Ethnobotanical, Medical, Therapeutical and Pharmacological Study of *Carapa guianensis* Aublet – a Review

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ABSTRACT – *Carapa guianensis*, popularly known as andiroba, belongs to the Meliaceae family of plants. The oil extracted from the andiroba seed is thick, dark yellow in color and is used as a raw material for illumination lamps and in the cosmetics industry for the manufacture of lotions, shampoos, creams and soaps. In addition, andiroba also has therapeutic and pharmacological attributes, with genotoxic, anthelmintic, healing, trypanocidal, leishmanicidal, repellent, larvicidal, anti-allergic, anti-inflamatory, acaricidal, antimalarial, antioxidant and antitumor. The present work reviewed the *Carapa guianensis* medical, therapeutic and pharmacological properties. For genotoxic activity, no toxicity was found for the DNA of the tested animals. The compounds responsible for healing activity in seed oil were taninins, saponins and alkaloids. No compounds responsible for trypanocidal activity were found. The compounds responsible for the leishmanicidal activity were fatty acids and phenolic compounds. No compounds responsible for repellent and larvicidal activity were found. Tetranortriterpenoids was found as responsible for the anti-allergic and anti-inflammatory activity. No compounds responsible for acaricidal activity were found. 6α-acetoxygedunin was the compound responsible for the antimalarial activity. In the antioxidant and antitumor activity from the seed oil were not found compounds involved.

Keywords: Ethnobotany of *Carapa guianensis*; pharmacological properties of andiroba; therapeutic and pharmacological activity of *Carapa guianensis*.

Estudo Etnobotânico, Médico, Terapêutico e Farmacológico de *Carapa guianensis* Aublet – uma Revisão

RESUMO – A *Carapa guianensis*, conhecida popularmente como andiroba, pertence à família das plantas Meliaceae. O óleo extraído da semente da andiroba é espesso, de cor amarelo-escura, e é utilizado como matéria-prima para iluminação de lamparinas e na indústria de cosméticos para fabricação de loções, xampus, cremes e sabonetes. Além disso, a andiroba também possui atributos terapêuticos e farmacológicos, com propriedades genotóxicas, anti-helmínticas, cicatrizantes, tripanocidas, leishmanicidas, repelentes, larvicidas, antialérgicas, anti-inflamatórias, acaricidas, antimaláricas, antioxidantes e antitumorais. O presente trabalho revisou as propriedades médicas, terapêuticas e farmacológicas de *Carapa guianensis*. Quanto à atividade genotóxica, não foi encontrada toxicidade ao DNA dos animais testados. Os compostos responsáveis pela atividade curativa no óleo de semente foram taninos, saponinas e alcalóides. Não foram encontrados compostos responsáveis pela atividade tripanocida. Os compostos responsáveis pela atividade leishmanicida foram ácidos graxos e compostos fenólicos. Não foram encontrados compostos responsáveis pela atividade repelente e larvicida. Tetranortriterpenóides foram considerados responsáveis pela atividade anti-alérgica e anti-inflamatória. Não foram encontrados compostos responsáveis pela atividade acaricida. 6α-acetoxiquedunina foi o composto responsável pela atividade antimalárica. Na atividade antioxidante e antitumoral do óleo de semente não foram encontrados compostos envolvidos.

Palavras-chave: Etnobotânica de *Carapa guianensis*; propriedades farmacológicas da andiroba; atividade terapêutica e farmacológica de *Carapa guianensis*.

Estudio Etnobotánico, Médico, Terapéutico y Farmacológico de *Carapa guianensis* Aublet – una Revisión

