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Review - Biological and Applied Sciences

Brief Review on *Piper aduncum* L., its Bioactive Metabolites and its Potential to Develop Bioproducts

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HIGHLIGHTS

- *Piper aduncum* L., which belongs to the Piperaceae family, is native to the Amazon region, Brazil.
- Extracts, essential oils (EOs) and compounds isolated from this species have exhibited remarkable biological activities.
- Its major chemical constituent is definitely dillapiole, an arylpropanoid.

Abstract: This literature brief review compiled the main biological activities and active chemical constituents that have already been isolated from *Piper aduncum* (Piperaceae), whose common name is spiked paper. In Brazilian Portuguese, it has been called *pimenta-longa, aperta-ruão, pimenta de macaco, matico, erva de jaboti, jaborandi do mato, pimenta-de-fruto-ganchoso* and *tapa buraco*. Extracts, essential oils (EOs) and compounds isolated from this species have exhibited remarkable fungicidal and insecticidal activities, besides antibacterial, antileishmanial, antioxidant, cytotoxic/antitumor, larvicidal, antiplatelet, molluscoidal and antiviral ones. *P. aduncum* is an endemic species in Brazil which has drawn researchers' attention because of high contents of EOs that are extracted from its leaves, inflorescences and twigs. This study aimed at analyzing data on *P. aduncum*, its EOs, extracts and isolated compounds found in 45 research papers. Its major chemical constituent is definitely dillapiole, an arylpropanoid. Findings were carefully compiled by this brief review which reinforces the chemical and biological potential of this botanic species.

Keywords: Essential oils; Plant extracts; Medicinal plants; Bioproducts; Dillapiole.

INTRODUCTION

Spiked pepper (*Piper aduncum* - Figure 1), which belongs to the Piperaceae family, is native to the Amazon region, Brazil. This species is economically important due to the fact that its essential oils (EOs) have bioactive secondary metabolites, such as dillapiole, linalool and nerolidol [1]. Its EOs exhibit several biological activities, such as fungicidal [1], insecticidal and larvicidal [2,3], molluscoidal [4], parasiticidal [5] and antibiotic [6] ones. When EOs are combined with conventional insecticides, they exhibit synergic potential and mitigate the ability insects have to develop resistance against insecticides. It improves product performance and decreases the amount needed for application [7].

The Piperaceae family comprises around 3,600 species which are distributed in tropical and subtropical regions in the northern and southern hemispheres. It includes herbaceous plants, shrubs and (less frequently) trees distributed in eight genera. The *Piper* genus is the most widely represented with around 2000 species [5]. Investigations into species of *Piper* L. have resulted in isolation of several chemical compounds, such as alkaloids, amides, propenylphenols, lignans, neolignans, terpenes, steroids, kawapyrones, piperolides, chalcones, dihydrochalcones, flavones and flavanones, with biological properties [8]. It should be mentioned that *P. aduncum* is a non-destructive sustainable crop since its EOs and extracts are collected in its aerial parts. Since this species has high resprouting ability, several cuttings may be carried out throughout a year. It characterizes an environmentally correct production system which outperforms other crops because it does not need to be planted every year [9].

Pharmacological effects of *P. aduncum* extracts (ethanol and methanol) and their EOs have been demonstrated, including antileishmanial, antibacterial, cytotoxic and antifungal activities [10]. Furthermore, isolated compounds from leaves have been shown to be very active against promastigote and intracellular amastigotes (which cause damage to DNA) mainly due to their antileishmanial, antimicrobial, molluscoidal, antitumor and antifungal activities [10]. Endophytic fungi isolated from *P. aduncum* also produce extracellular metabolites (found in the culture filtrate) that affect *Mycobacterium tuberculosis* growth [11]. In Brazil, when hexane, ethyl acetate and ethanol were extracted from its leaves and tested against *Anticarsia gemmatalis* and *Spodoptera frugiperda*, they exhibited promising activities [12]. Brazilian researchers have already described excellent results of activities of *P. aduncum* extracts against bacteria that cause dental decay (*Streptococcus mutans* and *Streptococcus sanguinis*) [13].

This brief review comprises all studies of different biological activities and chemical composition which mostly aimed to describe results that could be useful either as an alternative or a complementary strategy to treat diseases. considering that many diseases are still great challenges in many countries in both eastern and western tropical and subtropical regions. It should be highlighted that *P. aduncum* is a species that has a lot to offer in terms of medicinal properties. Thus, further in-depth studies are needed to unveil and apply its benefits to people worldwide.

Methodological development

The methodology used for compiling this paper was a systematic literature review. It was an investigation that focused on well-defined questions which aimed at identifying, selecting, evaluating and summarizing relevant and available evidence, i. e., it consisted in a movement that was based on pre-determined criteria and consistent evidence. Thus, the review was carried out with 45 papers published from 2017 to 2021 in the following databases: Chemical Abstracts Service (SciFinder), Scientific Electronic Library Online (SCIELO), Google Acadêmico and Pubmed. In the search, the following descriptors were used: Piperaceae, *Piper* and *Piper aduncum*.

