ORIGINAL ARTICLE

Phytochemical profile, traditional uses, and biological activities of *Duguetia furfuracea*: A review

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ABSTRACT

Duguetia furfuracea (A.St.–Hil.) Saff. has ancient descriptions in traditional medicine in the middle-western region of Brazil for multiple therapeutic uses and it is currently considered an invasive plant. The aim of this manuscript is to provide a review of published studies on botany, traditional uses, phytochemistry, biological effects and toxicology of *D. furfuracea*. Information was collected from databases Scielo, PubMed, Chemical Abstracts and Web of Science. There are several traditional uses of *D. furfuracea,* in treatment of rheumatism, menorrhagia, dysmenorrhea, pediculosis, renal colic, and stomachache. Based on a phytochemical investigation, over hundred compounds have been identified from the leaves, twigs, underground stem bark and wood of *D. furfuracea*, such as alkaloids, terpenes, flavonoids, phenolic acids and phenylpropanoids. This species present a broad spectrum of effects such as trypanocidal, leishmanicidal, larvicidal, antitumoral, anti-inflammatory, antimutagenic and cytoprotective. Data about the toxicity are limited, mainly for *in vivo* experiments. Phytochemical and pharmacological studies have demonstrated the therapeutic potential of *D. furfuracea*. However, the study of pharmacological mechanisms of its herbal medicinal product and isolated constituents should be further explored, since capsules containing material of this species have already been developed for renal colic.
Keywords: *Duguetia furfuracea*, phytochemistry, alkaloids, polyphenols, biological properties.

INTRODUCTION

Duguetia furfuracea (A.St.-Hil.) Saff. is one of the 80 native species of genus *Duguetia* belonging to the Annonaceae family (Muhammad et al. 2001). This species, commonly known as “araticum-seco” (Lorenzi 2000), is found in South America (POWO 2024) and it is used in the traditional medicine as anti-rheumatic (Pott and Pott 1994; Rodrigues and Carvalho 2001a), antidysmenorrheic, antidiarrheal (Lorenzi and Matos 2002) and parasiticide agents (Pio Corrêa 1978; Silberbauer-Gottsberger 1981, 1982; Lorenzi 2000). Additionally, the popular use of this plant for the treatment of renal colic (Rodrigues and Carvalho 2001a) might have inspired a product patent (da Silva Coelho 2003).

Substantial efforts have been made to describe the phytochemical profile of *D. furfuracea* and to date, over 100 constituents have been identified in the plant. Therefore, the phytochemical investigations have revealed the presence of alkaloids (Carollo et al. 2006a, 2006b; Silva et al. 2007; Carollo and Siqueira 2008; do Santos et al. 2018, Macedo et al. 2021), terpenes (Carollo et al. 2005; Silva et al. 2007; Valter et al. 2008), flavonoids

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(Santos and Salatino 2000; Carollo et al. 2006b; Pinho et al. 2014, 2016, Macedo et al. 2021) and other compounds (Carollo et al. 2006b; Silva et al. 2007; Pinho et al. 2014, 2016). The genus *Duguetia* has shown several isoquinolinic alkaloids, a targeted group of metabolites for the development of anticancer, antifungal, antiparasitic, cardiovascular and psychoactive drugs (Pérez and Cassels 2010).

Different extracts from *D. furfuracea* have exhibited a broad spectrum of biological properties including antitumoral (Silva et al. 2009), antimutagenic (Coelho et al. 2011; Silva et al. 2013), anti-inflammatory (do Santos et al. 2018; Saldanha et al. 2019a), cytoprotective (Silva et al. 2013; Lima et al. 2014), trypanocidal, leishmanicidal (Mesquita et al. 2005; Silva et al. 2009) and larvicidal (Rodrigues et al. 2006) effects. The aim of this manuscript is to provide a review of published studies on botany, ethnopharmacology, phytochemistry, biological, pharmacological effects and toxicology of *D. furfuracea*. This information might be useful in the future design studies, development of new drugs, and a better understanding of this species.

METHODS

Duguetia furfuracea-related information was collected from databases Scielo, PubMed, Chemical Abstracts and Web of Science. Keywords used to search included *Duguetia furfuracea*, chemical compounds, pharmacological effects, botany, phytochemistry, ethnopharmacology, toxicity, and biological effects. The manuscript was prepared using relevant data from different resources including books, patents, journals and websites. The article includes a total of 72 references from 1978 to 2021 out of which 57 were articles including *in vitro* and *in vivo* studies, in traditional uses, phytochemical analysis, botany information and toxicology, 2 patents, 11 books and 2 web references. No restriction was made on publication year or on the language of the papers identified.

RESULTS AND DISCUSSION

Botanical description and distribution

Duguetia furfuracea (A.St.-Hil.) Saff. [Synonyms: *Duguetia coriacea* Sond., *Aberemoa furfuracea* (A.St.-Hil.) Baill. var. *furfuracea, Aberemoa furfuracea* (A.St.-Hil.) Baill., *Duguetia fufuracea* (A.St.-Hil.) Saff., *Annona furfuracea* A.St.-Hil.] (Flora e Funga do Brasil 2024) is a shrub species (Figure 1), growing up to a height of 50 cm to 2 m (Pio Corrêa 1978; Maas et al. 2001; Martens 2008). Typically, the shoots open laterally near to the ground (Martens 2008). The flowers are solitary and axillary, with 3 sepals imbricate, 6 velvet hard and pink petals (Pio Corrêa 1984; Bontempo 1994; Barroso et al. 1999; Martens 2008), and its flowering period lasts from June to November (Martens 2008). Its bark is suberous and the fruit is a light green berry with an oval shape (Pio Corrêa 1978; Maas et al. 2001) fleshy in April-July, October-November, and February (Proença et al. 2000). The leaf bases, generally 9-14 cm long and 3-5 cm wide, are oblong-lanceolate to elliptic (Pio Corrêa 1978; Maas et al. 2001), petiolate,

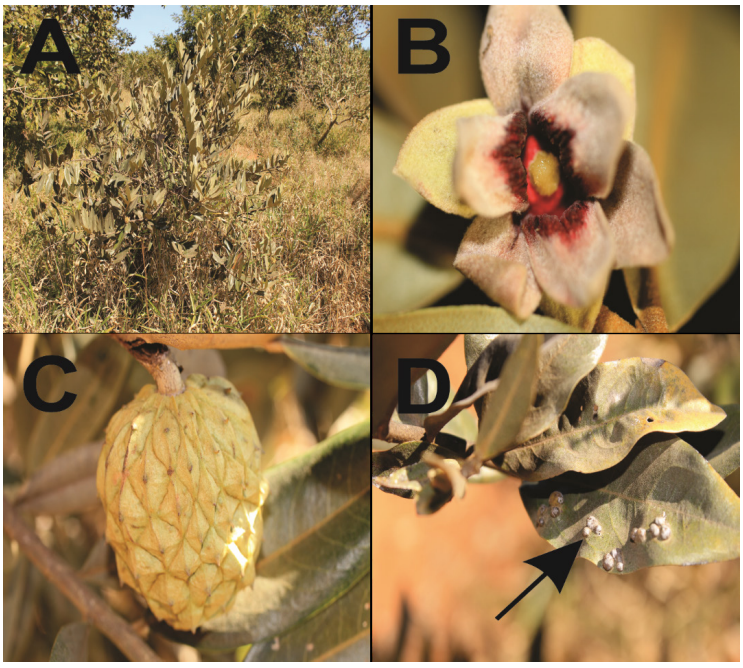


Figure 1. The whole plant (**A**), flower (**B**), unripe fruit (**C**), and leaves with galls (indicated by arrow) (**D**) of *Duguetia furfuracea*.

alternate, leathery, with acute apex, entire margins, and frequently exhibit galls (Pio Corrêa 1984; Bontempo 1994; Barroso et al. 1999).

