

Medicinal Uses, Phytochemistry, and Pharmacological Properties of *Piper aduncum* L.

(Kegunaan Perubatan, Fitokimia dan Sifat Farmakologi *Piper aduncum* L.)

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ABSTRACT

Piper aduncum L., commonly known as 'spiked pepper', has various uses in traditional medicine that include treating wounds, skin boils, infections, and diarrhoea. Its properties as an anti-parasitic, antimicrobial, insecticidal, antitumor, and anticancer agent indicates that it could have further therapeutic potential in treating infections and cancers. The aim of this review was to provide a comprehensive summary of the traditional uses, phytochemistry and pharmacological properties of *P. aduncum*. Data were collected from electronic databases from 1978 to 2019. The plant is traditionally used for treating diarrhoea in Peru and for its wound-healing properties in Brazil and Papua New Guinea. Phenolics, monoterpenes, sesquiterpenes, and chromene have been found in the *P. aduncum* plant, and these bioactive compounds contribute to its anti-parasitic, antimicrobial, insecticidal, antitumor, and anticancer properties. Several pharmacological activities of *P. aduncum* have been reported, most notably in the treatment of infectious diseases and cancer. However, information regarding its safety and efficacy in humans is lacking. Further study is needed to examine the benefits of *P. aduncum* and its potential applications in a clinical setting.

Keywords: Pharmacological properties; phytochemistry; *Piper aduncum*; traditional uses

ABSTRAK

Piper aduncum L., yang dikenali sebagai lada berduri, mempunyai pelbagai kegunaan dalam ubat tradisi termasuk merawat luka, bisul kulit, jangkitan dan cirit-birit. Sifatnya sebagai agen anti-parasit, antimikrob, insektisid, antitumor dan antikanser menunjukkan bahawa ia mempunyai potensi terapeutik dalam merawat jangkitan dan kanser. Tujuan kajian ini adalah untuk memberikan ringkasan komprehensif mengenai kegunaan tradisi, fitokimia dan sifat farmakologi *P. aduncum*. Data telah dikumpulkan dari pangkalan data elektronik dari tahun 1978 hingga 2019. Tumbuhan ini secara tradisinya digunakan untuk merawat cirit-birit di Peru serta menyembuhkan luka di Brazil dan Papua New Guinea. Fenol, monoterpena, sesquiterpena serta kromena telah dijumpai dalam tumbuhan *P. aduncum*, dan sebatian bioaktif ini menyumbang kepada sifatnya sebagai anti-parasit, antimikrob, insektisid, antitumor dan antikanser. Beberapa aktiviti farmakologi *P. aduncum* telah dilaporkan, terutamanya dalam rawatan penyakit berjangkit dan kanser. Walau bagaimanapun, maklumat mengenai keselamatan dan keberkesanannya pada manusia adalah kurang. Kajian lanjut diperlukan untuk mengkaji manfaat *P. aduncum* dan potensi pengaplikasiannya dalam persekitaran klinikal.

Kata kunci: Fitokimia; kegunaan tradisi; *Piper aduncum*; sifat farmakologi

INTRODUCTION

Many drugs that are available in the market nowadays have been discovered from natural products including plants. It has been known that plants have their own importance in human history with their interesting phytochemical and pharmacological properties (Flores et al. 2009).

The Piperaceae family comprises around 3600 species. Within this family, the large genus *Piper* comprises approximately 2000 plant species, including numerous bushes and herbs that can be found in hushed and humid areas, such as jungles and tropical rainforests (Bernuci

et al. 2016; Gutiérrez et al. 2016). *Piper aduncum* is a species in the *Piper* genus within the Piperaceae family (Ahmad & Rahmani 1993). It is known as *pimenta-demacaco* in the Amazon of Brazil and *aperta-ruao* in the Atlantic Forest of Brazil (de Almeida et al. 2009). It is believed that extracts from *P. aduncum*, which have been shown to have various pharmacological effects, including anti-parasitic, antimicrobial, insecticidal, antitumor, and anticancer properties, can cure many diseases and cancers (Lucena et al. 2017; Mee et al. 2009; Monzote et al. 2017; Ndjonka et al. 2013).

Although many studies have examined the pharmacological properties of *P. aduncum*, a systematic literature review of this potential therapeutic agent has not yet been conducted. This review reports on the traditional uses, phytochemistry, and pharmacological activities of *P. aduncum* in order to provide an overview of the research and a reference for the comprehensive therapeutic uses of this plant.

METHODS

Data on the background, traditional uses, phytochemistry, and pharmacological properties of *P. aduncum* were collected from published scientific journals from years 1978 to 2019, using the keywords ‘*Piper aduncum*’ and ‘*Piper* species’. Articles, websites, books, and electronic data were collected from academic search engines such as ScienceDirect, Scopus, PubMed, Google Scholar and ResearchGate. The species name of *P. aduncum* L. was validated by the database ‘The Plant List’ from www.theplantlist.org.

CHARACTERISTICS

P. aduncum, commonly known as ‘spiked pepper’, is considered the most invasive species of the genus *Piper*. *P. aduncum* grows as a small tree or shrub and can reach 6 to 8 m in height, with alternate leaves with short petioles and small fruits arranged in spikes (Ahmad & Rahmani 1993). The fruits of *P. aduncum* appear as berries that contain small, black seeds. The leaves are 10 to 18 cm long and have a narrow oval shape that tapers to a point and display a fine network of veins and smooth hairs on the underside (dos Santos et al. 2015). All parts of the *P. aduncum* plant have a peppery smell. The branches of the plant are commonly used as firewood and split easily when continuously exposed to moisture (Rali et al. 2007).

DISTRIBUTION

P. aduncum was mostly originally found in Central and South America, where it grows throughout a large part of the Amazon and Atlantic forests. It was introduced to Asia during the 19th century and is now commonly found throughout New Guinea, Indonesia, Malaysia and the Solomon and Christmas islands (de Almeida et al. 2009; Hartemink 2010; Orjala et al. 1994). It was introduced to the Botanical Gardens of Bogor, Indonesia, possibly as an ornamental (Hartemink 2010).

Due to the large amount of pollen it produces, it is easily spread by the wind. It is also carried efficiently in the faeces of mammals and birds. It grows in areas of evergreen vegetation and water courses in seasonally deciduous forests (Hartemink 2010). As such, *P. aduncum* can be found in increasingly large geographical areas today.

PHYTOCHEMISTRY OF *P. aduncum*

Previous studies have identified several bioactive constituents in *P. aduncum*, including flavonoids, monoterpenes and sesquiterpenes, chalcones, chromenes, phenylpropanoid, and benzoic acid derivatives (Lago et al. 2004; Moreira et al. 1998; Orjala et al. 1994; Rali et al. 2007). It has also been found to contain 23 essential oil components (Oliveira et al. 2013).

PHYTOCHEMICAL CONSTITUENTS IN THE LEAVES OF *P. aduncum*

P. aduncum contains a wide range of phytochemical compounds, such as flavonoids, monoterpenes, sesquiterpenes, chalcones and benzoic acid derivatives, as summarised in Table 1.

TABLE 1. Compounds from the leaves of *Piper aduncum*

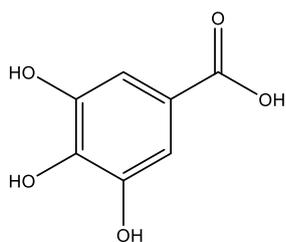
Class of compound	Compound	References
Flavonoids	Gallic acid (1)	(Escudero et al. 2008)
	Catechin (2)	
	Chlorogenic acid (3)	
	Epicatechin (4)	
	Quercetin-3-rutinoside (5)	
	Quercetin-3-rhamnoside (6)	
	Phloridzin (7)	
	Quercetin (8)	
	Phloretin (9)	

Mono- and sesquiterpenes	α -pinene (10) β -pinene (11) Limonene (12) (e)-ocimene (13) (z)-ocimene (14) Linalool (15) α -copaene (16) β -elemene (17) α -gurjunene (18) β -caryophyllene (19) Allo-aromadendrene (20) α -humulene (21) Undecanone (22) Germacrene d (23) bicyclogermacrene (24) α -muurolene (25) γ -cadinene (26) δ -cadinene (27) Germacrene b (28) Nerolidol (29) Spathulenol (30) Globulol (31) Safrole (32) β -gurjunene (33) β -sesquiphellandrene (34) Rosifoliol (35) Humulene epoxide ii (36) Epi-cubenol (37) α -muurolol (38) α -cadinol (39) Shyobunol (40) Piperitone (41)	(Bernuci et al. 2016; Navickiene et al. 2006; Oliveira et al. 2013; Rali et al. 2007)
Chalcones	Adunctins A (42) Adunctins B (43) Adunctins C (44) Adunctins D (45) Adunctins E (46) Cardamonin (47) Piperaduncin A (48) Piperaduncin B (49) Piperaduncin C (50) Asebogenin (51) 2',6'-dihydroxy-4'-methoxydihydrochalcone (52) Uvangoletin (53)	(Orjala et al. 1994)
Phenylpropanoid	Dillapiole (54)	(Rali et al. 2007)
Benzoic acid derivatives	3-(3,7-dimethyl-2,6-octadienyl)-4-methoxy-benzoic acid (55) 4-hydroxy-3-(3,7-dimethyl-2,6-octadienyl) benzoic acid (56) 4-hydroxy-3-(3-methyl-1-oxo-2-butenyl)-5(3-methyl-2-butenyl) benzoic acid (57) Methyl 4-hydroxy-3-(2'-hydroperoxy-3'-methyl-3'-butenyl)benzoate (58) Methyl 4-hydroxy-3-(2'-hydroxy-3'-methyl-3'-butenyl) benzoate (59) Aduncumene (60)	(Flores et al. 2009; Lago et al. 2009)

