids, terpenoids, and phenolic compounds, as well as flavonoids, and tannins, (Duduku et al., 2007).

Essential oils (EOs) are characterized as complex mixtures of compounds derived from the secondary metabolism of plants. Usually, volatiles present odors and may contain hundreds individual molecules formed essentially by monoterpenes, sesquiterpenes, phenylpropanoids, and isothiocyanates (Felipe and Bicas, 2017).

In general, monoterpenes, and sesquiterpenes, and their oxygenated derivatives are principal components of EOs. The concentration of these molecules varies, and some molecules can make up to 70% of the EO total, being thus principal components and therefore responsible for the EO´s attributed biological activity (Sharifi-Rad et al., 2017).

Increases in fungal resistance and the lack of therapeutic options to treat fungal infections has contributed to the advent of new, more effective, and less toxic therapies (Singh and Sharma, 2015). In the northeastern Caatinga, medicinal plants are widely used in folk medicine by local communities due to the presence of terpenes (Alves et al., 2016).

In addition to the development of fungal resistance, whether inherent or acquired, pharmacotherapy for fungal infections has been limited due to host toxicity, the struggle is to find an effective drug against eukaryotic fungal cells (Silva et al., 2012). This review aims to analyze scientific data from the principal published studies describing the use of terpenoids from Caatinga plants and their biological applications as antifungal agents.

2. Material and Methods

Our study consisted of a bibliographic review based on the following descriptors: Terpenoids, Antifungal activity, Caatinga, Northeast, and Essential Oils. The results were collected through the electronic databases Medline/PubMed and Science Direct, in Portuguese and English. Research inclusion criteria related to antifungal activity found in Brazilian Caatinga vegetation species were considered. However, the exclusion criteria were not applied, as articles are scarce. Papers with classic citations in the area between the years 1976 - 1995 were collected; and recent literature from 2003 to 2021 was also analyzed.

3. Results and Discussion

3.1. Caatinga ethnopharmacology

Many cultures maintain millennial traditions of using medicinal plants for different purposes and in different ways (Rodrigues et al., 2018). In ethnopharmacology, scientific proof concerning active principles and pharmacological activities of plant-derived products (which combat pathologies) can be obtained, and the manufacture of new medicines becomes possible (Dantas et al., 2018). The current growth in demand for natural products, in addition to social factors and economic constraints in needy communities and regional cultures, are related to the great diversity of pharmacological compounds being used today (Macedo et al., 2020).

The botanical diversity found in Brazil favors the use of medicinal plants, and the Caatinga is the only exclusive Brazilian domain containing these plants. The Caatinga represents about 10% of the national territory and about 60% of Northeastern Brazil. The Caatinga is characterized by its great diversity, (its diverse and endemic flora is composed mainly of annual herbaceous and woody shrub species, with 932 plant species recorded in the region, and of which 380 are endemic). Yet the Caatinga still suffers from a scarcity of ethnopharmacological study and/or scientific characterization (Torres et al., 2021), and legislative and practical problems in maintaining the biome are still frequently encountered (Vasconcelos et al., 2017).

Exploring the ethnobotanical diversity of the Caatinga, Roque et al. (2010) recorded the use of 62 native plants suitable for a pharmacological application based on the common knowledge of a rural community in the municipality of Caicó, Rio Grande do Norte. The most commonly mentioned species were aroeira (*Myracrodruon urundeuva* Alemão), cumaru (*Amburana cearensis*), marmeleiro (*Croton blanchetianus*), quebra-pedra (*Phyllanthus niruri*), and carrapicho (*Acanthospermum hispidum*).

Due to the known bioactive potential of their chemical compounds, certain Caatinga species have demonstrated pharmacological activity. Emiliano and Balliano (2019) evaluated the pharmacological activities of *Croton heliotropiifolius* and *Croton argyrophyllus*, which are traditionally used as antifungal and anti-inflammatory drugs, while Neri et al. (2021) evaluated the antioxidant activity of *Croton argyrophyllus*. Previously used in popular medicine as anti-inflammatories, another 15 plants from the Caatinga have also shown potential for sun protection.

