

CHEMICAL CONSTITUENTS AND BIOACTIVITIES OF ESSENTIAL OILS FROM PLANTS OF THE GENUS *Piper L.* (PIPERACEAE): A REVIEW

CONSTITUENTES QUÍMICOS E BIOATIVIDADES DE ÓLEOS ESSENCIAIS DO GÊNERO *Piper L.* (PIPERACEAE): UMA REVISÃO

Minelly Azevedo Da Silva^{1*}, Guilherme Matos Passarini², Leandro Do Nascimento Martinez³, Valdir Alves Facundo⁴, Carolina Garcia Bioni Teles⁵ And Christian Collins Kuehn⁶.

¹ Docente do Instituto Federal de Educação, Ciência e Tecnologia de Rondônia – campus: Porto Velho – Calama. Doutoranda da Universidade Federal de Rondônia – Programa de Pós Graduação em Biologia Experimental – UNIR;

² Doutorando da Universidade Federal de Rondônia – Programa de Pós Graduação em Biologia Experimental – UNIR;

³ Mestrando da Universidade Federal de Rondônia – Programa de Pós Graduação em Biologia Experimental – UNIR;

⁴ Doutor em Química Orgânica e Docente da Universidade Federal de Rondônia;

⁵ Pesquisadora da Fundação Oswaldo Cruz – Rondônia (FIOCRUZ –RO);

⁶ Docente da Universidade Federal de Rondônia – Programa de Pós Graduação em Biologia Experimental – UNIR.

* Correspondence to: minelly.silva@ifro.edu.br

RESUMO

Os óleos essenciais são objeto de estudos que objetivam a identificação de seus compostos e suas possíveis atividades biológicas. A presente investigação é uma revisão bibliográfica de óleos essenciais extraídos de espécies do gênero *Piper L.* que apresentaram atividades biológicas. As referências selecionadas relatam a extração de óleos de diferentes partes de plantas e suas bioatividades. As ações mais relatadas foram: antibacteriana, antifúngica, antioxidante e larvicida / inseticida. Esta revisão é de grande relevância para promover futuras investigações sobre os efeitos biológicos de compostos voláteis presentes nos óleos essenciais de espécies pertencentes à família Piperaceae, contribuindo para a pesquisa de novos produtos biotecnológicos, como medicamentos e pesticidas.

Palavras-chave: Óleo Essencial. *Piper*. Atividade biológica.

ABSTRACT

The essential oils are object of studies that aim the identification of its compounds and its possible biological activities. The present investigation is a literature review of essential oils extracted from species of the *Piper L.* genus that presented biological activities. The references selected reports the extraction of oils from different plant parts and its bioactivities. The most reported activities were: antibacterial, antifungal, antioxidant and larvicidal/insecticidal. This review is of great relevance to promote further investigations about the biological effects of volatile compounds present in the essential oils of species belonging to the family Piperaceae, hence contributing for the research on new biotechnological products, such as medicines and pesticides.

KEYWORDS: Essential Oil. *Piper*. Biological activity.

1. INTRODUCTION

The use of essential oils dates back to over 6000 B.C when they were obtained by Egyptians and Persians by dry distillation. During the Middle Ages, the Arabs improved the distillation method by employing the alembic, contributing with the quality of the essential oils obtained [1].

The essential oils are often complex mixtures of secondary metabolites, in which the terpene group is the most abundant. These molecules have been associated with defensive roles against predator by the plants, wound scarring in plant organs, protection against insects, resistance to microbial attacks and pollination. The oils can be extracted from any plant part, with their content varying depending on the part used for extraction. Factors such as the age of the plant, UV radiation, nutrients in the soils, pollution, the form of collection and storage of the plant material are known to affect the chemical composition of essential oils and contribute to the formation of different chemotypes [2].

The ability of plants to produce essential oils depends on several factors such as anatomy and the existence of secretory structures on the plant surface or within plant tissues [2,3]. In the Piperaceae, for example, secretory cells or lipid idioblasts are found in vegetative and reproductive organs [4-6].

Most of the essential oils are extracted by the method of steam distillation, but other methods can also be employed, such as: hydrodistillation, supercritical fluid extraction (CO₂), microwave distillation, solvent extraction, cold pressing, etc. [7,2]

These substances have been widely used in food, agronomic, sanitary and cosmetic industries. In the last years, the pharmaceutical industry has also demonstrated interest in essential oils, as many of their compounds have demonstrated desirable biological activities. Major compounds are of special interest since there is an evident relationship between their biological activities and their concentration in the oils. Depending on the chemical constitution, the compound might also promote either synergic/additive or antagonistic biological effects [8].

1.1 THE TERPENE CLASS

Terpenes constitute one of the major groups of natural products, as well as presenting the greatest variety of chemical structures, whose diversity is originated from methylethylol, mevalonate and shikimate pathways. Terpenes are constituted by isoprene units, which are non-active forms of the molecules. The active forms (isoprenyl pirophosphate – IPP and dimethylallyl pyrophosphate – DMAPP) are interchangeable isomers and generate other scaffolds, such as monoterpenes (C-10), irregular monoterpenes (C-10), sesquiterpenes (C-15), diterpenes (C-20), triterpenes (C-30), tetraterpenes (C-40), etc. [9,10].

Additionally, a new type of cyclic terpene has been obtained and identified from three non-pathogenic species of *Mycobacterium* sp. Classified as sesquiterpene (C-35), this was the

first example of biosynthesis of a natural triterpene through cyclization of a linear isoprenoid [11].

Monoterpenes, sesquiterpenes and phenylpropanoids are the most abundant terpene derivatives in essential oils, whose samples are analyzed through gas chromatography coupled to mass spectrometry (CG-MS), allowing the quantification and identification of these compounds.

1.2 *Piper* L. (PIPERACEAE) – CHEMICAL CONSTITUENTS OF ESSENTIAL OILS

The family Piperaceae belongs to the group of basal angiosperms and includes plants of the following life forms: lianas, shrubs and herbs, presenting glabrous or with various indumenta and with glands. This family possesses a great variety of purified secondary metabolites, such as: phenylpropanoids, aliphatic compounds, aromatic compounds, lignans, neolignans, pyrones, amides, alkaloids, polyketides, benzoic acid derivatives and benzopyrenes with economic and medical importance. The family has approximately 4000 species, which are distributed in five genera: *Macropiper*, *Zippelia*, *Piper*, *Peperomia* and *Manekia*, with the last three occurring in Brazil [12-19].

1.3 THE *Piper* GENUS

Piper L. has roughly 700 species distributed throughout tropical and subtropical regions of the globe. This genus includes shrubs, trees, lianas, herbs, and the species normally grow inside or at the edges of forests. Their leaves are alternated, complete, normally asymmetrical, palminerved or penninerved and are commonly found in woodlands of ombrophile tropical forests. *Piper* species are popularly known as ‘pimenteia’ and ‘jaborandi’ and have great economic and medicinal importance, with some of them used to treat various ailments. In India, a mixture of *P. nigrum*, *P. longun* and *Zengiber officinalis* (ginger) known as ‘Trikatu’, is also used by the Indian traditional medicine to treat some diseases. Other species, such as *Piper betle* L., *P. methysticum* G. Forst., are known masticatories [20,15,16]. Regarding chemical constituents, these species may present lignans, neolignans, terpenoids, propenyl phenols, chalcones, flavones, benzenopyrans and amides, of which piperidine and pyrrolidine are the most abundant [21,16].