RESUMEN – *Carapa guianensis*, conocida popularmente como andiroba, pertenece a la familia de plantas Meliaceae. El aceite extraído de la semilla de andiroba es espeso, de color amarillo oscuro y se utiliza como materia prima para la iluminación de lámparas y en la industria cosmética para la fabricación de lociones, champús, cremas y jabones. Además, la andiroba también tiene atributos terapéuticos y farmacológicos, con propiedades genotóxicas, antihelmínticas, cicatrizantes, tripanocidas, leishmanicidas, repelentes, larvicidas, antialérgicas, antiinflamatorias, acaricidas, antipalúdicas, antioxidantes y antitumorales. El presente trabajo revisó las propiedades médicas, terapéuticas y farmacológicas de *Carapa guianensis*. En cuanto a la actividad genotóxica, no se encontró toxicidad del ADN en los animales probados. Los compuestos responsables de la actividad curativa en el aceite de semilla fueron taninos, saponinas y alcaloides. No se encontraron compuestos responsables de la actividad tripanocida. Los compuestos responsables de la actividad leishmanicida fueron los ácidos grasos y los compuestos fenólicos. No se encontraron compuestos responsables de la actividad repelente y larvicida. Los tetranortriterpenoides se consideraron responsables de la actividad antialérgica y antiinflamatoria. No se encontraron compuestos responsables de la actividad acaricida. La 6α-acetoxiquedunina fue el compuesto responsable de la actividad antipalúdica. En la actividad antioxidante y antitumoral del aceite de semilla, no se encontraron compuestos involucrados.

Palabras clave: Etnobotánica de *Carapa guianensis*; propiedades farmacológicas de andiroba; actividad terapéutica y farmacológica de *Carapa guianensis*.

Introduction

Plant materials are used in whole world, such as home remedies, medicines and raw materials for the pharmaceutical industry, and represent a substantial part of the world medicine market (Sivapalan, 2013).

The andiroba (Aubl.) is a large tree native to the Amazon region, which is widely used in traditional medicine in the region (Lorenzi, 1998; Vieira, 1992). This specie is belonging to the Meliaceae family and is a large neotropical tree. It can be found in the north of South America, Central America, the Caribbean, and Sub-Saharan Africa (Costa-Silva *et al*., 2008; Henriques & Penido, 2014). There are in the Amazon with the name andiroba, two species of the family Meliaceae, *C. guianensis* A. and *Carapa procera* DC, occurring mainly in lowlands and flooded areas throughout the amazon region. Despite being known as andiroba, this tree also has several other popular names. In Brazil, it is known as andiroba, andirobinha, andiroba branca, andiroba-do-igapó, carape, jandiroba, penaiba. In South America it is known as karapa and in England it is known crab wood.

Andiroba is a word comes from the Tupi-Guarani and means bitter taste that. The tree is widely distributed along the Atlantic coast of Central America, in South America from Colombia to Brazil, Ecuador and in Amazonian Peru (Pennington *et al*., 1981). It reaches up to 30m in height, with white flowers, slightly fragrant, round, large and dark leaves and brown colored seeds and angled side (Enriquez *et al*., 2003).

In Guyana, Aublet was the first to describe the andiroba tree in 1775. The use of andiroba spread widely to Guatemala, Peru, Colombia, Panama, Venezuela, reaching Brazil. In Brazil, the development was such that the first andiroba oil industry was established, specifically in the city of Cametá, in the state of Pará (Leite, 1997). The plant has multiple uses with oil extracted from seeds being and wood the most relevant products. The oil, with international demand, is one of the best selling drugs in the Amazon, being exported to Europe and the United States. Despite this, there are no large areas for oil extraction and this action is carried out by small groups of families who harvest the fruits in the region (Amaral & Fierro, 2013).

Compounds like fatty acids, limonoids, triterpenes, steroids, coumarins, flavonoids, and diglycerides have been isolated from several parts of *C. guianensis* (Ambrozin *et al*., 2006). *C. guianensis* seed oils are rich source in limonoids, highly oxygenated tetranortriterpenoid compounds, that are reported to present several biological activities, such as antifungal, bactericidal, antifeedant, antimalarial, antiviral, anti-inflammatory, and growth-regulator on insects

(Nayak *et al*., 2010; Miranda Júnior *et al*., 2012), besides several medicinal effects in animals and humans (Henriques & Penido, 2014).

Seven limonoids was identified in oil sample of *C. guianensis* by Ambrozin *et al*. (2006): 17β-hydroxyazadiradione, gedunin, 6α-acetoxygedunin, 7deacetoxy-7-oxogedunin, 1,2-dihydro-3β-hydroxy-7-deacetoxy- 7-oxogedunin, methyl angolensate, and xyloccensin K, by chromatographic. The therapeutic effects of the oil are related to these bioactive compounds (Henriques & Penido, 2014).

