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Review

Compounds isolated from *Harpalyce brasiliana* Benth and their pharmacological properties

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***Harpalyce brasiliana* Benth, known as snakeroot, is one of the most popular herbal medicines against snakebite in South America. A hydroalcoholic solution is traditionally prepared from the roots of *H. brasiliana*. In the last two decades, understanding the pharmacological properties and the possible medicinal applications of *H. brasiliana* has increased considerably. *H. brasiliana* has antivenom activity and anticarcinogenic, antimicrobial and antioxidant properties. Various *in vitro* and *in vivo* studies have shown *H. brasiliana*'s diverse biological properties and its potential for disease treatment. The different biological effects of this plant may be attributable to the presence of secondary active metabolites such as pterocarpans, triterpenoids, chalcones and flavonoids. This overview presents different aspects of this plant and the pharmacological properties of its compounds through a review of the available literature. The results support the use of *H. brasiliana* in the treatment of snakebite and its potential for treatment of other diseases in folk medicine.**

Key words: Snake antivenom, medicinal plants, pterocarpans.

INTRODUCTION

Harpalyce brasiliana Benth (family Leguminosae), commonly known as snakeroot, is a shrub used in South America, particularly in northeastern Brazil to treat snake bite poisoning. The local people have reported that hydroalcoholic solution from the roots of *H. brasiliana* is an antidote against snakebite (Silva et al., 1999). Much of the activity of *H. brasiliana* is because of pterocarpans, which are major compounds present in the plant. Pterocarpans play an important role as phytoalexins and have significant pharmacological applications. Pterocarpans are present in the roots and leaves (Jiménez-González et al., 2008).

Initial studies using the roots of *H. brasiliana* showed two active compounds, betulinic acid and a prenylated pterocarpan (Silva et al., 1997). Subsequently, other bioactive pterocarpan derivatives were isolated, including 4′-dehydroxycabenegrin A-I, cabenegrin A-I, cabenegrin A-II, leiocarpin, medicarpin and maackiain (Silva et al., 2004; Militão et al., 2007). The active constituents isolated from this plant have pharmacological activities such as antiviral, antiophidic and anticarcinogenic activities. Two polyphenolic compounds, harpalycin and quercetin, were isolated from the *H. brasiliana* leaves (Silva et al., 1999). These compounds have numerous biological activities in animal cells, such as free radical scavenging properties and antioxidant and anticholinesterase activities

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Table 1. Compounds isolated from *Harpalyce brasiliana* Benth.

Extract type	Plant part	Compound	Reference
Ethanolic	Roots	4′-dehydroxycabenegrin A-I	Silva et al. (1997)
		3-hydroxy-4-isopentenyl-8,9-methylenedioxypterocarpan	Silva et al. (1999)
		3β-hydroxy-20(29)-lupen-28-oic acid or betulinic acid	Silva et al. (1997; 1999)
	Leaves	Harpalycin and quercetin 5,7,3′,4′-tetrahydroxyflavonol	Silva et al. (1999)
	Roots	Leiocarpin, medicarpin, maackiain, cabenegrin A-I and cabenegrin A-II	Militão et al. (2007)
		(-)-2-geranyl-3-hydroxy-8,9-methylenedioxypterocarpan	Vieira et al. (2008)
	Roots	(-)-6a*R*,11a*R*-2(4′,5′-dihydroxy-1′-isopentenyl)-3-hydroxy-8,9-methylenedioxypterocarpan and (-)-6a*R*,11a*R*-2(4′-hydroxy-1′-isopentenyl)-3-hydroxy-8,9-methylenedioxypterocarpan	Araújo et al. (2008)
		2-Geranyl-2,3′,4,4′-tetrahydroxychalcone	Vieira et al. (2008)
		(-)-7,8,3′,4′-trihydroxy-8-(3″,7 ″-dimethyl-octa-2″,6 ″-dienoyl)-flavanone	Araújo et al. (2008)

activities (Djeridane et al., 2006; Katalanić et al., 2010; Ximenes et al., 2012). Although few studies have been performed on this plant to date, the results show that *H. brasiliana* is a source of several bioactive compounds of medicinal interest. Here, an overview of the available literature on the main properties of this plant and the compounds isolated from this plant has been presented.