This species is found in South America, specifically in Brazil (Rondônia, Bahia, Ceará, Pernambuco, Distrito Federal, Goiás, Mato Grosso do Sul, Mato Grosso, Minas Gerais, Rio de Janeiro, São Paulo and Paraná States) (Flora do Brasil 2021; Flora e Funga do Brasil 2024), Bolivia (Santa Cruz) and Paraguay (Amambay, Caaguazú, Concepción, Presidente Hayes and San Pedro) (POWO 2024). In the state of Mato Grosso do Sul, this species is considered as an invasive plant (Lorenzi 2000). Importantly, the knowledge about the chemical composition of *D. furfuracea* can be useful to develop strategies for its dissemination (Silva et al. 2007).

Ethnopharmacology

The twigs and leaves of *D. furfuracea* have been used in traditional medicine as an anti-rheumatic agent and to treat renal colic (Rodrigues and Carvalho 2001a). The folk preparation techniques include infusion or tisane (Rodrigues and Carvalho 2001b). It is noteworthy that the patent protection of capsules containing "*D. furfuracea* material" (da Silva Coelho 2003), might be attributive to the medicinal use of this plant in the treatment of renal colic.

In addition, indications of its leaf tea include the treatment of dysmenorrhea, menorrhagia, and diarrhea (Lorenzi and Matos 2002). The seeds of *D. furfuracea,* powdered and diluted in water, also have medicinal value, and it is used as a parasiticide, principally to treat pediculosis (Pio Corrêa 1978; Silberbauer-Gottsberger 1981/1982; Lorenzi 2000). Barks and roots of this species can be traditionally used for the treatment of rheumatism (Pott and Pott 1994). Moreover, the *D. furfuracea* root is also used for relieving stomachaches (Silberbauer-Gottsberger 1981/1982).

Chemical compounds

Phytochemical investigations on *D. furfuracea* have revealed more than hundred constituents, including alkaloids, flavonoids, terpenes, phenolic acids and phenylpropanoids. Table 1 summarized these secondary metabolites and the plant parts which are obtained.

Figure 2 shows the occurrence of the different metabolites found in the *D. furfuracea*. Aporphine alkaloids, triterpenes, flavonols and flavanol are the metabolite class with higher occurrence reported in *D. furfuracea*. In addition, other metabolites have also been reported such as the alkaloids oxoaporphine, tetrahydroprotoberberine, quaternary protoberberine, (bis)benzyltetrahydroisoquinoline, sesquiterpene, phenylpropanoids and phenolic acids.

Recently, the leaves of *D. furfuracea* were harvested in different periods and analyzed by LC-DAD-MS to determine the impacts of seasonal variation on its chemical composition. Different metabolite classes were observed from leaves of *D. furfuracea*, such as alkaloids benzyltetrahydroisoquinoline, aporphine, proaporphine, tetrahydroprotoberberine, (bis) benzyltetrahydroisoquinoline, proanthocyanidins, and flavonoids (flavonols, dihydroflavonol, and flavones). The intensities of flavonoids were higher in the rainy seasons, while the alkaloids presented more stable intensities (Macedo et al. 2021).

Table 1. Compounds described from *Duguetia furfuracea.*

Class	Chemical component	Plant parts	Reference
ALKALOIDS			
Aporphine alkaloid	*N*-nitrosoanonaine (**1**)[1*]	Leaves and twigs	Carollo et al. (2006a)
	N-nitrosoxylopine (**2**)[1*]	Leaves and twigs	Carollo et al. (2006b)
	obovanine (**3**) - anonaine (**4**) mixture[1*]		
	xylopine (**5**)[1*]		
	(–)-asimilobine (**6**)[1*]		
	noriscorydine (**7**)[1*]		
	(+)-isocorydine (**8**)[1*]		
	(+)-8-nitrous-isocorydine (**9**)[1*]	Leaves and twigs	Carollo and Siqueira (2008)
	(-)-duguetine (**10**)[1,2*]	Leaves and underground stem bark	Silva et al. (2007), do Santos et al.(2018)
	(+)-*N*-methylglaucine (**11**)[1,2*]	Underground stem bark	Silva et al. (2007)
	(-)-duguetine β-*N*-oxide (**12**)[1*]		
Oxoaporphine alkaloid	aterospermidine (**13**)[1*]	Leaves and twigs	Carollo et al. (2006b)
	liriodenine (**14**)[1*]		
	lanuginosine (**15**)[1*]		
	dicentrinone (**16**)[1,2*]	Underground stem bark and leaves	Silva et al. (2007), do Santos et al.(2018)

continue

Table 1. *continuation*

Class	Chemical component	Plant parts	Reference
Tetrahydroprotoberberine alkaloid	(–)-discretamine (**17**)[1*]	Leaves and twigs	Carollo et al. (2006b)
	(-)-*N*-methyltetrahydropalmatine (**18**)[1*]	Underground stem bark	Silva et al. (2007)
Quaternary protoberberine alkaloid	staudine[1*] (**19**)	Roots	Santos et al. (2019)
(Bis) benzyltetrahydroisoquinoline alkaloid	isochondodendrine (**20**)[1*]	Leaves and twigs	Carollo et al. (2006b)
	(+)-reticuline (**21**)[1*]		
TERPENES			
Monoterpene	*p*-cimene (**22**)[3]	Leaves	Valter et al. (2008)
	α-phellandrene (**23**)[3]		
	β-phellandrene (**24**)[3]		
	criptone (**25**)[3]		
	1-hydroxy-linalool (**26**)[3]		
	limonene dioxide (**27**)[3]		
	myrcene (**28**)[3]		
	α-pinene **(29**)[3]		
	β-pinene **(30**)[3]		
	α-terpineol **(31**)[3]		
	terpinen-4-ol (**32**)[3]		
	cis-sabinene (**33**)[3]		
	trans-sabinene (**34**)[3]		
	santolinatriene (**35**)[3]	Underground stem bark	Saldanha et al. (2019a)
Triterpene	polycarpol (**36**)[1*]	Underground stem bark	Silva et al. (2007)
Sesquiterpene	(-)-ishwarane (**37**)[1*]	Leaves	Carollo et al. (2005)
	α-santalene **(38**)[1*]		
	(-)-α-santalen-11-one (**39**)[1*]		
	β-elemene (**40**)[3]	Leaves and underground stem bark	Valter et al. (2008), Saldanha et al. (2019a)
	germacrene D (**41**)[3]		
	ledol (**42**)[3]		
	δ-cadinene (**43**)[3]	Leaves	
	δ-cadinol (**44**)[3]		
	isospathulenol (**45**)[3]		Valter et al. (2008)
	α-cadinol (**46**)[3]		
	α-copaene (**47**)[3]		
	β-copaen-4-α-ol (**48**)[3]		
	Δ-guaiene (**49**)[3]		
	γ-muurolene (**50**)[3]		
	β-selinene (**51**)[3]		Favareto et al. (2019)
	α-thujene (**52**)[3]		
	alloaromadendrene oxide-1 (**53**)[3]		