The *Piper* genus

Piper genus constitutes one major class of medicinal plants used to manage pain and inflammatory disorders in folkloric practice and all genera are represented in the neotropical region, except the monotypic genus *Zippelia*, which is found in tropical Asia. In Brazil, Piperaceae is represented by about 450 taxa distributed in three genera; most are in both Atlântica and Amazon Forests, where approximately 280 and 230 taxa, respectively, can be found [14]. Its representatives may be epiphyte, terrestrial or rupicolous herbs, hemiepiphyte, vines, erect or scandent shrubs or small trees. Leaves are simple, alternate, opposite or verticillate, with entire margins and typical odor. Inflorescences are spikes or racemes, solitary or not, axillary, terminal or oppositifolia. Flowers are abundant, tiny, bisexual or unisexual, chlamydia and bracteate with bracts peltate. Every flower is formed by 2-6 free stamens with rimose anthers; gynoecium has 1-4 stigmata, sessile or with a pistil, superior ovary, sessile or pedicellate, unilocular and with a basal ovule. Fruit are drupes [14]. It should be mentioned that plants that belong to the *Piper* genus may also be found in the Brazilian *Cerrado* and occurs mainly in the States of Distrito Federal, Goiás, Minas Gerais (North of Minas), Mato Grosso do Sul and Mato Grosso [15].

About 180 species have been registered in Rio de Janeiro (RJ) state, Brazil, where 16 *Piper* may be found in the *restinga* vegetation. Due to the number of *Piper* species in *restinga* areas, it may be stated that they may have new physiological and morphological adaptation strategies to survive in this environment, an interesting topic for a chemical study [16]. Other *Piper* species were found in forests in lowlands and in mountains; two of them are strictly distributed in the Guiana Shield: *P. bolivaranum* (new record in Brazil) and *P. wachenheimii* [17]. Several species in this genus have been used in popular medicine in countries in South America, Asia, South Pacific and Africa to treat respiratory and gastrointestinal tract disorders and other diseases [18]. In the literature, there have been reports of anxiolytic, analgesic, anti-inflammatory, vasodilator, cytotoxic, immunomodulatory, antimicrobial and antifungal properties, besides promising antitumor activity. They also have remarkable importance in Phytochemistry and Ethnobotany [18].

Figure 1. *Piper aduncum* L. (Piperaceae) or *pimenta-de-macaco* in Brazilian Portuguese.

The Piperaceae family

The Piperaceae family comprises 10 genera and 1,400-2,000 species in tropical and subtropical regions worldwide. Most are shrubs, herbs and small trees. The family has stood out due to its pharmacological potential, attributed to its compounds, and its abundance in Brazil where several species have had their ethnomedicinal properties described [19]. Mexican researchers have also called attention to the ethnobotanical and medicinal importance of the Piperaceae family [20].

Piperaceae has been frequently studied due to its important characteristics, which enable it to be used in food, pharmaceuticals, cosmetics and perfumes. Several species have been used as spices (fruit), decoration and drugs as teas, infusions and aromatic baths. Stems, fruit, leaves and roots are the most used parts of plants [21, 41]. Piperaceae phytochemicals and EOs have shown higher antioxidant activity than synthetic antioxidants and exhibited antibacterial and antifungal activities against human pathogens [21]. In popular medicine, *P. aduncum* has been used for treating various disorders, such as asthma, bronchitis, cough, abdominal pain, diarrhea and rheumatism [22]. Several other *in vitro* studies confirmed its antibacterial, antifungal, anti-inflammatory, anthelmintic and antileukemic activities [22]. Considering so many benefits, the Piperaceae family keeps being a promising issue in scientific research.

Ethnobotanical studies and medicinal uses of *P. aduncum*

Ethnobotanical data have shown that *P. aduncum* has been used for treating several diseases. Data collected by Pohlit and coauthors (2006) have revealed that this plant is used in traditional formulations by peoples worldwide as an astringent, digestion stimulant, diuretic, antimalaria, sedative and laxative agent. Besides, it is a refreshing beverage and drugs against hemorrhoids, gonorrhea, leucorrhea (vaginal discharge), period cramps, diarrhea, dysentery and toothache [23]. This species also has been used against stomachache and as an insect repellent. In addition, Pohlit and coauthors (2006) have mentioned its traditional use as an antiseptic on skin cuts and as a hemostatic agent (bleeding management). Even more relevant is the hydroalcoholic extract from its leaves, which was officially acknowledged by the Brazilian government in the first Brazilian Pharmacopeia (Pharmacopéia dos Estados Unidos do Brasil, 1926). However, this fluid extract was suppressed from its second edition (2000) [23]. It should also be mentioned that Desmodium®, a compound tea produced by the Laboratório Flora Medicinal J. Monteiro da Silva (Rio de Janeiro, RJ) as a phytotherapeutic product. It is recommended for urinary infection, cystitis, urethritis, prostatitis and edema. It uses the whole *P. aduncum* plant in its formulation (both anti-inflammatory and diuretic activities of *P. aduncum* are mentioned). The manufacturer has sold it for about 70 years [23].