3.2. Phytochemistry

Many different phytochemical compounds are present in high concentrations in the Caatinga flora (Moura et al., 2019). The application of laboratory analysis, phytochemical typology, and experimental studies can determine the medicinal efficacy of their use, which is culturally disseminated by local populations. Secondary metabolites, the main phytochemical constituents with bioactive properties, combat many types of microorganisms, including filamentous fungi, yeasts, and bacteria. The principal secondary metabolites listed in the literature are the terpenes, phenolic compounds, nitrogen and organosulfur compounds, and alkaloids. However, in many medicinal plant groups, the terpene group (terpenoids) are prominent (Verruck et al., 2018).

3.3. Terpenoids

Terpenoids, are mostly found in plants as secondary metabolites, although they can also be found in animals as sterols and squalene. Currently, there are at least 60,000 terpenoids, making them the most significant and oldest family of natural products found on earth. (Cox-Georgian et al., 2019).

Terpenes play many roles in living organisms, they protect microorganisms, animals, and plants from both abiotic and biotic stress. Terpenoid compounds can help ward off pathogens, predators, and other natural plant competitors (Gershenzon; Dudareva, 2007), as well as serve medicinal purposes.

3.4. Classifications

Terpenes are classified according to the number of isoprene ($C_5 H_8$) units (Figure 1) present in their molecule, which can be: hemiterpenes ($C_5 H_8$), monoterpenes ($C_{10} H_{16}$) sesquiterpenes ($C_{15} H_{24}$), diterpenes ($C_{20} H_{32}$), sesquiterpenes ($C_{25} H_{40}$), triterpenes ($C_{30} H_{48}$), tetraterpenes ($C_{40} H_{64}$) or polyterpenes (C_{50} or >, and $H_{50\text{-}80}$ or >) (Mcgarvey and Croteau’, 1995).

3.5. Monoterpenes

The vast part of monoterpenes are volatile and primary constituents of essential oils or essences, such as menthol, linalool, and citral. Monoterpenes constitute 90% of essential oils and have many pharmacological activities already described in the literature, such as analgesic, anti-inflammatory, antidepressant, and anticonvulsant activity (Peixoto-Neves et al., 2010). Two monoterpenes that stand out for their antifungal activity and known in the literature are thymol and carvacrol (Figure 2) which are aromatic monoterpenes very present in plants such as *Lippia sidoides* (Verbenaceae) (Baldim et al., 2022).

3.6. Diterpenes

Diterpenes are part of a large and diverse class of unique metabolites that can be considered the result of natural factors, they can provide chemical defense against predators, mechanical injury, phytophages, pathogens, mechanical injury, and ecological interactions They often represent an alternative metabolic strategy to increase the average life of certain organic substances inside the cell, as well as other environmental factors. Diterpenes, mainly polycyclic with a carboxyl group, are present in various plant resins, such as copaiba (*Copaifera langsdorfii*, Fabaceae). There are several studies investigating and evaluating the activities of diterpenes isolated from copaifera, including copalic acid (Figure 3) as a therapeutic alternative for fighting against microorganisms. (Abrão et al., 2015).

3.7. Sesquiterpenes

The structural diversity of sesquiterpenes promotes a variety of pharmacological activities, not only through discovery of new molecules but also through improvements in drug development against emerging threats. Although sesquiterpenes are a class of terpenes, they can be categorized according to their biosynthetic origin, for example, carotenoids (MEP pathway cleavage products), drimanes, farnesene, and cyclic sesquiterpenes (FPP) (Chappell et al., 2010).

Some compounds originating from the MEP pathway (Figure 4), such as β-caryophyllene, can be found in a variety of plants, as an example, one of the most prominent constituents of the essential oils of *Pterodon emarginatus* and *Schinopsis brasiliensis*, exhibits antioxidant and anticancer activity (Donati et al., 2015). β-caryophyllene, also found in *Croton zehntneri* and *Eugenia uniflora* essential oils, presents antifungal activity (Santos et al., 2020; Costa et al., 2022).

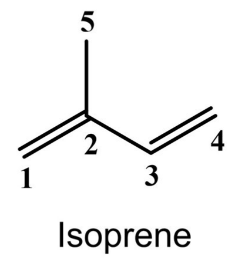

Figure 1. Formula of isoprene (Felipe and Bicas, 2017).

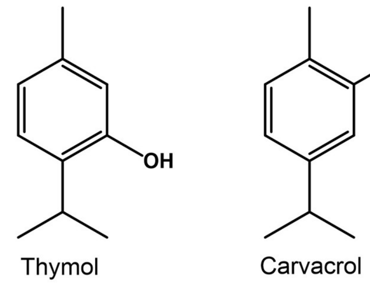

Figure 2. Formula of thymol and carvacrol (Felipe and Bicas, 2017).

