TRADITIONAL USES, CHEMICAL COMPOUNDS, BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES OF *Protium heptaphyllum* (AUBL.) MARCHAND

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Abstract: *Protium heptaphyllum* (Aubl.) Marchand is a tropical species native to South America and belongs to the Burseraceae family. This species has been widely used by traditional communities, particularly for its essential oils and the resin exuded from the stem, which have therapeutic properties. This review evaluated the chemical composition, biological activities, and ethnopharmacological aspects of *Protium heptaphyllum.* Fifty-four studies were analyzed following the PRISMA criteria and 230 chemical compounds were identified. The biological properties include anti-inflammatory, antimicrobial, larvicidal and anxiolytic activities. The results highlight this species' diverse biological activities and therapeutic and pharmacological potential in metabolism, vector control, tissue regeneration, and its cultural and ethnopharmacological applications. However, the predominant focus on resin indicates the need to investigate other botanical parts, such as leaves, fruits, and bark, to understand their bioactive properties comprehensively. Furthermore, this highlights the importance of integrating tradition and science to develop new pharmaceutical and biotechnological products.

Keywords: Amescla, Ethnopharmacology, Essential oil, Resin.

INTRODUCTION

Protium heptaphyllum (Aubl.) Marchand is a widely tropically distributed species and belongs to the Burseraceae family, one of the most diverse plant families worldwide, with ecological and economic importance due to its ability to produce resin and starch and a significant amount of essential oil (ABAD-FITZ *et al.*, 2022; DALY *et al.*, 2022). This family is subdivided into four main tribes: Garugeae, Bursereae, Protieae, and Beiselieae, comprising 19 genera and more than 800 species identified to date (DALY; FINE; MARTÍNEZ-HABIBE, 2012; COLE; GONZALEZ, 2023). Among these genera, the most representative are: *Commiphora* (~180 espécies), *Protium* (~150 espécies), *Bursera* (~120 espécies) e *Boswellia* (~23 espécies). In addition to its high species richness, this family is widely distributed across habitats ranging from tropical forests to semi-arid areas, reflecting evolutionary adaptations to diverse environmental conditions (DALY *et al.*, 2022).

Protium heptaphyllum is known as “Amescla” or “Breu-branco” in Brazil and is found across a wide geographical range, from the Amazon region (North) to the state of Bahia in the Northeast (CAMPOS FILHO; SARTORELLI, 2015a). Due to the country’s vast territorial extension and the distinct climatic conditions across regions, this broad distribution reflects the species’ high adaptability and ecological relevance across multiple biomes, making it a species of interest for conservation and the sustainable use of natural resources. Furthermore, *P. heptaphyllum* trees can reach up to 18 meters in height and 60 cm in diameter. The leaves are compound and alternate, and their wine-colored fruits are consumed by various animals, serving as a food source in forest ecosystems. The plant’s life cycle includes flowering between July and October and fruiting from July to November (CAMPOS FILHO; SARTORELLI, 2015a). However, many native species are under pressure from deforestation and timber extraction, such as *Protium bahianum*, *Protium glaziovii*, and *Protium occhionii*, which are classified as at risk of extinction (BRASIL, 2022).

The commercial uses of *P. heptaphyllum* are broad, particularly related to its wood and woodwork applications. In addition, an aromatic resin extracted from the stem has multiple uses, including in the cosmetics industry, as a sealant in civil construction, and, notably, for its cultural value, being traditionally used by Indigenous populations for body painting (CAMPOS FILHO; SARTORELLI, 2015b). Therefore, it is noteworthy that the importance of conserving and preserving the species is not only for biodiversity but also for its medical, commercial, and industrial applications.

The essential oils found in the resin of this species, as well as in other members of the Burseraceae family, have been extensively studied and used in traditional medicine due to their biological activities, which include analgesic, anti-inflammatory, antifungal, antioxidant, insecticidal, and larvicidal properties (MURTHY *et al.*, 2016). The major phytochemical compounds found in *P. heptaphyllum* are mainly terpenoids, including mono-, di-, tri-, and sesquiterpenoids, which are responsible for the plant's ecological interactions and potential applications in modern medicine (MURTHY *et al.*, 2016).

Due to the increasing appreciation of natural products and the search for sustainable alternatives in the medical and industrial fields, the study of *Protium heptaphyllum* (Aubl.) Marchand has become relevant. Research on its chemical compounds and biological activities may contribute to developing new products and promote sustainable management practices by integrating conservation and using natural resources.

RESULTS AND DISCUSSION

A total of 438 works were retrieved using descriptors. Subsequently, the inclusion and exclusion criteria were applied, and 55 articles remained for a comprehensive review (Figure 1). The temporal scale of the articles covers 44 years, from 1980 to 2024, with the majority published in the last 20 years. These results indicate that research on *P. heptaphyllum* has been recently conducted, most likely due to its relevance to biological, cosmetic, pharmacological, and traditional knowledge. The resin is the most commonly used botanical part, followed by bark, leaves and fruits. The main product obtained from the plant is the essential oil. The related biological activities were: acaricidal, anesthetic, antibacterial, antidepressant, antifungal, anti-hypercholesterolemia, antihyperglycemic, anti-inflammatory, antileishmanial, antimutagenic, antinociceptive, antiobesity, antioxidant, antipruritic, anxiolytic, biopesticide, cardioprotective, cytotoxicity, gastroprotective, hepatoprotection, hypolipidemic, larvicide, sedative, vasorelaxant and vibriocidal.

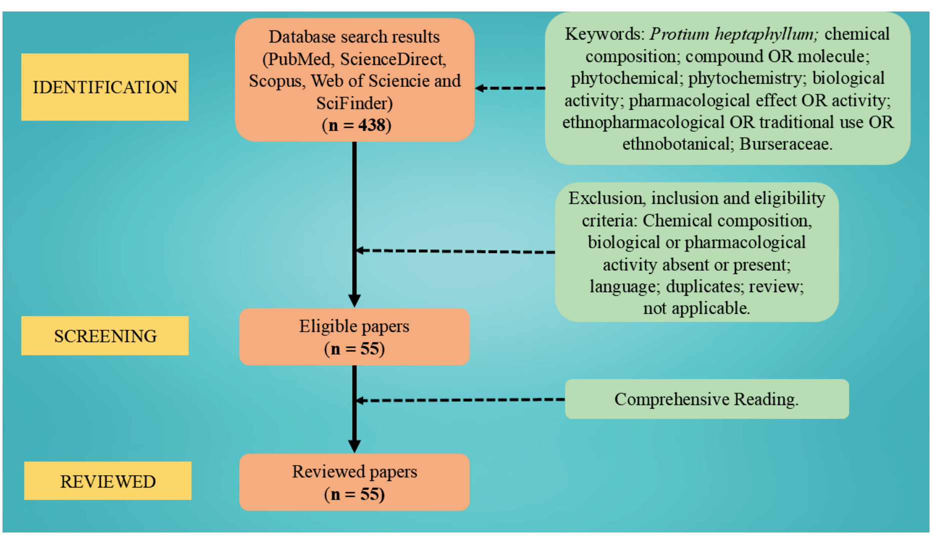

Figure 1. Identified process workflow: screening and review of *Protium heptaphyllum* studies, according to PRISMA.