continue

Table 1. *continuation*

Class	Chemical component	Plant parts	Reference
	caryophyllene oxide (**54**)[1,3*]	Leaves and underground stem bark	Carollo et al. (2005), Silva et al. (2007), Valter et al. (2008),
	β-caryophyllene oxide[3] (**55**)	Leaves	Favareto et al., 2019
	aromadendrene oxide-2[3] (**56**)		Favareto et al., 2019
	alloaromadendrene oxide-2[3] (**57**)		
	isoaromadendrene epoxide[3] (**58**)		
	α-gurjunene (**59**)[1,3*]		Silva et al. (2007), Valter et al. (2008), Saldanha et al. (2019a)
	bicyclogermacrene (**60**)[1,3*]	Leaves and underground stem bark	Silva et al. (2007), Valter et al. (2008)
	epi-α-cadinol (**61**)[3]	Leaves and underground stem bark	
	aromadendrene (**62**)[1,3 *]	Leaves and underground stem bark	Silva et al. (2007), Valter et al. (2008), Saldanha et al. (2019a)
	trans-caryophyllene (**63**)[3]		
	α-humulene (**64**)[3]		
	viridiflorol (**65**)[3]		
	spathulenol (**66**)[1,3*]	Leaves and underground stem bark	Carollo et al. (2005), Silva et al. (2007), Valter et al. (2008), Saldanha et al. (2019a), Favareto et al. (2019)
	γ-gurjunene (**67**)[3]	Underground stem bark	Silva et al. (2007), Saldanha et al., (2019a)
	γ-cadinene (**68**)[3]	Underground stem bark	Silva et al. (2007)
	palustrol (**69**)[3]		
	valerianol (**70**)[3]		
	epi-globulol (**71**)[3]		
	1-*epi*-cubenol (**72**)[3]		
	drima-7,9(11)-diene (**73**)[3]		
	cyperene (**74**)[3]	Underground stem bark	Saldanha et al. (2019a)
	β-chamigrene (**75**)[3]		
	α – muurolene (**76**)[3]		
FLAVONOIDS			
Flavonol	isorhamnetin (**77**)[1*]	Leaves and twigs	Carollo et al. (2006b)
	isorhamnetin-3-*O*-galactosylrhamnoside (**78**)[1]	Leaves	Santos and Salatino (2000)
	isorhamnetin-3-*O*-galactoside (**79**)[1]		
	isorhamnetin-3-*O*-rhamnosylglucoside (**80**)[1]		
	kaempferol-3-*O*-galactosylgalactoside (**81**)[1]		
	quercetin (**82**)[4]	Leaves	Pinho et al. (2014), Pinho et al. (2016)
	quercitrin (**83**)[4]		
	isoquercitrin (**84**)[4]		
	rutin (**85**)[4]		
	kaempferol (**86**)[4]		
Flavan-3-ol	catechin (**87**)[4]	Leaves	Pinho et al. (2014), Pinho et al. (2016)
PHENOLIC ACIDS	gallic acid (**88**)[4]	Leaves	Pinho et al. (2014), Pinho et al. (2016)
	ellagic acid (**89**)[4]		

continue

Table 1. *continuation*

Class	Chemical component	Plant parts	Reference
PHENYLPROPANOIDS	caffeic acid (**90**)[4]	Leves	Pinho et al (2014), Pinho et al. (2016)
	chlorogenic acid (**91**)[4]		
	α-asarone (**92**)[1,3*]	Roots and underground stem bark	Silva et al. (2007), Saldanha et al. (2019a), Santos et al. (2019)
	2,4,5-trimethoxystyrene (**93**)[1,3*]	Underground stem bark	Silva et al. (2007), Saldanha et al. (2019a)
	(*E*)-methylisoeugenol (**94**)[1]	Roots and underground stem bark	Silva et al. (2007), Santos et al. (2019)
	asaraldehyde (**95**)[1*]		
PHYTOSTEROL			
	β-sitosterol **(96)**[1]	Leaves and twigs	Carollo et al. (2006b)
	2-methylenocholestan-3-ol (**97**)[3, *]	Leaves	Favareto et al. (2019)
	3-deoxyestradiol(**98**)[3]		
UREIDE	allantoin (**99**)[1*]	Underground wood	Silva et al. (2007)
FATTY ACID AND DERIVATIVES	ethyl palmitate (**100**)[3]	Leaves	Favareto et al. (2019)
	methyl elaidate (**101**)[3]		
	palmitic acid(**102**)[3]		
	2-methylhexadecan-1-ol (**103**)[3]	Leaves	Favareto et al. (2019)
TOCOFEROL	α-tocoferol(**104**)[3]	Leaves	Favareto et al. (2019)
STEROIDAL GLICOSIDES	β-sitosterol 3-*O*- β-D-glucoside(**105**)[1*]		
	stigmasterol 3-*O*-β-D-glucoside(**106**)[1*]	Roots	Santos et al. (2019)

[1]Isolated compounds from *D. furfuracea*, and *spectral data available. [2]Observed by high-performance liquid chromatography coupled with diode-array detector (HPLC-DAD-MS). [3]Observed by gas chromatography and mass spectrometry (GC-MS). [4]Analysed by HPLC-DAD.

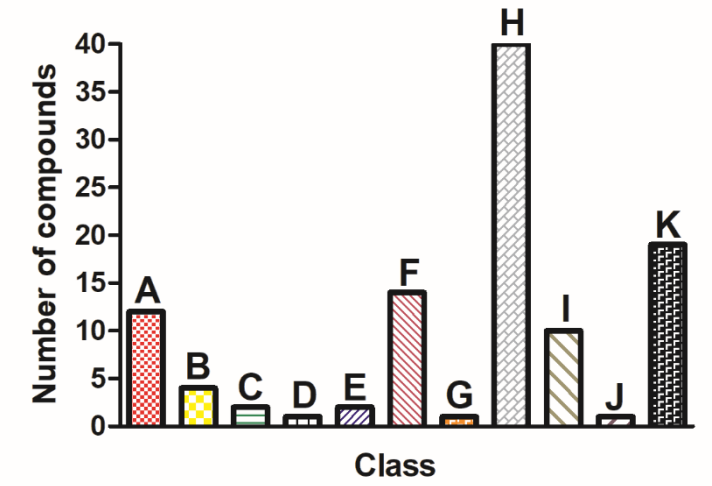


Figure 2. Isolated or identified metabolites in the *Duguetia furfuracea.* **A**) Aporphine alkaloid, **B**) Oxoaporphine alkaloid, **C**) Tetrahydroprotoberberine alkaloid, **D**) Quaternary protoberberine alkaloid, **E**) (Bis) benzyltetrahydroisoquinoline alkaloid, **F**) Monoterpene, **G**) Triterpene, **H**) Sesquiterpene, **I**) Flavonol, **J**) Flavan-3-ol, **K**) Other compounds.

Alkaloids (1-21)

Alkaloids are the characteristic compounds in Annonaceae family, mainly in the genus *Duguetia* (Pérez and Cassels 2010), and include one of the major classes of secondary metabolites present in the *D. furfuracea* (Figure 2). Twenty-one alkaloids have been identified from the leaves, twigs and underground stem bark of this plant. Based on the type of skeletons, they can be categorized into aporphine (**1-12**, structures can be found in the Supplementrary Material), oxoaporphine (**13-16**), tetrahydroprotoberberine (**17, 18**), quaternary protoberberine **(19)** and bisbenzyltetrahydro-isoquinoline (**20, 21**) (Figure 3). Despite the occurrence of the nitro-constituents in the plant kingdom is restricted, a minor aporphine alkaloid containing a nitrous functionality, (+)-8-nitrous-isocorydine or (+)-1,2,3-trymethoxy-11-hydroxy-8-nitrous-aporphine (**9**), was obtained from the aerial parts (leaves and twigs) of the *D. furfuracea* (Carollo and Siqueira 2008).

In addition, two new aporphine alkaloids with *N*-nitroso functionality, namely *N*-nitrosoanonaine (**1**) and *N*-nitrosoxylopine (**2**), were also isolated from the aerial parts of this species (Carollo et al. 2006a). To our knowledge, compounds in this class of alkaloids can be regarded as potential nitric oxide (NO)/nitrosonium ion (NO^+) donors (Ohwada et al. 2001). Drug discovery research demonstrated that the diclofenac derivates with *N*-nitroso-substitution in the skeleton are capable of reducing damages in the gastric mucosa (Pedrazzoli Jr. et al. 2004). Therefore, alkaloids with *N*-nitroso functionality might be promising for further research.

Another novel alkaloid, (-)-duguetine β-*N*-oxide (**12**), was identified from the underground stem bark of *D. furfuracea* and it showed a toxic effect in brine shrimp lethality test (Silva et al. 2007) and potent antileishmanial and antitumoral activities (Silva et al. 2009). Interestingly, (+)-*N*-methylglaucine (**11**) and (-)-*N*-methyltetrahydropalmatine (**18**) also characterized, and this study is the first report of them in Annonaceae family (Silva et al. 2007).

The alkaloids have a wide range of biological effects, including antimalarial, antimicrobial, cytotoxic activities (Muhammad et al. 2001) and antiprotozoal effect (Tempone et al. 2005; Carollo et al. 2006b).