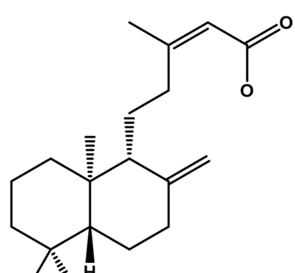

Figure 3. Molecular structure of copalic acid diterpene (Medeiros et al., 2021).

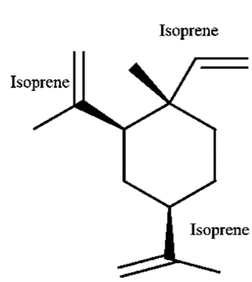

Figure 4. Sesquiterpene molecule (Dias and Amaro, 2020).

3.8. Triterpenes

Triterpenes are hydrocarbons that have relatively complex cyclic structures formed by the condensation of two FPPs, such as squalene (Figure 5). These are principally found in nature as 1-5 ring systems, and are formed in plants, animals, and fungi by numerous terpene synthases such as: squalene synthase, triterpene synthase, and oxidosqualene cyclase (OSC) (Garg et al., 2020).

3.9. Antifungal activity

There are a variety of terpenes that present antifungal activity. In Table 1, the results of the most recent studies can be found, summarized about terpenes whether extracted from Caatinga plants, or through synthetic processes. These molecules: terpinene-4-ol, limonene, γ-terpinene, E-cinnamaldehyde, Linalool, α terpineol, (-)-borneol, β-caryophyllene, germacrene D, and bicyclogermacrene present good antifungal activity, with significant biotechnological potential. However, overall, their mechanisms of action still need evaluation.

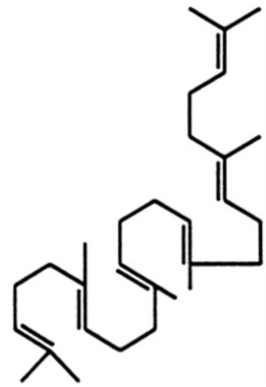

Figure 5. Structure of squalene (Dias and Amaro, 2020).

Table 1. Terpenes isolated from Caatinga species and related antimicrobial activities.

Species	Part of the Plant/ Extraction type	Terpenes	Activity investigated	Main results	Reference
Eugenia uniflora	Essential oil	β - Elemene, Caryophyllene, D-Germacrene, Bicyclogermacrene, α-Bulnesene, Germacrene B, Selina-1,3,7 (11)-trien-8-one, Germacrone, selina-1,3,7 (11)-trien-8-one epoxide	Antifungal activity and virulence inhibition against *Candida albicans, C. tropicalis* and *C. krusei*	High concentrations of essential oil were required to obtain an antifungal effect, with no synergism on the combination with fluconazole - regardless, good results were obtained in relation to *C. albicans* and *C. tropicalis*	(Santos et al., 2018)
Lippia gracilis	Essential oil, and essential oil emulsions	α-Thujene α-Pinene. Mircene, α Terpinene, p-Cimene, Limonene 1,8 Cineol, γ-Terpinene, Linalol, Terpinen-4-ol Metyl tymol, Tymol, Carvacrol, β-Cariofilene, α-Humulene, Viridiflorene, Biciclogermacrene, Espathulenol, Caryophyllene Oxide	Antifungal activity of the oil and its nanoemulsions against *Thielaviopis paradoxa*	MIC was 0.23 ± 0.3 mg/mL, and MFC 0.80 ± 0.08 mg/mL, the fungicide potential was maintained at the nanoemulsion developed.	(Cruz et al., 2018)
Lippia alba	Essential oil of leaves	Marjority: 6-methy-5-hepten-2-one, nerol/geraniol, citral (neral/geranial), E-caryophyllene	Antimicrobial activity (antifungal and antibacterial) against 16 microorganisms, and cytotoxic activity against cell lines B16F10Nex2, MCF-7, HUVEC, CT26WT, A549, MDA-MB-231, CACO 2, and CHO.	Cytotoxic activity was observed in tumor cell lines B16F10Nex2 and A549. The essential oil showed activity in all yeasts strains, except *C. albicans*.	(Santos et al., 2016)
R. echinus Schauer	Essential oil	Marjority: β-Caryophyllene and bicyclogermacrene	Antifungical activity against *Candida albicans, C. krusei* and *tropicalis*, and *E. coli,*	The essential oil itself was not relevant for clinical use, but it showed capability to enhance antibacterial and antifungal activity of nystatin and fluconazole.	(Duarte et al., 2016)

Table 1. Continued...