1.4 CONSTITUENTS OF ESSENTIAL OILS FROM *Piper* L.

The most frequently purified constituents from *Piper* were: sesquiterpene alcohols,

monoterpenes, cromenes, benzoic acid derivattves, arylpropanoids, safrol, apiol, dillapiol, β -pinene, bicyclogermacrene, spathulenol, α -pinene, trans-caryophyllene, α -humulene, α -selinene, β -selinene, , caryophyllene oxide, D-limonene, citral a (neral), citral b (geranial), geraniol, linalool, caryophyllene, p-cymene, β -caryophyllene, (E)-nerolidol, globulol, myrcene, β -eudesmol, α -eudesmol, guaiol, D-limonene, geraniol, myrcene, α -phellandrene, camphene, eugenol, sabinene, elemicin and isoelemicin [22, 29].

2. METHODS

The review was conducted through the periodic journal CAPES. As keywords, we searched for the terms “Chemical Constituents”, “biological activity”, “essential oil” and “*Piper*”. Only peer-reviewed articles from indexed journals, published from 2010 to december in 2018 were selected. Only papers written in English, Portuguese and Spanish were included in this review.

3. RESULTS AND DISCUSSION

The essential oils from these species present various biological activities, which include: antiprotozoal, antibactericidal, insecticidal, larvicidal, repellent, antifungal, anthelmintic, antiinflammatory, phytotoxic, toxicological, antinoceptive, antioxidant, acaricidal, antitumoral, cytotoxic etc. In respect to terpenic compounds, the most commonly reported activities are herbicidal, antimicrobial, cytotoxic, cytostatic and antitumoral [30-40].

Table I. Bioactivities of essential oils/coumpound from the genus *Piper*

	Biological Activity	Species studied	Oil source/ Compound tested	Bioassay model	Ref.
1	Antiprotozoal	<i>Piper auritum</i> Kunth	Essential oil from aerial parts major compound: safrole (87%).	<i>Piper auritum</i> essential oil inhibited the growth of <i>L. donovani</i> intracellular amastigotes with an IC ₅₀ value of 22.3 ± 1.8 µg /mL.	[41]

2		<i>Piper claussonianum</i> (Miq.) C. DC.	Essential oil from fresh and dried leaves and inflorescences major compounds: (E)-nerolidol in the leaves (83%) and linalol (50% in the inflorescences).	The essential oils of fresh leaves and inflorescences were assessed for their antiparasitic activity against a strain of <i>Leishmania amazonensis</i> ; Both samples showed biological activity, but the essential oil of fresh leaves of <i>P. claussonianum</i> , rich in (E)-stolid, presented effective inhibition of <i>L. amazonensis</i> growth due to the high percentage of this metabolite in the mixture.	[42]
3		<i>Piper demeraranum</i> (Miq.) C. DC. <i>Piper duckei</i> C. DC.	Essential oil from leaves (major compounds: β -elemene (33.1%) for <i>P. demeraranum</i> and trans-cariophyllene for <i>P. duckei</i>); Limonene; Caryophyllene.	The oils of <i>P. demeraranum</i> and <i>P. duckei</i> showed biological activity, with IC ₅₀ values ranging from 15 to 76 μ g/mL against two species of <i>Leishmania</i> , with <i>P. duckei</i> oil being the most active.	[43]
4		<i>P. tuberculatum</i> Jacq.	Essential oil from fruits.	The essential oil presented EC ₅₀ values of 133.97 μ g/mL and 143.59 μ g/mL against promastigotes of <i>L. infantum</i> and <i>L. braziliensis</i> , respectively. For <i>T. cruzi</i> , the oil showed an EC ₅₀ value of 140.31 μ g/mL against epimastigote forms.	[44]

5		<i>P. aduncum</i> L.	Essential Oil; Nerolidol.	The essential oil had an inhibitory effect on the growth of <i>L. braziliensis</i> promastigotes, with an $IC_{50/24\text{ h}}=77.9\ \mu\text{g/mL}$. The main constituent (nerolidol: 25.22%) presented an $IC_{50/24\text{ h}} = 74.3\ \mu\text{g/mL}$. Scanning and transmission electron microscopies revealed that the compounds caused cell shrinkage and morphological alterations in the mitochondrion, nuclear chromatin and flagellar pocket.	[45]
6		<i>P. aduncum</i> L.	Essential oil from leaves (major compounds: nerolidol (25.22%) and linalool (13.42%); Linalool; Nerolidol.	The essential oil was effective against cell-derived and metacyclic trypomastigotes, with IC_{50} 's of $2.8\ \mu\text{g/mL}$ and $12.1\ \mu\text{g/mL}$, respectively	[47]
7		<i>P. aduncum</i> L.	Essential oil from aerial parts Major compounds: camphor (17.1%), viridiflorol (14.5%), and piperitone (23.7%).	The essential oil presented IC_{50} values of $1.3\ \mu\text{g/mL}$ for <i>P. falciparum</i> , $2\ \mu\text{g/mL}$ for <i>T. brucei</i> , $2.1\ \mu\text{g/mL}$ for <i>T. cruzi</i> , $23.8\ \mu\text{g/mL}$ for <i>L. amazonensis</i> , $7.7\ \mu\text{g/mL}$ for <i>L. donovani</i> and $8.1\ \mu\text{g/mL}$ for <i>L. infantum</i> .	[48]
1	Antibacteria I	<i>P. bredemeyeri</i> Steyerm. <i>P. brachypodom</i> (Benth.) C. DC. <i>P. bogotence</i> C. DC.	Whole plant essential oil (<i>P. Brachypodom</i>) and leaves (<i>P. bredemeyeri</i> and <i>P. bogotence</i>).	The essential oils from <i>Piper bredemeyeri</i> , <i>Piper brachypodom</i> and <i>Piper bogotence</i> presented	[49]

				50% inhibitory concentration (IC ₅₀) for quorum sensing of 45.6 µg/mL, 93.1 µg/mL, and 513.8 µg/mL, respectively. In contrast, the essential oils did not exert antimicrobial activity, with their IC ₅₀ values being > 1000 µg/mL	
2		<i>Piper marginatum</i> Jacq.	Essential oil from fresh leaves (major compounds: isosafrol and notosmirnol (60,30%)	The components responsible for the antibacterial activity were the oxygen compounds, mainly the mixture of isosafrole and notosmirnol.	[50]
3		<i>Piper abbreviatum</i> Opiz <i>Piper erecticaule</i> Yunck. <i>Piper lanatum</i> Roxb.	<i>P. abbreviatum</i> oil were spathulenol (11.2%), (E)-nerolidol (8.5%) and β-caryophyllene (7.8%), whereas <i>P. erecticaule</i> oil mainly contained β-caryophyllene (5.7%) and spathulenol (5.1%). Borneol (7.5%), β-caryophyllene (6.6%) and α-amorphene (5.6%) were the most abundant components in <i>P. lanatum</i> oil.	Essential oils showed moderate antibacterial inhibition against Gram-positive and Gram-negative bacteria.	[51]
4		<i>Piper porphyrophyllum</i> (Lindl.) N.E. Br	Essential oil from leaves (major compounds: bicyclogermacrene (14.7 %), α-copaene (13.2 %) and β-phellandrene (9.5 %)) Essential oil from stems (major compounds: sabinene (15.5 %),	The test revealed that both oils were moderately active against all Gram-positive bacteria (<i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i>) and Gram-negative bacteria (<i>Pseudomonas aeruginosa</i> ,	[52]