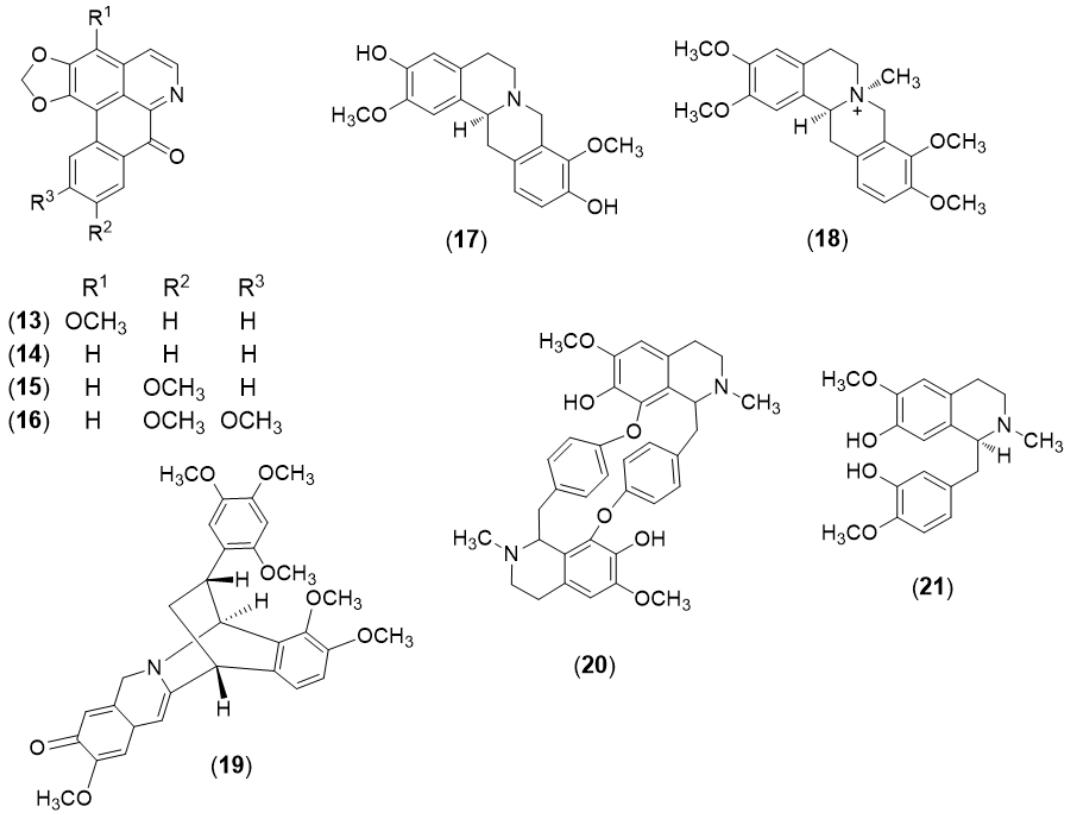


Figure 3. Alkaloids from *Duguetia furfuracea.*

Terpenes (22-76, structures can be found in the Supplementrary Material)

Terpenes are other important compounds on *D. furfuracea*. Currently, some terpenes have been identified from this species, they are mainly sesquiterpenes (**37-76**), followed by monoterpenes (**22-35**) and triterpenes (**36**) are the least abundant. Santalene sesquiterpenes are rare compounds (Ngo and Brown 1999) and the isolation of α-santalene (**38**) and α-santalen-11-one (**39**) from *D. furfuracea* was the first report of these compounds in a species belongs to the family Annonaceae.

The rare sesquiterpene (-)-ishwarane (**37**) was also isolated from *D. furfuracea* and described for the first time in this genus (Carollo et al. 2005). Moreover, it should be noted that the presence of the sesquiterpenes (-)-ishwarane (**37**), β-caryophyllene oxide (**54**), bicyclogermacrene (**60**) and (+)-spathulenol (**66**) in the *D. furfuracea* emphasizes the existence of chemotaxonomic relations between the families Annonaceae and Aristolochiaceae (Leboeuf et al. 1982; Priestap et al. 2003).

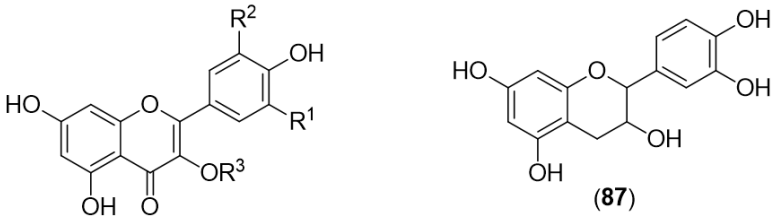
Furthermore, Valter et. al. (2008) evaluated the chemical composition of the essential oil of *D. furfuracea* leaves in the city of Campo Grande, located in Mato Grosso do Sul, Brazil. The compositional variations of the content of monoterpenes and sesquiterpenes observed could not attribute from the differences in the environment conditions, morphological characters and phenological state. The mentioned study showed that essential oil from the *D. furfuracea* leaves, harvested on Biome *Cerrado*, is dominated by the presence of non-oxygenated terpenes (Valter et al. 2008), corroborating with the information about the oxygenated constituents, which is the main compounds in the essential oil of Annonaceae species (Lago et al. 2003).

Flavonoids (77-87)

Flavonoids characterized from *D. furfuracea* (Figure 4) were mainly flavonols (**77-86**) and flavan-3-ols (**87**) with non-glycosylated and glycosylated forms, which showed sugars such as galactose, rhamnose and glucose. These secondary metabolites have a broad spectrum of biological and pharmacological properties including antimutagenic, antioxidant (Wozniak et al. 2006), hypoglycemic (Wu et al. 2011), antimicrobial, immunomodulatory and anti-inflammatory (Cao et al. 2015) effects. A previous study shows that the flavonol isorhamnetin (**77**), obtained in acid-base extraction of the ethanol extract from the *D. furfuracea* leaves, did not have anti-trypanosomal activity (Carollo et al. 2006b). On the other hand, the higher content of total phenols and flavonoids in the hydroalcoholic extract, methanolic and ethyl acetate fractions of *D. furfuracea* leaves, suggested that these compounds can be involved in their *in vitro* antioxidant activities (Pinho et al. 2016).

Other compounds (88-106)

Currently, only a few constituents other than those described above have been reported. Actually, four phenolic acids (**88-91**), three phytosterols (**96-98**), three fatty acids (**100-102**), one alcohol (**103**) and one tocoferol (**104**) have been identified from the leaves, while four phenylpropanoids (**92-95**) and one ureide (**99**) have been characterized from the underground parts, and two saponins (**105**,**106**) have been found in the roots of *D. furfuracea* (Figure 5).



(**87**)

	R1	R2	R3
(**77**)	OCH_3	H	H
(**78**)	OCH_3	H	galactosylrhamnosyl
(**79**)	OCH_3	H	galactosyl
(**80**)	OCH_3	H	rhamnosylglucosyl
(**81**)	H	H	galactosylgalactosyl
(**82**)	H	OH	H
(**83**)	H	OH	rhamnosyl
(**84**)	H	OH	glucosyl
(**85**)	H	OH	rutinosyl
(**86**)	H	H	H

Figure 4. Flavonoids from *Duguetia furfuracea*.

Phenolic acids that have been identified from this species can be categorized into derivates of benzoic acid (**88, 89**) and cinnamic acid (**90, 91**). According to Pinho et. al (2016) the phenolic compound, caffeic acid, was the main constituent quantified in both hydroalcoholic extract and methanol fraction of *D. furfuracea* leaves. Moreover, the total phenol contents in the extracts and fractions (Pinho et al. 2016) were similar to other Brazilian species belonging to the *Duguetia* genus (Dutra et al. 2012; Vendramin et al. 2013).

Among the other chemicals, phenylpropanoids-derived compounds and allantoin has been of great interest, since it has been correlated to chemical defense (Lane and Kubanek 2006), and transport and assimilation of nitrogen (Kahn and Tipton 2000), respectively.