Biological activities of *P. aduncum* extracts and their chemical constituents

Several classes of compounds, such as prenylated benzoic acid derivatives, chromenes or benzopyrans, flavonoids, alkaloids and amides, monoterpenes and sesquiterpenes and phenylpropanoids, have been isolated from *P. aduncum* (Figure 2 - compounds 1-42). Many research papers of *P. aduncum* extracts and isolated compounds, mainly in both Chemistry and Ethnopharmacology fields, have already been published (Table 1), according to Pohlit and coauthors (2006) [23]. This approach described by Pohlit and coauthors (2006) confirm several biological activities of extracts, fractions and active compounds isolated from *P. aduncum* leaves, fruit and twigs. The following biological activities have been described by the literature: antibacterial (Gram positive and Gram negative, even against *Neisseria gonorrhoeae*, the agent that causes gonorrhea) and antifungal (against *Crinipellis perniciosa,* the agent that causes the disease of cocoa, the witches' broom disease, besides pathogenic fungi from wheat, onion, cabbage, banana and others) ones [23].

Other activities include the antiprotozoal (against *Leishmania amazonensis*, the agent that causes leishmaniosis), larvicidal (against *Aedes* sp. or mosquito larvae), insecticidal (against *Cerotoma tingomarianus*, *Tribolium castaneum* and *Choristoneura rosaceana*) and molluscoidal (against *Biomphalaria glabrata*, the schistosomiasis vector) ones. Besides, it inhibits *in vitro* mycelial growth of *Fusarium solani* (Mart.) Sacc. *Fusarium* sp. *Piperis*, the pathogen that destroys *Piper nigrum* [23]. The summary is shown in Table 1. Antiproliferative activity of compounds 4 and 16-19 has already been confirmed *in vitro*. It should be highlighted that the broad spectrum of *in vitro* antimicrobial activities against some species, such as *Trichophyton mentagyrophytes*, *Candida albicans* and *Staphylococcus aureus*, is strong evidence of the potential of *P. aduncum* extracts, fractions and active chemical constituents 7, 8, 15, 21, 23 and 27, applied to several skin diseases. These *in vitro* activities are very relevant to validate drugs in the Dermatology field [23]. According to Brazilian researchers in Chemistry of natural products, *P. aduncum* leaves collected in Manaus, the capital of Amazonas state, Brazil, exhibited high contents of dillapiole (31.5 – 97.3 %) (active chemical constituents 1, Table 1), the compound whose antifungal, antibacterial, larvicidal, insecticidal and molluscoidal activities have already been confirmed by many research papers (Table 1). Some studies showed that dillapiole (1) exhibits synergism with pesticides pyrethroids (pyrethrins) and carbamates *in vitro*, a fact that increases its insecticidal activity when it is used against fruit flies (*Drosophila melanogaster*), *Aedes aegypti* larvae and flour beetles (*Tribolium castaneum*) [23]. When dillapiole is formulated with *Tanacetum vulgare* EOs, it has phagostimulant effect on *Choristoneura rosaceana* (Lepidoptera) larvae. It suggests that it may be mixed with the natural insecticide *Bacillus thuringiensis*, which is used against larvae [23]. Other studies showed that synergism among dillapiole and other compounds increases their biological activity. When dillapiole combines with gedunin (limonoid class), the antimalaria agent isolated from *Cedrela odorata* (Meliaceae) leaves, and with 7-methoxygedunin (semi-synthetic), it mitigates parasitemia in rats infected with *Plasmodium berghei* in *in vivo* assays. On the other hand, dillapiole does not have any significant antimalaria *in vitro* effect by itself. In addition, dillapiole was used for preventing metabolism of active compounds by the p450 cytochrome since it acts as a potential enzyme inhibitor in drug metabolism. The synergic effect was also shown by semi-synthetic derivatives of dillapiole *in vitro*. Derivatives 43-51 (Figure 2) were the ones that exhibited the highest level of synergism against *Tribolium castaneum* and *Aedes atropalpus* larvae. Finally, dillapiole may be used not only as raw material to prepare semi-synthetic derivatives against *Aedes aegypti* adult larvae, the vector of hemorrhagic dengue, but also as an important component of bioproducts.