Traditional use

The traditional use of *P. heptaphyllum* is widespread in resin applications. Some reports indicate that it is commonly used as a flavoring and anti-humidity agent, especially when mixed with *Erythroxylum coca* (coca) leaves, and is also applied in religious rituals and indigenous celebrations (SCHULTES, 1981; WILBERT, 1991). It can be used in baths, fumigation, or even by inhaling the smoke, which is released through burning in incense-like devices or during rituals involving the act of smoking (COELHO-FERREIRA, 2009). Accordingly, these applications act as purifying agents and provide protection, preserving the domestic environment against unwanted influences and negative energy. This traditional use integrates popular medicine and spiritual practices, revealing how deeply rooted these compounds are in various cultural traditions.

Furthermore, the resin is applied to disease conditions such as stroke and pulmonary problems, which include seizures, paralysis, respiratory diseases, tetanus, measles, viral hepatitis, and bacterial and fungal skin infections (SANTOS *et al.*, 2012b; PAGANI, SANTOS, RODRIGUES, 2017). Another application includes Chagas disease, hemorrhages, anxiety, bronchitis, sinusitis, dyspepsia, headaches, rheumatic pain, and wound healing treatments (COELHO-FERREIRA, 2009; RIBEIRO *et al.*, 2017). There are still uses of the bark for the treatment of uterus-related pathologies, including "mãe-do-corpo" conditions, which refers to uterine and abdominal region dysfunctions in popular knowledge (COELHO-FERREIRA, 2009; PAGANI, SANTOS, RODRIGUES, 2017).

Extraction methods

Steam distillation

Steam distillation was performed using three main methods, based on the type of contact with the matrix (PRADO *et al.*, 2021; MACHADO *et al.*, 2022): a) dry steam distillation: the steam is generated outside the distillation flask ("still") and directed to the sample (without direct contact); b) direct steam distillation: the sample is placed above the water level, and the steam flows through the matrix; c) hydrodistillation (direct contact). Several studies that applied these methods did not specify the type of distillation or the process's duration, making reproducibility difficult (ARAUJO *et al.*, 2011; SIANI *et al.*, 2012; MENDES *et al.*, 2019). According to the International Organization for Standardization (ISO 9235, 2021), this information is valuable, since essential oils must be obtained from natural plant materials by steam or dry distillation and subsequently separated from the aqueous phase. The absence of these data results in irreproducibility, which can be defined as the inability to replicate the same results using the same materials and methods of a study (FREEDMAN; COCKBURN; SIMCOE, 2015). Irreproducibility in the biosciences raises doubts about the reliability of published results and does not allow for comparison and discussion of the findings with other studies (FLIER, 2022).

Hydrodistillation with apparatus Clevenger (HC)

The Clevenger apparatus hydrodistillation is the Association of Official Analytical Collaboration (AOAC) official method for essential oil extraction without organic solvents (AOAC, 1990). This method involves some physicochemical processes: cellular lysis, steam distillation or co-evaporation, and decantation. The biological sample is mixed with water, then heated to the boiling point (100 °C), and the generated steam is carried to the condenser, thus obtaining the hydrolate and essential oil, which can be directly retrieved in the equipment through the separatory funnel (KAUR; KAUR, 2023).

Twelve studies used this method, and the authors differed in the extraction time parameter (1–8 hours), considering that 2 out of 12 did not indicate the extraction time in the methods section (RAO *et al*., 2007; HOUËL *et al*., 2015). Mobin *et al*. (2016) investigated the influence of extraction time on the chemical composition and yield. After 5 hours of extraction, 21 compounds were identified, with a 0.11% yield. However, continuous extraction for 6 hours provided a 1.38% higher yield and a lower chemical composition diversity, revealing only 16 compounds. The authors also showed that some compounds were detected only by the third hour of extraction, while other compounds were exclusively identified in the fourth or fifth hours.

Most extraction time ranges used were 2, 4, and 6 hours. The analysis of the articles indicates that some molecules can be detected within specific time ranges; nonetheless, it is not feasible to determine a direct association, since other conditions can influence and determine the absence of a compound or greater chemical diversity (PONTES *et al*., 2007; LIMA *et al*., 2016; Mobin *et al*., 2017; CABRAL *et al*., 2020; SILVA *et al*., 2020; ASTEGGIANO *et al*., 2021). Greater compositional variability tends to occur with longer extraction times; however, some genetic, environmental (soil, temperature, humidity, altitude, biogeochemical cycles), ecological (parasites, allelopathy), seasonal, and physiological (plant growth and development regulators) conditions determine the phytochemical composition (LOŽIENĖ; VENSKUTONIS, 2005; FIGUEIREDO *et al*., 2008; CLEMES *et al*., 2015; KHAN *et al*., 2023).

Concerning the yield versus extraction time, the values found are: 10.2% and 14.4% at 2 hours (LIMA *et al*., 2016), 9.9% to 20% at 4 hours (ALBINO *et al*., 2017), and 8.6% or 11.3% at 8 hours (MARQUES *et al*., 2010). Extractions performed at 1, 2, 3, 4, 5, and 6 hours showed yields ranging from 0.17% to 29% (PONTES *et al*., 2007; AMARAL *et al*., 2009; MOBIN *et al*., 2016; SILVA *et al*., 2016; FAUSTINO *et al*., 2020; CABRAL *et al*., 2021; RODRIGUES *et al*., 2022). Extraction times resulting in high yields (>45%) were not found, although 4-hour extractions showed the best results regarding time efficiency and compositional variety. The higher yields were limited and may be related to genetic, environmental, and physiological factors of the species, as well as the resin's air exposure time during collection or the handling of essential oil after extraction, since these are volatile products and such conditions directly affect yield and composition (SILVA *et al*., 2016).

A fundamental parameter in this process is the extraction duration, which must be adjusted according to the species and the equipment used. These necessary changes are because different species and plant botanical parts show variation in composition and extraction behavior. For instance, in the leaves of *Aquilaria malaccensis* and *Piper mikanianum* (Kunth), the optimal extraction time was determined to be 3.5 hours and 1 hour, respectively. For *Boswellia serrata* resin, the best yields were obtained after 3 hours (CLEMES *et al*., 2015; SAMADI *et al*., 2017; TURK *et al*., 2018). These examples highlight that extraction duration does not correspond to a fixed pattern; rather, it is a variable that depends on the species and the botanical part used (leaves, resin, trunk, bark, and roots).