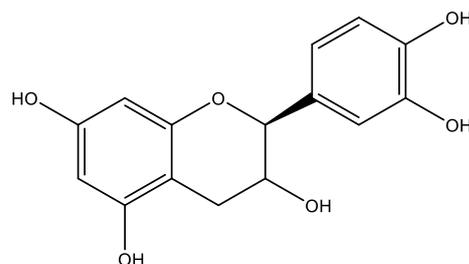
FLAVONOIDS

Ethanollic extracts of *P. aduncum* leaves have shown the presence of large amounts of flavonoids (Arroyo-Acevedo et al. 2015). Flavonoids, which are polyphenolic compounds, have antioxidant properties and are able to scavenge free radicals and therefore have utility in

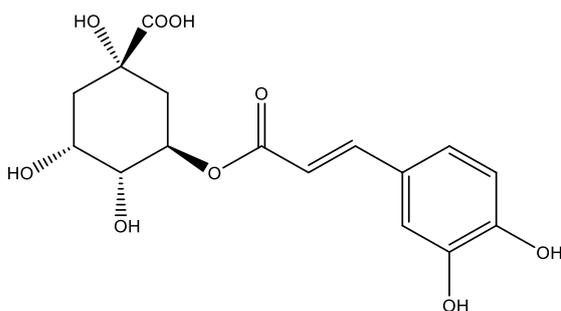
cancer treatment. As reported by Escudero et al. (2008), ethanollic extracts of *P. aduncum* leaves originating from the Peruvian rainforest showed flavonoid compounds as the predominant compounds in the plant. The flavonoid constituents identified in *P. aduncum* are shown in Figure 1.



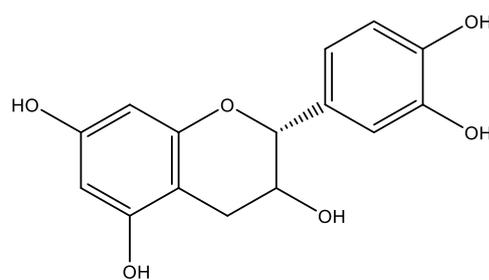
Gallic acid (1)



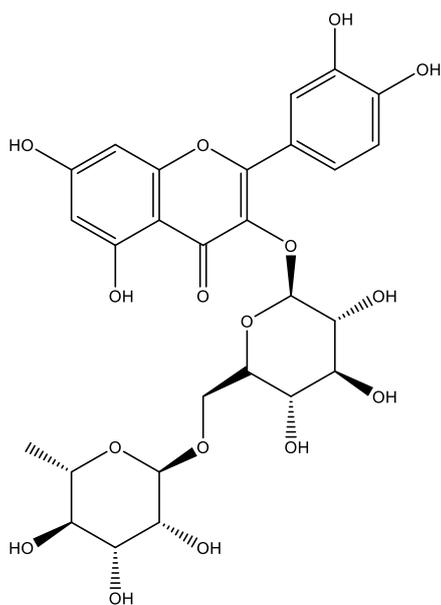
Catechin (2)



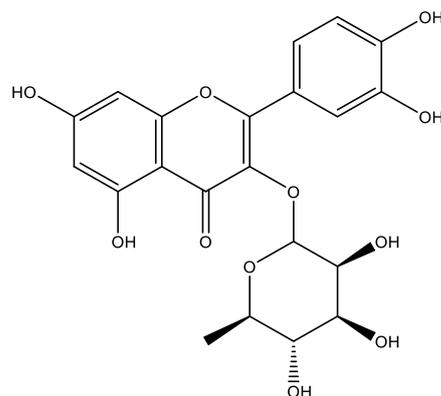
Chlorogenic acid (3)



Epicatechin (4)



Quercetin-3-rutinoside (5)



Quercetin-3-rhamnoside (6)

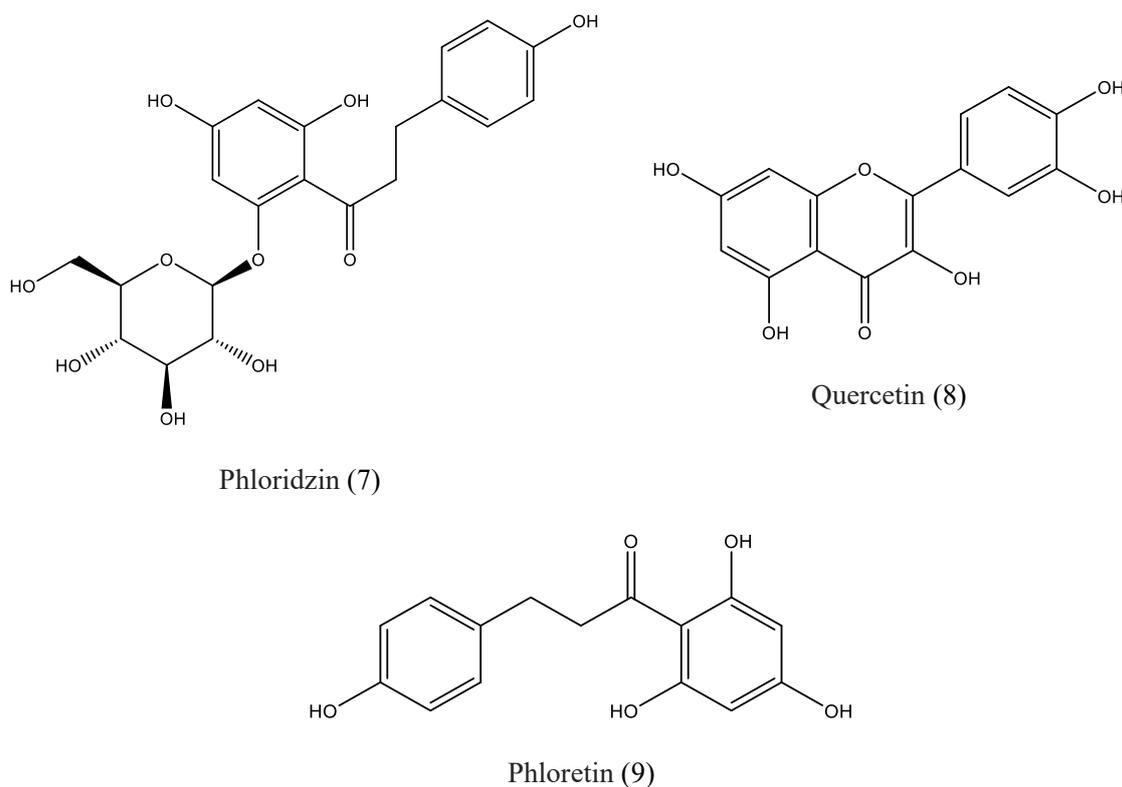


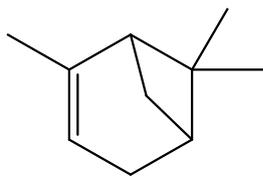
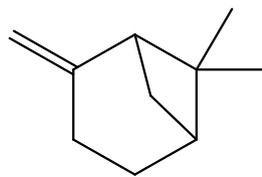
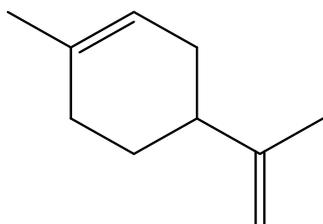
FIGURE 1. Flavonoid compounds identified in *Piper aduncum* leaves

MONOTERPENES AND SESQUITERPENES

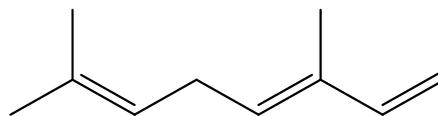
The presence of monoterpenes and sesquiterpenes (Figure 2) in the phytochemical analysis of *P. aduncum* leaves has been extensively reported (Escudero et al. 2008). The results obtained in separate studies all correlated with one another in terms of their finding that *P. aduncum* leaves contain larger amounts of sesquiterpene compounds (90.4%) than monoterpenes (7.0%). 1,8-Cineole has been found to be the major component of *P. aduncum* essential oil (Oliveira et al. 2013). The essential oil of *P. aduncum* leaves originating from Brazil has been shown to contain α -pinene (10), β -pinene (11), limonene (12), (E)-ocimene (13), (Z)-ocimene (14) and linalool (15) (Navickiene et al. 2006). The sesquiterpenes identified by GC-MS analyses are α -copaene (16), β -elemene (17), α -gurjunene (18), β -caryophyllene (19), allo-aromadendrene (20), α -humulene (21), undecanone (22), germacrene D (23), bicyclogermacrene (24), α -muurolene (25), γ -cadinene

(26), δ -cadinene (27), germacrene B (28), nerolidol (29), spathulenol (30) and globulol (31).