			bicyclogermacrene (12.3 %) and α -copaene (8.1 %))	<i>Pseudomonas putida</i> and <i>Escherichia coli</i> with minimal inhibitory concentration (MIC) with values of 125 - 1000 mg / mL.	
5		<i>P. malacophyllum</i> (C.Presl) C.DC.	Essential oil from leaves (major compound: (+)-camphor)	The essential oil showed activity against most of the microorganisms tested, especially the antifungal action, with MIC of 500 μ g/mL against <i>Trichophyton mentagrophytes</i> and <i>Cryptococcus neoformans</i> . This is the first study to report the composition and biological properties of the leaf essential oil of <i>P. malacophyllum</i> .	[53]
6		<i>Piper tuberculatum</i> Jacq.	Essential oil from seeds (major compound: α -Copaene)	The essential oil was shown to inhibit the growth of <i>Staphylococcus aureus</i> and <i>Bacillus subtilis</i> and, therefore, with a possible microbicidal effect, whereas for <i>Pseudomonas aeruginosa</i> and <i>Salmonella typhimurium</i> they showed no effect on their growth.	[54]
7		<i>Piper nigrum</i> L.	Essential oil from fresh and mature fruits (major compounds: β -caryophyllene (16.0 %), sabinene (12.6 %), limonene (11.9 %) and torreyol (9.3 %))	Chemical investigations revealed that β -caryophyllene was the major constituent of essential oil and showed effective antioxidant activity. In addition, it	[55]

				demonstrated remarkable antimicrobial activity.	
8	<i>Piper hispidum</i> C. DC.	Essential oil from fresh leaves (α -pinene (15.3 %), β -pinene (14.8 %), β -elemene (8.1 %), caryophyllene oxide (7.8 %) and δ -3-carene (6.9 %))		The antimicrobial activity was observed against Gram positive bacteria <i>S. aureus</i> ATCC 6538, <i>S. epidermidis</i> CECT232, <i>S. saprophyticus</i> CECT 235, <i>B. cereus</i> CECT496, <i>B. subtilis</i> CECT39 and <i>E. faecalis</i> CECT735 showing MIC values between 6.25 a 15 μ g/mL and MBC values of 12.5 to 15 μ g/mL, but a low activity was observed against <i>E. coli</i> bacterial strains CECT99, <i>P. mirabilis</i> CECT 170 and <i>P. aeruginosa</i> AK 958 with MIC and MBC of 200 μ g / mL.	[56]
9	<i>Piper caldense</i> C. DC.	(Major compounds: α -cardinol (19.0%), α -muurolol (9.0%), tujopsan-2- β -ol (7.4%), δ -cadiene (5.6%), linalool (3.2%), cubenol (3.2%), γ -amorphene (3.1%), α -terpineol (3.0%) in the leaves. Hydrocarbon pentadecane (35.7%), valencene (10.5%) and elina-3,7-11-diene- α -terpineol (5.4%) for the roots; terpine- 4-ol (18.5%), α -terpineol (15.3%), α -cadinol 2- β -ol (9.8%) for the stem.)		The essential oil presented antibacterial activity.	[36]

10	<i>Piper ilheusense</i> Yunck.	Essential oil from leaves (major compounds: E-caryophyllene (11.8 %), Patchouli alcohol (11.1 %) and Gleenol (7.5 %))	The oil showed no activity against the following bacteria: <i>K. pneumoniae</i> , <i>P. aeruginosa</i> and <i>E. coli</i> . However, it partially inhibited <i>B. subtilis</i> and <i>S. aureus</i> growth.	[57]
11	<i>P. cubeba L.</i>	Essential oil from fruits	It has antinociceptive activity and antipyretic activity. In addition, it showed strong antibacterial and antifungal activity. The findings of the study support the use of <i>P. cubeba</i> in patients with inflammatory conditions and confirm its use in traditional medicine.	[58]
12	<i>P. cubeba L.</i>	Essential oil from fruits	The essential oil presented activity against methicillin and oxacillin-resistant <i>Staphylococcus aureus</i>	[59]
13	<i>P. magnibaccum</i> C. DC.	Essential oil from leaves	The essential oil of the leaf showed moderate activity against <i>P. aeruginosa</i> , with a MIC of 250 µg/mL. None of the oils showed toxicity towards MCF-7 and A-549 cells	[60]
14	<i>P. nigrum L.</i>	Essential oil from fruits (limonene (18.59%), beta-pinene (11.51%), linalool (10.17%), alpha-pinene (9.96%))	The essential oil was not shown to be active against <i>S. aureus</i> (SR 196 and NCTC 1052) <i>Salmonella typhi</i> 15SA and <i>Salmonella enteritidis</i> , with minimal inhibitory concentrations starting at 10,000 ppm.	[61]

15	<i>P. arborescens</i> Roxb.	Essential oil from leaves and stems Leaves: β -phellandrene (24.3%), sabinene (16.3%), α -pinene (10.4%) and terpinen-4-ol (7.2%), Stems: β -phellandrene (20.4%), methyl eugenol (11.0%) and β -caryophyllene (9.0%)	The leaf oil showed significant activity towards <i>Staphylococcus aureus</i> with MIC value 250 μ g/ mL, whereas the stem oil showed activity against the Gram positive bacteria, <i>Pseudomonas aeruginosa</i>	[62]
16	<i>P. aduncum</i> C. DC.	Essential oil from leaves	A concentration-dependence effect was observed for the essential oil when tested against <i>Staphylococcus aureus</i> . <i>Escherichia coli</i> uropathogenic clinical isolates, on the other hand, had a lower sensitivity to the essential oil.	[63]
17	<i>P. hymenophyllum</i> Miq.	Essential oil from the fruits [Major compounds: (E) phytol (21.87%), dihydro terpineol (17.42), α - terpineol (13.93%), trans-piperitol (9.66%), endo-fenchol (4.09%), camphene (3.92%) and γ -terpinene (3.91%)]	<i>Salmonella typhimurium</i> , <i>Pseudomonas aeruginosa</i> and <i>Klebsiella pneumoniae</i> exhibited the highest sensitivity and strongly inhibited at very low MIC indicating the efficacy of the oil on the Gram negative bacteria. The oil was shown to have beneficial effects to inhibit tested human pathogenic organisms <i>in vitro</i> .	[64]

18		<i>P. caninum</i> Blume	Essential oil from stems (Major compound: safrole (25.5%)) Essential oil from leaves (Major compound: safrole (17.1%))	Evaluation of antimicrobial activity revealed that both oils exhibited strong activity against all bacteria strains with MIC values from 62.5 to 250 µg/mL, which suggest the essential oils can be used as antioxidant and antimicrobial agents for therapeutic purposes.	[65]
1	Insecticidal/ Larvicidal/ Repellent	<i>P. sarmentosum</i> Roxb.	Essential oil from young stems and leaves (major compounds: Myristicine (65.22%) and trans-caryophyllene (13.89%))	The results showed that the essential oil of <i>Piper sarmentosum</i> presents toxicity on the growth and development of <i>Brontispa longissima</i> . Myristicin exerted strong antifeedant and contact toxicity on 3rd instar larvae and imagoes of <i>Brontispa longissima</i> .	[66]
2		<i>P. capense</i> L.f.	Whole plant essential oil	The oil showed larvicidal activity against larvae of the third instar of <i>A. gambiae</i> , with LC ₅₀ and LC ₉₀ values of 34.9 and 85.0 ppm, respectively. Most of the larvae died in the first hours. The high larvicidal activity of this oil was explained by the fact that more than 80% of mortality was observed at a concentration of 100 ppm after 24 h. These results compared favorably with the commercial larvicide pylarvex®, which	[67]