The solid waste is a byproduct of the hydrodistillation process and, overall, is discarded. It may be used as a secondary material and submitted to re-extraction in organic solvents such as ethanol: water (1:1) or acetone: water (3:2) for the recovery of non-volatile compounds, such as phenolic molecules (OREOPOULOU *et al*., 2018; PSARROU *et al*., 2020; MILJANOVIĆ *et al*., 2023). Therefore, the waste is transformed into an additional source of bioactive molecules, increasing the process efficiency and promoting the full use of the material.

New combinations with Clevenger's apparatus are being developed, such as microwave-assisted distillation, which applies microwave energy to increase water temperature and promote the volatilization of compounds. These environmentally responsible methods may achieve higher yields and shorter extraction times than conventional techniques (LEBOVKA; VOROBIEV; CHEMAT, 2012; MORADALIZADEH; SAMADI; RAJAEI, 2013). On the other hand, no studies have been found regarding extracting essential oil from *P. heptaphyllum* using this method. It remains an open question for future investigations to improve material preparation and identify its active principles through biological activity analysis.

Organic solvent

The organic solvent extraction technique was described in 19 research articles. Five of these 19 focused on extracting non-volatile and total volatile compounds (VCs). A two-day hexane extraction was performed by Silva *et al*. (2009) and Rüdiger and Veiga-Junior (2013); however, only Silva *et al.* (2009) reported a 34% yield. Methanol, ethanol, and diethyl ether were applied to extract VCs, as well as acidic and neutral triterpenes. The total extraction time reached 20 minutes using a sonic bath, with 5%, 23.4%, and 48% yields, respectively (LAGO *et al*., 2016; ASTEGGIANO *et al*., 2021). A hydroalcoholic extract was also carried out, although no yield data were reported (MANNINO *et al*., 2021).

Six studies focused on pentacyclic triterpenoids α/β-amyrin using methanol: dichloromethane (4:1) mixed solvents (OLIVEIRA *et al*., 2004a; OLIVEIRA *et al*., 2005a; LIMA-JÚNIOR *et al*., 2005; OLIVEIRA *et al*., 2005b; SANTOS *et al*., 2012a; CARVALHO *et al*., 2015). Different protocols for triterpenoid extraction were reported, such as, for instance, extraction with hexane and chloroform (MAIA *et al*., 2000), dichloromethane in a Soxhlet apparatus (ALBINO *et al*., 2020), and direct chromatography of the resin on a silica gel column eluted with hexane, chloroform, ethyl acetate, methanol, and/or pentane (ALMEIDA; CONSERVA; LEMOS, 2002; ARAGÃO *et al*., 2006; BANDEIRA *et al*., 2007; LIMA *et al*., 2014; OLIVEIRA *et al*., 2022). Ethanol, methanol, chloroform, and ethyl acetate were also applied for the extraction of phenolic compounds (coumarins, coumarinolignoids, and flavonoids) (ALMEIDA; CONSERVA; LEMOS, 2002; LAGO *et al*., 2016; SINHORIN *et al*., 2020).

Organic solvents allow the extraction of different categories of molecules. For instance, ether and hexane are indicated for the extraction of mono- and sesquiterpenoids; chloroform and ether are used to obtain sesquiterpene lactones, diterpenes, sterols, and less polar triterpenes; high-oxygen compounds, flavones, flavonols, and aglycone flavonoids are most efficiently extracted with highly polar solvents such as n-butanol, acetone, ethanol, methanol, and water, or by using different polar solvents in sequence for a global extraction (AGUIAR; D'ONOFRIO; DAVID, 2022; MASYITA *et al*., 2022). Different polar and mixed solvent solutions or subsequent extractions using other solvents have proven to be a synergistic extraction process when applied in a greater distribution ratio of a single compound present in the mixture (RONCO; GAGLIARDI; CASTELLS, 2019).

The stability of the compounds must be considered during the process. Oxygen in the air leads to spontaneous chain radical reactions in terpene compounds containing double bonds, forming hydroperoxides and chemical decomposition (STEVANOVIC *et al*., 2020). Using inert gas to remove air from the flask is recommended in this context. Oxidative deterioration may also occur due to direct light exposure (ultraviolet and visible light) through photo-oxidation, auto-oxidation, thermal decomposition, and warming effects, as well as structural rearrangement processes such as isomerization, dehydrogenation, and polymerization (TUREK; STINTZING, 2013). Taken together, these conditions promote reduced or lost biological and pharmacological activity of the molecules (CHAABAN *et al*., 2017).

Purification

The essential oils purifying it is an uncommon practice, due to the volatile compounds' evaporation; therefore, it is commonly applied in non-volatile compounds extractions (CHIU *et al*., 2009; SILVA *et al*., 2016). The cryogenic separation and chromatography in silica gel column with eluent polarity gradient: Hexane: Ethyl Acetate (MAIA *et al*., 2000; BANDEIRA *et al.*, 2007; OLIVEIRA *et al.*, 2022); and Hexane:Chloroform: Ethyl Acetate: Methanol were the described methods (ALMEIDA; CONSERVA; LEMOS, 2002; ARAGÃO *et al.*, 2006), and Pentane: Dichloromethane (LIMA *et al.*, 2014). Chromatography is specially used to obtain non-volatile compounds such as pentacyclic triterpenoids (LUCHNIKOVA; GRISHKO; IVSHINA, 2020). This technique allows the separation and identification of compounds present in complex mixtures, providing robust and accurate data, and is widely used in natural product studies (ZHANG; LIN; YE, 2018). Cryogenic separation consists of cooling the sample to low temperatures under high pressure, which promotes physical separation of compounds, followed by water removal. Thus, it prevents the loss of volatile compounds but requires sophisticated equipment systems (HASSAN *et al.*, 2022; FU *et al.*, 2022; JAMES *et al.*, 2023).

Identification

The identification of non-volatile compounds was performed using the classic thin-layer chromatography technique (TLC) with development under ultraviolet light at wavelengths of 190–240, 254, and 399 nm, followed by spraying with Liebermann-Burchard reagent or infrared analysis (MAIA *et al.*, 2000; ARAGÃO *et al.*, 2006; OLIVEIRA *et al.*, 2022; PAULINO *et al.*, 2022). The most sensitive techniques reported in the articles employed various methods for compound identification, such as Nuclear Magnetic Resonance (NMR), High-Performance Liquid Chromatography (HPLC), Ultra-Performance Liquid Chromatography (UPLC), and/or Gas Chromatography (GC) coupled with Flame Ionization Detectors (FID), Mass Spectrometry (MS), and High-Resolution Mass Spectrometry (HRMS). The alternative ionization methods described include Atmospheric Pressure Chemical Ionization (APCI), Electron Impact (EI), and Electrospray Ionization (ESI). Only Mobin *et al.* (2016) reported using multidimensional gas chromatography (MDGC).

