Ethnobotanical and Pharmacological Study of *Ampelozizyphus amazonicus* Ducke (Rhamnaceae) – a Review

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ABSTRACT – *Ampelozizyphus amazonicus*, popularly known as "saracura-mirá", belongs the family plants Rhamnaceae. This plant it has limited occurrence to the of the Amazon region and have showing numerous ethnobotanical and pharmacological properties. In this review, among the pharmacological properties found are antiviral, antibacterial and antifungal, trypanocidal, antimalarial, larvicidal, immunobiological and anti-inflammatory, diuretic and antidiuretic, cytotoxic and antitumor, adaptogenic and immunomodulatory activities. Metabolites related to antiviral, antibacterial and antifungal activity were not found in the literature. The metabolites betulinic acid, 3ß-hydroxylup-20 (29) -eno-27,28-diioic acid and 2T, 3ß-dihydroxylup-20 (29) -eno-27,28 were found in the methanolic and ethyl acetate extract. -dioecious. For antimalarial and larvicidal activity, no metabolites were found for such activities. Complex saponins present in the aqueous extract were related to immunobiological and anti-inflammatory activities. Saponins and triterpenes mixed with saponins from the ethanolic extract of dry roots were related to diuretic and antidiuretic activity. The compounds 3ß-hydroxilup-20 (29) -en-27, 28-dioic acid and 2T, 3ß-dihydroxilup-20 (29) -eno-27,28-dioic acid found in the crude extract of hexane, ethyl- acetate, ethanolic, methanolic and aqueous from *A. amazonicus* demonstrated cytotoxic and antitumor activity. No compounds related to adaptogenic and immunomodulatory activity were found. The present work reviewed the ethnobotanical and pharmacological properties of *Ampelozizyphus amazonicus*.

Keywords: *Saracura-mirá* therapeutic activity; *indian beer* ethnobotany; pharmacological properties of curupiramirá beer.

Estudo Etnobotânico e Farmacológico de *Ampelozizyphus amazonicus* Ducke (Rhamnaceae) – uma Revisão

RESUMO – A *Ampelozizyphus amazonicus*, conhecida popularmente como "saracura-mirá", pertence à família das plantas Rhamnaceae. Esta planta tem ocorrência limitada à região amazônica e possui inúmeras propriedades etnobotânicas e farmacológicas. Nesta revisão, entre as propriedades farmacológicas encontradas estão as atividades antiviral, antibacteriana e antifúngica, tripanocida, antimalárica, larvicida, imunobiológica e antiinflamatória, diurética e antidiurética, citotóxica e antitumoral, adaptogênica e imunomodulatória. Não foram encontrados na literatura metabólitos relacionados à atividade antiviral, antibacteriana e antifúngica. No extrato metanólico e de etil-acetato foram encontrados os metabólitos ácido betulínico, ácido 3ß-hidroxilup-20 (29) -eno-27,28-diioico e ácido 2T, 3ß-diidroxilup-20 (29) -eno-27,28-dioico. Também não foram encontrados metabólitos para atividade antimalárica e larvicida. Saponinas complexas presentes no extrato aquoso foram relacionadas às atividades imunobiológicas e antiinflamatórias. Já as saponinas e os triterpenos misturados com saponinas do extrato etanólico de raízes secas foram relacionados a atividade diurética e antidiurética. Os compostos 3ß-hidroxilup-20(29)-en-ácido 27,28-dióico e 2T,3ß-di-hidroxilup-20(29)-eno-27,28-ácido dióico encontrados no extrato cru de hexano, etil-acetato, etanólico, metanólico e aquoso de *A. amazonicus* demonstraram atividade citotóxica e antitumoral. Não foram encontrados compostos relacionados à atividade adaptogênica e imunomodulatória. O presente trabalho revisou as propriedades etnobotânicas e farmacológicas de *Ampelozizyphus amazonicus*.

Palavras-chave: Atividade terapêutica de saracura-mirá; etnobotânica da cerveja-da-amazônia; propriedades farmacológicas da cerveja de curupiramirá.

Estudio Etnobotánico y Farmacológico de *Ampelozizyphus amazonicus* Ducke (Rhamnaceae) – una Revisión

RESUMEN – *Ampelozizyphus amazonicus*, conocida popularmente como "saracura-mirá", pertenece a la familia de las plantas Rhamnaceae. Esta planta ha ocurrido limitada a la región amazónica y tiene numerosas propiedades etnobotánicas y farmacológicas. En esta revisión, entre las propiedades farmacológicas encontradas se encuentran las actividades antivirales, antibacterianas y antifúngicas, tripanocidas, antipalúdicas, larvicidas, inmunobiológicas y antiinflamatorias, diuréticas y antidiuréticas, citotóxicas y antitumorales, adaptógenas e inmunomoduladoras. No se encontraron en la literatura metabolitos relacionados con la actividad antiviral, antibacteriana y antifúngica. Los metabolitos ácido betulínico, ácido 3ß-hidroxilup-20(29)-eno-27,28-diioico y ácido 2T, 3ß-dihidroxilup-20(29)-eno-27,28 se encontraron en el extracto de acetato de etilo y metanólico. También no se encontraron metabolitos para la actividad antipalúdica y larvicida. Las saponinas complejas presentes en el extracto acuoso se relacionaron con actividades inmunobiológicas y antiinflamatorias. Las saponinas y triterpenos mezclados con saponinas del extracto etanólico de raíces secas se relacionaron con la actividad diurética y antidiurética. Los compuestos 3ß-hidroxilup-20 (29) -en-27, ácido 28-dioico y ácido 2T, 3ß-dihidroxilup-20 (29) -eno-27,28-dioico que se encuentran en el extracto crudo de hexano, etil- acetato, etanólico, metanólico y acuoso de *A. amazonicus* demostraron actividad citotóxica y antitumoral. No se encontraron compuestos relacionados con la actividad adaptogénica e inmunomoduladora. El presente trabajo revisó las propiedades etnobotánicas y farmacológicas de *Ampelozizyphus amazonicus*.