Biological properties

Duguetia furfuracea exhibits a wide spectrum of biological activities, proving the effect on pain and inflammation and the biocide effects of some extract and fractions obtained from the aerial and subterranean parts. Moreover, different chemical models of antioxidant activity were used to evaluate extracts and fractions obtained from *D. furfuracea* leaves. Table 2 summarizes the biological effects documented, with details on the plant part, concentration or dose, and experimental model. Information on the *in vivo* biological effects of this species is limited since *in vitro* tests were mostly reported.

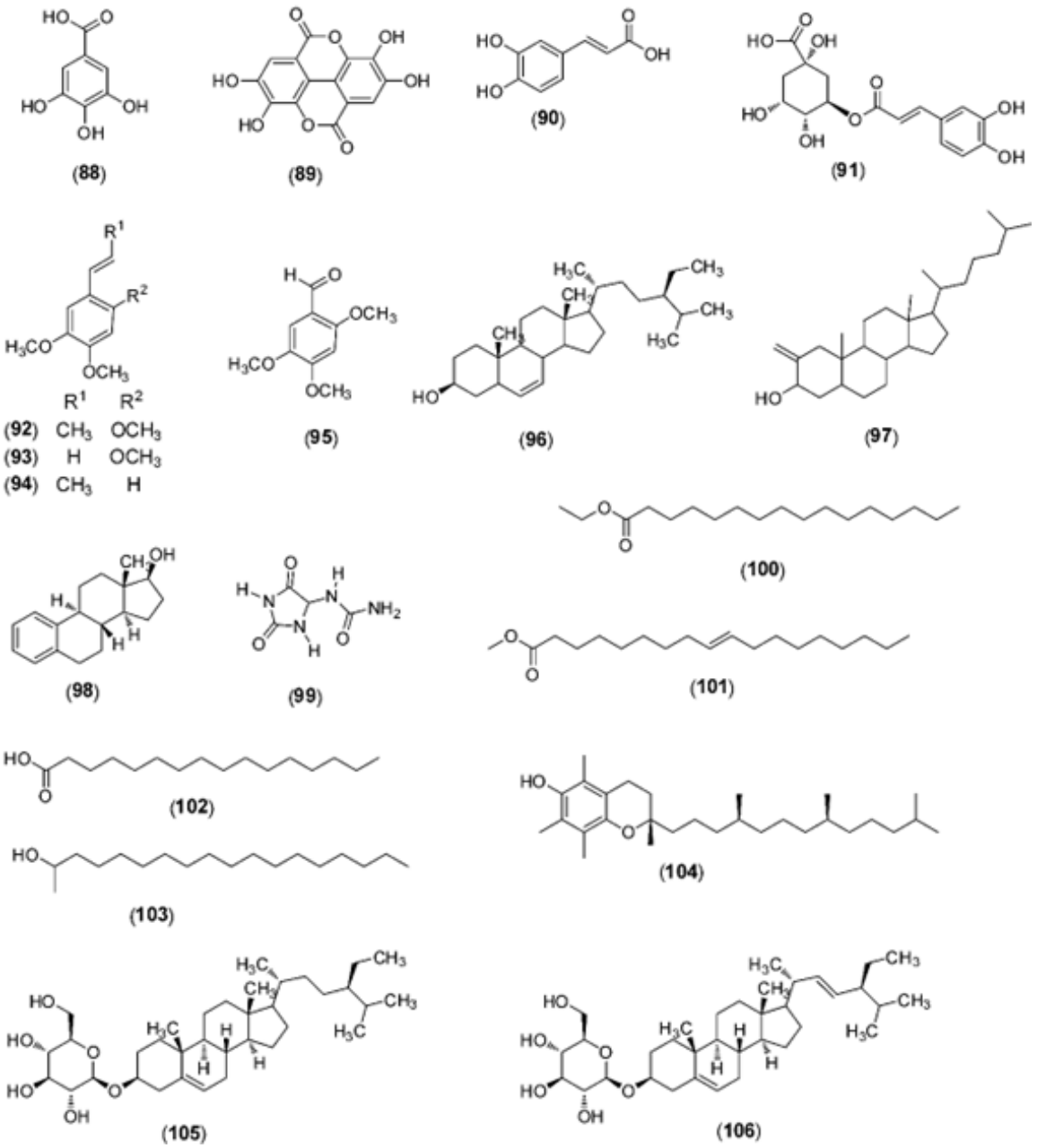


Figure 5. Other compounds described from *Duguetia furfuracea*.

Table 2. Biological and antioxidant effects from extracts and fractions of *Duguetia furfuracea*.

	Activity	Extract or fraction	Plant Part	Experimental test	Dosage (or concentration) and administration route	Results	Reference
In vitro tests							
	Trypanocidal	EtOH and Hex extracts	S, RB and RW	β-galactosidase-expressing parasite	-	Hexane extract from stem - IC_{50}=50±1.6 µg/ml; ethanol extract from root bark - IC_{50}=30.4±1.3 µg/ml; hexane extract from root bark - IC_{50}=6.6±0.6 µg/ml; ethanol from root wood - IC_{50}=25.6±1.5 µg/ml	Mesquita et al. (2005)
		Alk extract	USB	Spectrophotometric	0.5, 2, 8, and 32 µg/ml	Half maximal inhibitory concentration (IC_{50})=22.44 µg/ml	Silva et al. (2009)
	Leishmanicidal	EtOH and Hex extracts	S, RB and RW	MTT assay	Initial concentration of 15 µg/ml	Ethanol and hexane extracts were not active	Mesquita et al. (2005)
		Alk extract	USB	Colorimetric	0.5, 2, 8, and 32 µg/ml	IC_{50}=16.32 µg/ml	Silva et al. (2009)
	Larvicidal	EtOH and Hex extracts	L, S, RW and RB	Adult immersion	500, 250, 125, 62.5, and 31.2 µg/ml	Lethal concentration 50 LC_{50}=56.6 µg/ml (at 500 µg/ml)	Rodrigues et al. (2006)
		EO, fraction, PE extract and Alk extract	USB and UHW	Larvae of the third and fourth instars of *Culex quinquefasciatus* - lethal concentrations	300, 150, 75, and 37.5 µg/ml	LC_{50} of essential oil, fraction and petroleum ether extract from underground stem bark were 88.95, 86.02, 71.14 µg/ml, respectively. The alkaloid extract from underground stem bark was inactive. LC_{50} of essential oil and petroleum ether extract from underground heartwood were 94.36 and 94.35 µg/ml, respectively.	Maia et al. (2020)
	Antitumoral	Alk extract	USB	MTT assay	0.03-25 µg/ml	90.2±1.1, 85.1±0.6, and 99.6±0.4% of inhibition of colon (HCT-8), glyoblastoma (SF-295) and melanoma (MDA/MB-435) human cancer, respectively	Silva et al. (2009)
	Antimutagenic	Aq extract	L	Ring-X-loss test	0.085, 0.042, and 0.014 g/ml	Modulatory effect in *Drosophila melanogaster* against urethane in both standard and high bioactivation crosses	Coelho et al. (2011)
		Aq extract	L	Prophage λ induction test (SOS-Inductest)	0.5, 1, 2, 5, and 10 mg	All concentrations promoted a decrease in the induction of prophage λ	Silva et al. (2013)
				Mouse bone marrow micronucleus test	100, 200, and 300 mg/kg, oral route	All doses caused a reduction in the number of micronucleated polychromatic erythrocytes, at 24 and 48 h	
	Cytoprotective	Aq extract	L	SOS-Inductest	0.5, 1, 2, 5, and 10 mg	Extract at 0.5, 1, 2, and 5 mg promoted an increase of the surviving *Escherichia coli* WP2s (λ) colonies	Silva et al. (2013)
				Mouse bone marrow micronucleus test	100, 200, and 300 mg/kg, oral route	All doses caused an increase the polychromatic and normochromatic erythrocyte ratio at 24 and 48 h	
		EtOH extract, Hex, EA and MeOH fractions	L	MIC and MBC and metal modulation	Initial concentration of 1024 µg/ml	Ethanol extract, ethyl acetate and methanol fractions had cytoprotective effect against mercury chloride in *Escherichia coli*	Lima et al. (2014)
	Acaricidal	Hex extract	L	Larval packet test and adult immersion test	100%	6.03% of *Rhipicephalus microplus* larval mortality	Valente et al. (2014)
	Antifungal	HA extract, MeOH and EA fractions	L	MIC and modulation of standard antifungal action	1024 – 0.5 µg/ml	All extract and fractions showed minimum inhibitory concentration (MIC) ≥1024 µg/ml against all the fungi strains tested and synergism with fluconazole	Pinho et al. (2016)
	Free radical scavenging	HA extract, MeOH and EA fractions	L	DPPH assay	-	Hydroalcoholic extract - IC_{50}=33.15 µg/ml; methanol fraction - EC_{50}=42.32 µg/ml; ethyl acetate fraction - IC_{50}=39.32 µg/ml	Pinho et al. (2016)
				FRAP	-	Hydroalcoholic extract -166.73±5.13 µ*M* Fe^{+2}/g of sample; methanol fraction 126.43±4.98 µ*M* Fe^{+2}/g of sample; ethyl acetate fraction 118.20±1.08 µ*M* Fe^{+2}/g of sample	