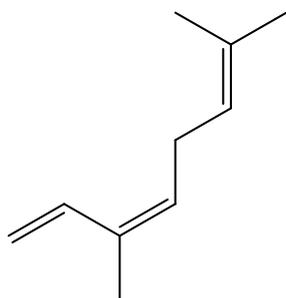
Bernuci et al. (2016) showed that the essential oil of fresh *P. aduncum* leaves from Santa Catrina, Brazil, is rich in sesquiterpenes. The monoterpene compounds identified were (E)-ocimene (13), (Z)-ocimene (14), linalool (15) and safrole (32). The sesquiterpenes identified were β -caryophyllene (19), β -gurjunene (33), α -humulene (21), allo-aromadendrene (20), bicyclogermacrene (24), γ -cadinene (26), β -sesquiphellandrene (34), spathulenol (30), rosifoliol (35), humulene epoxide II (36), epi-cubenol (37), α -muurolol (38), α -cadinol (39) and shyobunol (40). Analysis conducted by Rali et al. (2007) showed that the dominant compounds in *P. aduncum* leaf essential oil from Papua New Guinea were β -caryophyllene (19), piperitone (41) and α -humulene (21). Figure 2 shows the monoterpenes and sesquiterpenes identified in the analysis of *P. aduncum* leaves.

 α -pinene (10) β -pinene (11)

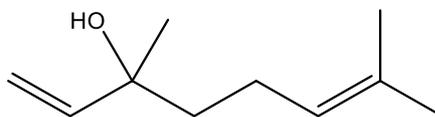
Limonene (12)



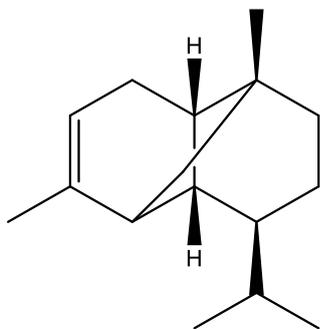
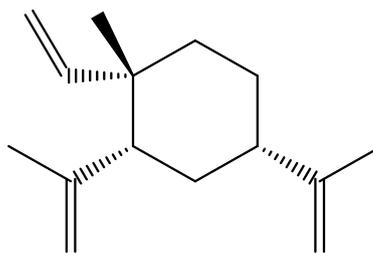
(E)-ocimene (13)

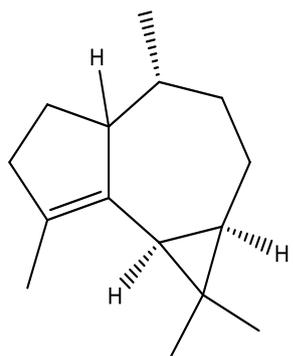
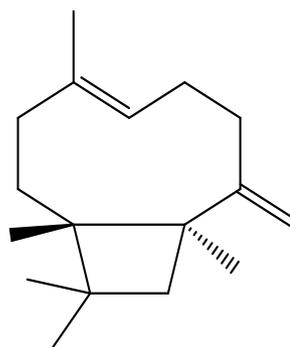
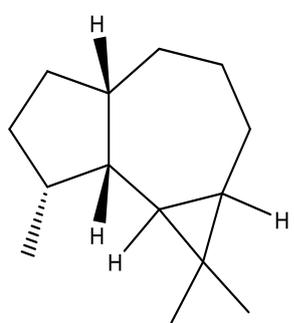


(Z)-ocimene (14)

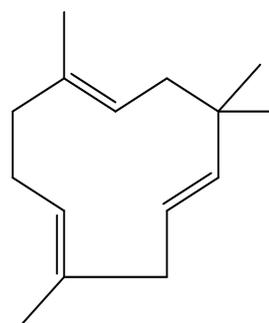
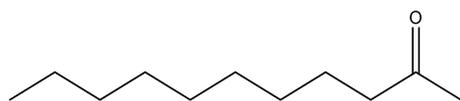


Linalool (15)

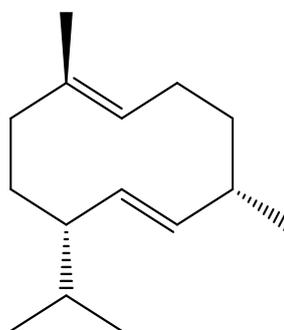
 α -copaene (16) β -elemene (17)

 α -gurjunene (18) β -caryophyllene (19)

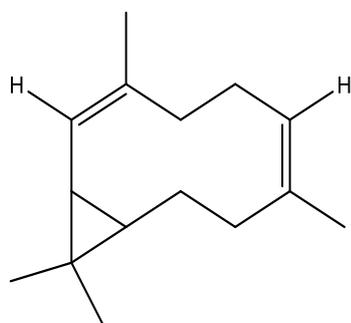
Allo- Aromadendrene (20)

 α -humulene (21)

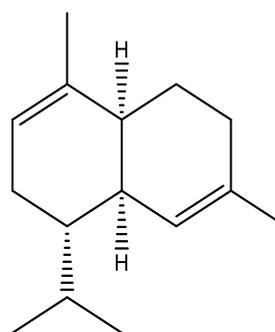
Undecanone (22)

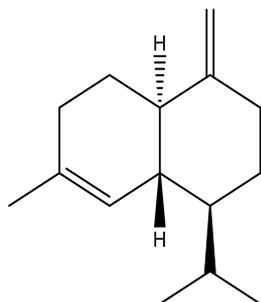
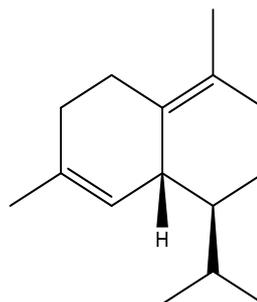
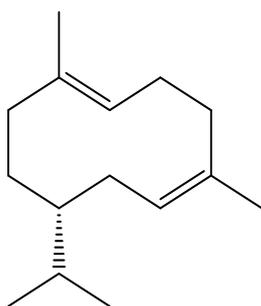


Germacrene D (23)

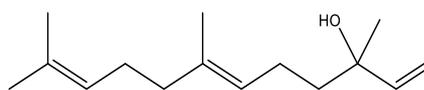


Bicyclogermacrene (24)

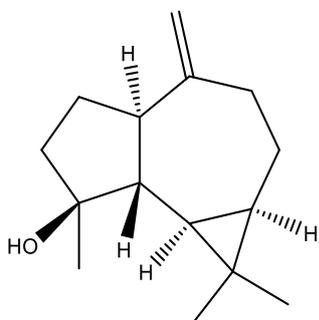
 α -murolene (25)

 γ -cadinene (26) δ -cadinene (27)

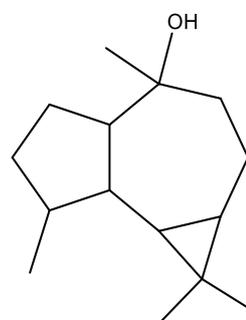
germacrene B (28)



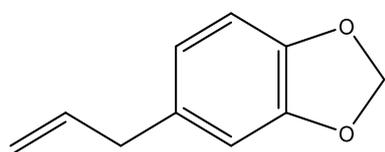
Nerolidol (29)



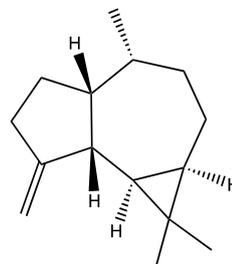
Spathulenol (30)

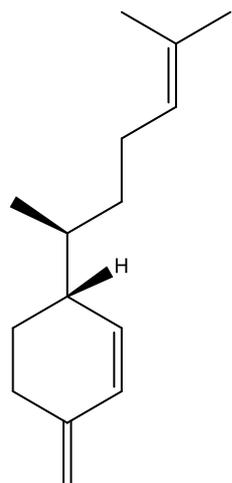
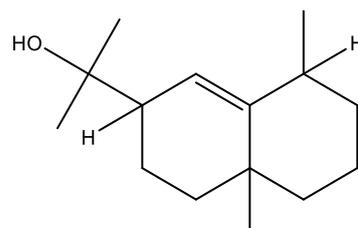


Globulol (31)

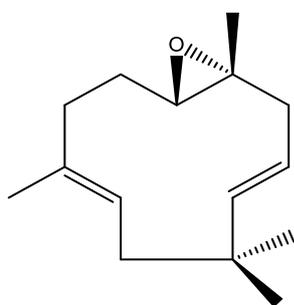


Safrole (32)