Palabras clave: Actividad terapéutica de saracura-mirá; etnobotánica de la cerveza amazónica; propiedades farmacológicas de la cerveza curupiramirá.

Introduction

Ampelozizyphus amazonicus Ducke (Rhamnaceae) is a plant family Rhamnaceae. The species differs from the other species of the genus called *Ampelozizyphus* due to its arborescent habit (climbing plant), its inflorescence and the presence of nectaries at the base of the leaf blades (Meier *et al*., 2008). When young, the plant takes the form of a small shrub and eventually becomes a vine that spreads over other trees (Santos *et al*., 2005).

The occurrence *A. amazonicus* is limited to the territories of the Amazon region (Revilla, 2002). According to Lima (2006), the species has an endemic distribution in South America passing through the territories of the Brazilian, Venezuelan, Colombian and Peruvian Amazon, reaching as far as Ecuador. The plant is found in upland forests and its occurrence in Brazil is limited to the states of Amazonas, Pará and Roraima, preferably in the vicinity of streams and waterfalls (Lima, 2006).

The plant *A. amazonicus* is widely known as saracura-mirá, curupiramirá beer (brewery), beer-of-the-bush, beer (Santos *et al*., 2005), beer-of-indian (Santos *et al*., 2005; Milliken, 1997) and saracuracorá (Milliken, 1997) and stands out in the use of amazonian folk medicine as a herbal medicine. This fact is verified in a survey carried out among the inhabitants of the Rio Solimões and the Manaus region by Hidalgo (2003). The author made a survey of the repertoire of leaves, roots, vines and bark of plants used by riverside populations to prevent or mitigate the suffering caused by malaria. Of the 126 plants mentioned in the survey by riverside populations, the carapanaúba (*Aspidosperma nitidum* Benth ex Müll) stood out, the most remembered plant, and the saracura-mirá (*A. amazonicus*) was the second most mentioned species by the interviewees, being the only one indicated for the prevention of disease in question.

In traditional medicine, preparations for *A. amazonicus* root infusions are commonly used for the treatment and prevention of malaria, as an antidote for snake venom, and as an anti-inflammatory (Brandão *et al*., 1992; Krettli *et al*., 2001). The bark or roots of this plant are traditionally used by local communities as an aqueous extract. This extract has a very bitter taste and forms abundant foam when stirred because the presence of the high content of saponins in the plant (Brandão *et al*., 1992; Brandão *et al*., 1993).

Silva *et al*. (2009) demonstrated the presence of 48.4% of saponins in an aqueous extract of the plant's roots. Some substances have already been isolated and described in the literature, such as: 3-O-[β-D-glycopyranosil(1→2)a-Larabinopyranosil] - 20-OaL-ramnopyranosyl-jujubogenin (Brandão

et al., 1992), and ampelozigenin- 15a-O-acetyl-3-Oa-L-ramnopyranosyl-(1→2)-β-D-glycopyranoside (Brandão *et al*., 1993). Other substances have been described, such as triterpenes: melaleuucic acid, 3β, 27a-dihydroxylup-20 (29) -em-28β-oic acid, betulinic acid, betulin, lupeol (Brandão *et al*., 1992); and phytosteroid (Rosas *et al*., 2007).

In addition, species of the family of the referred plant (Rhamnaceae) showed an inhibitory effect on alcohol-induced muscle relaxation. There are also reports that extracts and pure compounds from other species of the Rhamnaceae family have cytotoxic, genotoxic, neurotoxic, anti-inflammatory, antipyretic and hepatoprotective activity to theirs (Popoca *et al*., 1998; Chang *et al*., 1996).

Pharmacological studies carried out with the extract of *A. amazonicus* have indicated other activities related to this species besides the prevention of malaria, such as: trypanosomicide, antifungal, antibacterials and antivirals (Amaral *et al*., 2008). The plant also showed activity against the trypomastigote form of *Trypanosoma cruzi* (Rosas *et al*., 2007) and is used in cases of snake bites (Brandão *et al*., 1992). The same plant was considered hepatoprotective in cases of injury induced in the liver (Sparg *et al*., 2004). *In vivo* studies have also demonstrated the antidiuretic effect of a fraction of saracura-mirá extract containing saponins and also a diuretic effect of a fraction of the same species without saponins (Diniz *et al*., 2009; Diniz *et al*., 2012).

Thus, the objective of this review was to report the ethnobotanical and pharmacological properties of *Ampelozizyphus amazonicus*. For this review, databases of *A. amazonicus* were consulted, such as Google, Scielo, Periódicos CAPES and Coordination for the Improvement of Higher Education Personnel (CAPES) in the period from 15 to 19 August 2020, based on the ethnobotanical and pharmaceutical attributions of the plant.

Ethnobotanical Study of *Ampelozizyphus amazonicus*

Ampelozizyphus amazonicus also known as saracura-mirá is a plant in widespread popular use. It is used in several amazonian regions including the Negro River Region and even urban centers (Santos *et al*., 2005; Rodrigues, 2006). The scholar Le Cointe (1947) made a description indicating the root sap against malaria fever. In addition, there are reports of preparation made from the roots of Indian beer (*A. amazonicus*) in the Brazilian Army as a preventive use against malaria (Institute de Recherce pour le Développement) (Table 1).

From the barks and roots of *A. amazonicus*, a water-based drink can be made with abundant foam and a bitter taste, very similar to beer, which gives it the names of "Cervejinha", "Cervejainha", "Cerveza-do-mato" and "beer-of-Indian" (Rodrigues, 1989; Vieira, 1992; Ducke & Martinez, 1994; Revilla 2002; Krettli & Andrade-Neto 2004; Santos *et al*., 2005).

Throughout the Amazon region, *A. amazonicus* is considered a species of extreme importance in prevention (Brandão *et al*., 1985; Vieira, 1992; Krettli *et al*., 2001; Krettli & Andrade-Neto, 2004; Silva *et al*., 2009) and in the treatment of malaria (Rodrigues, 1989; Ducke & Martinez, 1994; Santos & Muaze, 2002; Oliveira, 2004; Rodrigues, 2006).