				presented LC ₅₀ and LC ₉₀ values of 3.7 and 7.8 ppm, respectively.	
3	<p><i>P. aduncum</i> L., <i>P. marginatum</i> Jacq. <i>P. divaricatum</i> G.Mey. <i>P. callosum</i> Ruiz & Pav.</p>	<p>Essential oil from arial parts of all species investigated (Major compounds: dillapiole (64.4%) for <i>P. aduncum</i>; <i>p</i>-mentha-1(7),8-diene (39.0%), 3,4-methylenedioxypropophenone (19.0%), and (<i>E</i>)-β-ocimene (9.8%) for <i>P. marginatum</i> – chemotype A and (<i>E</i>)-isoosmorhizole (32.2%), (<i>E</i>)-anethole (26.4%), isoosmorhizole (11.2%), and (<i>Z</i>)-anethole (6.0%) for <i>P. marginatum</i> – chemotype B; methyleugenol (69.2%) and eugenol (16.2%) for <i>P. divaricatum</i>; safrole (69.2%), methyleugenol (8.6%), and β-pinene (6.2%) for <i>P. callosum</i>)</p>	<p>Insecticidal activity was evaluated against the fire ant (<i>Solenopsis saevissima</i>). <i>P. aduncum</i> obtained a LC₅₀ = 58.4 mg/L, whereas <i>P. marginatum</i> type A, <i>P. marginatum</i> type B, <i>P. divaricatum</i> and <i>P. callosum</i> obtained LC₅₀ values of 122.4, 167, 301.7 and 312.6 mg/L, respectively</p>	[39]	
4	<p><i>P. aduncum</i> L.</p>	<p>Essential oil from fresh leaves (Major compound: 1,8-cineol (53,9%))</p>	<p>The essential oil was shown to be efficient at inhibiting <i>H. contortus</i> hacth, with a LC₉₀ of 8.9 mg / mL.</p>	[68]	
5	<p><i>P. klotzschianum</i> (Kunth) C. DC.</p>	<p>Essential oil from roots, stems, leaves and seeds (major compounds: 1-butyl-3,4-methylenedioxybenzene and 2,4,5-</p>	<p>The present study indicated that the essential oil from <i>P. klotzsdhianum</i> and the pure compound 1-butyl-3,4-methylenedioxybenze</p>	[69]	

			trimethoxy-1-propenylbenzene in the roots, 1-butyl-3,4-methylenedioxybenzene in stems and leaves and 1-butyl-3,4-methylenedioxybenzene, limonene and α -phellandrene in the seeds	ne may constitute alternative tools for the larval control of <i>A. aegypti</i> . This was the first report on the biological activity of the essential oil and the isolated compound from this species against <i>A. Aegypti</i> .	
6	<i>P. guineense</i> Schumach. & Thonn.	Essential oil from fruits [Major compounds: copaene (99%), caryophyllene (99%), eugenol (98%), α -cubebene (98%), γ -elemene (94%)] n-hexane fraction Chloroform fraction Ethyl acetate fraction Methanol fraction	All fractions of the essential oil caused significant ($P < 0.001$) mortality of the weevils by contact toxicity. All doses of the n-hexane fraction were highly toxic to the test insect than the control, causing 100% mortality after five days of exposure. All the fractions produced a strong repellent activity against <i>Sitophilus oryzae</i> . These results suggest show that the essential oil may be promising for the development of insecticides.	[70]	
7	<i>P. auritum</i> Kunth; <i>P. multiplinervium</i> C. DC.	Essential oil from fresh leaves (Major compounds: safrole (93.2%) and miristicine (4.3%) (<i>P. auritum</i>); B-elemene (9.0 %), trans-B-caryophyllene (5.3 %) and caryophyllene oxide (4.1%) (<i>P. multiplinervium</i>))	This study evaluated the repellent activity and toxicity of two essential oils isolated from these plants against <i>Tribolium castaneum</i> , which were determined using the method of area preference and contact toxicity, respectively. The essential oil of <i>P. auritum</i> presented a higher repelence than <i>P. Multiplinervium</i> . The former presented	[24]	

				100% lethality in the shortest period of exposition (24 h), while the latter caused 16% at 72 h. It is believed that the repellent effect of <i>P. auritum</i> can be related to the content of safrole, a known repellent. These results showed that the species of <i>Piper</i> could be used for the development of repellents against <i>T. castaneum</i> .	
8		<i>Piper hispidinervium</i> C. DC.	Essential oil from leaves (Major compounds safrole (82.07%), terpinolene (5.71%), and bicyclogermacrene (3.16%))	The study tested the combination of long pepper (<i>Piper hispidinervium</i> L.) and clove (<i>Syzygium aromaticum</i> L.) oils at two concentrations. The combination affected the biological and reproductive parameters of the larvae, leading to changes in the levels of nitric oxide and phenoloxidase in the hemolymph of the pest.	[71]
9		<i>P. arboreum</i> Aubl. <i>P. marginatum</i> Jacq. <i>P. aduncum</i> L.	Essential oils from leaves (Major compounds: <i>Piper arboreum</i> : germacrene D (31.83%) and bicyclogermacrene (21.40%); in <i>Piper marginatum</i> : (E)-methyl isoeugenol (27.08%), (E)-anethole (23.98%) and (Z)-methyl isoeugenol (12.01%); and in <i>Piper</i>	The essential oils extracted from the Piperaceae studied resulted in lethal concentrations (LC ₅₀) at the range of 34-55 ppm, whereas the LC ₉₀ was greater than 100 ppm, except for <i>P. marginatum</i> (85 ppm).	[72]

			<i>aduncum</i> : (E)-isocroweacin (29.52%), apiole (28.62%) and elemicin (7.82%)	
10	<p><i>P. augustum</i> Rudge <i>P. corrugatum</i> Kuntze <i>P. curtispicum</i> C. DC. <i>P. darienense</i> C. DC. <i>P. grande</i> Vahl. <i>P. hispidum</i> Sw. <i>P. jacquemontianum</i> Kunth <i>P. longispicum</i> C. DC. <i>P. multiplinervium</i> C. DC. <i>P. reticulatum</i> L. <i>P. trigonum</i> C. DC.</p>	<p>Essential oils from leaves (Major compounds: cembratrienol (25.4%) in <i>Piper augustum</i>; β-pinene (26.6%) in <i>Piper corrugatum</i>; α-pinene (19.4%) in <i>Piper curtispicum</i>; <i>trans</i>-β-farnesene (63.7%) in <i>Piper darienense</i>; <i>p</i>-cymene (43.9%) in <i>Piper grande</i>; dillapiole (57.7%) in <i>Piper hispidum</i>; linalool (14.5%), α-phellandrene (13.8%), and limonene (12.2%) in <i>Piper jacquemontianum</i>; β-caryophyllene (45.2%) in <i>Piper longispicum</i>; linalool (16.5%), α-phellandrene (11.8%), limonene (11.4%), and <i>p</i>-cymene (9.0%) in <i>Piper multiplinervium</i>; β-selinene (19.0%), β-elemene (16.1%), and α-selinene (15.5%) in <i>Piper reticulatum</i>; and germacrene D (19.7%) in <i>Piper trigonum</i>)</p>	<p>The larvicidal activity was evaluated for essential oils of six species. The essential oils of <i>P. hispidum</i> and <i>P. longispicum</i> at a concentration of 250 μg / mL showed larvicidal activity against <i>Aedes aegypti</i>, while the oils of <i>P. curtispicum</i>, <i>P. multiplinervium</i>, <i>P. reticulatum</i> and <i>P. trigonum</i> were not shown to be active (LC₁₀₀ \geq 500 μg / mL). The essential oils of <i>P. grande</i>, <i>P. jacquemontianum</i> and <i>P. multiplicinervium</i> showed no significant fungicidal activity (MIC > 250 μg / mL) against several strains of fungi.</p>	[73]
11	<i>P. corcovadensis</i> (Miq.) C. DC.	Essential oils from leaves (major compounds : 1-butyl-	The essential oil presented larvicidal activity. This article	[74]