Recent findings have reinforced that *P. aduncum* extracts have exhibited antileishmanial, antibacterial, cytotoxic and antifungal activities [24]. Furthermore, compounds isolated from its leaves have shown to be very active against promastigote and intracellular amastigotes (which cause damage to DNA), mainly due to their antileishmanial, antimicrobial, molluscoidal, antitumor and antifungal activities [24]. A study of ethanolic extract from *P. aduncum* leaves which was carried out in Dourados, Mato Grosso do Sul (MS) state, Brazil, revealed its antidepressant and anxiolytic activities [25]. Philippine researchers also showed antibacterial potential of ethanolic extract from *P. aduncum* leaves when they incorporated it into liquid hand soap [26]. In addition, its aqueous extract exhibited toxicological effect on *Raoiella indica* in laboratory conditions [27]. Hexane, dichloromethane and ethanolic extracts from *P. aduncum* led to 100% death of *A. aegypti* larvae [28]. Santos and coauthors (2013) showed that hexane and ethanolic extracts from *P. aduncum* are active against dermatophytes *Trichophyton rubrum* and *Trichophyton interdigitale* [29]. Finally, methanolic extract from its leaves exhibited satisfactory anti-inflammatory activity and four new flavonoids [30].

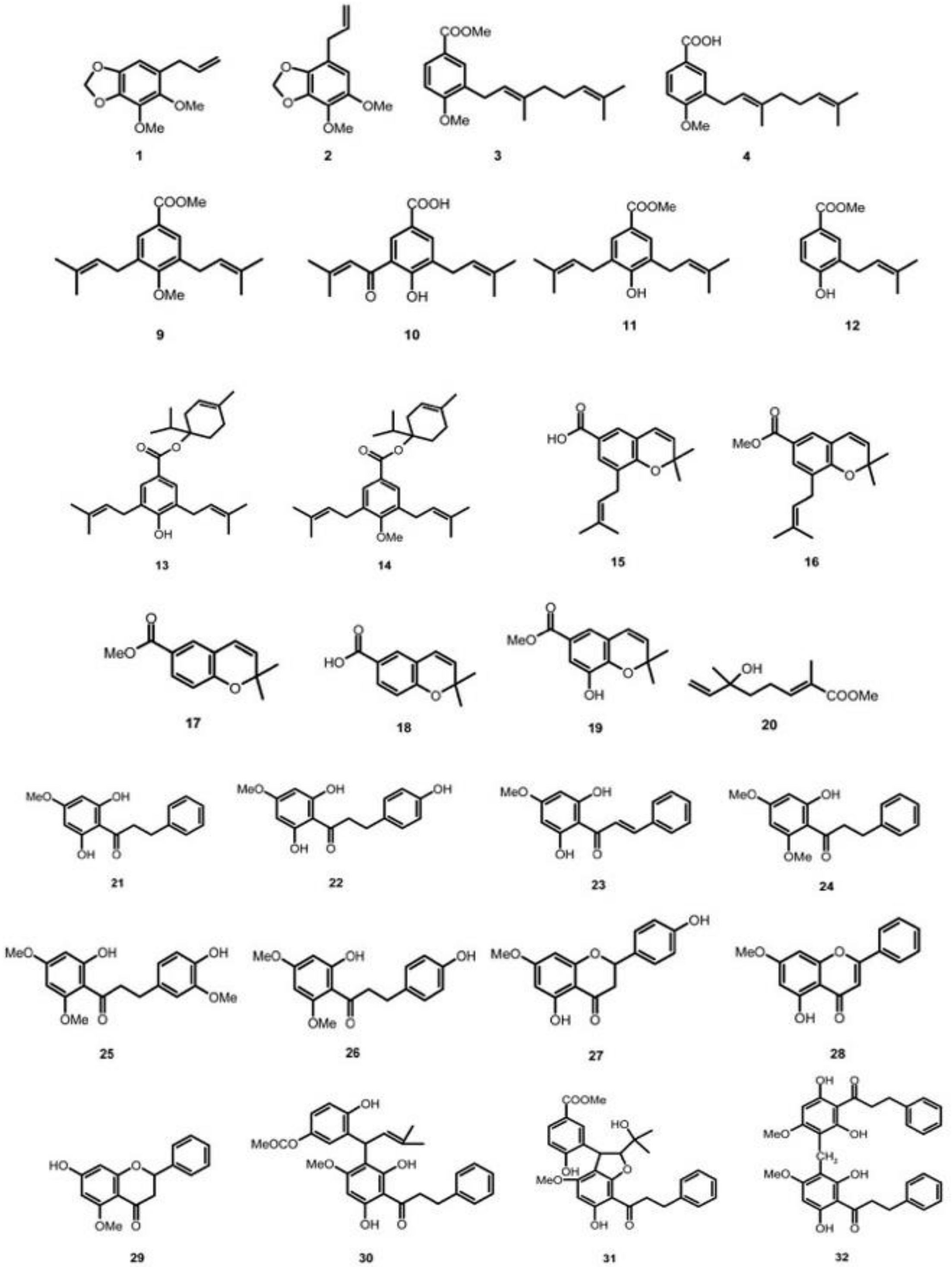

Figure 2. Chemical constituents isolated from *P. aduncum*: **1:** dillapiole (4,5-methyl-1-nodioxy-2,3-dimethoxy-allyl-benzene); **2:** pseudo-dilla-2-piole (2,3-methylenodioxy-4,5- dimethoxy-allyl-benzene); **3:** 3-(3',7'-dimethyl-2',6'-octa-dienyl)-4-methoxy-methyl benzoate; **4:** 3-(3',7'-dimethyl-2',6'-octa-dienyl)-4-methoxy-benzoic acid; **5:** 3-(6'-hydroxy-3',7'-dimethyl-2',7'-octa-dienyl)-4-methoxy- methyl benzoate; **6:** 3-(2'-hydroxy-3'-methyl-3'-butenyl)-4-hydroxy-methyl benzoate; **7:** 4-methoxy-3,5-bis(3'-methyl-2'-butenyl)-benzoic acid; **8:** nervonic acid (4-hydroxy-3,5-bis(3-methyl-2-butenyl) benzoic acid); **9:** 3,5-bis(3-methyl-2-