ISOLATED COMPOUNDS

Studies have been performed, particularly during the past two decades, to isolate and identify bioactive compounds from *H. brasiliana* (Table 1). Phytochemical studies using leaves and roots of *H. brasiliana* showed the presence of several substances belonging to the class of flavonoids, particularly pterocarpans and some triterpenoids. Ethanolic extract from roots showed a prenylated pterocarpan, namely 4′-dehydroxycabenegrin A-I (Silva et al., 1997). The structure of this pterocarpan is similar to that of the known snake venom antidote, cabenegrin A-I (Figure 1), a compound initially isolated by Nakagawa et al. (1982) from a hydroethanolic beverage called “Específico Pessôa,” a Brazilian folk medicine used against snakebite. Subsequently, other pterocarpans were also isolated from the ethanolic extract roots. They are 3-hydroxy-4-isopentenyl-8,9-methylenedioxypterocarpan (Silva et al., 1999); leiocarpin, medicarpin, maackiain, cabenegrin A-, and cabenegrin A-II (Militão et al., 2007); (-)-2-geranyl-3-hydroxy-8,9-methylenedioxypterocarpan (Vieira et al., 2008); (-)-6a*R*,11a*R*-2(4′,5′-dihydroxy-1′-isopentenyl)-3-hydroxy-8,9-methylenedioxypterocarpan and (-)-6a*R*,11a*R*-2(4′-hydroxy-1′-isopentenyl)-3-hydroxy-8,9-methylenedioxypterocarpan (Araújo et al., 2008). The compounds isolated from the roots included the triterpenoid 3β-hydroxy-20(29)-lupen-28-oic acid or betulinic acid (Silva et al., 1997; Silva et al., 1999); the chalcone 2-geranyl-2,3′,4,4′-tetrahydroxychalcone (Vieira et al., 2008) and the flavanone (-)-7,8,3′,4′-trihydroxy-8-(3″,7″-dimethyl-octa-2″,6″-dienoyl)-flavanone (Araújo et al., 2008). The isoflavone harpalycin and the flavonol quercetin 5,7,3′,4′-tetrahydroxyflavonol were isolated from the leaves of *H. brasiliana* (Silva et al., 1999).

PTEROCARPANS

Pterocarpans are phytoalexins, that is substances produced *de novo* by plants to provide resistance against stress factors such as microbial infections or stress of abiotic origin. The second largest class of natural isoflavonoids found in the Leguminosae family is characterized by the presence of a tetracyclic system of benzofuran-benzopyran rings with two chiral centers in the 6a and 11a positions in *H. brasiliana* (Jiménez-González et al., 2008). All natural pterocarpans have a junction of *cis*-fused rings. Computational studies have shown that the *trans* isomers are