In the studies by Andrade-Neto *et al*. (2008), the prophylactic activity of *A. amazonicus* has already been demonstrated, both in vivo and in vitro, against the sporozoite form of malaria contagion corroborating the popular indication of the plant in the Amazon region. The *A. amazonicus* species is considered an extremely important plant in the prevention and cure of malaria throughout the Amazon region (Rodrigues, 1989; Vieira, 1992; Ducke & Martinez, 1994; Krettli *et al*., 2001; Santos & Muaze, 2002; Krettli & Andrade-Neto, 2004; Oliveira, 2004; Santos *et al*., 2005; Rodrigues, 2006; Silva *et al*., 2009; Oliveira *et al*., 2011).

According to Santos *et al*. (2005), the *A. amazonicus* is considered stimulating and energetic. The plant also has other properties as in its roots considered as purifying (Rodrigues, 1989; Vieira, 1992; Almeida, 1993). The roots are also used in the treatment of gastrointestinal disorders, inflammation and fever (Rodrigues, 2006) (Table 1).

The powder from the leaves of *A. amazonicus* is indicated as a healing agent (Almeida, 1993; Berg, 1993). The barks of the plant also has another properties, they are used in the preparation of a fortifying tonic (MEB, 1993), as an aphrodisiac (Berg, 1993; Santos *et al*., 2005), and in cases of snake bites (Brandão *et al*., 1992) (Table 1). Reports also indicate that the barks are used in the treatment of gastritis, joint pain, "inflammation of women", like inflammation of the uterus and

ovaries for example, anemia and diabetes, as a revitalizer, depurative and diuretic (Oliveira, 2004) (Table 1). The diuretic effect of *A. amazonicus* in rats has been demonstrated in an in vivo study made by Diniz *et al*. (2009).

Acoording to Santos *et al*. (2005), in addition to use of prevent malaria, *A. amazonicus* roots are used to cure colds and as an energy stimulant, "which improves endurance". Reports from ribeirinhas population describe a drink prepared with a mixture of phloem roots and fresh stalk of saracura-mirá to recover from the effects of fatigue and hunger (Table 1). The plant is also indicated before heavy tasks, long walks in the forest or just to work as a stimulant. It is said among people in the local community that the body, whether weak or tired, recovers with saracuramira (Table 1). Users of *A. amazonicus* in São Gabriel da Cachoeira-Amazonas also mention other indications: rheumatism, liver, aphrodisiac, pneumonia, worms, itching, pain, diarrhea, inflammation, wounds and AIDS (Table 1). In the city of Manaus, Amazonas, uses of the plant have been described against malaria, liver problems and sleep disorders (Table 1).

An investigative study was carried out by a researcher Rodrigues (2006) residing in Jaú Nacional Park, in the State of Amazonas. He examined the therapeutic practices of local residents through interviews in the period from May to December 1995. Of the 519 plant species of registered uses 81 were indicated for therapeutic purposes, which were grouped into 15 categories of use according to the expected effects. Within this context, the species *A. amazonicus* was mentioned against fever, tropical diseases (roots), gastrointestinal disorders (bark/roots) (Table 1).

In Colombia, the bark that is in the soil is mixed with water and shaken vigorously. After this process, the resulting foamy preparation is applied as an antiseptic to wounds (Lopez *et al*., 2001) (Table 1). In addition, this species is used as a febrifuge in Peru (Miliken, 1997) (Table 1). There are several reports stating that the plant is not hallucinogenic or toxic (Santos *et al*., 2005), although it is narcotic when ingested in large quantities (Pontes, 1999).

According to Santos *et al*. (2005) *A. amazonicus* is widespread with widespread use in all locations visited in the Rio Negro region in the state of Amazonas, Brazil. This plant is considered among the inhabitants of that region as stimulating, energetic and with the property of increasing the resistance in addition to other properties (Table 1). *A. amazonicus* traditionally used among the Indians and caboclos of the Rio Negro region and also in other areas of the Amazon including the central urban region. The use of this species is always associated with the well-being and purification of the body, having a symbolic context of action with the power of "inducing property", uniting myth, shamanism and the plant in rituals.

In 1993, two researchers reported direct contact with the plant on the outskirts of São Gabriel da Cachoeira on the Rio Negro, Amazonas. With the help of two indigenous people from the Tukano group and after a long walk in the forest, *A. amazonicus* was collected and prepared in a mixture with the roots and stems in the water (Table 1). In all ingested portions of the drink recovery from physical exhaustion, fatigue and hunger was reported. At that time, there was knowledge of the widespread use of the mixture not only by Indians and Caboclos, but also by prospectors, soldiers in training in the jungle and residents of the local city, exhausted by physical fatigue in long walks in the Forest (Santos *et al*., 2005) (Table 1).

According to Santos *et al*. (2005), the most well-known activity of the plant is energetic with reports of habits of drinking the preparations based on the plant before heavy work. The local report is that when the body is weakened or intoxicated, it recovers with *A. amazonicus*. The use of the plant-based preparation is used in case of excessive intake of alcohol or fatty foods. In patients suffering from malaria, drinking is also used to recover the patient's energy. In addition, there is a great possibility that this practice is present for patients affected with other diseases such as rheumatism, liver disease, STDs (sexually transmitted diseases), pneumonia, worms, diabetes. There are also reports of use of the plant as an aphrodisiac, for "wild sore", "pereba", "all pain", itching, diarrhea and inflammation.