Species	Part of the Plant/ Extraction type	Terpenes	Activity investigated	Main results	Reference
Eremanthus arboreus	Essential oils	Main component: α-Bisabolol	Chemical composition and literature review of its antimicrobial activities	As the main component of the essential oil, is α-Bisabolol, it has pharmaceutical potential to present antimicrobial, larvicide, anti-inflammatory and antinociceptive.	(Macedo et al., 2020)
Lippia gracilis	Leaves/ hydrodistilled	Carvacrol, thymol	Antifungal activity	The biomass formation of the *F. oxysporum* biofilm was inhibited completely at essential oils concentrations ranging from 0.3125 to 10 mg ml^{-1} .	(Oliveira et al., 2021)
Lippia sidoides, Lippia gracilis	Leaves/ hydrodistillation	Thymol, carvacrol	Antifungal activity	At concentrations of 0.3 µL mL^{-1}, both the essential oils of L. gracilis and *L. sidoides* inhibited 100% mycelial growth of *Colletotrichum sp.*	(Araújo et al., 2018)
Eugenia uniflora L.	Leaves/ hydro-distillation	Mono- and sesquiterpenes	Antifungal activity and potential anti-virulence	The concentration that reduced microorganismal growth was ≥8,192 µg/mL while the IC50 varied, this being between 1892.47 and 12491.80 µg/ mL (oil), 10.07 – 80.78 µg/mL (fluconazole) and 18.53 – 295.60 µg/mL (fluconazole + oil). 295.60 µg/mL (fluconazole + oil).	(Santos et al., 2018)
Lippia alba (Mill.) N.E.Br. ex Britton & P. Wilson (Verbenaceae)	Leaves/ hydro-distillation	Linalool, trans-ocimenone and caryophyllene oxide	Antifungal activity	The essential oils showed antifungal activity, mainly against *S. slerotiorum*, a fungi species related with diseases in soybean plants, with 100% of growth inhibition.	(Arruda et al., 2019)
Croton tricolor	Stems/ hydrodistillation	Epiglobulol, α-bisabolol, α-trans-bergamotol and β-caryophyllene.	Antifungal activity	Essential oils concentrations from 1.0 to 1024 µg/mL inhibited the growth of all tested strains,	(Miranda et al., 2019)
Nectandra, and *Ocotea* genera	Seeds, leaves, stem barks, and twigs/ hydrodistillation	β-caryophyllene, germacrene D, bicyclogermacrene, caryophyllene oxide, α-bisabolol, bicyclogermacrenal, phenylpropanoids, safrole, 6-methoxyelemicin, apiole, limonene, α-pinene, β-pinene, 1,8-cineole, and camphor.	Antimicrobial activity	Several biological activities have been attributed to these oils, especially cytotoxic, antioxidant and antifungal potential, among other pharmacological applications.	(Xavier et al., 2020)

Table 1. Continued...

Species	Part of the Plant/ Extraction type	Terpenes	Activity investigated	Main results	Reference
Mentha piperita L.	Essential oils, and citral and limonene	The chemical nature of the essential oils were not studied. Citral and Limonene.	Screening and selection the best product with antifungal activity against *C. albicans* strains isolated from dental prostheses	Of all essential oils and molecules, citral presented the best antifungal activity, against strains nystatin resistant	(Freire et al., 2017)
Algrizea minor	The essential oil was extracted by hydrodistillation of the leaves	b-Pinene and a-Pinene (monoterpene)	The antimicrobial activity of *Algrizea minor* essential oil, which contains as main constituents b-Pinene and a-Pinene	*Candida albicans* ATCC 10231 (500 mg/mL) and *Candida glabrata* ATCC 15126 (1000 mg/mL)	(Veras et al., 2020)
Schinus terebinthifolia	Essential oils from leaves by hydrodistillation	Terpenes	Antichemotactic and Antifungal Action of the Essential Oils from *Cryptocarya aschersoniana*, *Schinus terebinthifolia,* and *Cinnamomum amoenum*	Resulting in MIC ranging from 125 µg/mL to over 500 µg/mL. C. aschersoniana oil inhibited the growth of species of the genera *Trichophyton* and *Microsporum* and combined terbinafine resulted in an additive interaction effect	(Maciel et al., 2019)
Eugenia uniflora	Leaves extract	Terpenes	Antifungal potential of plant species from brazilian caatinga against. Dermatophytes.	An inhibitory effect on dermatophytes growth was observed for essential oil from leaves of E. uniflora cultivated in the Brazilian cerrado for AcE of E. uniflora, which exhibited moderate activity against most clinical isolates (MIC90 of 125.0 µg/mL)	(Biasi-Garbin et al., 2016)