butenyl)-4-methoxy-methyl benzoate; **10:** 4-hydroxy-3-(3-methyl-2-butenoyl)-5-(3-methyl-2-butenyl)-benzoic acid; **11:** 4-hydroxy-3,5-bis(3'-methyl-2'-butenyl)-11-methyl benzoate; 12: 4-hydroxy-3-(3-methyl-2-butenyl)-methyl benzoate; **13:** 1-(1-methylethyl)-4-methyl-3-cyclohexanol 3,5-bis(3-methyl-2-butenyl)-4-hydroxy-benzoate; **14:** 1-(1-methylethyl)-4-methyl-3-cyclohexanol 3,5-bis(3-methyl-2-butenyl)-4-methoxy-benzoate; **15:** 2,2-dimethyl-8-(3'-methyl-2'-butenyl)-2H-chromeno-6-carboxylic acid; **16:** 2,2-dimethyl-8-(3'-methyl-2'-butenyl)-2H-chromeno-6-methyl carboxylate; **17:** 2,2-dimethyl-2H-chromeno-6-methyl carboxylate; **18:** 2,2-dimethyl-2H-chromeno-6-carboxylic acid ; **19:** 8-hydroxy-2,2-dimethyl-2H-chromeno-6-methyl carboxylate; **20:** (6S)-2-trans-6- hydroxy-2,6-dimethyl-2,7-octadienoate; **21:** 2',6'-dihydroxy-4'-methoxy-dihydrochalcone; **22:** 2',4,6'-trihydroxy-4'-methoxy-dihydrochalcone; **23:** 2', 6'-dihydroxy-4'-methoxy-chalcone; **24:** 2'-hydroxy-4',6'-dimethoxy-dihydrochalcone; **25:** 2',4-dihydroxy-4',6',3-trimethoxy-dihydro-chalcone; **26:** 2',4-dihydroxy-4',6'-dimethoxy-dihydrochalcone; **27:** sakuranetin; **28:** 5-hydroxy-7-methoxy-flavone; **29:** 7-hydroxy-5-methoxy-dihydro-flavone; **30:** piperaduncina A (3-(1-[2,4-dihydroxy-6-methoxy-3-(3-phenylpropanol)-phenyl]-3-methyl-2- butenyl)-4-hydroxy-methyl benzoate); **31:** piperaduncina B (4-hydroxy-3-[2,3-dihidro-2-(1-hydroxy-1-methyl-ethyl)-6-hydroxy-4-methoxy-7-(3-phenyl-propanoil)-benzo[b]furan-3-il] methyl benzoate); **32:** piperaduncina C (bis-[a, b-dihidro-2',6'-dihydroxy-4'-methoxy-chalcone-5'-il] methane) [23].