According to Coelho-Ferreira (1992) *A. amazonicus* also fights insomnia in addition to having activity against malaria and liver problems. Santos *et al*. (2005) also reported that in the second half of 1995, researchers obtained several testimonies in places visited of the wide use of the plant throughout the Rio Negro Valley. With this, the authors were able to affirm that saracura-mirá composes an entire collection that is both therapeutic and cultural within the community of Rio Negro and that the use of the plant is redefined

over time, establishing itself from generation to generation. Thus, Tukano Anacleto Indian 46-year-old, from São Gabriel da Cachoeira affirms that the knowledge of this plant is ancient, that is, since ancient times. Already a resident of Barcelos named Raimundo Golçalves Martins, 26, reports knowing the plant since he was born through his parents. The prayer in Novo Arião Irineu Pereira da Silva, 72, claims that he received a book from his father and that it contains the indication of saracura-mirá as a strengthener for the body for many years.

According to Santos *et al*. (2005), the plant's reports are not limited to the Amazon region only. *A. amazonicus* together with six plants is mentioned by Pontes (1993) in his Manual of Survival of the Jungle by IBGE (Instituto Brasileiro de Geografia e Estatística) as a plant species for medicinal use. In the manual, the hepatoprotective function was emphasized, also bringing as information the narcotic characteristic of the plant when ingested in excess.

According to Dultra (1993) in his publication in the newspaper "O Liberal", the *A. amazonicus* plant stood out for its energetic potential. The plant had the descriptions like: foamy like beer, bitter like chimarrão being sweet when it reaches the mouth. The plant was also highlighted in the text of the publication for its immediate effect against fatigue, making the work available. According to the publication, saracura-mirá was not described as hallucinogenic or even toxic. It was also pointed out in the text that *A. amazonicus* has been used by the Indians of the upper Rio Negro for millennia, with the caboclos having been using it for 200 years and the border military and prospectors for a decade and a half. The plant was also compared to eastern ginseng and amazonian guarana, with a perception of the difference between the male and female plant due to the sinuousness of the stem. According to the publication's text, the researchers who used the plant-based drink walked 3 and a half hours in the forest without any signs of tiredness.

According to Santos *et al*. (2005) the report had great repercussions in the locality, in the entire region and in the entire country. After this report, there was a lot of demand for the plant and the report itself was used as advertising for marketing the plant. However, in the state of Pará the use of the plant is scarce, not having the ethnobotanical tradition found in the Rio Negro Valley, where the tradition is not only maintained but also updated. Still according to Santos *et al*. (2005), the plant is considered as cultural heritage in the symbolic and natural sense in the entire Rio Negro Valley. It's relevant to note that the species is considered a sacred healing plant in the Santo Daime sect, in Vila do Céu do Mapiá, Purus river, near Boca do Acre. In this way, the collection, preparation and use are made according to the ritual procedures.

A. amazonicus is also used by the amazonian population to combat digestive problems, malaise and diarrhea (Rocha & Scarda, 2003), as an anti-inflammatory agent, antidote for snake venom (Rosas *et al*., 2007), colds and as a purifier (Ribeiro *et al*., 1999) (Table 1). The root has a purifying effect and the leaf powder is detersive and caustic and its new stems when beaten in water provide a sparkling drink due to the presence of saponin, hence the name Indian beer (Silva, 1977), being mainly used in popular medicine as antimalarial (Brandão *et al*., 1992; Hidalgo, 2003) (Table 1).

According to Rocha & Scarda (2003) according to popular medicine to ingest *A. amazonicus* tea, it is important to clean the part to be used (root or stem) and then to remove the outermost bark, so that you can use the bark between the bark and the wood. So, you must scrape the place and put the contents in a little water and let it season, beating with a fork or with the plant's own branch until it forms a foam, allowing it to rest for 15 to 20 minutes before consumption. Ingestion is done mainly before entering the forest, before heavy work and for the prevention and treatment of malaria (Santos *et al*., 2005) (Table 1).

In addition to the indications for use against malaria, *A. amazonicus* is also used for liver disorders, intoxications, gastritis, joint pain, kidney pain, such as depurative, purgative, diuretic, revitalizing, as a nerve tonic, for "woman inflammation", anemia and diabetes (Oliveira, 2004; Oliveira *et al*., 2011) (Table 1). In addition, other indications can be mentioned, such as memory, lack of appetite, constipation, prostate inflammation, and intoxication treatment (Oliveira, 2009) (Table 1).

A. amazonicus is considered a stimulating and vigorous plant (Santos *et al*., 2005, Oliveira *et al*., 2012) and from the barks a fortifying and aphrodisiac tonic is obtained (Berg, 1993; MEB, 1993; Santos *et al*. 2005; Oliveira *et al*., 2011) (Table 1). Another indications of popular use of *A. amazonicus* are the use of its roots indicated for the cure of colds and malaria (Lima, 2006) (Table 1). The roots are also used as purifiers

(Rodrigues, 1989; Vieira, 1992; Almeida, 1993; Oliveira *et al*.; 2011) and are also used in the treatment of gastrointestinal disorders, inflammation in general, rheumatism and other types of pain and fever (Santos, 2005; Rodrigues, 2006; Rodrigues *et al*., 2010) (Table 1). Another popular use is the powder from the leaves of that plant, which is indicated as a healer (Almeida, 1993; Berg, 1993) (Table 1).

The drink is also prepared with the *A. amazonicus* species in quilombola communities in the municipality of Oriximiná (Pará/Brazil) by the traditional method. The method consists of cleaning the vine and scraping the bark, then placing it in a container with water and shaking vigorously with a spoon until it forms an abundant and persistent foam. This formed foam is then removed and discarded, repeating this procedure six more times (Oliveira *et al*., 2011).

There is the possibility of using *A. amazonicus* to fight malaria both in the healing process and in an indirect way, preventing relapses, according to the uses reported by quilombolas related to fighting and preventing diseases (Table 1). The species is also used to combat pain and inflammation. It is used as a fortifier, stimulant and depurative and has the description of having an anabolic effect by individuals who consume the drink (Oliveira *et al*., 2011) (Table 1). In addition, it is important to note that the use of *A. amazonicus* by patients with malaria is not specifically aimed at curing, but at restoring energy (Santos *et al*., 2005).