Zheng et al. (2015) investigated Citral´s action mechanism against *Penicillium digitatum*. Mitochondria were extracted and visualized using scanning electron microscopy. Intracellular and extracellular ATP levels were evaluated, as well as effects on respiratory metabolism, citric acid (CA), and enzymatic activity related to TCA metabolism. The study results revealed that citral was involved in inhibiting respiratory metabolism by affecting mitochondrial morphology and function. According to the study, citral diminished enzymatic activity related to TCA and its metabolic functions. The same species, *P. digitatum*, presented sensibility against another terpene, citronellal. However, its mechanism of action was different. Ouyang et al. (2021) showed that *P. digitatum* membrane integrity was affected in cells treated with citronellal, and ergosterol biosynthesis was modified.

Further, citronellal inhibitory activity was diminished when exogenous ergosterol was added to restore ergosterol to normal levels. Consequently, membrane structure was also restored, and an accumulation of ergosta-7,22-dienol was observed, which made the authors suppose that this terpene, citronellal, down regulates the ERG3 gene. The ERG3 gene is involved in lanosterol conversion into ergosterol, a fundamental component of the fungal membrane. Therefore, through this mechanism, citronellal interferes in fungal plasmatic membrane integrity. These examples show how certain terpenes act depending on their molecular structures and the peculiarity of the targeted cell.

As shown before, the same cell can be affected differently by distinct molecules with differing mechanisms. Shi et al. (2019) demonstrated how derivatives of the same molecule, β-pinene, can act differently. This type of study helps to understand which portion of a molecule interacts with the target cell. The β-pinene derivatives presented better results against some species than others. The study also showed both moderate and significant antifungal activity through pinene skeleton fusion with the amide portion of acylthiourea.

In analysis of structure-activity relationships, it was shown that a trifluoromethyl group at the benzene ring of the derivatives, or a fluor atom and nitro group, could significantly improve activity.

Brilhante et al. (2019) demonstrated the effects of Terpinen-4-ol against species of *Sporothrix schenckii* complex, a human pathogen that causes sporotrichosis. The authors investigated its effects against the planktonic and biofilm forms of *S. schenckii*. Terpinen-4-ol was effective against both fungi forms, being responsible for membrane alterations through ergosterol reductions. The authors also combined the terpene with other drugs, such as ergosterol synthesis inhibitors, such as ITC (14-α-demethylase inhibitor), and TRB (squalene epoxidase inhibitor). Synergism was observed for both associations, with distinct inhibition points in the ergosterol biosynthesis cascade.

Besides the mechanisms discussed here, many others still need elucidation. Research for alternatives to infections caused by drug-resistant strains makes this field of research fundamental. It is also essential to focus on combination therapeutics, as was discussed in the literature (Brilhante et al., 2019), it is a worldwide tendency, and is becoming an important focus in modern pharmacology. Since terpenes represent a class of molecules with diverse structures and many activities that still need elucidation, they are also a promising discovery field for further research.

4. Future Perspectives

Knowledge concerning bioactive molecules has increased significantly over the past few years, and phytochemicals isolated from plants can be found which have various applications in the food, cosmetics, and pharmaceutical industries (antifungal applications). Terpenoids are found in such diverse applications, this review analyzes data from studies describing the fungicidal activity of terpenes and prospects for future use. Terpenoids present differing mechanisms of action, and can interfere with microbial membrane functions, or suppress virulence factors such as production of enzymes and toxins, or by acting against fungal biofilm formation.

Due to its large territory, Brazil has a rich and diverse flora that can be studied and explored. The Caatinga, as a Brazilian exclusivity, still presents plants that are little known. Such resources may provide new molecules and a diversity of applications for industry. Preservation of this biome and new bio-prospective research of its grand potential are of great importance.

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