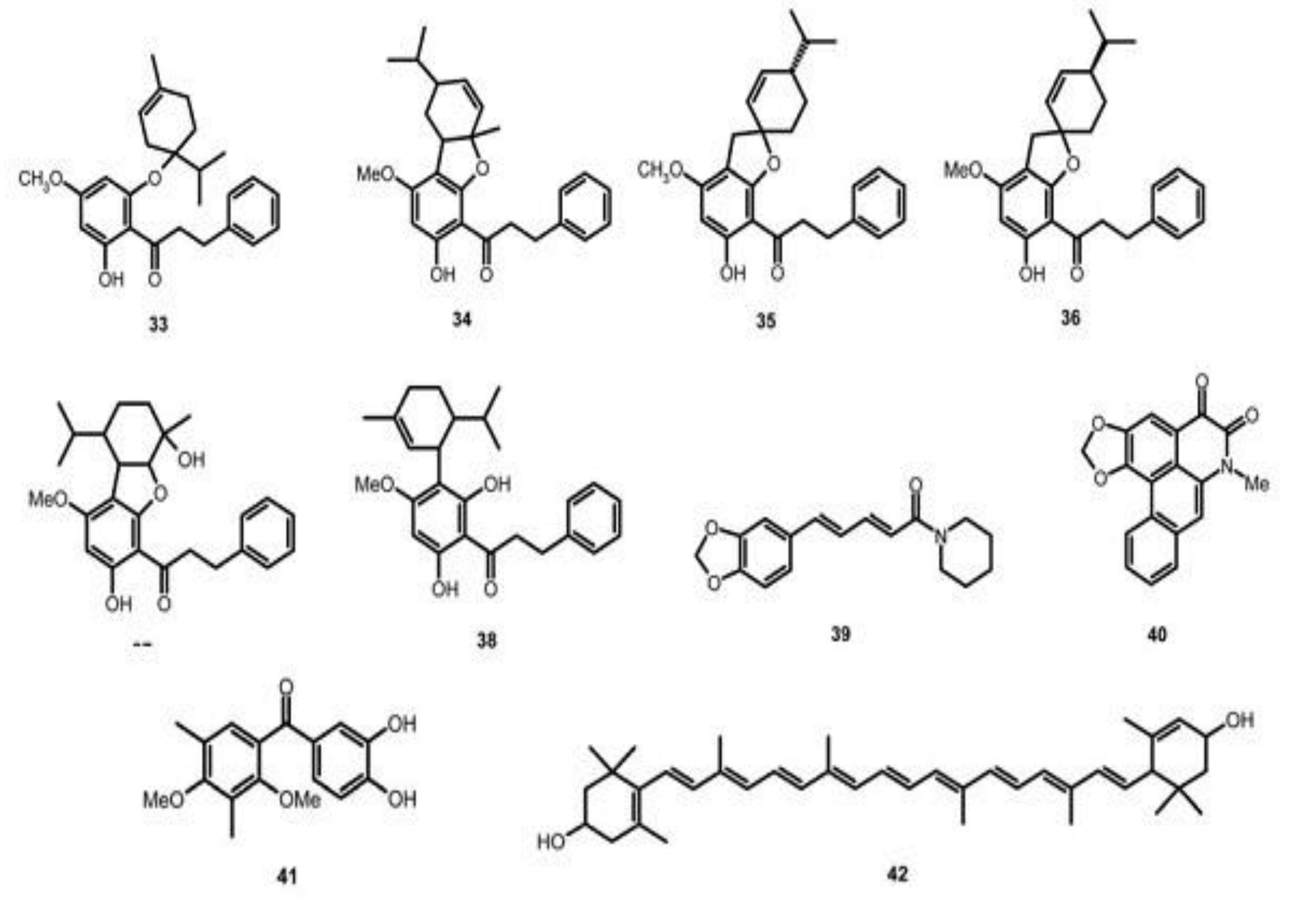

Figure 2 (Continuation). Chemical constituents isolated from *P. aduncum*: 33: adunctin A (1" S)-1-{2'-hydroxi-4'-methoxy-6'-[4"-methyl-1"-(1"'-methylethyl)cyclohex-3"-em-1"-iloxi]phenyl}- 3-phenylpropan-1-ona); 34: adunctin B ((5a 34 R*,8R*,9aR*)-3-phenyl-1-[5'a,8',9',9'a-tetrahydro-3'-hydroxy-1'-methoxy-8'-(1"-methyl ethyl)- 5'a-methyl-dibenzo[b,d] furan-4'-il]propan-1-ona); 35: (2R*,4"S*)-1-{6'-hydroxy-4'-methoxy-4"-(1"'-methylethyl)spiro[benzo[b]furan-2'-(3'H),1-cyclohex-2"-en]-7'il}-3-phenyl-propan-1-ona); 36: adunctin D ((2' R*,4"R*)-1-{6'-hydroxy-4'-methoxy-4"-(1"'-methylethyl)espiro[benzo[b]furan-2'(3'H),1"-cyclohex-2"- en]-7'-il}-3-phenyl-propan-1-ona); 37: adunctin E ((5'a R*,6'S*,9'R*,9'aS*)-1-[5'a,6',7',8',9',9'a-hexahydro-3',6'-dihydroxi-1'-methoxy-6'-methyl-9'-(1"-methylethyl)dibenzo[b,d]furan-4'-il]-3-phenylpropan-1-ona); 38: (-)-methyl-lindaretin; 39: piperine; 40: cefaradiona; 41: 3',4'-dihydroxi-3,5-dimethyl-4,6-dimethoxy-benzophenone; 42: lutein [23].

Table 1. Previously described biological activities of *P. aduncum* L [23].