According to the reports of the community in the Amazon region, the evidence strongly points to the *A. amazonicus* adaptogenic properties and this effect may be related to the high saponin content. According to studies, this class of substances has a proven adaptogenic effect, associated with an immunostimulating effect attributed to the triterpenes present such as betulinic acid (Oliveira *et al*., 2011; Oliveira *et al*., 2012).

Table 1 – Ethnobotanical properties of *Ampelozizyphus amazonicus*.

Ethnobotanical Properties				
Activity	**Used form**	**Part of the plant used**	**Who use**	**References**
Malaria fever	Sap	Root	Amazonian communites	Le Cointe (1947)
To prevent malaria	Beer	Root	Brazilian army	Institute pour Le Dévelopment
Stimulating and energetic, Purifying, To treat gastrointestinal disorders, inflammations and fever	Unknown	Root	Amazonian communities	Santos *et al*. (2005), Rodrigues (1989), Vieira (1992), Almeida (1993), Rodrigues (2006)
Healing agent	Powder	Leaves	Amazonian communities	Almeida (1993), Berg (1993)
Fortifying tonic, aphrodisiac and in cases of snake bites	Unknown	Bark	Amazonian communities	MEB (1993), Berg (1993), Santos *et al*. (2005), Brandão *et al*. (1992)
Gastritis, joint pain, "inflammation of women", anemia, diabetes, as a revitalize, depurative and diuretic	Unknown	Bark	Amazonian communities	Oliveira (2004)
To cure cold, to prevent malaria	Unknown	Unknown	Amazonian communities	Santos *et al*. (2005)
Stimulant	Drink with phloem roots and fresh stalk	Root, stalk	Amazonian communities	Santos *et al*. (2005)
Rheumatism, liver, aphrodisiac, pneumonia, worms, itching, pain, diarrhea, inflammation, wound, AIDS	Unknown	Unknown	Community in São Gabriel da Cachoeira, Amazonas	Santos *et al*. (2005)

Against malaria, liver problems, sleep disorders	Unknown	Unknown	Community in Manaus, Amazonas	Santos et al. (2005)
Against fever, tropical diseases	Unknown	Root	Local residents in Jaú National Park	Rodrigues (2006)
Gastrointestinal disorders	Unknown	Bark, root	Local residents in Jaú National Park	Rodrigues (2006)
Antiseptic to wounds	Bark with water resulting foamy preparation	Bark	Community in Colombia	Lopez *et al.* (2001)
Febrifuge	Unknown	Unknown	Community in Peru	Miliken (1997)
Stimulant, energetic and with property to increasing the resistence	Unknown	Unknown	Community in Rio Negro region, Amazonas	Santos *et al.* (2005)
To recover physical exhaustion, fatigue and hunger	Mixture with the roots and stems in the water	Root, stem	Community in São Gabriel da Cachoeira, Amazonas, indians, caboclos, soldiers in training in the jungle	Santos *et al.* (2005)
To combat digestive problems, malaise and diarrhea, anti-inflammatory agent, antidote for snake venom, colds and as purifier	Unknown	Root	Amazonian population	Rocha & Scarda (2003), Rosas *et al.* (2007), Ribeiro *et al.* (1999)
Antimalarial	Powder	Leaf	Amazonian population	Brandão *et al.* (1992), Hidalgo (2003)
Before heavy work, to prevent malaria	Tea	Root, stem	Amazonian population	Santos *et al.* (2005)
Liver disorders, intoxications, gastritis, joint pain, kidney pain, depurative, purgative, diuretic, revitalizing, nerve tonic, woman inflammation, anemia and diabetes	Unknown	Unknown	Unknown	Oliveira (2004), Oliveira *et al.* (2011)
Memory, lack of apetite, constipation, prostate inflammation and intoxication treatment	Unknown	Unknown	Unknown	Oliveira *et al.* (2009)
Stimulating and energetic, aphrodisiac	Unknown	Bark	Amazonian population	Santos *et al.* (2005), Oliveira *et al.* (2012), Berg (1993), MEB (1993), Oliveira *et al.* (2011)
To cure cold and malaria	Unknown	Root	Amazonian population	Lima (2006)
As purifier, to the treatment of gastrointestinal disorders, inflammations in general, rheumatism and other types of pain and fever	Unknown	Root	Amazonian population	Rodrigues (1989), Vieira (1992), Almeida (1993), Oliveira *et al.* (2011), Santos *et al.* (2005), Rodrigues (2006), Rodrigues *et al.* (2010)
Healer	Powder	Leave	Amazonian population	Almeida (1993), Berg (1993)
To fight malaria, to fight pain and inflammation, fortifier, stimulating and depurative	Drink with water	Bark	Quilombola community in Oriximiná, Pará	Oliveira *et al.* (2011), Santos *et al.* (2005)

Pharmacological Activities of *A. amazonicus*

According to Amaral *et al*. (2008), several pharmacological studies of *A. amazonicus* have been carried out. The main purpose of these studies is to check the effectiveness of the species used as a house made remedy.

Antiviral activity

Khan & Ather (2005) tested the methanol extract from the dry leaves of *A. amazonicus* against HSV1 (*Herpes Simplex* virus type 1) and *Poliovirus* (agent that causes polio in humans) (Table 2). The authors The authors assessed the antiviral activity of the extract through periodic inspection of viruses induced by cytopathic effects on culture. In the test of *A. amazonicus* extract against HSV1, complete cell destruction required 4 days. For *Poliovirus*, only 2 days were necessary for the extract of *A. amazonicus* to destroy it. The minimum inhibitory concentration (MIC) of the extract corresponded to complete inactivation of the virus infectivity. A MIC of 22Qg/mL of the studied extract of *A. amazonicus* was active against HSV1 but showed no activity against the Poliovirus.The authors were also able to conclude that the extract of *A. amazonicus* was active against the HSV1 virus (Khan & Ather, 2005).