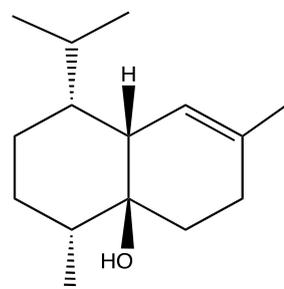
 β -gurjunene (33)

 β -sesquiphellandrene (34)

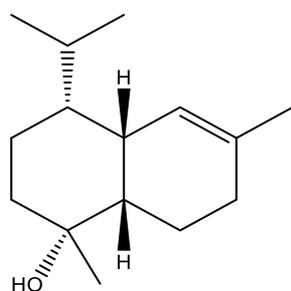
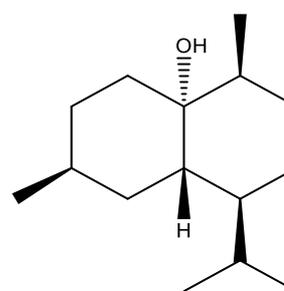
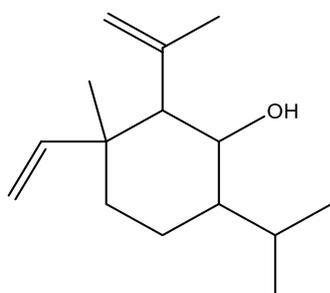
Rosifoliol (35)



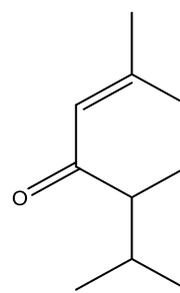
Humulene epoxide II (36)



Epi-cubenol (37)

 α -muurolol (38) α -cadinol (39)

Shyobunol (40)



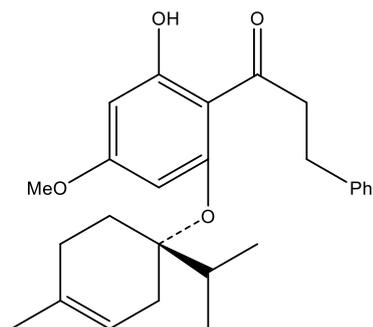
Piperitone (41)

FIGURE 2. Chemical structures of mono- and sesquiterpenes found in *Piper aduncum* leaves

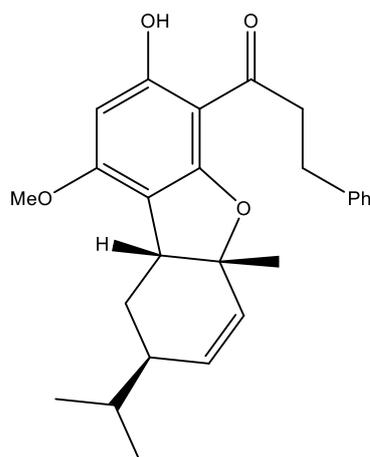
CHALCONES

Orjala et al. (1994) isolated chalcones and previously unidentified monoterpenes-substituted dihydrochalcones from the leaves of *P. aduncum*, which were adunctins A-E (42-46). Piperaduncin A-C (48-50), asebogenin (51) and 2',6'-dihydroxy-4'-methoxydihydrochalcone (52) were

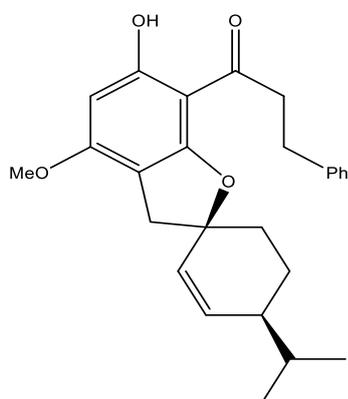
also isolated from the leaves of *P. aduncum* (Orjala et al. 1994). Cardamonin (47) and uvangoletin (53) (Figure 3) were isolated from *P. aduncum* leaves originating from Brazil by solvent extraction with CH_2Cl_2 (de Castro et al. 2015).



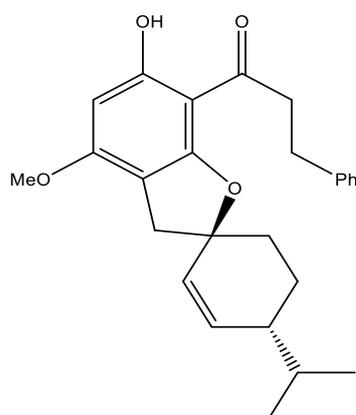
Adunctins A (42)



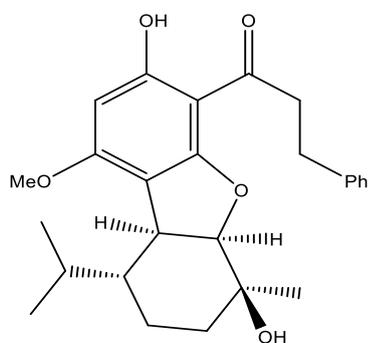
Adunctins B (43)



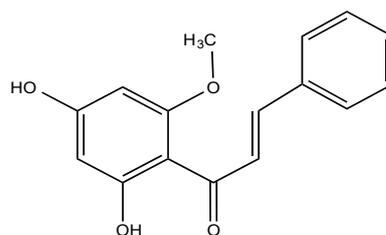
Adunctins C (44)



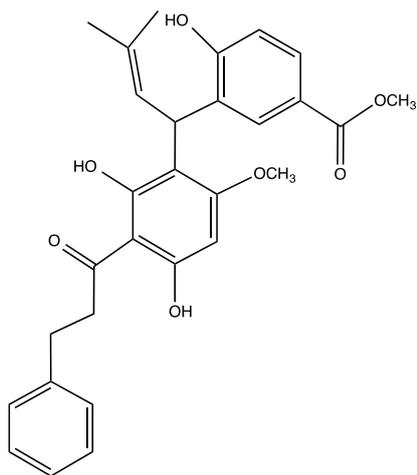
Adunctins D (45)



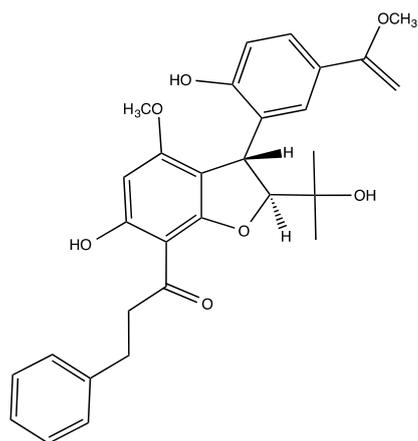
Adunctins E (46)



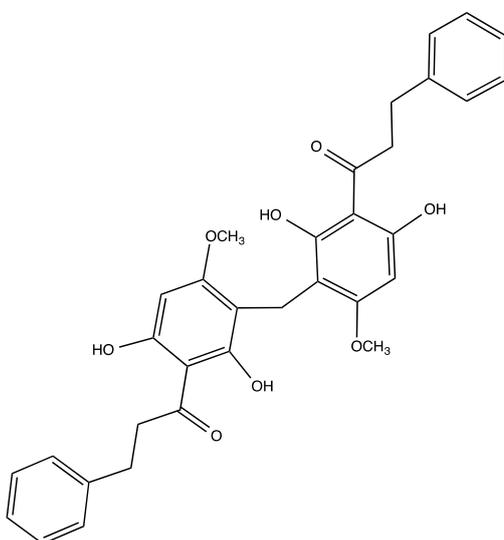
Cardamonin (47)



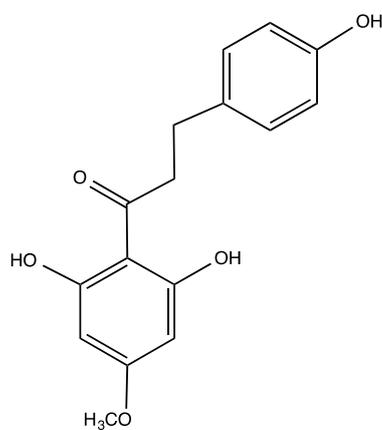
Piperaduncin A (48)



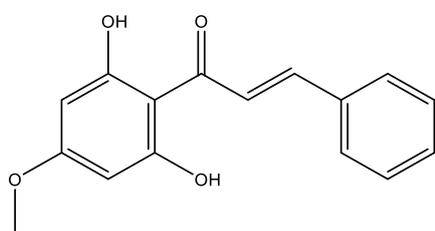
Piperaduncin B (49)



Piperaduncin C (50)

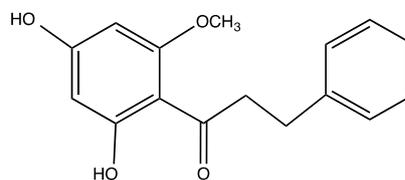


Asebogenin (51)



2',6'-dihydroxy-4'-methoxydihydrochalcone

(52)



Uvangoletin (53)

FIGURE 3. Chemical structures of chalcones isolated from *Piper aduncum* leaves

PHENYLPROPANOID

The essential oil of *P. aduncum* is rich in dillapiole (54) (Figure 4), which is a derivative of phenylpropene. Rali et al. (2007) identified dillapiole as the main volatile constituent of the essential oil from the leaves of *P. aduncum* from the Brazilian Amazon rainforest, Costa Rica, Cuba, Malaysia, and Fiji. Ahmad and Rahmani (1993) also identified dillapiole as the main constituent (43.3%) in *P. aduncum* leaves from Puchong, Malaysia.