Thus, the objective of this review was to report the medicinal, therapeutic and pharmacological properties of *Carapa guianensis*. For this review about *Carapa guianensis* databases such as Google, Scielo, Periódicos Capes and Coordination for the Improvement of Higher Education Personnel (CAPES) thesis database were consulted, based on the plant's ethnobotanical and pharmaceutical attributions.

Ethnobotanical study: Popular and/or traditional uses

The ethnopharmacological approach is essential precisely because it is through it that it is possible to investigate how medicinal plants and combine information acquired in local communities that make use of medicinal flora with phytochemical and pharmacological studies carried out in specialized laboratories. This tactic is allowed the selection of plant species and constitutes a precious shortcut for the discovery of new drugs (Koehn *et al*., 2005; Braz-Filho, 2010).

In traditional herbal medicine from the Amazon for the treatment of skin diseases crude andiroba (*C. guianensis*) oil is recommended due to anti-microbial and anti-inflammatory properties (Nayak *et al*., 2011). Against muscle strains and other skin tissue changes, the oil is used in small amounts (Pinto, 1963).

Andiroba oil is extremely bitter and is used as a fuel in lighting and to prepare soap and cosmetics. In addition, the oil is also used as an insect repellent in some indigenous groups and traditional populations (Pinto, 1963). Andiroba candles were recently launched on the market by the Osvaldo Cruz Foundation with the aim of repelling mosquitoes that transmit diseases such as dengue and malaria. In the fight against bacterial infections, tea from the bark and flowers can also be used. Heartwood is commonly used as a fungicide (Hammer & Johns, 1993).

Andiroba oil is also used in folk medicine as a fever, painkiller, antibacterial and antiparasitic, as well as to treat upper respiratory tract infections, dermatitis, abrasions (Tropical Plant Database, 2012). Very commercialized in the Amazon, andiroba seed produces oil with many medicinal properties. In the 70's there was a demand of up to 350 tons/year for export between Europe and the United States and its industrialization originated in the city of Cametá/PA (Shanley *et al*., 1998).

The oil is used by extractivists, Indians and riverside dwellers for various purposes, such as snake bites, scorpions and bees, to combat worms and protozoa, arthritis, tetanus, rheumatism, kidney infection, hepatitis, jaundice and other liver infections, dyspepsia, fatigue muscle, foot pain, colds, flu, cough, psoriasis, scabies, ringworm, leprosy, malaria, tetanus, herpes and severe ulcers, and to cure mumps. In order to have a repellent action against insects, the oil is mixed with the annatto dye (*Bixa orellana* L.) by the indigenous people. In contrast, the Mundurucus Indians used oil to mummify the enemies' heads. The Wayãpi and Palikur Indians used the oil to remove ticks and lice. For combating fever, worms, bacteria, tumors, such as antidiarrheal, antianemic, against bronchitis and respiratory tract infections, analgesic and for use as balsamic, the bark and flower tea is generally widely used. Mixed with other repellent plants such as neem, eucalyptus and citronella, andiroba extract is indicated to repel ants, termites, spiders, cockroaches and moths (Pio Correa, 1931; Prance & Silva, 1975; Berg, 1982; Rodrigues, 1989; Shanley *et al*., 1998; NatuScience, 2000; Revilla, 2000; Sampaio, 2000).

The natives of the Amazon rainforest have for many years used plant parts of the *C. guianensis*, as well as their derivatives for different purposes. For the treatment and treatment of illnesses, a plant has been used in isolation or associated with other drugs/chemicals (Ministério da Saúde, 2014).

In the researched literature, reports were found of the realization of a medicinal soap containing crude andiroba oil, wood ash and cocoa skin residues made by the caboclos, traditional inhabitants of the Amazon forest who live on the river bank. This product was recommended for the treatment of skin diseases. Applied directly on the joints, andiroba oil is related to the relief of arthritis

pain. The oil is commonly used to treat arthritis on the Marajó island/PA. When mixed with hot water and human milk, it is used in drops for ear infections (Hamer & Johns, 1993; Nayak *et al*., 2010; Nayak *et al*., 2011).

The oil extracted from the seeds has the most ethnobotanical properties besides the popular use of bark, flower, leaf and seed in the form of tea or by decoction. Table 1 is an update from the Ministério da Saúde (2015).