continue

Table 2. *continuation*

	Activity	Extract or fraction	Plant Part	Experimental test	Dosage (or concentration) and administration route	Results	Reference
		MeOH extract, $CHCl_3$, EA and HMeOH fractions	L	DPPH assay	5-250 µg/ml	Methanol extract - IC_{50}=22.46 µg/ml; chloroform fraction - IC_{50}=17.88 µg/ml; ethyl acetate fraction - IC_{50}=60.56 µg/ml and hydromethanolic fraction - IC_{50}=28.21 µg/ml	do Santos et al. (2018)
		MeOH extract, $CHCl_3$, EA and HMeOH fractions		ABTS	5-250 µg/ml	Methanol extract – IC_{50}=25.41 µg/ml; chloroform fraction - IC_{50}=183.40 µg/mL; ethyl acetate fraction - IC_{50}=88.55 µg/ml and hydromethanolic fraction - IC_{50}=24.12 µg/ml	
		MeOH extract, $CHCl_3$, EA and HMeOH fractions		β-carotene method	5-250 µg/ml	Methanol extract - IC_{50}=87.64 µg/mL; chloroform fraction - IC_{50}= >250 µg/mL; ethyl acetate fraction - IC_{50}=184.44 µg/mL and hydromethanolic fraction - IC_{50}=100.77 µg/ml	
		MeOH extract, $CHCl_3$, EA and HMeOH fractions Extract obtained by supercritical CO_2 and Hex and EtOH extracts	L	Malondialdehyde method ABTS	5-250 µg/ml	Methanol extract – IC_{50}=78.99 µg/mL; chloroform fraction - IC_{50}= >250 µg/ml; ethyl acetate fraction - IC_{50}= not detected, and hydromethanolic fraction - IC_{50}=96.43 µg/ml Ethanol and hexane extracts: 606 and 531 µ*M* Trolox g^{-1} extract, respectively	Favareto et al. (2019)
In vivo tests							
	Anti-inflammatory	MeOH extract, $CHCl_3$, EA and HMeOH fractions	L	Carrageenan induced paw edema	30, 100, and 300 mg/kg, oral route	Methanol extract (30, 100, and 300 mg/kg), chloroform, ethyl acetate and hydromethanolic fractions (all at dose of 100 mg/kg) inhibited paw edema induced by carrageenan.	do Santos et al. (2018)
		MeOH extract	L	Air pouch model	30, 100, and 300 mg/kg, oral route	Methanol extract (300 mg/kg) reduced plasma leakage into the air pouch and inhibited leukocyte recruitment	do Santos et al. (2018)
	Antinociceptive	EO and phenylpropanoid-enriched fraction	USB	Formalin test	3, 10, and 30 mg/kg, oral route	The essential oil and phenylpropanoid-enriched fraction at 10 and 30 mg/kg exhibited central (with participation of the adenosinergic and opioidergic systems) and peripheral (involvement of the opioidergic system) effects.	Saldanha et al. (2019a); Saldanha et al. (2020)
		EO and phenylpropanoid-enriched fraction	USB	LPS-induced thermal hyperalgesia test	3, 10, and 30 mg/kg, oral route	Confirmation of central antinociceptive activity (essential oil and phenylpropanoid-enriched fraction at 10 and 30 mg/kg) and participation of opioidergic system.	

S: stem; RB: root bark; RW: root wood; USB: Underground stem bark; L: leaves; UHW: underground heart-wood; MTT: Dimethylthiazol-diphenyltetrazolium bromide; MIC: Minimum inhibitory concentration; MBC: Minimum bactericidal concentration; DPPH: 2,2-diphenyl-1-picryl-hydrazyl-hydrate; FRAP: Ferric reducing ability of plasma; ABTS: 2,2-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid; EtOH: ethanol; Hex: hexane; Alk: alkaloid; EO: essential oil; PE: petroleum ether; Aq: Aqueous; EA: ethyl acetate; MeOH: methanol; HA: Hydroalcohol; $CHCl_3$: chloroform; HMeOH: hydromethanol; EtOH: ethanol.

In vitro evaluations

Trypanocidal activity

Mesquita et al. (2005) investigated the trypanocidal activity of the ethanol (root bark and root wood) and hexane (stem and root bark) extracts from *D. furfuracea*. All extracts tested inhibited *Trypanosoma cruzi* amastigotes and the most active was the hexane extract from root bark, with a weakly cytotoxic effect on mammalian L6 cells.

The trypanocidal activity of alkaloid extract from *D. furfuracea* underground stem bark and the duguetine (**10**), duguetine β-*N*-oxide (**12**) and dicentrinone (**16**) isolated from this extract was demonstrated by Silva et al. (2009). Importantly, duguetine (**10**) exhibited the most significant effect against *T. cruzi* trypomastigote forms of the Y strain with half maximal inhibitory concentration (IC_{50}) of 9.32 µ*M*. Future studies with alkaloids *N*-oxide are promising (Silva et al. 2009) since synthetic compounds have shown to inhibit the nicotinamide adenine dinucleotide (NADH)-fumarate reductase, an enzyme presents only in the parasite (Turrens et al. 1999).

Leishmanicidal activity

Thirty-one extracts of thirteen species from the Brazilian Cerrado were evaluated against

Leishmania donovani (MHOM/ET/L82/LV9) promastigotes. The ethanol (root bark and root wood) and hexane (stem and root bark) extracts from *D. furfuracea* did not exhibit the leishmanicidal effect (Mesquita et al. 2005).

Another study reported that alkaloid extract obtained from the underground stem bark of *D. furfuracea* and the duguetine (**10**), duguetine β-N-oxide (**12**), dicentrinone (**16**), *N*-methyltetrahydropalmatine (**18**) and *N*-methylglaucine (**11**) isolated from this extract have a leishmanicidal effect. Among these alkaloids, the higher inhibition of *Leishmania braziliensis* (MHOM/BR175/M2904) was obtained with duguetine β-*N*-oxide (**12**) (IC_{50} = 0.11 μ*M*) and dicentrinone (**16**) (IC_{50} = 0.01 μM) (Silva et al. 2009). The leishmanicidal activity of isoquinoline alkaloids has been well described (Queiroz et al. 1996).

Larvicidal activity

Rodrigues et al. (2006) evaluated the larvicidal of the ethanol and hexane extracts obtained from *D. furfuracea* leaves, stem, root wood, and root bark were tested against the third stage *Aedes aegypti* larvae. This species showed excellent larvicidal activity and the hexane extract from root wood resulted in a lethal concentration of 50% (LC_{50}) of 56.6 μg/ml. This action may be attributed to the presence of constituents in the underground organs synthesized by defense pathways. Another study of Maia et al. (2020) evaluated the larvicidal effect of essential oil, its fraction, and petroleum ether and alkaloid extracts of *D. furfuracea* obtained from underground stem bark and underground heartwood. The essential oils, petroleum ether (from underground stem bark and underground heartwood) and fraction (from essential oil underground stem bark) showed moderate activity against *C. quinquefasciatus* with LC_{50} ranging from 71.14 to 94.36 μg/ml. However, the alkaloid extract from the underground stem bark was inactive. (*E*)-asarone (**92**) showed larvicidal activity against *C. quinquefasciatus* with LC_{50} of 42.72 μg/ml, and it is a constituent present in active samples such as essential oil from underground stem bark, and its fraction, and essential oil from underground heartwood.