High-performance liquid and gas chromatography are highly sensitive techniques that separate complex matrices, allowing for the characterization and isolation of compounds. When hyphenated to MS detectors, they enable precise structural determination (SKALICKA-WOŹNIAK; WIDELSKI; GŁOWNIAK, 2008; HARRIS, 2012). Both techniques are efficient for compound identification, especially when coupled to mass spectrometry (MS), which provides molecular mass information and fragmentation patterns, thereby enhancing structural elucidation capacity (APARICIO-RUIZ *et al.*, 2018).

GC-MS and GC-FID are the most commonly used techniques for identifying volatile and semi-volatile chemical compounds in the essential oil of *P. heptaphyllum*. In these methods, a small amount of sample is injected into the chromatographic column; under programmed heating and carrier gas flow, the molecules are volatilized and separated with high efficiency (SADGROVE; PADILLA-GONZÁLEZ; PHUMTHUM, 2022). The identification is confirmed by mass spectral libraries (NIST, EPA, NIH, WILEY, MassFinder), based on fragmentation pattern profiles and supported by other scientific articles. GC-FID allows identification based on retention indices, using homologous series, especially alkanes (C8–C40) according to the Kovats index. Although efficient for quantifying compounds, GC-FID is often combined with techniques such as GC-MS for structural confirmation.

The most commonly used columns in GC-MS and/or GC-FID analyses were low-polarity or apolar columns (Table 1). The column type influences the separation capacity of compounds in the complex matrices of essential oils and, consequently, may result in different extraction times and/or coelutions. The most common apolar columns applied in essential oil analyses are methylpolysiloxane (HP-1, OV-101, SE-30, etc.) or methyl-phenyl-polysiloxane (SE-52, DB-5, HP-5, etc.), mainly used for separation based on boiling point. Conversely, polar polyethylene glycol columns (Carbowax 20M, Carbowax 4000) or semi-polar cyanopropyl-phenyl polysiloxane columns are the most appropriate for the analysis of terpenes and their oxygenated derivatives, using polarity differences as a separation parameter (CAGLIERO *et al*., 2022; SADGROVE; PADILLA-GONZÁLEZ; PHUMTHUM, 2022).The analysis patterns of Liquid Chromatography (LC) described in the articles involved the use of C18 apolar columns, with water as part of the mobile phase and acetonitrile, or a mixture of water and acetonitrile:methanol (20:80), containing additives such as formic acid (0.1%) or trifluoroacetic acid (0.05%), and employing either gradient and/or isocratic elution (LAGO *et al*., 2016; ALBINO *et al*., 2020; SINHORIN *et al*., 2020; ASTEGGIANO *et al*., 2021; MANNINO *et al*., 2021).

Polarity	Columns	References
Apolar	DB-5, HP-5, DB-1, CP-sil5CB, VF-1, Elite1-ms, OV-5, VF-5, EquityTM-1	Siani *et al*., 1999; Pontes *et al*., 2007; Rao *et al*., 2007; Amaral *et al*., 2009; Silva *et al*., 2009; Marques *et al*., 2010; Araujo *et al*., 2011; Siani *et al*., 2012; Rüdiger; Veiga-Junior, 2013; Lima *et al*., 2014; Houël *et al*., 2015; Lago *et al* 2016; Lima *et al*., 2016; Silva *et al*., 2016; Albino *et al* 2017; Mendes *et al* 2019; Albino *et al*., 2020; Silva *et al*., 2020; Asteggiano *et al*., 2021; Mannino *et al*., 2021.
Low-polarity	Rtx-5, Rxi-5	Faustino *et al*., 2020; Asteggiano *et al*., 2021; Cabral *et al*., 2021; Mannino *et al*., 2021; Oliveira *et al* 2022; Paulino *et al*., 2022; Rodrigues *et al*., 2022.

Table 1 – List of columns used in GC-MS and/or GC-FID with different polarities for the analysis of *P. heptaphyllum* essential oil.

At last, NMR identification allows structural elucidation, including the conformation and configuration of isolated chemical species. However, this method is not commonly used for complex essential oil samples due to the extensive signal overlap, particularly in the aliphatic region (ALENCAR *et al*., 1997). NMR has been employed for the elucidation of pentacyclic triterpenoids, particularly α/β-amyrin and phenolic compounds, in concentrated or purified samples (ALMEIDA, CONSERVA, LEMOS, 2002; OLIVEIRA *et al.*, 2004a; OLIVEIRA *et al.*, 2004b; ARAGÃO *et al.*, 2006; BANDEIRA *et al.*, 2007; SANTOS *et al.*, 2012a; RÜDIGER; VEIGA-JUNIOR, 2013; CARVALHO *et al.*, 2015; LAGO *et al.*, 2016; OLIVEIRA *et al.*, 2022).

2.5 Chemical composition

A total 230 compounds were identified in the extracts from the botanical parts of *P. heptaphyllum*. Of these, 124 were found exclusively in the resin, 26 in the leaves (young and mature), 23 in the fruits (ripe and unripe), and 6 in the bark. The studies that reported the highest numbers of compounds were Siani *et al.* (1999), Pontes *et al.* (2007), Albino *et al.* (2017), and Silva *et al.* (2016), which identified 59, 57, 48, and 46 compounds, respectively. Concerning the essential oils, the major organic classes were terpenes, phenylpropanoids, and isothiocyanates (SADGROVE; PADILLA-GONZÁLEZ; PHUMTHUM, 2022). As a result of this chemical diversity, the compounds were classified into five distinct groups in this review: volatile terpenes, non-volatile terpenes, oxidized terpenes, phenylpropanoids, and flavonoids (Figure 2).

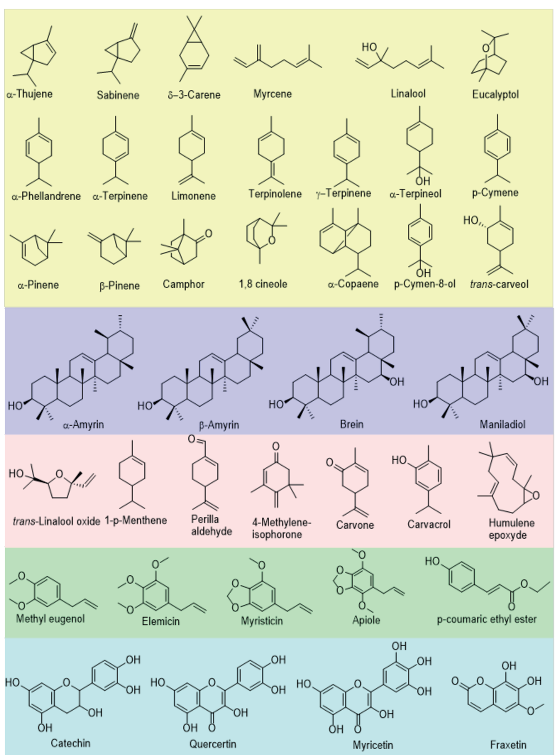

Figure 2. Classes of chemical compounds identified in resin, leaves, and/or bark of *P. heptaphyllum*: volatile terpenes (yellow), non-volatile terpenes (lilac), oxidized terpenes (pink), phenylpropanoids (green), and flavonoids (blue).