Table 2. Compounds and their pharmacological activities

Compound	Pharmacological Activity	Reference
Pterocarpan		
Cabenegrin A-I and A-II	Anti-inflammatory, antifungal, antimicrobial, antiparasitic, antimitotic, anticarcinogenic, and antiophidic against *Bothrops atrox*	Nakagawa et al. (1982), Jiménez-González et al. (2008), Zhou et al. (2009), Harinantenaina et al. (2010) and Dey and De (2012)
4′-dehydroxycabenegrin A-I	Antimyotoxic, antiproteolytic, and PLA2 inhibitor against *B. jararacussu* (*in vitro*)	Ishiguro et al. (1982) and Silva et al. (2004)
Leiocarpin C	Cytotoxic activity against several tumor cell lines	Yadav et al. (2008)
Maackiain	Inhibitor of aryl hydrocarbon hydroxylase	Gelboin et al. (1981)
	Inhibitory action on lymphoblastoid cell lines I	Skinnider and Stoessl (1986)
	Induction of apoptosis of the DNA of human promyelocytic leukemia HL-60 cells	Aratanechemuge et al. (2004)
Medicarpin	Inhibitor of mixed function oxidase (P450) (*in vitro*)	Friedman et al. (1985)
	Suppressor of osteoclastogenesis	Tyagi et al. (2010)
	Stimulator of osteoblast differentiation	Bhargavan et al. (2012)
Triterpenoid		
Betulinic acid	Anticarcinogenic	Chintharlapalli et al. (2007)
Chalcones	Anti-inflammatory, antimicrobial, antioxidant, and anticarcinogenic	Hijova (2006) and Perjési and Rozmer (2011)
Chalcone 2-hydroxychalcone	Anticarcinogenic	Makita et al. (1996)
	Preventive effect on diabetic complications	Jamal et al. (2009)
Flavonoids		
Quercetin	Antioxidant	Day et al. (2000)
	Inhibitor of butyrylcholinesterase	Katalinić et al. (2010)
4′-chloroflavanone	Antiproliferative activity	Choi et al. (2010)
Naringenin	Antioxidant (*in vitro*)	Cavia-Saiz et al. (2010)
Naringenin and Hesperidin	Inhibition of bone resorption	Habauzit et al. (2011)
Naringenin flavanone	Antihyperglycemic and activity on bone metabolism	Annadurai et al. (2012)
Harpalycin 2 isoflavone	Anti-inflammatory	Ximenes et al. (2012)

energetically unfavorable, which explains the reason for all pterocarpans of natural origin possessing the 6a, 11a-*cis* configuration (Van Aardt et al., 2001).

The main bioactivities of pterocarpans (Table 2) included anti-inflammatory, antifungal, antimicrobial, antiparasitic, antimitotic, anticarcinogenic and antiophidic activities (Nakagawa et al., 1982; Jiménez-González et al., 2008; Zhou et al., 2009; Harinantenaina et al., 2010; Dey and De, 2012).

Cabenegrins A-I and A-II were isolated initially by Nakagawa et al. (1982) from “Específico Pessôa,” a northeast Brazilian folk medicine used against snakebite and spider venom. According to the authors, it was a hydroethanolic extract from the root of the plant popularly known as “black head”. Cabenegrin A-I and cabenegrin A-II showed antiophidic activity at a dose of 2.0

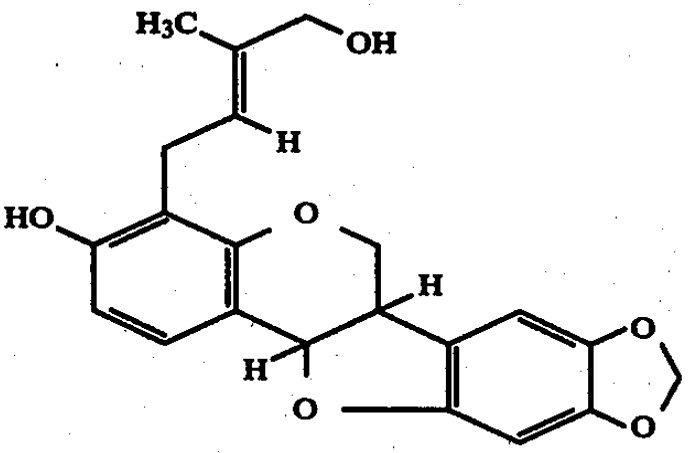

Figure 1. Cabenegrin A-I, a compound initially isolated by Nakagawa et al. (1982) and Darko (1984).

to 2.8 mg/kg in mice and at a dose of 1.0 mg/kg in beagle dogs previously envenomed using the venom of *Bothrops atrox* (Viperidae). Further, on the basis of spectroscopic analysis of cabenegrins, other pterocarpans were obtained by synthesis. The compound 4′-dehydroxycabenegrin A-I obtained by synthesis showed antimyotoxic, antiproteolytic and PLA2 inhibitor activities against *Bothrops jararacussu* (Viperidae) crude venom *in vitro* (Ishiguro et al., 1982; Silva et al., 2004).