Antibacterial and antifungal activities

Lopez *et al*. (2001) tested the antibacterial and antifungal actions of methanol dry leaf extract (1%w/v) of *A. amazonicus* using the disk diffusion assay method, and using gentamicin and nystatin as controls for the inhibition growth (Table 2). Antifungal and antibacterial activities have been studied against *Candida albicans* and *Bacillus subtilis*, *Streptococcus faecalis, Staphylococcus aureus* K147, *Escherichia coli* DC10, *Klebsiella pneumoniae, Pseudomonas aeruginosa* 187, *Salmonella typhimurium* and *Mycobacterium phlei*, respectively. The authors evaluated the results based on the evaluation of growth inhibition. These studies were also carried out in duplicate, one in the dark and the other under UV exposure to test the light activation in the extract activity. As a result, Lopez *et al*. (2001) were able to conclude that the methanolic extract at a concentration of 100mg/mL had no antibacterial or antifungal activity against the species of microorganisms studied, either in the dark or under UV activation (Table 2).

Kim *et al*. (2000) also used the methanolic extract of the leaves of *A. amazonicus* and also using the paper disk agar diffusion method only under anaerobic conditions (Table 2). The *in vitro* test was carried out through the growth inhibitory activity against the human intestinal bacteria *Bifidobacterium longum*. The authors applied a sample of this extract to a paper disc (20mg/disc) using a glass microcapillary. After evaporation of the solvent, the disc was placed on the agar surface inoculated with the bacteria test. It is important to note that the authors performed all tests in triplicate. In addition, all plates were incubated anaerobically at 37°C for 2 days. As a result, the authors were able to see that the extract strongly inhibited the growth of the *Bifidobacterium longum* bacteria under test.

Trypanocidal activity

Rosas *et al*. (2007) tested the crude extracts of hexane, ethyl acetate, ethanolic, methanolic and aqueous from the stems of *A. amazonicus* and their fractions were tested *in vitro* against the trypomastigote blood forms of *Trypanosoma cruzi*. The above authors performed the bioassays on infected blood of mice at the peak of parasitemia (7 days of *T. cruzi* infection) diluted to a concentration of 2 x 106 trypomastigote forms/mL. The extracts and fractions were tested at final concentrations of 100, 250 and 500μg/mL. Rosas *et al*. (2007) were able to conclude that all samples (extracts and fractions) had trypanocidal activity against the trypomastigote blood forms in the tested concentrations. The results showed, however, different levels of activity, with various extracts and fractions, exhibiting more than 50% of parasite lysis at the highest concentration (500μg/mL). Rosas *et al*. (2007) still claim that in some samples, although with less efficiency, presented active compounds, namely one of the fractions obtained from ethyl acetate and methanolic extracts whose trypanocidal activity was mainly due to betulinic acid, 3ß-hydroxylup-20 (29) -eno-27,28 -diioic and 2T, 3ß-dihydroxylup-20 (29) -eno-27,28-dioic acid (Table 2).

Antimalarial activity

Krettli *et al*. (2001) carried out experiments to assess the antimalarial capacity of *A. amazonicus* using blood from rodents and birds for the stages of *Plasmodium berghei* and *Plasmodium gallinaceum*, respectively. The authors used aqueous and ethanolic extracts from freshly ground roots and made purified fractions with or without saponins (Table 2). The above test results showed no activity. In addition, there was also no effect against blood stages of *Plasmodium falciparum* in *in vitro* cultures. The extracts and fractions were tested against sporozoites (invasion or development) in chickens infected with *P. gallinaceum* previously treated orally for 5 to 8 days with 200mL/kg of *A. amazonicus* samples. The aforementioned authors were able to conclude in the study that the freshly prepared ethanol from the extract reduced tissue parasitemia (condition of the parasite present in the tissue) by about 67%, while sulfadiazine (used as a reference medicine) reduced parasitemia in 97% host tissues tested.

Researchers from the Federal University of Minas Gerais (UFMG) together with other researchers from the Oswaldo Cruz Foundation (FIOCRUZ) carried out tests with the crude extract of the *A. amazonicus* bark, to verify its antimalarial activity in the blood phase of the disease with *in vivo* tests on rats and chickens infected with *P. falciparum, P. berghei* and *P. gallinaceum*. As a result, the extract showed no activity in the blood phase of the disease, however, it was observed that the crude extract of the barks inhibited the development of the sporozoite (Krettli, 2003) (Table 2). In the other way, the same author noted in a previous study that the aqueous extract works more to prevent than to treat the symptoms of the disease (Krettli, 2001). In this way, this plant has great medicinal potential for the treatment of malaria and needs studies aimed at its domestication.

In the studies by Andrade-Neto *et al*. (2008), the ethanolic extract of *A. amazonicus* was tested *in vitro* and the results were measured in the effect on the growth of liver cell schizonts (parasite form) (Table 2). The results of the study above showed that in cultures of HepG2 hepatoma cells infected with *P. berghei* sporozoites and incubated with *A. amazonicus* extracts, there were fewer parasites. This number was significantly lower than the parasites present in the control group. Still in the same study, the rats were previously treated with 100, 200 and 400mg of *A. amazonicus* per kilogram of body weight, for 6 days. These rats were later infected with sporozoites by exposure and by feeding in the laboratory. The results were evaluated daily by the authors by microscopy in search of invasion of blood cells and development of the parasite. The authors concluded that there was a reduction in parasitemia and mortality. In the second week of infection, the authors perceived that all untreated controls died, the treated mice had low parasitemia. It is important to note that some animals pretreated with higher doses were never infected, indicating that the extracts of *A. amazonicus* also had a prophylactic effect.

Several studies have reported the popular use of *A. amazonicus* in the treatment and prevention of malaria (Krettli & Andrade-Neto, 2004; Oliveira *et al*., 2012; Oliveira *et al*., 2015; Silva *et al*., 2009). According to Andrade-Neto *et al*. (2008), despite the absence of an effect of these plant extracts on the blood stage forms of Plasmodium (*in vivo* or in red blood cell cultures), this natural product has been shown to be effective in to control sporozoite-induced infection in mice. This study confirms that the *A. amazonicus* protects against natural infections, however, it does not cure vertebrates that have already been infected. In addition, the preventive activity of the use of the saracura-mirá species has been demonstrated both in vivo and *in vitro* against the sporozoite form of malaria contagion (Andrade-Neto *et al*., 2008). Even with the negative results for the activity against blood forms of the (Brandão, 1985; Andrade-Neto *et al*., 2008; Oliveira, 2009), some studies point to a prophylactic activity of the plant against malaria (Krettli *et al*., 2001; Andrade-Neto *et al*., 2008).