Type of activity	Organism under evaluation	Derivative under evaluation
Antibacterial	*Actinobacillus actinomycetemcomitans*	Alcoholic extract
	Bacillus cereus	Ethanolic extract
	Bacillus subtilis	Alcoholic extract, dichloromethane extract, petroleum ether extract, active chemical constituents 1, 3, 5-15,19, 21-23, 27, 30-32
	Enterococcus faecalis	Ethanolic extract
	Escherichia coli	Alcoholic extract, petroleum ether extract, dichloromethane extract, active chemical constituent 19
	Fusobacterium nucleatum	Alcoholic extract
	Micrococcus luteus	Petroleum ether extract, dichloromethane extract, active chemical constituents 5-8, 10, 12, 13, 15, 19, 21, 22, 30-32,34-36, 38
	Mycobacterium intracellulare	Alcoholic extract, active chemical constituents 7, 8,15, 21, 23
	Neisseria gonorrhoeae	Hydroalcoholic extract
	Prevotella intermedia	Alcoholic extract
	Pseudomonas aeruginosa	Active chemical constituents 7, 8, 15, 21, 23
	Staphylococcus aureus	Alcoholic extract, active chemical constituents 7, 8, 15, 21, 23, 27
	Staphylococcus epidermidis	Ethanolic extract
	Streptococcus pyogenes	Ethanolic extract
	Streptococcus sanguis	Ethanolic extract
	Xanthomonas compestris	Active chemical constituent 2
	Xanthomonas carotae	Active chemical constituent 2
Antifungal	*Alternaria brassicicoli*	Active chemical constituent 2
	Alternaria chrysanthemi	Active chemical constituent 2
	Aspergillus flavus	Alcoholic extract
	Aspergillus fumigatus	Alcoholic extract
	Candida albicans	Alcoholic extract, active chemical constituents 7, 8,15, 21, 23
	Cladosporium herbarum	Active chemical constituent 2
	Cladosporium sphaerospermum	Active chemical constituents 16, 17, 19, 21 e 37
	Cladosporium cladosporioides	Active chemical constituents 16, 17, 19, 21 e 37
	Cryptococcus neoformans	Alcoholic extract, active chemical constituents 7, 8,15, 21, 23
	Erysiphe graminus	Active chemical constituent 2

Cont.

Cont.

	Helminthosporum carbonum	Active chemical constituent 2
	Penicillium oxalicum	Petroleum ether extract, active chemical constituents 15 and 19
	Pyrenochaeta terrestris	Active chemical constituent 2
	Saccharomyces cerevisiae	Alcoholic extract, active chemical constituent 4, 16-19
	Trichophyton mentagrophytes	Alcoholic extract
Antioxidant	DPPH	Hydroalcoholic extract
Antitumor	*Saccharomyces cerevisiae*	Active chemical constituent 4
Antiviral	Poliovirus	Methanolic extract
KB cell/carcinoma	*Homo sapiens* (human cells)	Dichloromethane extract, active chemical constituents 27, 30, 31, 38
Cytotoxic	Murino	Active chemical constituents 21 and 22
Inseticidal	*Tribolium casteneum*	Active chemical constituent 1
	Cerotoma tingomarianus	Active chemical constituent 1
	Choristoneura rosaceana	Active chemical constituent 1
Inhibition of epoxidase activity	-	Active chemical constituent 1
Inhibition of p450 3A4 cytochrome	-	Active chemical constituent 1
Larvicidal	*Aedes atropalpus*	Active chemical constituent 1
Antileishmanial	*Leishmania amazonensis*	active chemical constituent 23
	Leishmania braziliensis	Active chemical constituents 21 and 22
	Leishmania tropica	Active chemical constituents 21 and 22
	Leishmania infantum	Active chemical constituents 21 and 22
Molluscoidal	*Biomphalaria glabrata*	Petroleum ether extract, active chemical constituents 1, 7-10, 15, 19, 22

Biological activities of *P. aduncum* EOs and their chemical constituents

Regarding EOs, they are usually extracted from different parts of a plant (such as leaves, fruit, root and flower) by hydrodistillation with the use of a Clevenger-type apparatus. In this system, which heats the plant material that is in contact with distilled water in a heating mantle, temperature increases gradually and generates vapor that holds volatile compounds found in plants. The vapor generated by temperature increase in the balloon goes through cooling in the glass condenser, forming two liquid phases that may be separated at the end of the process, resulting in EOs [31].

P. aduncum EOs, for instance, have monoterpenes (piperitone), sesquiterpenes (nerolidol, β-caryophyllene) and phenylpropanoid (dillapiole) as their major constituents [1]. These EOs affect permeability and functioning of membranes of pathogenic microorganisms but they may also inhibit formation of cell walls, cell division and processes of transcription and translation [32]. In medicine, EOs from leaves have been used for direct and indirect fight against several human diseases [33]. In addition, EOs have been applied to agriculture due to their insecticidal, larvicidal, antileishmanial, molluscoidal, antibacterial and antifungal activities [33, 40].