Terpenes considered volatile include hemiterpenes (C_5), monoterpenes (C_{10}), sesquiterpenes (C_{15}), some diterpenes (C_{20}), and terpenoids. Greater volatility is associated with a lower number of carbon atoms and the presence of oxygen atoms (ROSENKRANZ; SCHNITZLER, 2016; NINKUU *et al*., 2021; ROSENKRANZ *et al*., 2021). Non-volatile terpenes include diterpenes, triterpenes/steroids (C_{30}), tetraterpenes/carotenoids (C_{40}), and other polyterpenes ($C > 40$) (BREITMAIER, 2006; LORETO *et al*., 2014). Terpene-derived compounds that contain oxygen atoms in their structure—such as alcohols, carboxylic acids, aldehydes, ketones, esters, epoxides, or phenols—are known as terpenoids and are formed through enzymatic reactions, oxidation, or degradation (BRAHMKSHATRIYA; BRAHMKSHATRIYA, 2013).

The abundant volatile monoterpenes and sesquiterpenes in *P. heptaphyllum* were α-thujene, α-pinene, α-phellandrene, α-terpinene, sabinene, δ-3-carene, myrcene, terpinolene, limonene, camphor, linalool, eucalyptol, α-copaene, and spathulenol. The non-volatile compounds included pentacyclic triterpenoids such as α-amyrin, β-amyrin, lupeol, brein, maniladiol, elemonic acid, and lupeol. The terpenoids and oxidized terpenes identified and described in this review were p-cymene and carvacrol (MOBIN *et al*., 2016); humulene epoxide, limonene epoxide, caryophyllene oxide, and α-pinene oxide (PONTES *et al*., 2007; MOBIN *et al*., 2017; CABRAL *et al*., 2021); carvone and perilla aldehyde (PONTES *et al*., 2007; MENDES *et al*., 2019). These molecules can be formed through oxidation reactions such as dehydrogenation, double-bond cleavage, epoxidation, and allylic oxidation, resulting in the formation of alcohols, ketones, and aldehydes, or through enzymatic reactions (MCGRAW *et al*., 1999).

Mobin *et al*., (2017) analysed the oxidation of monoterpenes in fresh and aged oleoresins of *P. heptaphyllum* and hey identified that over time chemical oxidations occur, converting terpinolene into p-cymene, and subsequently into p-cymmene-8-ol. They suggest that structural changes may result from various enzymatic reactions. Another factor contributing to the formation of oxidized compounds is the elevated temperature during extraction, combined with prolonged heating of the sample, which triggers thermal degradation and oxidation reactions (MOBIN *et al*., 2016). Mobin *et al*. (2016) detected that extended heating induced secondary reactions, leading to a decrease in some compounds and an increase in α-terpineol, thereby altering the chemical composition of the essential oil.

The phenylpropanoids (methyl eugenol, elemicin, myristicin, apiole) and flavonoids (catechin, quercetin, myricetin, and fraxetin) were less frequently reported than terpenes. Moreover, they were found in different contexts and plant parts according to the articles; however, they were consistently described in the aerial parts of P. heptaphyllum (SIANI et al., 1999; ALMEIDA, CONSERVA, LEMOS, 2002; MARQUES et al., 2010; LAGO et al., 2016; MOBIN et al., 2016; SINHORIN et al., 2020). In addition, glycosylated compounds such as 3-O-β-D-glycopyranosyl-β-sitosterol and quercetin-3-β-D-glucoside were also described (ALMEIDA, CONSERVA, LEMOS, 2002; SINHORIN et al., 2020); along with alkanes such as bicycloheptane, tridecane, tetradecane, pentadecane, and hexadecane (MARQUES et al., 2010); the alkadiene 1,3-pentadiene; and the ethoxybenzenes 3,5-dimethoxybenzene, 2,5-dimethoxybenzene, and O-methyl anisole (SIANI et al., 1999).

Concerning the chemical composition of leaf extracts, Cabral *et al.* (2021) did not identify significant differences between young and mature leaves, except for three unquantified components: (Z)-β-ocimene, *p*-cymen-8-ol, and (E)-carveol. The authors also reported the presence of additional compounds in young leaves, such as α-thujene, camphene, β-pinene, terpinolene, β-bourbonene, and camphor, among others. Likewise, in resin/oil-resin extracts, the chemical composition of this species may vary depending on environmental conditions, geography, genetics, and physiological factors (CLEMES *et al.*, 2015; KHAN *et al.*, 2023).

The essential oil extracts from immature and mature fruits showed different chemical compositions. In the study by Cabral et al. (2020), germacrene D, α-cadinol, and β-elemene were found exclusively in immature fruits, whereas limonene, trans-nerolidol, and spathulenol were reported in mature fruits. Pontes et al. (2007) identified more than 20 compounds in immature fruits, such as chrysanthenone, karahanaenone, and p-cymen-9-ol. The changes in chemical composition are attributed to enzyme activation, pH variations, temperature, humidity, and plant development, which may promote the formation of reactive oxygen species (TOSUN; USTUN; TEKGULER, 2008; BOURGOU et al., 2012; NOROUZI et al., 2019).

Biological and pharmacological activities

Biopesticide (Acaricidal, Larvicide, and repellent)

Essential oils possess larvicidal and repellent activities that act on multiple targets. These mechanisms include inhibiting key enzymes in insect metabolism, such as acetylcholinesterases, through interactions with olfactory receptors. This process interferes with the insect's odor detection capacity and leads to the dysregulation of ion channels, which affects nerve conduction and may result in neurological collapse. These effects lead to paralysis, disorientation, or death of the organisms, making essential oils effective biopesticides (CORRÊA *et al.*, 2023).

Rodrigues *et al.* (2022) investigated the essential oil biopesticide activity from *P. heptaphyllum* resin against the *Callosobruchus maculatus*, the insect parasite of the feijão-caupi. The repellent effect was evaluated, together with the fumigation and toxicity by contact, and the highest toxicity reported was 14.23 μL/20g in the contact test and 191.28 μL.L-1 of air for fumigation. The repellent effect was detected in all tested concentrations, and at 35 μL/20 g, no reported insect rise. The authors suggest that activity is associated with the D-limonene, the most prevalent compound in the essential oil (40.1%).