Immunobiologic and Antiinflammatory activity

Based on the reported properties of this plant and its uses in folk medicine, Peçanha *et al*. (2013) suggested in this study that *A. amazonicus* could improve the function of the immune system and alleviate inflammatory disorders caused by malaria. The authors investigated the toxicity of *A. amazonicus* and its effects on the immune system's response, as well as its anti-inflammatory

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properties. The effect of an aqueous extract of the plant on the immune response was investigated by measuring the immunoglobulin production induced by antigen immunization in mice infected with *Plasmodium chabaudi*. The treatment with the plant extract increased levels of antigen-specific IgM and IgG in immunized mice. During the study, the authors also realized that the response of B cells during malaria infection was also modified by the aqueous extract of *A. amazonicus*. The authors were able to conclude with the research that the aqueous extract of the plant has immunomodulatory properties, inducing a modified in vivo response of the B lymphocyte. In addition, the plant extract also has anti-inflammatory properties, which probably occur due to a reduction in cell migration and inhibition of the production of inflammatory mediators. Preliminary HPLC-ESI-MS/MS analysis of the aqueous extract of *A. amazonicus* reveals a complex saponin profile with a deprotonated molecule (Table 2).

Diuretic and antidiuretic activities

Diniz (2006) evaluated the diuretic activity of the ethanolic extract of the dry roots of *A. amazonicus* and the fraction of saponins obtained after partition and chromatography of the ethanolic extract in rats (Table 2). As a result, the author realized that the extract increased dieresis (Table 2). In the other way, the fraction of saponins decreased diuresis in a dose-dependent manner. In the experiment, the rats were previously kept under two conditions of hydration (12-hour water restriction or free access to water). The different concentrations of the ethanol extract and the fraction of saponins were also analyzed (Table 2). The dose of 150mg/kg of the extract caused a slight increase in the urine volume, when compared to the control group of rats (without expansion) and with expansion only with 0.9% NaCl. On the other hand, the fraction with saponins, even under water restriction, showed an inhibition of the increase, even if slight, in urinary volume. This inhibition was dose dependent and peaked at a dose of 200mg/kg of saponins. In the second experiment (rats with free access to water), the extract allowed an increase in diuresis produced by expansion with 0.9% NaCl. An effect similar to that observed in the first experiment, the fraction of saponins also had the same profile inhibiting the diuresis produced by the expansion with 0.9% NaCl in rats with free access to water. The author concluded that the maximum antidiuretic effect of the saponin fraction was observed at 90 minutes of expansion at concentrations of 50 and 1000mg/kg of *A. amazonicus* extract.

Diniz *et al*. (2009) showed in that a triterpene mixed with saponins isolated from the roots of *A. amazonicus* (SAPAaD) reduced the excretion of urine from normal mice in a dose-dependent manner (Table 2). According to Matsubara (2004), there is a need for the discovery of new oral antidiuretics to treat diseases such as diabetes insipidus and nephrogenic diabetes insipidus. However, investigations of other compounds than arginine vasopressin (AVP) or desmopressin are lacking. According to the same author, it is well known that diuresis is regulated by endogenous and exogenous compounds that act in several intra-renal sites influencing the formation of urine.

Diniz *et al*. (2012) investigated whether atrial natriuretic peptides (ANP) and renal ATPases would play a role in the antidiuresis induced saponins isolated from the roots of *A. amazonicus* in rats. To assess the effect of SAPAaD on furosemide-induced diuresis, Diniz *et al*. (2012) used Wistar rats received an oral loading dose of saline (0.9% NaCl, 4ml/100g body weight) to impose a uniform state of water and salt. The solution containing furosemide was administered 30min after the rats were treated orally with 50mg/kg of saponins isolated from the roots of *A. amazonicus*. The animals were housed individually in metabolic cages, and the urine volume was measured every 30min throughout the experiment (3h). To investigate the role of ANP and renal Na + pumps in the antidiuretic effects promoted by SAPAaD, the rats received the solution containing SAPAaD (50mg/kg). After 90min, urine and blood samples from the last 30min were collected. Kidneys and atria were also removed after previous anesthesia. As a result, Diniz *et al*. (2012) observed that saponins isolated from the roots of *A. amazonicus* inhibited diuresis induced by furosemide. In addition, the authors also concluded that the antidiuretic effect of saponins isolated from *A. amazonicus* roots may be due to an increase in renal activities of Na + - and (Na +, K +) - ATPases and/or a decrease in renal ANP.

Larvicidal activity

According to Jang *et al*. (2002) the methanolic extract of the leaves of *A. amazonicus* were placed in contact with groups of 25 larvae of the 4th instar of *Aedes aegypti* and *Culex pipiens pallens* (Table 2). Jang *et al*. (2002) assessed larvicidal activity 24 hours after treatment. The same authors were able to conclude in their studies that between these two species of larvae tested, only a moderate activity was observed in *C. pipiens pallens*, which reached 53.4% mortality with 400ppm of the stock solution of *A. amazonicus* extract.

Cytotoxic and antitumor activity

Lopez *et al*. (2001) evaluated the cytotoxicity of *A. amazonicus* leaf extract by monolayers of African green monkey kidney cells, which were exposed to sample dilutions (Table 2). The treated cells were examined microscopically, after a 24-hour incubation, they showed no toxic effects, such as cell damage or lysis.