Antitumoral activity

Alkaloid extract from *D. furfuracea* underground stem bark exhibited cytotoxic activity with an IC_{50} of 1.2, 0.6, and 3.4 μ*M* against human tumor cell lines SF-295 (glyoblastoma), HCT-8 (colon cancer), and MDA/MB-435 (melanoma), respectively. The antitumoral activity of five alkaloids isolated from the extract was also investigated. *N*-methylglaucine (**11**) and *N*-methyltetrahydropalmatine (**18**) showed weak activity, while duguetine (**10**) and duguetine β-*N*-oxide (**12**) had high cytotoxicity against all tumor lines evaluated. Interestingly, the duguetine β-*N*-oxide (**12**) (IC_{50} = 7.27 μM) revealed more potent cytotoxic effect than the observed for duguetine (**10**) (IC_{50} = 12.39 μM) against the MDA/MB-435 cells. On the other hand, dicentrinone (**16**) did not exhibit a significant cytotoxic effect (Silva et al. 2009).

Antimutagenic activity

The antimutagenic effect of aqueous extract from *D. furfuracea* leaves on the damage induced by urethane in *Drosophila melanogaster* somatic cells was demonstrated by Coelho et al. (2011). This modulatory effect was observed in both standard and high bioactivation crosses descendants. The compounds identified from this evaluated extract, such as flavonoids and terpenoids, could be contributing for the antimutagenic effects.

Silva et al. (2013) investigated the antigenotoxic action of aqueous extract of *D. fufuracea* leaves by measuring the inhibitory effect on mitomycin C-induced mutagenesis prophage λ induction test (SOS-Inductest) model. The antimutagenic effect was evidenced by suppression of the induction of prophage λ (*Escherichia coli* WP2s (λ) colonies) promoted by all concentrations of extract (0.5, 1, 2, 5, and 10 mg) co-administered with mitomycin C (0.5 μg). Importantly, the antimutagenic effect was more pronounced at 2 mg (Silva et al. 2013). This result agrees with those obtained by Coelho et al. (2011). This effect is partly due to the presence of sesquiterpenes and flavonoids in this species (Silva et al. 2013).

Cytoprotective properties

Silva et al. (2013) also demonstrated the anticytotoxic effect of the aqueous extract from *D. furfuracea* leaves. The extract at concentrations of 0.5, 1, 2, and 5 mg significantly attenuated the cytotoxic effects induced by mitomycin C (0.5 μg), increasing the number of surviving *E. coli* WP2s (λ) colonies. However, this effect was not observed with 10 mg, indicating a possible cytotoxic effect (in higher dose) against *E. coli*, corroborating with Silva et al. (2012).

The cytoprotective effect of ethanol extract, hexane, ethyl acetate and methanol fractions from *D. furfuracea* leaves against mercury chloride in *Escherichia coli* (ATCC 11105) was investigated by Lima et al. (2014). All extract and fractions showed no significant antibacterial effect on the microdilution method (minimum inhibitory concentration, MIC ≥ 1.024 μg/ml). The protective activity was not evidenced only for hexane fraction. The presence of flavonoids in the ethanol extract, ethyl acetate and methanol fractions can explain, at least in part, the cytoprotective effect observed (Lima et al. 2014). These compounds are able to chelate metals (Behling et al. 2004).

Acaricidal activity

The study evaluated the acaricidal effect of extracts of eleven Brazilian flora species against *Rhipicephalus microplus,* which were previously selected based on the ethnopharmacological and chemosystematics data. Among the species tested the *D. furfuracea,* and its hexane extract showed lower larval mortality (mean larval mortality of 6.03%) (Valente et al. 2014).

Antifungal activity

The hydroalcoholic extract, and its fractions (methanolic and ethyl acetate) from *D. furfuracea* leaves revealed low antifungal activity against some *Candida* species. However, the combination of them and the drug fluconazole indicated a synergism, which was observed higher inhibition of *C. krusei* (hydroalcoholic extract and methanolic fraction), *C. tropicalis* (methanolic fraction), and *C. albicans* (ethyl acetate fraction) strains. The high-performance liquid chromatography coupled to diode-array detector (HPLC-DAD) analysis showed the presence of rutin (**85**) and chlorogenic acid (**91**) in this extract and fractions (Pinho et al. 2016). These compounds can also be related to the antifungal effect (Lee et al. 2008; Orhan et al. 2010).

Antioxidant properties by chemical essays

Antioxidant activity of the hydroalcoholic extract and its fractions (methanol and ethyl acetate) from *D. furfuracea* leaves was demonstrated by ferric reducing antioxidant power (FRAP) and scavenging of 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical methods. It is noteworthy that the activity of this extract was more pronounced compared to its fractions. The presence of other phenolic compounds than those detected may have contributed for these effects. This hypothesis is raised since it was not possible to positively correlate this activity and the total index of phenols and flavonoids identified (Pinho et al. 2016).

Do Santos et al. (2018) evaluated the antioxidant effect and inhibition of lipid peroxidation of the methanolic extract, and some fractions from *D. furfuracea* leaves, using the DPPH and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) essays, which the antioxidant activity of methanolic extract and its hydromethanolic fraction were the most pronounced. These results corroborate with the findings of the study by Pinho et al. (2016). In addition, do Santos et al. (2018) also investigated the possible inhibition of lipid peroxidation promoted by extract and fractions using the peroxidation β-carotene/linoleic acid and malondialdehyde (MDA) assays. Moderate inhibition of lipoperoxidation was observed with methanol extract. The presence of phenolic compounds and flavonoids may contribute to antioxidant action and inhibition of lipid peroxidation.

Favareto et al. (2019) demonstrated that *D. furfuracea* leaves extract obtained by supercritical fluid extraction did not show significantly different values, which indicates that factors such as pressure, temperature and volumetric flow did not influence the antioxidant activity.

***In vivo* evaluations**

Antimutagenic activity

Silva et al. (2013) demonstrated the antigenotoxic action of the aqueous extract of *D. furfuracea* leaves. Oral treatment with extract at doses of 100, 200, and 300 mg/kg associated with mitomycin C (4 mg/kg, intraperitoneally) suppressed the number of micronucleated polychromatic erythrocytes, at 24 and 48 h. This protection against DNA damage can be attributed to compounds such as flavonoids and sesquiterpenoids found in the *D. furfuracea* (Silva et al. 2012).

Cytoprotective effect

The anticytotoxic effect of the aqueous extract of *D. furfuracea* leaves was evaluated by the mouse bone marrow micronucleus test. Oral treatment with extract of 100, 200, and 300 mg/kg associated with mitomycin C (4 mg/kg, intraperitoneally) increased the polychromatic and normochromatic erythrocyte ratio at 24 and 48 h (Silva et al. 2013). It is known that compounds such as flavonoids and sesquiterpenoids may contribute to the cytoprotective effect (Silva et al. 2012).

Anti-inflammatory activity

The anti-inflammatory activity of methanolic extract and chloroform, ethyl acetate, and hydromethanolic fractions from *D. furfuracea* leaves was evaluated by carrageenan-induced paw edema model. Importantly, the alkaloid dicentrinone (**16**) was isolated from the chloroform fraction and tested. Methanolic extract at doses 100 and 300 mg/kg (orally) inhibited paw edema by 22 ($p<0.01$) and 39% ($p<0.001$) 2 h after inflammatory stimulus, respectively. In addition, inhibition of paw edema 4 h after carrageenan injection was also promoted by methanolic extract at doses of 100 (25%, $p<0.01$) and 300 mg/kg (40%, $p<0.001$). All tested fractions and dicentrinone (**16**) exhibited antiedematogenic activity at the dose of 100 mg/kg (orally), 2 and 4 h after carrageenan injection (do Santos et al. 2018). Do Santos et al. (2018) also demonstrate the anti-inflammatory effect of methanolic extract obtained from leaves of D. furfuracea and of the alkaloid dicentrinone (**16**), using the air pouch model of inflammation. The methanolic extract (30-300mg/kg) and dicentrinone (**16**) (100mg/kg) inhibited

leukocyte migration and plasmatic leakage in this model.