The acaricidal activity was analyzed in the study by Pontes *et al*. (2007). Essential oil extracts from leaves and fruits were applied against the mite Tetranychus urticae. The most toxic effects in fumigation and repellent actions were observed with the fruit essential oil, causing 63% mortality at 10 $\mu L \cdot L^{-1}$ of air after 72 hours, while the repellent action started at 0.5%. The leaf essential oil showed lower effectiveness, requiring higher concentrations and longer exposure times to achieve similar effects. In this context, the major compounds in the fruit essential oil were α-terpinene (47.6%) and trans-9-epicaryophyllene (21.4%) in the leaves. Faustino *et al*. (2020) tested the larvicidal activity of a nanoemulsion against *Aedes aegypti* larvae. The activity reached significant mortality with parameters of lethal concentration (LC_{50}) of 2.91 $\mu g.mL^{-1}$ and LC_{90} of 12.44 $\mu g.mL^{-1}$ after 24 hours, with residual effects up to 72 hours. Chemical characterization of the resin oil showed that p-cymene (27.7%) and α-pinene (22.3%) were the main compounds.

Antimicrobial (Antibacterial and Antifungal)

A possible antibacterial and antifungal mechanisms of action of terpenes and terpenoids involve interactions with biological membranes, in which the hydrophobic molecules accumulate, inducing structural and functional disturbances (PATRA; BAEK, 2016). These changes lead to cell swelling, increased membrane fluidity and/or permeability, loss of ion homeostatic control, inhibition of enzymatic pathways related to biosynthesis, and suppression of germination and sporulatio, resulting in cellular dysfunction, cell wall disruption, and bacterial and fungal death (NAZZARO *et al*., 2017). The antibacterial activity was tested by Cabral *et al*. (2020), using the essential oil extract from leaves and mature and immature fruits against seven species of bacteria associated with caries and periodontitis. The leaf essential oil exhibited potent activity against *Streptococcus mutans* and *Streptococcus mitis*, with minimum inhibitory concentrations (MICs) of 50 $\mu g.mL^{-1}$ and 62.5 $\mu g.mL^{-1}$, respectively, while the essential oil from mature and immature fruits exhibited notable activity against *Prevotella nigrescens* (MIC = 50 $\mu g.mL^{-1}$). The MICs for the other tested bacterial species ranged from 100 to 400 $\mu g.mL^{-1}$, depending on the plant matrix**.**

In the study by Lima *et al*. (2016), a weak antibacterial activity was reported using the resin essential oil against *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *S. mutans*, and *C. albicans*, with MIC values ≥ 0.5 $mg.mL^{-1}$. This value was lower than those reported in other studies involving the same species and was attributed to differences in compound composition (MOBIN *et al*., 2016; CABRAL *et al*., 2020). Accordingly, Lima *et al*. (2016) suggested that the composition and ratio of compounds significantly influenced the antimicrobial activity. The antimicrobial activity of the resin essential oil Against *Vibrio parahaemolyticus* (an enteropathogenic bacterium) was evaluated by Mendes *et al*. (2019), and a MIC of 0.25 $mg.mL^{-1}$ proved to be effective. Among the main compounds identified were β-phellandrene (60.68%), followed by *p*-cymene (13.63%) and α-pinene (4.47%).

Melo *et al*. (2023) evaluated the essential oil activity against *Klebsiella pneumoniae* and observed MIC values ranging from 256 to 512 μg.mL^{-1}. This effect was associated with the presence of δ-carene (21.5%) and β-pinene (9.56%).

Mobin *et al*. (2016) evaluated the antifungal activity of resin essential oil against dermatophyte fungi cultures (*Candida krusei*, *C. albicans*, *C. parapsilosis*, *C. metapsilosis*, *C. rugosa*, *C. guilliermondii*) for potential application in the treatment of onychomycosis. The disc diffusion test indicated that all species were inhibited, with inhibition zones ≥ 14 mm at 1000 μg.mL^{-1} concentration. The main compounds identified were L-limonene (21.2%) and α-terpineol (26.1%). Houël et al. (2015) analyzed the effect of immature fruit essential oil on *Trichophyton mentagrophytes*, *Microsporum gypseum*, and *M. canis*. The microdilution test yielded IC_{50} values ranging from 31 to 62 μg.mL^{-1}. Limonene (82%) was the most abundant compound, followed by other monoterpenes such as α-pinene (5.4%), β-pinene (2.5%), and p-cymene (1.5%). The authors highlighted the promising results due to the high antifungal potential of the oil.

Action on the Nervous System (Antidepressant and Anxiolytic)

Aragão *et al*. (2006) described the antidepressant and anxiolytic activity of a mixture of α/β-amyrin extracted from resin in mice. The authors highlighted the antidepressant effects by significantly reducing immobility time in the forced swimming test, using doses of 2.5 and 5 mg. kg^{1}, indicating a positive response to treatment. This effect was blocked when reserpine, an agent that depletes neurotransmitter stores, was previously administered, supporting the involvement of noradrenergic mechanisms in the antidepressant response. The Elevated Plus Maze (EPM) test evaluated the anxiolytic activity. In this assay, the authors observed that 10 and 25 mg.kg^{-1} doses increased both the time spent in the open arms and the number of open arm entries, consistent with those observed when diazepam is used. Flumazenil (2.5 mg.kg^{-1}) was administered, reversing the anxiolytic effect of α/β-amyrin, suggesting the involvement of benzodiazepine receptor modulation.

Antinociceptive (Anesthetic and sedative)

Rao *et al*. (2007) evaluated the resin essential oil antinociceptive activity in mice using the chemical stimulus induced by formalin and capsaicin. The antinociceptive effect was reported after the oral administration of 50 and 100 mg.kg^{-1}. In the test with formalin, the activity reveals a significant effect only in the second phase, and this phase is associated with inflammatory pain, suggesting an anti-inflammatory action in the essential oil. The capsaicin test promotes pain through the TRPV1 receptors, and the essential oil demonstrated a strong antinociceptive effect, highlighted by Suppression of the hind paw-licking response, indicating a possible modulatory action on these receptors.

Silva *et al*. (2020) tested the anesthetic and sedative actions in *Colossoma macropomum*, a fish species. The fruit essential oil promotes sedative effects, observed at a concentration of 250 mg.L^{-1}, intensifying the response at higher concentrations. The authors highlighted research aimed at the anesthetic potential of herbal medicines in fishes, given that MS-222 (tricaine methanesulfonate), benzocaine, and propofol are expensive, frequently imported, and have restricted use, especially in hospitals. Aragão *et al*. (2006) also evaluated sedative effects in mice using an extracted resin α/β-amyrin mixture at doses of 10 and 25 mg.kg^{-1}, which induced sedation in the open field test. Compared with diazepam, it promotes similar effects. The authors also applied flumazenil to evaluate a possible mechanism of action and verified that animals showed behavior comparable to the control group, indicating a benzodiazepine-mediated sedative mechanism.