			3,4-methylenedioxybenzene (30.62%), terpinolene (17.44%) and <i>trans</i> -caryophyllene (6.27%)	constituted the first report on the biological activities associated with the essential oil of leaves of <i>P. corcovadensis</i> .	
12		<i>P. aduncum</i> L.	Essential oil from leaves	The oil resulted in a 90% mortality when assessed by the ingestion bioassay after 24h of application. However, no significant differences were observed in the topical application of the oil until the end of the life cycle of <i>Chrysodeixeis includens</i> . The results highlight the potential of <i>P. aduncum</i> essential oil as a tool for <i>C. includens</i> control.	[75]
13		<i>P. aduncum</i>	Dillapiol-rich Essential oils from stems and leaves) L. Dillapiol	All treatments caused 90–100% mortality in nymphs of <i>Diaphorina citri</i> . The Topical treatments with oil containing 79.9 and 85.4% dillapiol at 0.75% and 1% dilutions were effective in adults, with mortality being mortality $\geq 80\%$). However, no residual activity by the oil against adults (mortality $\leq 30\%$) was observed. The present study demonstrated the high efficacy of the essential oil in the control of <i>D. citri</i> .	[76]

14		<i>P. aduncum</i> L.	Semisolid formulations of the essential oil (ointment, cream and gel)	The three semisolid essential oil formulations repelled >65% of the <i>A. aegypti</i> after 4h of application. The ointment, gel and cream formulation provided protection time of 182.5 ± 16.01 , 97.5 ± 14.93 min and 162.5 ± 6.29 min, respectively.	[77]
15		<i>P. betle</i> L.	Essential oils from leaves	Both strains (Laboratory Strain - LS and Wild Strain - WS) (1.5 mg/L) displayed steady larval mortality rate across all instars when treated with the essential oil. The LC_{50} of the oil was observed at 0.72 and 0.64 mg/L for LS and WS strains respectively.	[78]
16		<i>P. nigrum</i> L.	Essential oil (Plant part not cited)	The essential oil repelled nymph and adult stages of German cockroaches (<i>Blattella germanica</i>), with a rate of repellence of $65.19 \pm 6.90\%$ and $55.00 \pm 8.56\%$ at 6 and 12 h, respectively, demonstrating its potential for the management of German cockroaches.	[79]

17		<i>P. hispidinervum</i> C. DC.	Essential oil from fresh leaves and thigs [Safrole was the major component (78 - 81 %) followed by terpinolene (5 – 9 %)] Combinations of safrole and terpinolene	The essential oils were effective as insect antifeedants. The results of the study demonstrated that when binary combinations were tested, low ratios of safrole improved the activity of terpinole The essential oil caused a higher mortality of <i>Meloidogyne javanica</i> than the isolated compounds. When tested in binary combinations, low ratios of terpinole improved the nematicidal activity of safrole. EO treatment strongly suppressed nematode egg hatching and juvenile infectivity.	[80]
18		<i>P. gaudichaudianum</i> (Kunth) Kunth ex Steud.	Essential oils from the leaves Major compounds: germacrene B, δ -cadinene, γ -elemene, (Z)-cariophyllene, α -copaene, (E)-cariophyllene, α -calacorene, α -humulene and (E)-nerolidol.	The essential oil had LC ₅₀ values of 3.69 (24h) and 2.19 (48h) against <i>Lucilia cuprina</i> when solubilized in ethanol, and 9.14 and 6.05 μ L/cm ² when solubilized in acetone, respectively.	[81]
19		<i>P. betle</i> L.	Essential oils from leaves	When treated with the essential oil, both strains of <i>Aedes aegypti</i> (Laboratory Strain and Wild Strain) displayed larval mortality across all instars, with the LC ₅₀ values of 0.72 and 0.64 mg/L (for LS and WS, respectively)	[78]

20		<i>P. crassinervum</i> Kunth	Essential oil (plant part not cited)	The results obtained indicate that <i>P. crassinervum</i> has a repellent effect on the adults of <i>Sitophilus zeamais</i> . Because of the concentrations used, the percentage of insects attracted was lower than those of the respective controls. Within these, the most effective was of 2uL / g, presenting the lowest preference value (13.01%)	[82]
1	Antifungal	<i>P. betle</i> L.	Essential oils from leaves (major compounds: eugenol (63.39%) and acetil-eugenol (14.05%))	The essential oil obtained a MIC of 0.7 µl/mL against <i>Aspergillus flavus</i> and completely inhibited the production of aflatoxin B ₁ at 0.7 µl/mL	[83]
2		<i>P. hispidum</i> Sw.	Essential oil from fresh leaves (α-pinene (15.3 %), β-pinene (14.8 %), β-elemene (8.1 %), caryophyllene oxide (7.8 %) and δ- 3-carene (6.9 %))	The essential oil from fresh leaves presented moderate activity against <i>Candida albicans</i> , with a MIC of 100-200 µg / mL.	[56]
3		<i>P. diospyrifolium</i> Kunth	Essential oil from leaves	The <i>in vitro</i> activity of the essential oil of the leaves of <i>Piper diospyrifolium</i> was tested using disk diffusion techniques. The antifungal test showed activity with significant antifungal potential. The oil was effective against several clinical strains of fungi. Most of the compounds in the essential oil were	[84]

				identified as sesquiterpenes by GC-MS and GC-FID.	
4	<i>P. malacophyllum</i> (C.Presl) C.DC.	Essential oil from leaves (major compound: (+)-camphor)		The essential oil showed activity against most of the microorganisms tested, especially the antifungal action, with a MIC of 500 µg / mL against <i>Trichophyton mentagrophytes</i> and <i>Cryptococcus neoformans</i> .	[53]
5	<i>P. hispidum</i> Sw. <i>P. aleyreanum</i> C. DC. <i>P. anonifolium</i> (Kunth) Steud.	Essential oil from aerial parts (Major compounds: Selin-11-en-4-ol - 20.0 % (<i>P. anonifolium</i>); B-Caryophyllene - 10.5 % - (<i>P. hispidum</i>); B-elemene -16.3% - (<i>P. aleyreanum</i>))		All essential oils testes displayed antifungal activity, with detection limit (DL) from 0.1 to 1.0 µg against <i>Cladosporium cladosporioides</i> and <i>Cladosporium sphareospermum</i>	[85]
6	<i>P. aduncum</i> L.	Essential oil from fresh leaves (major compounds: Dillapiole (45.92%), trans-E-ocimene (10.39 %), piperitone (8.47 %)		The essential oil of <i>P. Aduncum</i> at its maximum concentration presented the highest percentages of inhibition against <i>F. solani</i> (94%) and <i>Phytophthora sp.</i> (91%).	[86]
7	<i>P. ilheusense</i> Yunck	Essential oil from leaves (Major compounds: E-caryophyllene (11.8 %), Patchouli alcohol (11.1 %) and Gleenol (7.5 %))		The oil was active in fungal combat, but showed no activity against the following bacteria: <i>K. pneumoniae</i> , <i>P. aeruginosa</i> and <i>E. coli</i> , however, partially inhibited <i>B. subtilis</i> and <i>S. aureus</i> .	[57]