Table 1 – Ethnobotanical properties of *Carapa guianensis* Aublet.

Indications in Popular Medicinal			
Activity	**Used form**	**Part of the plant used**	**Source**
Analgesic, pain relief in cases of uterine cancer, arthritis, rheumatism	Bark	Stalk	Gomes (2010), Tapim *et al*. (2008), Hammer & Johns (1993), Tapim *et al*. (2008), Silva (2002)
Anti-inflammatory, throat inflammation, bruises, skin inflammations, splenitis	Bark	Stalk	Barros (2011), Pessoa (2009), Gonçalves (2007), Hammer & Johns (1993), Tappin *et al.* (2008), Costa-Silva *et al*. (2006), Hammer & Johns (1993), Tappin *et al*. (2008), Pessoa (2009), Tappin (2007), Costa-Silva *et al*. (2006), Gonçalves (2007), Silva (2002), Tavares (2005)
Antipyretic	Bark	Stalk	Gomes (2010), Tavares (2005), Oliveira *et al*. (2003)
Healing, used in general wounds and insect bites	Bark	Stalk	Barros (2011), Hammer & Johns (1993), Tappin *et al*. (2006), Pessoa (2009), Tappin (2007), Costa-Silva *et al*. (2006), Gonçalves (2007), Silva (2002)
Antiseptic	Bark	Stalk	Barros (2011)
Against infections, airway, respiratory infections, skin infections, ear infections, bacterial infections, hepatitis, fungicide	Bark	Stalk	Pessoa (2009), Gomes (2010), Tavares (2005), Almeida *et al*. (2012), Tappin *et al*. (2008), Tavares (2005), D'Alessandro (2008), Tavares (2005), Hammer & Johns (1993)
Insect repellent, insecticide	Bark	Stalk	Tappin *et al*. (2008), Costa-Silva *et al*. (2006), Gonçalves (2007), Tavares (2005), Barros (2011)
Anthelmintic, antiparasitic, worms, scabies (canine)	Bark	Stalk	Carvalho (2011), Tavares (2005), Gomes (2010), Silva (2002), Ritter *et al*. (2012)
Antianemic, antidiarrheal, reduces blood glucose level (diabetes), digestive stimulant	Bark	Stalk	Gomes (2010), Hammer & Johns (1993), Tappin *et al*. (2008), Tappin (2007), Gomes (2010), Tavares (2005), Tappin *et al*. (2008), Tappin (2007), Hammer & Johns (1993), Tappin (2007)
Analgesic, pain relief in cases of rheumatism, skin problems, bruises, antipyretic, healing, pharyngitis, against intestinal worms, insect repellent	Leaf	Leaf	Brito *et al*. (2006), Silva (2002), Nayak *et al*. (2010), Brito *et al*. (2006), Nayak *et al*. (2010), Oliveira *et al*. (2003), Brito *et al*. (2006), Brito *et al*. (2006), Nayak *et al*. (2010), Silva (2002), Silva (2002)
Analgesic, pain relief in cases of arthritis, anti-inflammatory, bruises, antipyretic, healing, used in cuts, insect bites, emollient, against bacterial infections, insect repellent	Seed	Seed	Hammer & Johns (1993), Hammer & Johns (1993), Pessoa (2009), Ritter *et al*. (2012), Monteiro *et al*. (2011), Pessoa (2009), Oliveira *et al*. (2003), Ritter *et al*. (2012), Monteiro *et al*. (2011), Pessoa (2009), Silva *et al*. (2004), Prophiro *et al*. (2012), Silva *et al*. (2004), Prophiro *et al*. (2012), Silva *et al*. (2004), Prophiro *et al*. (2012), Silva *et al*. (2004), Prophiro *et al*. (2012), Silva *et al*. (2004), Prophiro *et al*. (2012), Silva (2002), Monteiro *et al*. (2011)