Energy metabolism (Anti-hypercholesterolemia, hypolipidemic, antiobesity, and antihyperglycemic)

All activities related to energy metabolism were evaluated with pentacyclic terpenoids, especially the resin extract α/β-amyrin. Santos *et al*. (2012a) reported that total cholesterol, triglycerides, low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), and blood glucose were reduced using a 100 mg.kg^{-1} dose; besides, insulin levels and high-density lipoprotein (HDL) were increased. The authors suggest that the cannabinoid system interacts with blood glucose levels and improves these levels; meanwhile, the hypolipidemic action would be related to insulin sensitivity; however, the molecular mechanism needs further investigation.

Carvalho *et al*. (2015) expanded these findings, corroborating the reductions in lipid and glycemic parameters with the α/β-amyrin mixture, which regulates ghrelin, leptin, and resistin levels, and reduces pro-inflammatory mediators such as TNF-α, IL-6, and MCP-1. In addition, it promotes the inhibition of lipid accumulation in adipocytes. These results indicate that the antiobesity potential is due to enzymatic and hormonal secretory modulation, affecting lipid and carbohydrate metabolism and obesity-related inflammation. The ethanolic leaf extract shows antihyperglycemic activity; however, reductions in cholesterol and triglyceride levels have not been reported. These findings suggest that the leaves contain other compounds absent in the resin, which may also act as blood glucose-reducing agents, but not in lipid metabolism (SINHORIN *et al*., 2020). Phenolic compounds are implicated in all of the mechanisms described above.

Mannino *et al*. (2021) evaluated the anti-hypercholesterolemic potential of a hydroalcoholic resin extract in THLE-3 (ATCC) cell cultures treated with 200 μg of the extract for 12 hours. They reported reduced cholesterol levels, with an effect similar to that of lovastatin (10 μg). Genetic analyses revealed significant modulation of gene expression, with most of the downregulated genes related to lipid metabolism regulation, such as LDL receptor, inducible degrader of the LDL receptor (IDOL), and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR). These findings suggest a probable hypolipidemic effect.

Antiparasitário (Antileishmanial)

The antileishmania activity (*Leishmania amazonensis*) was evaluated in the studies by Houël *et al*. (2015) and Cabral *et al*. (2021). Houël *et al*. (2015) reported that the essential oil from immature fruits had an IC_{50} = 3.7 μg.mL^{-1}, and attributed this effect to the major compound, limonene (82%). In tests with leaf essential oil, an IC_{50} = 9.02 μg.mL^{-1} was observed against the promastigote form, whereas the young leaf essential oil showed an IC_{50} = 28.88 μg.mL^{-1}. These differences may be due to the chemical composition, as the young leaves showed a slightly higher proportion of caryophyllene oxide (7.1%) and limonene (6.5%) compared to mature leaves (5.8% and 5.6%, respectively). Caryophyllene oxide is a terpene that inhibits complex III of the electron transport chain in *Leishmania*, while limonene promotes lysis of the parasite's plasma membrane (MONZOTE *et al*., 2018).

Cellular actions (Cytotoxicity, Antimutagenic, and Anti-Inflammatory)

Lima *et al*. (2014) and Lima *et al*. (2016) analyzed the cytotoxic effect of the resin essential oil on MCF-7 cancer cells, and no significant effect was reported at the concentration of 40 μg.mL^{-1}. Nonetheless, the α/β-amyrin-enriched fraction promoted potent cytotoxicity and apoptosis, indicating that the fractions may have oncogenic activity. In the genotoxicity test using cyclophosphamide, a reduction in the number of micronuclei in polychromatic erythrocytes (MN-PCE) was observed, revealing a normal cytotoxicity index across all administered doses (25, 50, and 100 mg. kg^{-1}) (Lima *et al*., 2016). These results suggest that the oil reduced genetic damage and did not induce significant cytotoxic effects, supporting a chemopreventive action. All of these effects are attributed to the monoterpenes.

Oliveira *et al*. (2004a) demonstrated subacute anti-inflammatory activity using the cotton pellet-induced granuloma model with a resin extract obtained in methanol: dichloromethane (4:1). The 200 and 400 mg.kg^{-1} doses resulted in 13% and 14% inhibition, respectively. The study by Amaral *et al*. (2009) used resin essential oil (100 and 200 mg.kg^{-1}). It showed a significant reduction in paw edema, peritoneal vascular permeability, and leukocyte migration, in addition to inhibiting granuloma formation and mast cell degranulation. These results suggest their potential in the treatment of inflammatory conditions, and the major constituent compounds are limonene (49.9%), trans-β-ocimene (11.8%), and eucalyptol (10.9%).

Siani *et al*. (1999) used the resin essential oil in the zymosan-induced protein extravasation model. At a dose of 100 mg.kg^{-1}, the inhibition of the inflammatory response was significant. The authors also investigated the oil's inhibitory capacity on cell proliferation lineages. They found complete inhibition of the neuroblastoma lineage (Neuro-2a), with a

75% reduction in the plasmacytoma lineage (SP2/0) and the monocytic cell line (J774). Terpinolene (21%) and dillapiole (16%) were the main compounds identified in both cases. Cabral *et al*. (2021) conducted a cytotoxicity assay with *Artemia salina* and the essential oil from young and adult leaves showed IC_{50} values of 490.5 $\mu g.mL^{-1}$ and 488.3 $\mu g.mL^{-1}$, respectively. According to Nguta *et al*. (2011), plant extracts with LC_{50} between 100–500 $\mu g.mL^{-1}$ are considered moderately toxic.

Tissue action (Gastroprotective, Hepatoprotection, Vasorelaxant, Cardioprotective, and Antipruritic)

The gastroprotective action was evaluated in ethanol- and acidified ethanol- The gastroprotective action was evaluated in ethanol- and acidified ethanol-induced gastric lesion models (0.3 M HCl) (OLIVEIRA *et al.*, 2004b). Mice were treated with 200 or 400 mg.kg, resulting in 45% and 89% lesion reductions, respectively. This effect may be attributed to the antioxidant capacity of α/β-amyrin (45.25%). The non-protein sulfhydryl (NP-SH) recovery assay yielded negative results, suggesting the involvement of alternative mechanisms of action. Araujo *et al*. (2011) also investigated this effect using essential oils from bark and leaves. The results highlighted a significant inhibition of ulcer formation, attributed to increased cyclooxygenase-2 (COX-2) and epidermal growth factor (EGF) in ethanol, indomethacin, and acetic acid-induced models.