8		<p><i>P. augustum</i> Rudge <i>P. corrugatum</i> Kuntze <i>P. curtispicum</i> C. DC. <i>Piper darienense</i> C. DC. <i>P. grande</i> Vahl. <i>P. hispidum</i> Sw. <i>P. jacquemontianum</i> Kunth <i>P. longispicum</i> C. DC. <i>P. multiplinervium</i> C. DC. <i>P. reticulatum</i> L. <i>P. trigonum</i> C. DC.</p>	<p>Essential oil from leaves (Major compounds: cembratrienol (25.4%) in <i>Piper augustum</i>; β-pinene (26.6%) in <i>Piper corrugatum</i>; α-pinene (19.4%) in <i>Piper curtispicum</i>; <i>trans</i>-β-farnesene (63.7%) in <i>Piper darienense</i>; <i>p</i>-cymene (43.9%) in <i>Piper grande</i>; dillapiole (57.7%) in <i>Piper hispidum</i>; linalool (14.5%), α-phellandrene (13.8%), and limonene (12.2%) in <i>Piper jacquemontianum</i>; β-caryophyllene (45.2%) in <i>Piper longispicum</i>; linalool (16.5%), α-phellandrene (11.8%), limonene (11.4%), and <i>p</i>-cymene (9.0%) in <i>Piper multiplinervium</i>; β-selinene (19.0%), β-elemene (16.1%), and α-selinene (15.5%) in <i>Piper reticulatum</i>; and germacrene D (19.7%) in <i>Piper trigonum</i>)</p>	<p>The larvicidal activity was evaluated for essential oils of six species. The essential oils of <i>P. hispidum</i> and <i>P. longispicum</i> at a concentration of 250 μg / mL showed larvicidal activity against <i>Aedes aegypti</i>, whereas the oils of <i>P. curtispicum</i>, <i>P. multiplinervium</i>, <i>P. reticulatum</i> and <i>P. trigonum</i> were not active ($LC_{100} \geq 500 \mu$g / mL). The essential oils of <i>P. grande</i>, <i>P. jacquemontianum</i> and <i>P. multiplicinervium</i> showed no significant fungicidal activity ($MIC > 250 \mu$g / mL) against various yeasts and fungal strains.</p>	[73]
9		<p><i>P. cubeba</i> L.</p>	<p>Essential oil from fruits</p>	<p>The essential oil exhibited a strong antimicrobial potential.</p>	[58]
10		<p><i>P. betle</i> L.</p>	<p>leaf essential oil based microemulsion.</p>	<p>The essential oil presented E_{max} and MIC values of 2.01 and 3.55 ppm in tomato paste against the <i>Aspergillus flavus</i></p>	[87]

				mould, which suggest it has potential as a natural food preservative.	
11		<i>P. betle</i> L.	Essentil oil from leaves	The essential oil-based microemulsion inhibited the growth of <i>Aspergillus flavus</i> and <i>Penicillium expansum</i> in raw apple juice. The oil also induced morphological alterations on treated spores, which highlights its potential as an antifungal agent in food system.	[88]
12		<i>P. arborescens</i> Roxb.	Essential oil from leaves and stems Leaves: β -phellandrene (24.3%), sabinene (16.3%), α -pinene (10.4%) and terpinen-4-ol (7.2%), Stems: β -phellandrene (20.4%), methyl eugenol (11.0%) and β -caryophyllene (9.0%)	The stem oil presented antifungal activity against <i>Aspergillus niger</i> with s MIC value of 500 μ g/mL	[62]
13		<i>P. betel</i> Linn.	Essential oil from the leaves	<i>Piper betel</i> essential oil was shown to possesses antifungal activity producing a zone of inhibition of 17 mm (fluconazole control, > 35 mm) and an inhibitory concentration = 1.6% (fluconazole control, 0.8%) against <i>C. albicans</i> .	[89]

14		<i>P. aduncum</i> L.	Essential oil from the leaves	A concentration-dependence nature of the activity was revealed in the essential oil when tested against <i>C. albicans</i> .	[63]
15		<i>P. hymenophyllum</i> Miq.	Essential oil from the Fruits. [Major compounds: (E) phytol (21.87%), dihydro terpineol (17.42), α - terpineol (13.93%), trans-piperitol (9.66%), endo-fenchol (4.09%), camphene (3.92%) and γ -terpinen (3.91%)]	The leaf oil was shown to present a significant activity against <i>Aspergillus niger</i> , with MIC value of 500 μ g/mL. In addition, the fruit essential oil strongly inhibited <i>C. albicans</i> and <i>S. aureus</i> growth.	[64]
16		<i>P. mosenii</i> C. DC. <i>P. rivinoides</i> Kunth <i>P. arboretum</i> Roxb. <i>P. aduncum</i> L. <i>P. diospyrifolium</i> Kunth	Bycyclogermacrene - 11.8 % (<i>P. rivinoides</i>); Caryophyllene Oxide - 12.1 % (<i>P. mosenii</i>); Spathulenol - 11.5 % (<i>P. cernuum</i>); Selin-11-en-4- α -ol - 17.7 % (<i>P. diospyrifolium</i>); (E)-Caryophyllene - 12.6 % (<i>P. arboretum</i>); Bicyclogermacrene - 20.9 % (<i>P. aduncum</i>); δ -Cadinene - 45.3 % (<i>P. gaudichaudianum</i>); β -Phellandrene - 22.6 % (<i>P. xylosteoides</i>); Safrole - 72.4 % (<i>P. mikanianum</i>).	The species <i>P. rivinoides</i> , <i>P. cernuum</i> and <i>P. diospyrifolium</i> showed moderate activity against <i>Mycobacterium tuberculosis</i> H37 Rv, with a minimum inhibitory concentration (MIC) of 125 μ g/mL. These results are relevant and suggest their potential for therapeutic purposes.	[46]
1	Ant-helmintic	<i>P. cubeba</i> L.	Essential oil from fruits (major compounds: sabinene (19.99%), eucalyptol (11.87%), 4-terpineol (6.36%), β -pinene	The results suggested that the essential oil of <i>Piper cubeba</i> has an effect against cercariae, schistosomiasis and	[90]

			(5.81%), camphor (5.61%), and δ -3-carene (5.34%))	adult worms of <i>S. mansoni</i> .	
2		<i>P. malacophyllum</i> (C.Presl) C.DC	Essential oil from leaves (major compound: (+)-camphor)	The essential oil showed activity against most of the microorganisms tested, especially the antifungal action, with MIC of 500 μ g / mL against <i>Trichophyton mentagrophytes</i> and <i>Cryptococcus neoformans</i> . This is the first study to report the composition and biological properties of the leaf essential oil of <i>P. malacophyllum</i> .	[53]
3		<i>P. aduncum</i> L.	Essential oil from fresh leaves (major compound 1,8-cineole – 55,8%)	The essential oil inhibited the hatchability of <i>Haemonchus contortus</i> , with a calculated LC ₉₀ of mg / mL, which highlight the potential of this essential oil as an alternative to control <i>H. contortus</i> .	[68]
1	Antiinflammatory	<i>P. aduncum</i> L.	Dillapiole and dihydrodillapiole	Dillapiole and dihydro dillapiole exhibited moderate antiphlogistic properties, indicating that they can be used as prototypes for the development of anti-inflammatory compounds.	[35]
2		<i>P. nigrum</i> L.	Essential oil from fresh and mature fruits (Major compounds: β -caryophyllene (16.0 %), sabinene (12.6 %), limonene (11.9	The chemical investigations revealed that β -Caryophyllene was the major constituent and presented an efficient antioxidant activity.	[55]