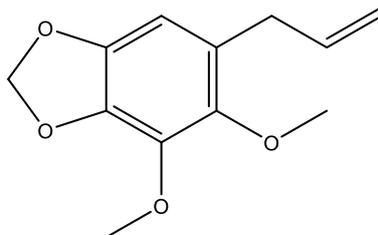
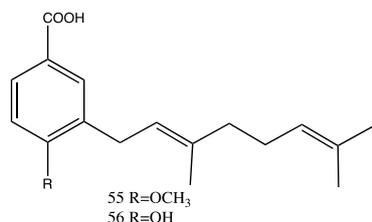


FIGURE 4. Chemical structure of dillapiole (54)

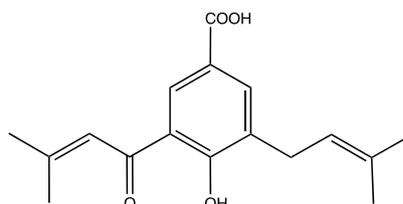
BENZOIC ACID DERIVATIVES

Flores et al. (2009) conducted a phytochemical analysis of the leaves of *P. aduncum* and isolated the prenylated hydroxybenzoic acid derivatives namely 3-(3,7-dimethyl-2,6-octadienyl)-4-methoxy-benzoic acid (55), 4-hydroxy-3-(3,7-dimethyl-2,6-octadienyl) benzoic acid (56) and 4-hydroxy-3-(3-methyl-1-oxo-2-butenyl-5(3-methyl-2-

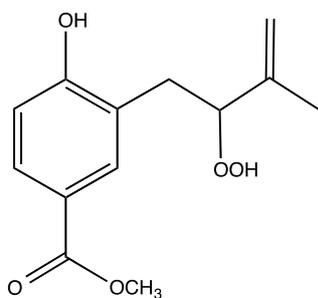
butenyl) benzoic acid (57) (Figure 5). Additional two prenylated methyl benzoates have also been isolated from *P. aduncum* leaves which are methyl 4-hydroxy-3-(2'-hydroperoxy-3'-methyl-3'-butenyl)benzoate (58) and methyl 4-hydroxy-3-(2'-hydroxy-3'-methyl-3'-butenyl) benzoate (59) (Lago et al. 2009). Aduncumene (60) was isolated after successive extractions using different solvents and column chromatography.



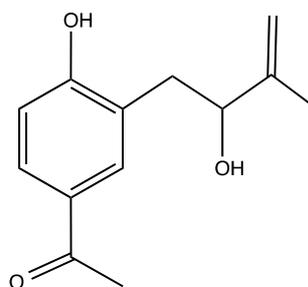
3-(3,7-dimethyl-2,6-octadienyl)-4-methoxy-benzoic acid (55) and 4-hydroxy-3-(3,7-dimethyl-2,6-octadienyl) benzoic acid (56)



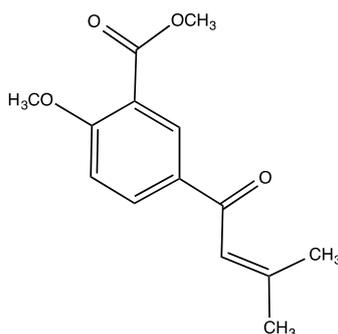
4-hydroxy-3-(3-methyl-1-oxo-2-butenyl-5(3-methyl-2-butenyl) benzoic acid (57)



Methyl 4-hydroxy-3-(2'-hydroperoxy-3'-methyl-3'-butenyl)benzoate (58)



Methyl 4-hydroxy-3-(2'-hydroxy-3'-methyl-3'-butenyl)benzoate (59)



Aduncumene (60)

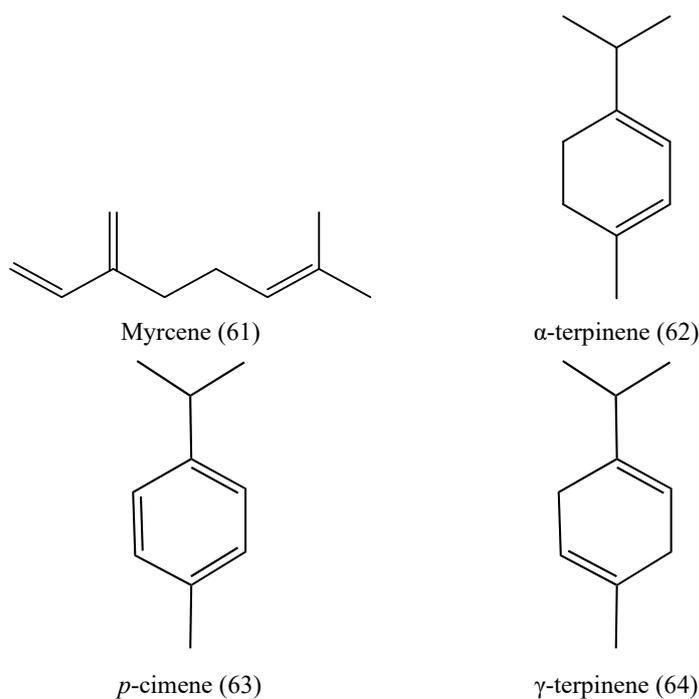
FIGURE 5. Isolated benzoic acid derivatives from *Piper aduncum* leaves

PHYTOCHEMICAL CONSTITUENTS IN THE STEMS OF

P. aduncum

Several monoterpenes, including α -pinene (10), β -pinene (11), myrcene (61), α -terpinene (62), *p*-cimene (63), limonene (12), (*E*)-ocimene (13), (*Z*)-ocimene (14), γ -terpinene (64) and linalool (15), have been identified in the stems of *P. aduncum*, in addition to the sesquiterpenes β -caryophyllene, α -humulene, germacrene D, and nerolidol (Navickiene et al. 2006). A separate study identified

monoterpenes and sesquiterpenes such as β -pinene (11), myrcene (61), α -terpinene (62), α -phellendrene (65), *m*-cimene (66), 1,8-cineole (67), bornyl acetate (68), neryl acetate (69), geranyl acetate (70), and copaene (71) (Moreira et al. 1998). The chromenes eupatoriochromene (72) and methyl 2,2-dimethyl-8-(3-methyl-2-butenyl)-2H-chromene-6-carboxylate (73) have also been identified. The chemical structures of bioactive compounds isolated from the stems of *P. aduncum* are shown in Figure 6.