In the studies by Rosa *et al*. (2007), the crude extracts of hexane, ethyl acetate, ethanolic, methanolic and aqueous from the stems of *A. amazonicus* and the compounds: 3ß-hydroxylup-20 (29) -ene- Acid 27, 28-dioic [compound 1] and 2T, 3ß-dihydroxilup-20 (29) -eno-27,28- dioic acid [compound 2], isolated from ethyl acetate extract were tested *in vitro* against SKBR-3 (human adenocarcinoma) and tumor cells of melanoma lineage (C-8161) by the diphenyltetrazolium bromide (MTT) method (Table 2). Rosa *et al*. (2007) were able to conclude that compound 1 showed selective cytotoxicity against SKBR-3, while ethyl acetate extract and compound 2 demonstrated this activity against both tumor cell lines (Rosas *et al*., 2007).

Adaptogenic and immunomodulatory activity

Among the properties of *A. amazonicus* in ethnopharmacological studies carried out in the Amazon region, it was demonstrated that the plant is also used as a stimulant and tonic (Oliveira *et al*., 2012), as well as fortifying and aphrodisiac (Oliveira *et al*., 2011). Based on this information, Siemens *et al*. (2016) inferred that this plant could promote a general increase in the immune response, and can act as an adaptogen. The adaptogens of this plant are be able increase an organism's ability to adapt to environmental factors and prevent damage from such factors (Panossian & Wagner, 2005). Adaptogens are interesting in increasing non-specific resistance against stressors, thus improving the ability to adapt to stress (Panossian *et al*., 1999).

In fact, it has already been demonstrated in studies by Peçanha *et al*. (2013) that *A. amazonicus* has immunomodulatory properties that induce an *in vivo* modification of the B lymphocyte response and anti-inflammatory properties, which corroborates the author's hypothesis that this plant acts as an adaptogen, increasing the function of the immune system.

According to Simen *et al*. (2016), *A. amazonicus* is a medicinal plant used in the Amazon region in beverage preparations with tonic, immunomodulatory and adaptogenic properties. Because of the growing interest in creating dietary supplements with these properties and providing a new functional ingredient, the barks of *A. amazonicus* were extracted and used in the study. The extract was dried into a powder.

In previous studies, the extract of powdered barks from *A. amazonicus* had an immunomodulatory effect because mice treated with this powder modified the function of B cells after infection with *P. chabaudi*. In addition, the treatment with the bark of the plant powder increased the levels of antigen-specific IgM and IgG in TNPficoll-immunized mice (Peçanha *et al.,* 2013). In another study, increased antibody production was observed in mice treated orally with red ginseng extract (Xu *et al*., 2012), which has been described as a prototypic adaptogenic substance.

In the studies by Simen *et al*. (2016) the potential immunomodulator of the plant was also investigated by its effects on the production of antibodies. During the investigation of the effect of the dry extract of the bark of *A. amazonicus* on the production of antibodies it was observed that it increased the basal levels of several types of antibodies (Table 2). No increase in antibody titers was observed after treatment with the barks extract dried into a powder in immunized mice. According to these results, Simens *et al*. (2016) suggested that dry extract from the bark of *A. amazonicus* could

be a new functional ingredient for food applications or pharmaceutical products.

Still, according to the aforementioned authors, the results are in accordance with the description of adaptogen plants with compounds that increase non-specific resistance against stressors, improving the ability to adapt to stress related to the increase in antibodies promoted by the plant (Panossian *et al*., 1999). Siemens *et al*. (2016) observations also corroborate the popular use of *A. amazonicus* bark extract as a stimulant and energizer (Oliveira *et al*., 2012) and as a fortifying tonic (Oliveira *et al*., 2011).

Table 2 – Pharmacological properties of *Ampelozizyphus amazonicus*.

Pharmacological Properties			
Activity	**Related metabolite**	**Used form**	**References**
Antiviral activity	Unknown	Methanolic extract from the dried leaves	Khan & Ather (2005)
Antibacterial and antifungal activity	Unknown	Methanolic extract from the dried leaves	Kim *et al*. (2000), Lopez *et al*. (2001)
Trypanocidal activity	Betulinic acid, 3ß-hydroxylup-20 (29) -eno-27,28 -diioic and 2T, 3ß-dihydroxylup-20 (29) -eno-27,28-dioic acid	Ethyl acetate and methanolic extract	Rosas *et al*. (2007)
Antimalarial activity	Unknown	Aqueous and ethanolic extracts from de roots, crude extract of the barks	Krettli *et al*. (2001), Krettli (2003), Andrade-Neto *et al*. (2008)
Immunobiologic and antiinflammatory activity	Complex saponin	Aqueous extract	Peçanha *et al*. (2013)
Diuretic and antidiuretic activity	Saponins, Triterpenes mixed with saponins	Ethanolic extract of the dried roots	Diniz (2006), Diniz *et al*. (2009), Diniz *et al*. (2012)
Larvicidal activity	Unknown	Methanolic extract of the leaves	Jang *et al*. (2002)
Cytotoxic and antitumor activity	Unknown, 3ß-hydroxylup-20 (29) -ene- Acid 27, 28-dioic and 2T, 3ß-dihydroxilup-20 (29) -eno-27,28- dioic acid	Leaf extract, crude extract of hexane, ethyl acetate, ethanolic, methanolic and aqueous	Lopez *et al*. (2001), Rosas *et al*. (2007)
Adaptogenic and immunomodulatory activity	Unknown	Barks extract dried into a powder	Siemens *et al*. (2016)

Conclusion

It is important to emphasize that the ethnobotanical study is essential for the pharmacological study because it serves as a basis for initial pharmacological researches. Despite scientific studies be demonstrating antiviral, antibacterial and antifungal, trypanocidal, antimalarial, immunobiologic and anti-inflammatory, diuretic and antidiuretic, larvicidal, citotoxic and antitumor activities as well as adaptogenic and immunomodulatory activities of the *Ampelozizyphus amazonicus* that could be useful in the treatment of several human diseases, more clinical studies in humans are necessary. There is a need for these studies are precisely to confirm all plant properties and to avoid possible side effects in humans. In addition, protocols for the use of the plant are necessary in relation to the quantities and concentrations of the formulations presented.

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