			%) and torreyol (9.3 %))	
3	<i>P. aleyreanum</i> C. DC.	Essential oil from aerial parts [Major compounds: Caryophyllene oxide (11.5%), β -pinene (9%), spathulenol (6.7%), camphene (5.2%), β -elemene (4.7%), myrtenal (4.2%), verbenone (3.3%) and pinocarvone (3.1%)]	The essential oil (10-1000 mg/kg, oral administration) inhibited both neurogenic and inflammatory phases of formaline-induced licking (ID ₅₀ = 281.2 and 70.5 mg/kg, respectively). The antinociception caused by the oil was not reversed by naxolone in the formalin test. It did not affect animal motor coordination at concentrations ranging from 100-300 mg/kg, p.o.) in an open-field model. In carrageenan-induced pleurisy (1-100 mg/kg, p.o.) the oil significantly decreased the total cell count, neutrophils and mononuclear cells with mean ID ₅₀ values of 53.6, 21.7 and 43.5 mg/kg, respectively.	[92]
4	<i>P. guineense</i> Schumach. & Thonn.	Essential oil from the fresh fruits	The activity was measured in albumin-induced rat paw edema. The oil caused a significant reduction in albumin-induced edema. The study showed that the essential oil has significant antiinflammatory effects	[93]

5		<i>P. vicosanum</i> Yunck	Essential oil from the leaves	The oil significantly reduced the formation of edema and also inhibited leucocyte migration. The results indicate that this oil has potential as an antiinflammatory agente.	[94]
1	Antioxidant	<i>P. betle</i> L.	Essential oil from leaves (major compounds : eugenol (63.39%) and acetyl-eugenol (14,05%))	The essential oil obtained an IC ₅₀ value of 3.6 µg/mL, being comparable to that of ascorbic acid (3.2 µg/mL) and lower than those of synthetic antioxidants such as butylated hydroxytoulene (BHT) (7.4 µg/mL) and butylated hydroxyanisole (BHA) (4.5 µg/mL).	[83]
2		<i>P. nigrum</i> L.	Essential oil from seeds (β-caryophyllene (25.38±0.62%), limonene (15.64±0.15%), sabinene (13.63±0.21%), 3-carene (9.34±0.04%), β-pinene (7.27±0.05%), and α-pinene (4.25±0.06%))	The radical elimination activity of the extracts obtained by SC-CO ₂ and hydrodistillation showed an EC ₅₀ of 103.28 and 316.27 µg / mL, respectively.	[30]

3		<p><i>P. hispidum</i> Sw. <i>P. aleyreanum</i> C. DC. <i>P. anonifolium</i> (Kunth) Steud.</p>	<p>Essential oil from aerial parts (Major compounds: Selin-11-en-4-ol - 20.0 % (<i>P. anonifolium</i>); B-Caryophyllene - 10.5 % - (<i>P. hispidum</i>); B-elemene -16.3% - (<i>P. aleyreanum</i>))</p>	<p>The most expressive result as obtained by the essential oil of <i>P. aleyreanum</i>, with DPPH = 412.2 mg/mL</p>	[85]
4		<p><i>P. marginatum</i> Jacq.</p>	<p>Essential oil from roots (Major compounds: Canphene (10.10 %), Bicyclogermacrene (9.40 %) and Germacrene D (8.83 %))</p>	<p>The essential oil displayed antioxidant activity, with an EC₅₀ of 75.26 mg/L.</p>	[91]
5		<p><i>P. magnibaccum</i> C. DC.</p>	<p>Essential oil from the leaves</p>	<p>The leaf oil had an IC₅₀ = 20.5 µg/mL in the scavenging activity assay of DPPH and of 11.7 µg/mL in the scavenging activity of ABTS. Antityrosinase activity of the leaf oil using the mushroom tyrosinase resulted in a I% = 49.50±0.6 The stem oil had an IC₅₀ = 17.5 µg/mL in the scavenging activity assay of DPPH and of 12.9 µg/mL in the scavenging activity of ABTS. Antityrosinase activity of the leaf oil using the mushroom tyrosinase resulted in a I% = 57.01±0.8.</p>	[60]

6		<i>P. caninum</i> Blume	Essential oil from stems (Major compound: safrole (25.5%)) Essential oil from leaves (Major compound: safrole (17.1%))	The stem oil showed a high inhibitory activity towards lipid peroxidation ($114.9 \pm 0.9\%$), when compared to the control BHT ($95.5 \pm 0.5\%$) The oils showed weak activity in the DPPH free-radical scavending assay The results of the study suggest the oil may be used to develop antioxidant agents.	[65]
1	Acaricidal	<i>P. aduncum</i> L.	Essential oil from leaves (major compounds: camphene, camphor, piperitone and viridiflorol)	The acaricidal effect of <i>Piper aduncum</i> essential oil was evaluated by complete exposure and by vapors. The oil was considered a promising candidate for the development of a botanical acaricide, causing 100% mortality of <i>Varroa destructor</i> adults in Petri dish (25 μ L).	[95]
2		<i>P. aduncum</i> L.	Essential oil from fresh leaves dillapiole α -humulene (<i>E</i>)-nerolidol caryophyllene	The acaricidal activity and repellency of essential oil and its components [dillapiole (0.28 g/mL), α -humulene (0.016 g/mL), (<i>E</i>)-nerolidol (0.0007 g/mL) and β -caryophyllene(0.0021 g/ mL)] were evaluated in laboratory against adults of <i>Tetranychus urticae</i> . Repellent	[96]

				activity was attributed to (E)-normolide, α -humulene and β -caryophyllene, while fumigation and contact toxicity was attributed to β -caryophyllene.	
1	Antitumoral	<i>P.cernuum</i> Vell.	Essential oil from fresh branches a-pinene Camphene Limonene Carvacrol Tymol Myrcene p-cyemne a-terpineol linalol	It has been found that camphene exerted antitumor activity <i>in vivo</i> by inhibiting subcutaneous tumor growth of highly aggressive melanoma cells in a syngeneic model, suggesting a promising role for this compound in cancer therapy.	[97]
1	Cytotoxic	<i>P. auritum</i> Kunth	Essential oil from aerial parts (major compounds: safrole (87%))	The <i>essential</i> presented a CC_{50} value of $106.4 \pm 3.4 \mu\text{g/mL}$ against peritoneal macrophages from BALB/c mice.	[41]
2		<i>P.demeraranum</i> (Miq.) C.DC. <i>P. duckei</i> C. DC.	Essential oil from leaves (Major compounds: β -elemene (33.1%) for <i>P. demeraranum</i> and trans-caryophyllene for <i>P. duckei</i>) Limonene Caryophyllene	The cytotoxicity of the essential oils in mouse peritoneal macrophages cells was insignificant compared to the toxicity of pentamidine.	[43]
3		<i>P. hispidum</i> Sw. <i>P. aleyreanum</i> C. DC. <i>P. anonifolium</i> (Kunth) Steud.	Essential oil from aerial parts (major compounds: Selin-11-en-4-ol - 20.0 % (<i>P. anonifolium</i>); B-Caryophyllene - 10.5 % - (<i>P. hispidum</i>); B-	The most expressive result was obtained by the essential oil of <i>P. aleyreanum</i> , that displayed high cytotoxic activity against the human	[85]

			elemene -16.3% - (<i>P. aleyreanum</i>))	melanoma cell line SKMEL-19, with an IC ₅₀ = 7.4 µg/mL.	
4		<i>P. magnibaccum</i> C. DC.	Essential oil from the leaves	The essential oils did not exhibited acute cytotoxicity against MCF-7 and A-549 cell lines.	[60]
1	Sedative	<i>P. guineense</i> Schumach. & Thonn.	Essential oil from dried fruits (major compounds: linalool (41.8%) and 3,5-dimethoxytoluene (10.9%))	These two main compounds (linalol (41.8%) and 3,5-dimethoxytoluene (10.9%)), showed an important role in the sedative activity of <i>P. guineense</i> essential oil. These results suggest that the inhalation of <i>P. guinean</i> essential oil may induce a mild tranquilizing effect.	[70]
1	Antiulcer	<i>P. aleyreanum</i> C. DC.	Essential oil from aerial parts [Major compounds: Caryophyllene oxide (11.5%), β-pinene (9%), spathulenol (6.7%), camphene (5.2%), β-elemene (4.7%), myrtenal (4.2%), verbenone (3.3%) and pinocarvone (3.1%)]	The essential oil (30 mg/kg, p.o.) protected rats against ethanol-induced gastric lesions, with an ID ₅₀ value of 1.7 mg/kg, and increased the mucus and GSH levels of the gastric mucosa to levels similar to those of the control (non-lesioned) group.	[92]
1	Enzyme inhibition	<i>P. hispidum</i> Sw. <i>P. aleyreanum</i> C. DC. <i>P. anonifolium</i> (Kunth) Steud.	Essential oil from aerial parts (major compounds: Selin-11-en-4-ol - 20.0 % (<i>P. anonifolium</i>); B-Caryophyllene - 10.5 % - (<i>P. hispidum</i>); B-	The oils of <i>P. anonifolium</i> and <i>P. hispidum</i> presented a significant anticholinesterase action, with detection limits (DL) of 0.01 ng.	[85]