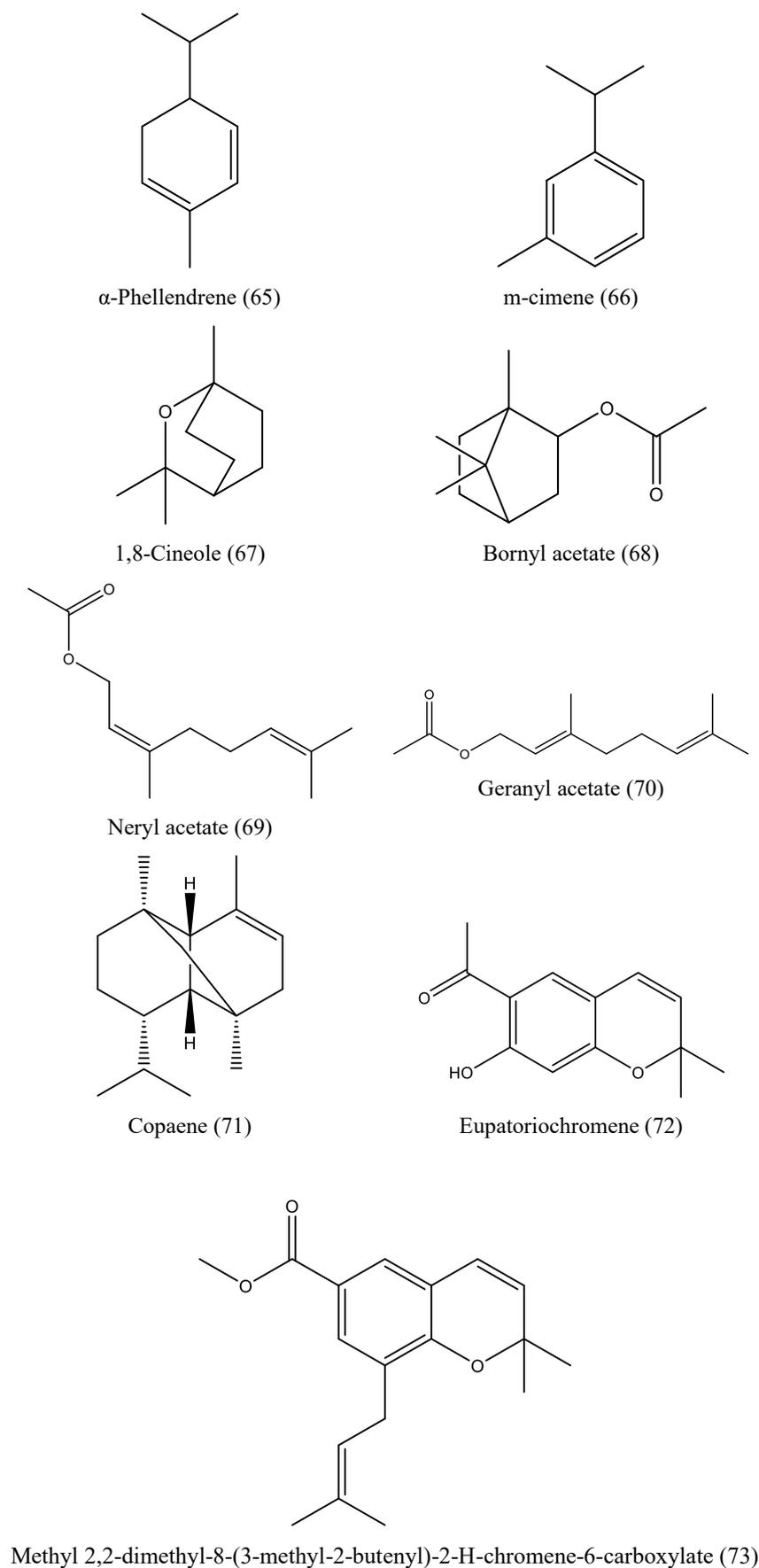


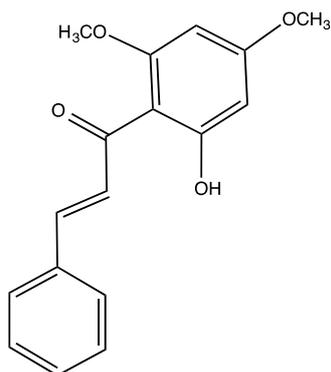
FIGURE 6. Compounds found in *Piper aduncum* stems

PHYTOCHEMICAL CONSTITUENTS IN THE FRUITS OF

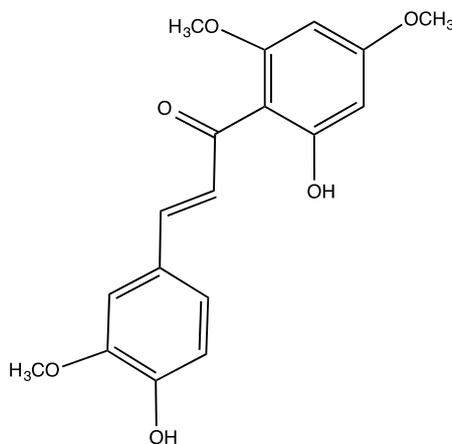
P. aduncum

The fruits of *P. aduncum* have been analysed using a chemical extraction process and have been shown to contain both monoterpenes and sesquiterpenes (Navickiene et al. 2006). The specific compounds identified in the fruits are α -pinene (10), β -pinene (11), myrcene, α -terpinene, limonene (12), 1,8-cineole, (E)-ocimene (13), (Z)-ocimene (14), γ -terpinene (64), linalool (15), β -caryophyllene (19),

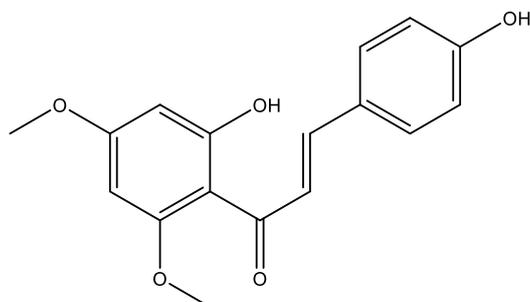
α -humulene (21), germacrene D (25) and nerolidol (29). Other dihydrochalcone compounds, including 2'-hydroxy-4',6'-dimethoxydihydrochalcone (74), 2',6'-dihydroxy-4',6'-trimethoxydihydrochalcone (75) and 2',4-dihydroxy-4',6'-dimethoxydihydrochalcone (76), have been isolated from hexane extracts of *P. aduncum* fruits (Moreira et al. 1998). The chemical structures of these dihydrochalcones are shown in Figure 7.



2'-hydroxy-4',6'-dimethoxydihydrochalcone (74)



2',4-dihydroxy-4',6',3-trimethoxydihydrochalcone (75)



2',4-dihydroxy-4',6'-dimethoxydihydrochalcone (76)

FIGURE 7. Chemical structures of dihydrochalcones found in *Piper aduncum* fruits

Different phytochemical constituents have been found in varying quantities in different parts of the *P. aduncum*

plant, and different parts of the plant have been shown to contain different types of compounds (Table 2).

TABLE 2. Summary of the compounds from the leaves, stems, and fruits of *P. aduncum*

Leaves	Stems	Fruits
Gallic acid (1)	α -pinene (10)	α -pinene (10)
Catechin (2)	β -pinene (11) Limonene (12)	β -pinene (11)
Chlorogenic acid (3)	(E)-ocimene (13)	Myrcene (61)
Epicatechin (4)	(Z)-ocimene (14)	α -terpinene (62)
Quercetin-3-rutinoside (5)	Linalool (15)	Limonene (12)
Quercetin-3-rhamnoside (6)	β -caryophyllene (19)	1,8-cineole (67)
Phloridzin (7)	α -humulene (21)	(E)-ocimene (13)
Quercetin (8)	Germacrene d(23)	(Z)-ocimene (14)
Phloretin (9)	Nerolidol (29)	γ -terpinene, linalool (15)
α -pinene (10)	Myrcene (61)	β -caryophyllene (19)
β -pinene (11)	α -terpinene (62)	α -humulene (21)
Limonene (12)	<i>p</i> -cimene (63)	Germacrene D (25)
(e)-ocimene (13)	γ -terpinene (64)	Nerolidol (29)
(z)-ocimene (14)	α -phellendrene (65)	2',6'-dihydroxy-4'-
Linalool (15)	<i>m</i> -cimene (66)	methoxydihydrochalcone (52)
α -copaene (16)	bornyl acetate (68)	2'-hydroxy-4',6'-
β -elemene (17)	neryl acetate (69)	dimethoxydihydrochalcone (74)
α -gurjunene (18)	geranyl acetate (70)	2'4-dihydroxy-4',6',3-
β -caryophyllene (19)	copaene (71)	trimethoxydihydrochalcone (75)
Allo-aromadendrene (20)	eupatoriochromene (72)	2'.4-dihydroxy-4'-6'-
α -humulene (21)	methyl 2,2-dimethyl-8-(3-methyl-2-butenyl)-	dimethoxydihydrochalcone (76)
Undecanone (22)	2H-chromene-6-carboxylate (73)	
Germacrene d (23)		
Bicyclogermacrene (24)		
α -muurolene (25)		
γ -cadinene (26)		
δ -cadinene (27)		
Germacrene b (28)		
Nerolidol (29)		
Spathulenol (30)		
Globulol (31)		
Safrole (32)		
B-gurjunene (33)		
B-sesquiphellandrene (34)		
Rosifoliol (35)		
Humulene epoxide ii (36)		
Epi-cubenol (37)		
A-muurolol (38)		
A-cadinol (39)		

Shyobunol (40)
 Piperitone (41)
 Adunctins A (42)
 Adunctins B (43)
 Adunctins C (44)
 Adunctins D (45)
 Adunctins E (46)
 Cardamonin (47)
 Piperaduncin A (48)
 Piperaduncin B (49)
 Piperaduncin C (50)
 Asebogenin (51)
 2',6'-dihydroxy-4'-
 methoxydihydrochalcone (52)
 Uvangoletin (53)
 Dillapiole (54)
 3-(3,7-dimethyl-2,6-octadienyl)-4-
 methoxy-benzoic acid (55)
 4-hydroxy-3-(3,7-dimethyl-2,6-
 octadienyl) benzoic acid (56)
 4-hydroxy-3-(3-methyl-1-oxo-2-butenyl-
 5(3-methyl-2-butenyl) benzoic acid (57)
 Methyl 4-hydroxy-3-(2'-hydroperoxy-3'-
 methyl-3'-butenyl)benzoate (58)
 Methyl 4-hydroxy-3-(2'-hydroxy-3'-
 methyl-3'-butenyl)benzoate (59)
 Aduncumene (60)

TRADITIONAL USES OF *P. aduncum* TREATMENT OF DIARRHOEA

In traditional folk medicine, *P. aduncum* is widely used in Jamaica for treating stomach aches, in Peru for treating diarrhoea and in Colombia as a remedy for dysentery (Luyen et al. 2017; Orjala et al. 1994; Thao et al. 2016). Traditionally, an infusion of *P. aduncum* leaves is used by Peruvian people as an alternative therapy for treating diseases with symptomatic diarrhoea, due to the plant's antimicrobial, astringent, diuretic, stimulant, and stomachic properties (Duarte et al. 2007; Morandim et al. 2005). The essential oil of *P. aduncum* has been shown to ameliorate diarrhoea caused by *Escherichia coli*. A minimal inhibitory concentration (MIC) of 1000 µg/mL *P. aduncum* essential oil successfully inhibited enterohaemorrhagic *E. coli*, 900 µg/mL enteropathogenic *E. coli* and enteroinvasive *E. coli* (Duarte et al. 2007).