Other studies evaluated the anti-inflammatory activity of *D. furfuracea* underground stem bark essential oil and phenylpropanoid-enriched fraction. Oral treatment with essential oil and phenylpropanoid-enriched fraction both at 3 and 10 mg/kg inhibited lipopolysaccharide (LPS)-induced paw edema at all time points (1 to 6 h after inflammatory stimulus). In addition, the essential oil at 10 mg/kg and phenylpropanoid-enriched fraction at 3 mg/kg were able to inhibit polymorphonuclear leukocyte migration, expression of inducible nitric oxide synthase (iNOS), and tumor necrosis factor alpha (TNF-α) production (Saldanha et al. 2019a; Saldanha et al. 2020). The phenylpropanoid-enriched fraction showed an increase in the anti-inflammatory activity when compared with the essential oil (Saldanha et al. 2020). One of the constituents that may contribute to the essential oil's anti-inflammatory effect is its major compound, (*E*)-asarone (**92**). Oral treatment with this phenylpropanoid (at 3 mg/kg) inhibited paw edema, polymorphonuclear leukocyte recruitment, expression of iNOS and TNF-α level induced by LPS (Saldanha et al. 2019b). Other studies also described the anti-inflammatory effect of the (*E*)-asarona (**92**) (Shin et al. 2014; Kim et al. 2015).

Antinociceptive activity

The central and peripheral antinociceptive activity of the underground stem bark essential oil and phenylpropanoid-enriched fraction were demonstrated. Oral treatment with essential oil and phenylpropanoid-enriched fraction (both at 10 and 30 mg/kg) inhibited both phases of the formalin test, presenting the central and peripheral effects. The central activity was confirmed on the LPS-induced thermal hyperalgesia test by increased reaction time 1 to 6 h after oral treatment with essential oil and phenylpropanoid-enriched fraction both at 10 and 30 mg/kg. Adenosinergic and opiodergic systems participate in central antinociception, while opioidergic system is involved in peripheral antinociceptive effect (Saldanha et al. 2019a; Saldanha et al. 2020). One of the major compounds, (*E*)-asarone (**92**), may contribute to this effect, since the oral treatment at 10 and 30 mg/kg showed antinociceptive activity by formalin and LPS-induced thermal hyperalgesia model (Saldanha et al. 2019b). Other previous data corroborate the antinociceptive action of this phenylpropanoid (Filho et al. 2004). However, a possible synergism resulting from other constituents' actions, such as (*E*)-caryophyllene (**63**) (Paula-Freire et al. 2014), should be considered.

Toxicity studies

Previous reports evaluated the possible toxicity of *D. furfuracea*, including investigations of embryotoxicity effect, mutagenic action and toxicity on brine shrimp (*Artemia salina*). Embryotoxicity effects of aqueous extract of *D. furfuracea* leaves obtained by maceration using cold and hot methods was evaluated by Toledo et al. (2006). Pregnant Wistar rats were orally treated with extract at a concentration of 5, 10 or 20% p/v. The *in vivo* effects were similarly independent of the maceration method used. Pregnant rats showed diarrhea, itch, epistaxis, reduction of body weight and hepatomegaly. Furthermore, for all concentrations tested, external fetal abnormalities, visceral and skeletal malformations were observed, especially in the organogenesis.

The mutagenic effect of aqueous extract of *D. furfuracea* leaves (0.085, 0.042 or 0.014 g/ml) was evaluated in the somatic mutation and recombination test (SMART) somatic mutation and recombination test (SMART)/wing test. Therefore, three *Drosophila melanogaster* somatic cell lines (mwh, flr^3, and ORR) were used. Negative results for mutagenesis were observed in both standard and high bioactivation crosses. Thus, no significant increase occurred in the frequency of single small spots, large single spots, twin spots, or total spots (Coelho et al. 2011).

Silva et al. (2012) studied the genotoxic and cytotoxic effects of aqueous extract of *D. furfuracea* leaves using prophage λ induction (SOS-Inductest) in lysogenic strain *Escherichia coli* WP2s(λ) and mouse bone marrow micronucleus tests. The extract exhibited the absence of genotoxic activity in both *in vitro* and *in vivo* assays. However, the cytotoxic action of this extract was verified by the reduction of bacteria number of the culture incubated with extract at concentrations of 5 and 10 mg/0.1 ml. Moreover, this toxic effect also occurred in mice that orally received the extract at doses of 100, 200 and 300 mg/kg, being observed the decrease of polychromatic erythrocytes/normochromatic erythrocytes ratio at both times, 24 and 48 h after treatments (Silva et al. 2012).

Silva et al. (2007) evaluated the toxicity of fresh volatile oil, petroleum ether and alkaloid extracts (at 500, 50, 5, and 0.5 µg/ml) of *D. furfuracea* underground parts (stem bark and wood) against second instar larvae of *Artemia salina* Leach (brine shrimp). The fresh volatile oil exhibited more pronounced larval mortality (lethal dose 50 - LD_{50} = 2.6 µg/ml) than the petroleum ether (LD_{50} = 6.1 µg/ml) and alkaloids (LD_{50} = 36.9 µg/ml) extracts. In the mentioned study, the phytochemical profile showed the presence of 2,4,5-trimethoxystyrene (in both fresh volatile oil and petroleum ether extract), polycarpol (petroleum ether extract) and

oxoaporphine alkaloids (alkaloid extract). Previously studies demonstrated that these compounds have toxicity in the brine shrimp lethality bioassay (Wang et al. 1988; Siqueira et al. 2001; Jung et al. 1990). Maia et al. (2020) demonstrated the toxicity of essential oil, Df10-12 fraction, petroleum ether and alkaloid extracts from *D. furfuracea* underground stem bark, and of the essential oil and petroleum ether extract from underground heartwood of this species by brine shrimp lethality bioassay. The lethal concentration (LC_{50}) of essential oil, Df10-12 fraction, petroleum ether and alkaloid extract from underground stem bark were 9.98, 36.74, 15.23, and 66.49 µg/ml, respectively. Furthermore, the LC_{50} of essential oil and petroleum ether extract from underground heartwood were 7.79 and 21.97 µg/ml, respectively. Most of these tested samples showed high toxicity (<37 µg/ml) against *A. salina*, and in their composition is found (*E*)-asarone (**92**), a phenylpropanoid with LC_{50} of 12.48 µg/ml against this microcrustacean (Maia et al. 2020).

Patent information on *D. furfuracea*

Herbal drug composition containing "*D. furfuracea* material" has been patented for the treatment of the renal colic by da Silva Coelho (2003) (Patent nº: BR 200202030-A) and the recommended dosage is 25 mg three times per day for about ninety days.

Soap and moisturizer obtained from the alcoholic extract of the leaves of *D. furfuracea*, with antimicrobial and antioxidant potential, has been patented by Marques (2023) (Patent nº: BR102023008837A2), for the prophylaxis of infections, as well as antioxidant to prevent and reduce the oxidative process, for external and topical application.

CONCLUSION

Phytochemical and pharmacological studies have demonstrated the therapeutic potential of *D. furfuracea*. However, the study of pharmacological mechanisms of its herbal medicinal product, isolated constituents and toxicity should be further explored, since capsules containing material of this species have already been developed for renal colic. In addition, the plant raw materials from *D. furfuracea* are easily obtained since it is considered an invasive plant.

AUTHORS' CONTRIBUTIONS

All authors contributed to the conception and design of the study, and also drafting the work and revising it critically for important intellectual content. Final approval of the version to be published was performed by all authors.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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