The α/β-amyrins were associated with hepatoprotective and antipruritic activities using a resin extract obtained with methanol: dichloromethane (4:1) (OLIVEIRA *et al.*, 2004a; OLIVEIRA *et al.*, 2004b; OLIVEIRA *et al.*, 2005a). The hepatoprotective activity was evaluated using acetaminophen (500 $mg.kg^{-1}$), which induces fulminant liver failure, histological and biochemical alterations, and severe mortality. Pretreatment with the α/β-amyrins mixture at doses of 50 and 100 mg.kg reduced AST and ALT levels in a dose-dependent manner, restored hepatic glutathione levels, and reduced hepatic tissue damage. The authors attributed these effects to anti-inflammatory activity, reduced oxidative stress, and cytochrome P450 inhibition.

Pruritus was evaluated using dextran T40 (75 $mg.kg^{-1}$) or compound 48/80 (3 $mg.kg^{-1}$), compared to 100 and 200 $mg.kg^{-1}$ of α/β amyrins. Oliveira *et al*. (2004b) showed a significant reduction in mice’s scratching behavior. The mechanism involved comprises the blockade of mast cell degranulation since histamine, once released, acts as a mediator that stimulates the nerve endings of the skin, leading to the scratching sensation. This result may be compared to the anti-histaminic effect and ketotifen, a mast cell stabilizer, which may be used in atopic allergy and would possess a significant clinical effect. Mobin *et al*. (2017) tested a vasorelaxant action on rat mesenteric artery rings and noticed that 10 $\mu mol.L^{-1}$ of the resin essential oil reduces and inhibits phenylephrine-induced muscle contraction. The authors associated this effect with the blockade of Ca^{2+} channels, suggesting that the pharmacological action may be related to more than one secondary metabolite, since three major compounds were identified: limonene (34%), eucalyptol (20.64%), and p-cymene (17.04%).

The cardioprotective action was evaluated by Paulino *et al*. (2022) using α-terpineol extracted from the resin. The cardiac toxicity test was performed with isoproterenol, which induces ischemia, hypoxia, ventricular hypertrophy, and membrane lesions (SIDDIQUI *et al*., 2016). The results indicate a positive response when applying α-terpineol at doses of 25, 50, and 75 $mg.kg^{-1}$, reducing infarct size, necrotic zone, leukocytic infiltrate, edema, cytoplasmic vacuolization, myocardial inflammation, cardiac enzymatic markers (creatine kinase, C-reactive protein, and calcium), tachycardia, and hypertrophy. These data indicate that α-terpineol exhibits preventive mechanisms such as calcium channel blockade, coronary vasodilation, and cardiovascular protection.

Atividade Antioxidant

The antioxidative activity was evaluated using ethanolic and ethyl acetate leaf extracts by applying the free-radical test, 2,2-diphenyl-1-picrylhydrazyl (DPPH□) (SINHORIN *et al*., 2020). Overall, the ethyl acetate fraction showed positive results, especially in the phenol and flavonoid content ratio, with 371 g of gallic acid equivalents per gram (GAE g^{-1}) and rutin equivalents per gram (RE g^{-1}), respectively. These values indicate a high content of bioactive compounds can to combat oxidative stress. LC-UV and LC-MS/MS analyses detected quercetin, quercetin-3-β-d-glucoside, and myricetin, which may be associated with this phenolic antioxidant potential.

EXPERIMENTAL

The literature review used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. The authors created a flowchart summarizing the workflow (LIBERATI *et al*., 2009). The article search was conducted in each database using the breadth and depth method. The first search was performed with all descriptors, and the subsequent ones combined the descriptors, always maintaining the main keyword: "*Protium heptaphyllum*" (TRAINA; TRAINA JÚNIOR, 2009). The following descriptors were: "chemical composition"; "compound OR molecule"; "phytochemical"; "phytochemistry"; "biological activities OR activity"; "pharmacological effect OR activities OR activity"; "Burseraceae"; "ethnopharmacological" OR "traditional use" OR "ethnobotanical". Boolean operators in uppercase (AND/OR) were used to refine the search. Example: (("*Protium heptaphyllum*") AND ("Biological activities" OR "Biological activity")).

The articles identified by the method described above were evaluated regarding the botanical aspect based on the following criteria: (1) chemical composition; (2) compounds and extracts with biological activity; (3) pharmacological and medical data; (4) language of the article. The exclusion criteria were duplicate publications, review articles, taxonomic and/or ecological studies without chemical and/or pharmacological data, citations without additional information, inaccessible documents, and editorials. Articles, books, and book chapters published in English, Spanish, or Portuguese were included in the research. The sources were available in PubMed, ScienceDirect, Scopus, Web of Science, and SciFinder, with no time range restrictions.

Data collection was performed through research summaries and exploratory reading to confirm the use of each data point, evaluating the presence of relevant information or inconsistencies, and interpretative reading to extract the data (LIMA; MIOTO, 2007). The data were analyzed and classified according to chemical group, botanical part used, biological activity, extraction and purification methods, and identification technique. The chemical structures were drawn using ChemDraw Professional © (v. 15.1), following standard conventions for bond lengths and angles, stereochemistry, and atom labeling. Manual adjustments were made when necessary.

CONCLUSIONS

Protium heptaphyllum reveals a considerable chemical diversity with promising pharmacological applications. The predominance of studies of the resin highlights their importance, biological activities, and applications; however, they demonstrate a need for further investigation of other botanical parts of the plant, such as bark, leaves, flowers, and fruits, allowing for a comprehensive chemical characterization and evaluation of bioactive properties. Concerning the identified and quantified methods and techniques employed, intrinsic limitations may underestimate the obtained results. Therefore, it is recommended that additional analyses using different approaches, such as gas and liquid chromatography, coupled with mass spectrometry or nuclear magnetic resonance, be carried out to corroborate the obtained data. In addition, the use of this plant by traditional communities, originating from Indigenous peoples, persists to the present day in geographical regions where the plant-human interaction remains strong. Further investigations are necessary to broaden scientific knowledge to conserve and appreciate the associated cultural and genetic patrimony.

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AUTHOR CONTRIBUTIONS

M. P. Miranda was responsible for Investigation, Data curation, Formal analysis, and Writing – original draft.; R. C. Oliveira and M. B. Loureiro contributed to Formal analysis and Writing - review & editing; A. Lucchese contributed to Supervision, Methodology, Validation, Data curation, and Writing – review & editing, and L.G. Fernandez was responsible for Conceptualization, Project administration, Funding acquisition, Supervision, and Writing – review & editing.

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DECLARATION OF INTEREST

The authors have no relevant financial or non-financial interests to disclose.

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