TREATMENT OF WOUNDS

P. aduncum is used in traditional Brazilian and Papua New Guinean folk medicine for treating wounds due to its antiseptic and anti-inflammatory properties (Morandim et al. 2005). The leaves are used in herbal remedies in two ways. The first involves making an infusion of the leaves, which is then used to wash the bleeding area. The second method is to crush the leaves and sprinkle them onto a wound (Dal Picolo et al. 2014; Mee et al. 2009). Recent studies have found that the essential oil of *P. aduncum* has strong antimicrobial activity against many common microorganisms that cause wounds to become infected, such as *Staphylococcus epidermis*, *S. aureus* and *Pseudomonas aeruginosa*. In one study, the MIC value of isolated compounds for *P. aeruginosa*, *Bacillus subtilis*, and *S. aureus* was reported to be more than 100 µg/mL (Okunade et al. 1997). In addition, one *in vitro* study

demonstrated a highly significant anti-inflammatory effect of a methanolic extract of *P. aduncum*, with an inhibition value of 20 µg/mL (Thao et al. 2016).

PHARMACOLOGICAL PROPERTIES OF *P. aduncum*

Table 3 provides a summary of the pharmacological properties of *P. aduncum*.

TABLE 3. Summary of pharmacological properties of *P. aduncum*

Pharmacological Properties	Plant Parts	Extracts	Methods	Mechanisms	Concentration / dose	Constituents	References
Anti-fungal	Leaves	Ethanol	<i>In vitro</i> on <i>C. cladosporioides</i> and <i>C. sphaerospermum</i>	n.a	MIC: 0.5-5.0 µg	Benzoic acid derivatives and chromenes	(Lago et al. 2004)
	Fruits	n.a	Direct bioautography on TLC plate against <i>C. cladosporioides</i> and <i>C. sphaerospermum</i>	n.a	MIC: 10 µg	Monoterpenes (Linalool)	(Navickiene et al. 2006)
	Aerial part	n.a	<i>In vitro</i> against <i>Clinipellis perniciosus</i> (witches _ broom)	n.a	MIC: 0.6-1.0ppm	Dillapiole	(de Almeida et al. 2009)
	Leaves	Ethanol	<i>In vitro</i> inhibitory activity against <i>Cryptococcus neoformans</i> and <i>Candida albicans</i>	n.a	MIC: > 100 µg/mL	Benzoic acid, chalcones and chromenes	(Okunade et al. 1997)
Anti-bacterial	Leaves	Dichloromethane	<i>In vitro</i> on <i>Bacillus subtilis</i> and <i>Micrococcus luteus</i>	n.a	MIC: Sakuranetin: 0.5-2 µg/mL Chalcones: 0.1-3 µg/mL	Sakuranetin and chalcones	(Orjala et al. 1994)
	Leaves	n.a	<i>In vitro</i> against <i>S. aureus</i>	n.a	IC ₅₀ : 18.2 µg/mL	Piperitone, camphor and viridiflorol	(Monzote et al. 2017)
	Leaves	Ethanol	<i>In vitro</i> inhibitory activity against <i>Mycobacterium intracellulare</i>	n.a	MIC: > 100 µg/mL	Benzoic acid, chalcones and chromenes	(Okunade et al. 1997)

Insecticidal	Leaves	n.a	<i>In vitro</i> on the larvae and pupae of <i>A. aegypti</i>	Mortality of larvae and normal abnormalities in cells of pupae	200-400 µg/mL	Dillapiole	(Rafael et al. 2008)
	Leaves	n.a	<i>In vitro</i> against larvae and adult insects of <i>Anopheles marajoara</i> and <i>Aedes aegypti</i>	n.a	Mortality: 100 ppm (larvae) 600 ppm(insects)	Dillapiole	(de Almeida et al. 2009)
	Leaves	Hexane and ethyl acetate	<i>In vitro</i> on <i>Antircasia gemmatalis</i>	Synergistic action of the phenylpropanoids, apiol and myristicin by inhibiting the function of cytochrome P450	LC ₅₀ : Hexane extract: 6.35 mg/mL Ethyl acetate: 5.79 mg/mL	Apiol	(Lucena et al. 2017)
	Leaves	n.a	Adulticidal bioassay by topical application on <i>Musca domestica</i>	Alterations in a specific physiological processes that take place upon contact with toxicant	LC ₅₀ : 6.2 - 23.8 µg/fly LC ₉₀ : 13.3 - 50.5 µg/fly	n.a	(Mee et al. 2009)

ANTI-PARASITIC ACTIVITY AGAINST GENUS *Leishmania*

Leishmaniasis is an infectious disease caused by diverse flagellate kinetoplastids of the genus *Leishmania* (Dal Picolo et al. 2014). The essential oil from the hydro-distillation of fresh *P. aduncum* leaves showed that the high content of sesquiterpenes present possessed antileishmanial activity in an *in vitro* test on promastigote forms of *Leishmania amazonensis*, where the IC₅₀ after 24 h demonstrated a value of 25.9 µg/mL, though no explanation for the mechanism of action was proposed (Bernuci et al. 2016). Nerolidol, which is a sesquiterpene compound, has been found to exert antileishmanial activity, where the IC₅₀ after 24 h in an *in vitro* test on *Leishmania braziliensis* demonstrated a value of 74.3 µg/mL, whereas the IC₅₀ after 24 h for *P. aduncum* essential oil was reported to be effective at 77.9 µg/mL (Ceole et al. 2017). Scanning electron microscopy showed severe morphological changes, such as cell shrinkage and alterations in the mitochondria, nuclear chromatin, and flagella pocket on promastigotes, following treatment with nerolidol.

Chalcone derivatives have also been reported to possess antileishmanial activity (Dal Picolo et al. 2014; Torres-santos et al. 1999). Adunchalcone has been obtained from an ethanolic extract of *P. aduncum* leaves, whereas 2',6'-dihydroxy-4'-methoxychalcone has been obtained from a dichloromethane extract of *P. aduncum* leaves. An *in vitro* test of adunchalcone on promastigote

forms of *L. amazonensis* and *Leishmania shawi* obtained an EC₅₀ of 11.03 and 11.26 µM, respectively, whereas an *in vitro* test on 2',6'-dihydroxy-4'-methoxychalcone obtained an EC₅₀ of 0.5 µg/mL against promastigotes and 24 µg/mL against amastigotes of *L. amazonensis*. It has been suggested that the presence of two aromatic rings linked by three carbons containing carbonyl group with a hydrophilic and lipophilic substituent forms the structure of adunchalcone, which inhibits the growth of parasites (Dal Picolo et al. 2014). The mechanism of action for the cytotoxicity of 2',6'-dihydroxy-4'-methoxychalcone has been suggested as being due to the enlargement and disorganisation of mitochondria in *L. amazonensis* promastigote (Torres-santos et al. 1999). Flores et al. (2009) found that benzoic acid derivatives from ethanol and water extracts of *P. aduncum* leaves also possessed antileishmanial activity and reported that the IC₅₀ against *L. braziliensis* was 6.5 µg/mL *in vitro*. *P. aduncum* extracts from the Atlanta forest have been reported to contain 4-hydroxybenzoic acid, dihydrochalcones and chromenes that contribute to the plant antileishmanial effects (de Almeida et al. 2009). However, none of these studies discussed the potential mechanism of action for this antileishmanial activity.

ANTI-PARASITIC ACTIVITY AGAINST *Plasmodium falciparum*

Pink et al. (2005) reported that the essential oil from *P. aduncum* has antiprotozoal activity against *P. falciparum*,

which is the causal agent of malaria. The essential oil from *P. aduncum* collected in Cuba showed high antiprotozoal activity, where the IC_{50} value was reported as 1.3 $\mu\text{g}/\text{mL}$. The antiprotozoal activity may be attributable to the components piperitone, camphor and viridiflorol found in *P. aduncum* essential oil. It has been suggested that the mechanism of action for the cytotoxicity could be the decrease in mitochondrial membrane potential following treatment (Monzote et al. 2017; Villamizar et al. 2017).