			elemene -16.3% - (<i>P. aleyreanum</i>))		
2		<i>P.sarmentosum</i> Roxb.	Essential oil from roots, leaves and fruits The phenyl propanoid myristicin was identified as the major compound comprising 83.4% in the leaf oil, 84.2% in the fruit oil and 81.2% in the root oil. Myristicin	The antimicrobial activity of myristicin was evaluated <i>in vitro</i> and <i>in silico</i> against the FtsZ protein. The <i>in vitro</i> assay showed 13.0% FtsZ inhibition by 200- μ M myristicin. The molecular docking results supported the <i>in vitro</i> activity of myristicin.	[98]
1	Antinociceptive	<i>P. cubeba</i> L.	Essential oil from fruits	The essential oil caused a prominent antinociceptive effect (17, 30 and 54%) and an increase in reaction time in mice in the flick tailed and hot-plate tests. Its also presented antipyretic effects. Decrease of Brewer's yeast induced hyperpyrexia was observed in a dose dependent manner.	[58]
2		<i>P.aleyreanum</i> C. DC.	Essential oil from aerial parts [Major compounds: Caryophyllene oxide (11.5%), β -pinene (9%), spathulenol (6.7%), camphene (5.2%), β -elemene (4.7%), myrtenal (4.2%), verbenone (3.3%) and pinocarvone (3.1%)]	The oral administration of the essential oil (10–1000 mg/kg) significantly inhibited both the neurogenic and inflammatory phases of formalin-induced licking, presenting ID ₅₀ values of 281.2 and 70.5 mg/kg, respectively. The antinociception	[92]

				caused by this essential oil (100 mg/kg, p.o.) was not reversed by naloxone (1 or 5 mg/kg, i.p.) in the formalin test. The oil (100–300 mg/kg, p.o.) did not affect the animal motor coordination in an open-field model. In the carrageenan-induced pleurisy assay, the oil (1–100 mg/kg, p.o.) significantly decreased the total cell count, neutrophils and mononuclear cells with mean ID ₅₀ values of 53.6, 21.7 and 43.5 mg/kg, respectively.	
3		<i>P. guineense</i> Schumach. & Thonn.	Essential oil from the fresh fruits	The oil (50 a 200 mg/kg i.p.) was tested in hot plate model and induced writhings, and was shown to prolong the time of reaction of mice in the hot plate and inhibited writhings induced by acetic acid. The study demonstrated that the essential oil has significant antinociceptive effects.	[93]
4		<i>P. mollicomum</i> Kunth ex Steud. <i>P. rivinoides</i> Kunth	Essential oil from leaves (Major compounds: β -ocimene for <i>P. mollicomum</i> and α -pinene for <i>P. rivinoides</i>)	In the test of writhing induced by acetic acid (0.8%), in order to assess the antinociceptive activity, the essential oil from <i>Piper mollicomum</i> and <i>Piper</i>	[98]

				<i>rivinoides</i> , at 1 mg/kg, showed significant inhibition of writhing, presenting 20.90 and 50.25% inhibition respectively.	
1	Toxicological evaluation	<i>P. nigrum</i> L.	Essential oil from fruits (limonene (18.59%), β -pinene (11.51%), linalool (10.17%), α -pinene (9.96%))	The administration of a combination of gentamicin and <i>Piper nigrum</i> essential oil did not caused alterations in the weight of Balb/c mice. As for the AST and ALT enzymes, the only differences were observed in ALT levels of females after the administration of high doses of the essential oil.	[61]
2		<i>P.elongatum</i> Vahl	Essential oil from leaves	Essential oil of <i>Piper elongatum</i> concentrations below 0.5% (w/v) did not produce genotoxic damage when evaluated by the SMART technique.	[99]
3		<i>P. guineense</i> Schumach. & Thonn.	Essential oil from fresh fruits	Results of acute toxicity indicate that the LD ₅₀ of the essential oil was calculated at 693 and 1265 mg / kg for the intraperitoneal and oral routes, respectively. The study showed that the essential oil was moderately toxic.	[93]

4		<p><i>P. vicosanum</i> Yunck</p>	<p>Essential oil from leaves</p>	<p>No toxicity was observed (LD₅₀ probably greater than 2000 mg/kg) The comet assay did not detect any increase in the frequency of DNA damage in the test groups. In the micronucleus assay, no signs of toxicity and genotoxicity were observed in peripheral blood erythrocytes. The results indicate the oil is safe regarding the genotoxicity.</p>	[94]
5		<p><i>P. tuberculatum</i> Jacq.</p>	<p>Essential oil from leaves Major compounds: germacrene D, germacrene B and <i>iso</i>-caryophyllene)</p>	<p>The essential oil inhibited about 60 % of Ethoxyresorufin <i>O</i>-Deethylase activity <i>in vitro</i> with 12.5 µL per mL of reaction médium. However, it did not inhibit the 7-Ethoxycoumarin <i>O</i>-Deethylase activity even with 100 µL per mL of reaction medium. The enzyme assays showed that there was Ethoxyresorufin <i>O</i>-Deethylase inhibition by the essential oil, but no inhibition of 7-Ethoxycoumarin <i>O</i>-Deethylase.</p>	[100]

1	Phytotoxic	<i>P. hispidinervum</i> C. DC.	Essential oil from fresh leaves and thigs [Safrole was the major component (78 - 81 %) followed by terpinolene (5 – 9 %)] Combinations of safrole and terpinolene	The oils affected the germination of the plants <i>Solanum lycopersicum</i> and <i>Lactuca sativa</i> at 24h of treatment, with <i>L. sativa</i> being the most affected. Safrole moderately affected germination and root growth of <i>L. sativa</i> , <i>S. lycopersicum</i> and <i>Lolium perene</i> . Terpinole affected only the root growth of <i>S. lycopersicum</i> .	[80]
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This literature search resulted in 99 peer review articles describing the extraction of essential oils from species of the genus *Piper* and their respective biological activities and chemical constituents. The major biological activities reported were: antimicrobial/antibacterial, antifungal, larvicidal/insecticidal and antioxidante. Most of the studies reported the biological activities of only the essential oils and did not isolate a purified compound, with the activities observed being associated with the major compounds present in their oils in most investigations, whereas a few studies fractioned the essential oils and reported biological activities of both the oils and/or purified substances from them.

CONCLUDING REMARKS

This review summarized and characterized the importance of essential oils in species of the *Piper* genus. Most of the studies on biological activities of their essential oils and compounds isolated from the essential oils reported insecticidal, antibacterial and antifungal actions. Most of these studies, however, did not investigate the effect of purified constituents of the screened species. The information presented in this review serves as a reference for researchers that work in the fields of ethnopharmacology and pharmacology related to the genus *Piper*.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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