The pterocarpan medicarpin is naturally found in dietary legumes and has also been synthesized for pharmacological studies. Studies on rat liver microsomes showed that medicarpin can inhibit mixed-function oxidase (P450) activity, particularly the cytochrome P-450-dependent aryl hydrocarbon hydroxylase (AHH) and ethoxycoumarin deethylase (ECD) activities (Friedman et al., 1985). Recent studies have shown that medicarpin affects osteoclastogenesis. Tyagi et al. (2010) showed that medicarpin at a dose of 10^{-10} mol/L suppresses osteoclastogenesis in bone marrow cells and induces apoptosis of mature osteoclasts in ovariectomized mice. The mechanism of action appeared to be independent of estrogen receptor activation. Medicarpin acted as an estrogen receptor agonist; however it showed no uterine estrogenicity. Medicarpin stimulates osteoblast differentiation and promotes achievement of peak bone mass in rats (Bhargavan et al., 2012).

Various studies have shown that maackiain inhibits different forms of aryl hydrocarbon hydroxylase in human and rat livers (Gelboin et al., 1981), besides its inhibitory effect on the growth of human lymphoblastoid cell line I (Skinnider and Stoessl, 1986) and induction of apoptosis in the DNA of human promyelocytic leukemia HL-60 cells (Aratanechemuge et al., 2004). Leiocarpin C, isolated from the stem bark of the *Goniothalamus leiocarpus* (Annonaceae), also possesses cytotoxic activity against several human tumor cell lines (Yadav et al., 2008). Studies on three human cells lines, namely HL-60 (leukemia cells), HCT-8 (colon cancer cells) and MDA-MB-435 (melanoma cells) showed that leiocarpin is cytotoxic and its half-maximal inhibitory concentration (IC_{50}) values are 5.5, 6.9 and 13.7 µg/ml, respectively (Militão et al., 2007). Studies on understanding the synthesis of this compound have been reported (Yadav et al., 2008; Krishna and Alivelu, 2011).

TRITERPENOIDS

Triterpenoids are natural products, with thirty carbons, derived from a squalene skeleton or enzymatic reaction by cyclization products of squalene, oxidosqualene and bis-oxidosqualene. They are found either in the acyclic or cyclic forms and tetracyclic and pentacyclic triterpenoids the most common forms of triterpenoids (Xu et al., 2004). Triterpenoids from natural origin and their synthetic derivatives are pharmacologically active (Table 2) and have anti-inflammatory and anticarcinogenic activities (Bishayee et al., 2011). The triterpenoid 3β-hydroxy-20(29)-lupen-28-oic acid, betulinic acid inhibits the growth of multiple tumors, including human melanomas. In an experimental model of prostate cancer, betulinic acid treatment decreased the growth of the cancer cells and its IC_{50} value was 1 to 5 µmol/L (Chintharlapalli et al., 2007). In addition, the anticarcinogenic effect of betulinic acid on colon cancer cells has also been investigated. The results showed that the betulinic acid at a concentration of ≥ 5 µmol/L inhibited the growth of cancer cells and down-regulated the specificity protein (Sp) transcription factors (Chintharlapalli et al., 2011).

CHALCONES

Chalcones, 1,3-diphenyl-2-propenones, considered as precursors of flavonoids and isoflavonoids, are also known as benzalacetophenone or benzylidene acetophenone. They play an important role in plants for the pigmentation flowers, and act against pathogens and insects (Batovska and Todorova, 2010). Studies with chalcones and their analogues have shown several biological activities such as anti-inflammatory, antimicrobial, antioxidant and anticancer activities (Table 2) (Hijova, 2006; Perjési and Rozmer, 2011). A previous study showed that diets containing 500 ppm of chalcone and 2-hydroxychalcone showed an inhibitory effect on oral carcinogenesis induced using 4-nitroquinoline-1-oxide in F344 rats (Makita et al., 1996). Another study showed that chalcones had a preventive effect on diabetic complications. The effect of several chalcones at a dose of 25 mg/kg on glycogen contents in rats showed marked inhibition of aldose reductase, which affected the rate of glycogenolysis by decreasing the glycogen content of the liver (Jamal et al., 2009). These data indicate the importance

of chalcones and their analogues as an emerging class of preventive and therapeutic agents for diabetes.