ANTI-PARASITIC ACTIVITY AGAINST *Trypanosoma brucei* AND *T. cruzi*

The parasitic protozoa for trypanosomiasis ('morning sickness') have been identified as *T. brucei* and *T. cruzi*. The antiprotozoal activity of the essential oil from *P. aduncum* leaves showed high activity against *T. brucei* and *T. cruzi*, where the IC_{50} gave values of 2.0 and 2.1 $\mu\text{g}/\text{mL}$, respectively (Monzote et al. 2017). The antiprotozoal activity may be attributable to the presence of piperitone, camphor, and viridiflorol. It has been suggested that the mechanism of action for the antiprotozoal activity could be the reduction in mitochondrial membrane potential of the parasite after treatment (Villamizar et al. 2017).

ANTI-PARASITIC ACTIVITY AGAINST *Rhipicephalus* (*boophilus*) *microplus*

Silva et al. (2009) reported that a hexane the extraction of *P. aduncum* leaves possessed anti-parasitic activity and reported an LC_{50} of 9.3 mg/mL test against *R. microplus* larvae and adult females *in vitro*. GC-MS analysis indicated that the main compound responsible for the anti-parasitic activity was dillapiole. The cytotoxic effect was shown to be caused by alterations in development and physiological disturbances in the metabolism of the parasite (Silva et al. 2009).

ANTI-PARASITIC ACTIVITY AGAINST *Schistosoma mansoni*

de Castro et al. (2015) showed that dichloromethane extracts of *P. aduncum* at concentrations of 25, 50, and 100 μM caused 100% mortality in *S. mansoni* adult worms *in vitro*. GC-MS analysis showed that chalcone was the major compound responsible for the anti-parasitic activity. Treatment with cardamonin caused mortality, and tegumental altered and reduced the oviposition and motor activity of *S. mansoni* worms by inhibiting ATP diphosphohydrolase (de Castro et al. 2015).

ANTIMICROBIAL PROPERTIES ANTIFUNGAL

Research conducted by Lago et al. (2004) showed that an ethanolic extract of *P. aduncum* leaves possesses fungicidal activity against *Cladosporium sphaerospermum* and *Cladosporium cladosporioides*, where the MIC values have been reported to be between 0.5 and 5.0 $\mu\text{g}/\text{mL}$. Nerolidol obtained from the essential oil of the fruits of

P. aduncum has also demonstrated antifungal properties with an MIC value of 10 $\mu\text{g}/\text{mL}$ against *C. cladosporioides* and *C. sphaerospermum* (Navickiene et al. 2006).

A hydro-distillation of the aerial parts of *P. aduncum* showed that dillapiole possesses antifungal activity, where MIC values in an *in vitro* test against *Clinipellis perniciosus* ('witches-broom') were reported to be between 0.6 and 1.0 ppm (de Almeida et al. 2009). In addition, benzoic acid, chalcone, and chromene from ethanolic extracts of *P. aduncum* were shown to kill *Cryptococcus neoformans* and *Candida albicans* with MIC values of more than 100 $\mu\text{g}/\text{mL}$ (Okunade et al. 1997). No mechanism of action for the antifungal properties of these compounds was proposed in these studies.

ANTIBACTERIAL PROPERTIES

The crude of *P. aduncum* leaves from a dichloromethane extract demonstrated significant antibacterial activity towards *Bacillus subtilis* and *Micrococcus luteus* (Orjala et al. 1994). In addition, the *in vitro* inhibitory activity against *Mycobacterium intracellulare* has been demonstrated with an MIC value of higher than 100 $\mu\text{g}/\text{mL}$ (Okunade et al. 1997). *P. aduncum* taken from the Ciego de Avila Province, which is rich in camphene and isborneol constituents, has also been shown to have moderate to poor antimicrobial activity against *E. coli* and *S. aureus* (Gutiérrez et al. 2016). The mechanism of action for the antibacterial properties was not discussed in these studies.

INSECTICIDAL PROPERTIES

INSECTICIDAL ACTIVITY AGAINST MOSQUITOES

Previous studies have shown that the genus *Piper* is an important pesticide against the genus *Aedes* due to the presence of phenylpropanoids, lignoids, and flavonoids. Rafael et al. (2008) reported that dillapiole treatment at concentrations of 200 and 400 $\mu\text{g}/\text{mL}$ reduced survival and reproduction in *Aedes aegypti*. The chromosomal damaged and nuclear alterations have been induced by dillapiole treatments in larvae and pupae (Rafael et al. 2008). Dillapiole has also been shown to cause mortality in *Anopheles marajoara* and *A. aegypti*, where one study found that 100 and 600 ppm killed larvae and adult insects, respectively (de Almeida et al. 2009). However, no explanation for the mechanism of action was proposed in this study. Oliveira et al. (2013) reported an anti-larvicidal activity of *P. aduncum* essential oil against *A. aegypti*.

Research on the topical application of *P. aduncum* against *Musca domestica* has found that the essential oil from *P. aduncum* leaves has insecticidal properties against houseflies (Mee et al. 2009). However, this study did not discuss the compounds responsible for the insecticidal properties of the essential oil. The mechanism could be explained as resulting from alterations in a specific physiological process that occurs upon contact

with the toxicant. The insecticidal activity was tested on male and female houseflies of the same species, which were collected from either Chow Kit or the Institute of Medical Research. Houseflies from Chow Kit showed a lower susceptibility to the insecticidal effect of the *P. aduncum* extract. Cossolin et al. (2019) reported that the essential oil from *P. aduncum* showed toxicity against the brown stink bug *Euschistus heros*, which usually attacks soy bean plants. It exerted its effect by changing the insects' tissues and mitochondria population and through glycogen and lipid reduction in the body fat cells (Cossolin et al. 2019).

INSECTICIDAL ACTIVITY AGAINST CATERPILLARS

Hexane and ethyl acetate crude extracts of *P. aduncum* leaves have been shown to possess insecticidal activity against *Antircasia gemmatalis* caterpillars (Lucena et al. 2017). GC-MS analysis showed that apiol is the major bioactive compound responsible for the insecticidal properties, as it inhibits the function of cytochrome P450. The LC₅₀ of both hexane and ethyl acetate extracts were reported as 6.35 and 5.79 mg/mL, respectively.

ANTITUMOR AND ANTICANCER PROPERTIES

Research on the flavonoid constituents of the ethanolic extracts of *P. aduncum* leaves showed that concentrations of 50 to 300 mg/kg body weight had anticancer properties in DMBA-induced rats *in vivo* (Arroyo-Acevedo et al. 2015). Dihydrochalcone from the dichloromethane extract of *P. aduncum* leaves was also found to possess anticancer activity, inhibiting human glioma and carcinoma of the nasopharynx, human large cell lung carcinoma and human breast cell carcinoma (Wang et al. 2014). In an *in vitro* study on the cytotoxic activity of *P. aduncum* against human nasopharynx carcinoma cells, the IC₅₀ was reported as 2.3 µg/mL, whereas *in vitro* cytotoxic activity on glioma and carcinoma of human large cell lung and human breast cell tissues obtained an IC₅₀ of between 23 and 27 µg. The antioxidant capacity of an ethanolic extract of the leaves of *P. aduncum* was tested using a DPPH radical scavenging assay, and IC₅₀ values of between 82 and 220 µg/mL were obtained (Escudero et al. 2008). The antioxidant properties were said to be attributable to gallic acid, chlorogenic acid, catechin and quercetin, which act as free radical scavengers.

OTHER ACTIVITIES

The major component of *P. aduncum* essential oil, dillapiole exhibited antiviral against West Nile virus (WNV) is a mosquito-borne flavivirus (Radice et al. 2019) and poliovirus (Lohézic-Le Dévéhat et al. 2002). The ethanolic extracts of *P. aduncum* has a gastroprotective effect in mice and antisecretory effect in rats (Arroyo et al. 2013).

CONCLUSION AND PERSPECTIVES

P. aduncum is used as an alternative medicine in the world. It is the most ethnobotanical uses among Piper

species. It is particularly important as a traditional medicine for diarrhoea caused by *E. coli* infection and for inducing wound healing. Studies on the phytochemistry of *P. aduncum* have shown that the plant contains many bioactive constituents, including flavonoids, monoterpenes and sesquiterpenes, chalcones, chromenes, phenylpropanoid, and benzoic acid derivatives. Extracts of *P. aduncum* leaves, stems, and fruits have been found to possess anti-parasitic properties against *Leishmania*, *Plasmodium falciparum*, *Trypanosoma brucei*, *T. cruzi*, *Rhipicephalus microplus* and *Schistosoma mansoni*, in addition to their antifungal, antibacterial, insecticidal, antitumor, and anticancer properties. However, the mechanism of action and specific constituents responsible for the biological properties of *P. aduncum* are yet to be fully explored. Further studies on *P. aduncum*, which shows potential utility in treating and preventing infectious diseases are warranted.

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