Therefore, EOs from *P. aduncum* are natural products which have been deeply studied due to their high biological activities against several biological targets. Many biological proprieties of EOs from *P. aduncum* have been studied. For instance, their antibacterial and antifungal activities showed good results against problematic agents of nosocomial infections, such as *Staphylococcus aureus*, *S. epidermidis* and *S. lentus* [34]. Besides, there are promising results of prevention of infection in immunocompetent or immunocompromised patients regarding their activity against *Cryptococcus neoformans*. There are also antioxidant, anti-inflammatory and antiplatelet activities, among others [34]. Chemical composition of EOs shown by several studies mainly includes two large groups: phenylpropanoids and monoterpenes. The following constituents were found in EOs from *P. aduncum*: dillapiole, myristicin, carpacin, apiole, safrole, sarisan and 1,8-cineole [35]. Different classes of bioactive secondary metabolites confer excellent results of *in vitro* and *in vivo* activities to species of the Piperaceae family. Examples are studies that aim at evaluating medicinal uses, phytochemistry and pharmacological properties of *P. aduncum* [35].

Concerning *P. aduncum* EOs, dillapiole has frequently been the main component that characterizes them, followed by myristicin. However, papers highlight variable abundance mainly due to the different growth conditions and geographical origins, which inevitably affect qualitative and quantitative profile of the phytocomplex. Dillapiole was the most cited component and the one that had the most promising proprieties, but it showed better activities as a component of the entire EO than as an isolated compound [36]. *P. aduncum* EOs appear to have promising properties in terms of insecticidal activity since they have been tested against a wide range of insects and reached positive results. Findings support the possibility of discovering suitable substitutes for chemical insecticides [37]. In sum, promising antileishmanial, antituberculosis and antifungal (*Aspergillus niger* and *Cladosporium* sp.) activities have already been acknowledged [38-39]. In addition, the main chemical constituents identified in the EOs of *P. aduncum* are shown in Figure 3.

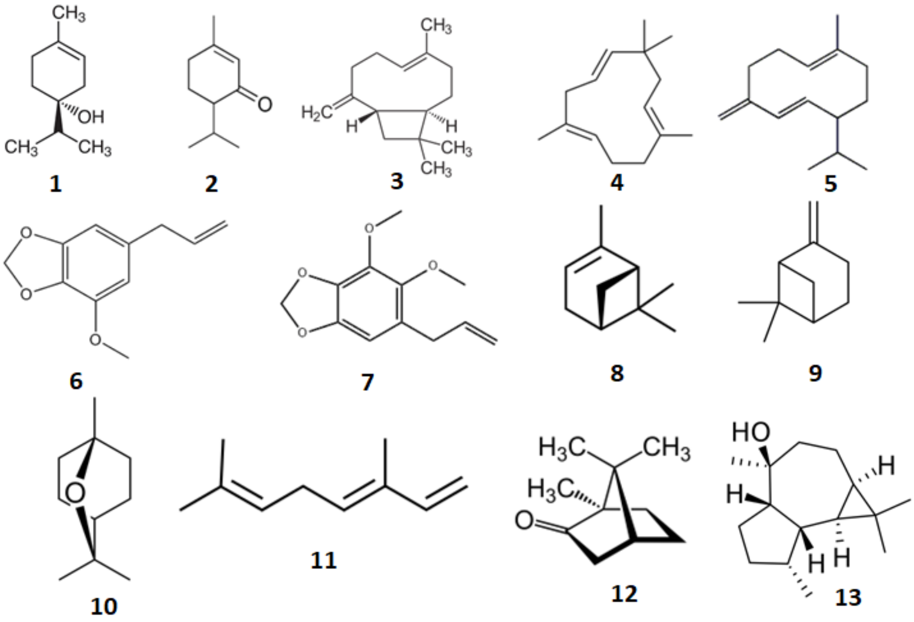

Figure 3. Main chemical constituents found in the EOs of *P. aduncum* (Piperaceae) [1, 2, 5]: terpinene-4-ol (**1**); piperitone (**2**); β-caryophyllene (**3**); α-humulene (**4**); germacrene D (**5**); myristicin (**6**); dillapiole (**7**); α-pinene (**8**); β-pinene (**9**); 1,8-cineole (**10**); *trans*-ocimene (**11**); camphor (**12**) and viridiflorol (**13**).

CONCLUSION

This literature review enabled to conclude that the *P. aduncum* species exhibited relevant chemical and biological potential when it was studied by researchers worldwide. Its extracts and EOs have been deeply studied *in vitro* and *in vivo* due to the fact that they are rich in bioactive secondary metabolites, such as dillapiole. The chemical diversity of compounds produced by this species of Piperaceae justifies its broad biological applicability, mainly regarding its fungicidal and insecticidal activities.

P. aduncum has been a remarkably promising plant which needs further in-depth studies of its mechanisms of action that result in excellent biological activities against several targets that have already been described by the literature.

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