FLAVONOIDS

Flavonoids are a class of polyphenolic compounds synthesized in plants. In general, flavonoids are compounds characterized by three rings; two aromatic rings linked to one heterocyclic ring. Flavonoids can be divided into flavonols, flavones, flavanones, isoflavonoids, catechins and anthocyanins (Hollman and Katan, 1997; Peterson and Dwyer, 1998). These compounds generally are considered safe because of favorable pharmacological activity and low toxicity (Table 2). Many compounds possess anti-inflammatory, antioxidant, anticarcinogenic and antiallergenic activities (Khairullina et al., 2010). In addition, the antiproliferative effect of the analogue 4′-chloroflavanone was observed in MCF-7 and MDA-MB-453 cells. The synthetic flavanone at a concentration of > 50 µmol/L inhibits cell proliferation through disruption of the G1/S phase and by induction of apoptosis (Choi et al., 2010). Additional biological activities were described for compounds belonging to the class of flavonoids. Recent studies with flavanone compounds showed antihyperglycemic action and an effect on bone metabolism. In an experimental model of diabetes, the flavanone naringenin (50 mg/kg) significantly decreased the levels of fasting blood glucose and glycosylated hemoglobin and increased the serum insulin levels. The same study showed an increase in the activities of the pancreatic enzymatic antioxidants and plasma non-enzymatic antioxidants (Annadurai et al., 2012). Another study showed favorable effects of naringenin and hesperidin on bone metabolism. Naringenin 0.5%, hesperidin 0.5% and naringenin 0.25% + hesperidin 0.25% were administered to male gonad-intact senescent rats, and systemic parameters of bone metabolism were evaluated. The results showed that the flavanones exerted a protective effect on the bone in senescent male rats through inhibition of bone resorption (Habauzit et al., 2011).

In vitro assays showed that the antioxidant capacity of naringenin was higher than that of its glycoside naringin (Cavia-Saiz et al., 2010). In addition, a study on lipid peroxidation in mouse liver homogenates showed that both glycosides naringin and hesperidin had no antioxidant activity. On the other hand, quercetin at a concentration of 1 µmol/L showed antioxidant action (Day et al., 2000). Quercetin, the most abundant flavonoid, is recognized for its antioxidant action; however, several studies have also shown that quercetin has prooxidant activity (Constantin and Bracht, 2008). Moreover, similar to other flavonoids, quercetin showed reversible inhibition of butyrylcholinesterase, an enzyme linked to scavenging (Katalinić et al., 2010).

Studies with harpalycin 2 isoflavone on enzymatic, edematogenic and myotoxic activities of secretory phospholipase A2 (sPLA2) isolated from *B. pirajai* (Viperidae), *Crotalus durissus* (Viperidae), *Apis mellifera* (Apidae) and *Naja naja* (Elapidae) venoms showed inhibition of all sPLA2s tested, edema and myotoxic activity. These results suggest that harpalycin 2 possesses anti-inflammatory activity mainly in disorders that involve sPLA2 (Ximenes et al., 2012).

CONCLUSION

Plants extracts have been used for the treatment of several human diseases. Although few studies have been performed using *H. brasiliana*; studies show that this plant represents a particularly rich source of pharmacologically active compounds and possesses more than one bioactivity. This plant has anti-inflammatory, antivenom, antimicrobial, anticarcinogenic and antioxidant activities. Finally, further studies should be performed to identify the clinical applications of this plant for the benefit of mankind.

Conflict of Interest

Authors declare no conflict of interest.

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