Analgesic, pain relief in cases of uterine cancer, rheumatism, anti-inflammatory, throat inflammation, bruises, skin inflammations, including psoriasis, muscle tensions, arthritis	Oil	Seed	Chicaro (2009), Santos *et al*. (2012), Ambrozin *et al*. (2006); Silva *et al*. (2009), Silva *et al*. (2012), Mirada Júnior *et al*. (2012), Costa-Silva (2006), Penido *et al*. (2006), Penido *et al*. (2005), Hammer & Johns (1993), Tappin *et al*. (2008), Tappin (2007), Sehorini (2010), Costa-Silva *et al*. (2007), Hammer & Johns (1993), Tappin *et al*. (2008), Tappin (2007), Sehorini (2010), Costa-Silva *et al*. (2007), D'Alessandro (2009), Nayaki *et al*. (2010), Menezes (2008), Penido *et al*. (2006), Penido *et al*. (2005), Andrade *et al*. (2001), Barros *et al*. (2012), Barros (2011), Andrade (2008), Farias *et al*. (2010), Farias *et al*. (2007), Farias (2007), Penido *et al*. (2006), Penido *et al*. (2005), Brito *et al*. (2006), Silva (2002), Souza Júnior *et al*. (1999), Brito *et al*. (2001), Medonça & Ferraz (2007), Tappin (2007), Brito (2006), Silva (2002), Brito *et al*. (2001), Hammer & Johns (1993), Miranda Júnior (2010), Barros (2011), Tanaka *et al*. (2011), Pessoa (2009), D'Alessandro (2008), Nayak *et al*. (2010), Nayak *et al*. (2011), Menezes (2008), Brito (2006), Silva (2002), D'Alessandro (2008), Nayak *et al*. (2010), Nayak *et al*. (2011), Menezes (2008), Pinto (1963), Hammer & Johns (1993)
Antipyretic, healing, used in general wounds, insect bites, ulcers, bactericide, fungicide	Oil	Seed	Andrade *et al*. (2001), Barros *et al*. (2012), Chicaro (2009), Barros (2011), Mendonça & Ferraz (2007), Farias *et al*. (2010), Farias *et al*. (2007), Farias (2007), Miranda Júnior *et al*. (2012), Brito *et al*. (2001), Andrade *et al*. (2001), Hammer & Johns (1993), Miranda-Júnior (2010), Barros (2011), Mendonça & Ferraz (2007), Andrade (2008), Tanaka *et al*. (2011), Tappin *et al*. (2008), Golynski (2003), Nayak *et al*. (2010), Nayak *et al*. (2011), Mendonça *et al*. (2005), Brito *et al*. (2006), Silva (2002), Brito *et al*. (2001), Chicaro (2009), Chicaro (2009), Barros (2011), Farias (2007)
Against infections Respiratory tract infections, skin infections, ear infections, bacterial infections, insect repellent, insecticide, anthelmintic, antiparasitic, lice and tick, antidiarrheal, reduces blood glucose level (diabetes)	Oil		Chicaro (2009), Chicaro (2009), Silva (2002), Hammer & Johns (1993), Tappin *et al*. (2008), Tappi (2007), Sehorini (2010), Nayak *et al*. (2010), Barros *et al*. (2012), Barros (2011), Farias *et al*. (2010), Farias *et al*. (2007), Farias (2007), Santos *et al*. (2012), Ambrozin *et al*. (2006), Silva *et al*. (2009), Mirada Júnior *et al*. (2012), Menezes (2008), Hammer & Johns (1993), Barros *et al*. (2012), Chicaro (2009), Barros (2011), Medonça *et al*. (2007), Andrade (2008), Tanaka *et al*. (2011), Tappin *et al*. (2008), Farias *et al*. (2010), Farias *et al*. (2007), Farias (2007), Tappin (2007), Senhorini (2010), Dantas (2009), Miranda Júnior *et al*. (2012), D'Alessandro (2008), Costa-Silva (2006), Golynski (2006), Nayak *et al*. (2010), Nayak *et al*. (2011), Menezes (2008), Silva (2002), Freire *et al*. (2006), Ribas & Carreño (2010), Ambrozi *et al*. (2006), Silva *et al*. (2009), Miranda Júnior *et al*. (2012), Andrade *et al*. (2001), Brito *et al*. (2001), Chicaro (2009), Santos *et al*. (2012), Ambrozin *et al*. (2006), Silva *et al*. (2009), Miranda Júnior *et al*. (2012), Mendonça *et al*. (2006), Pessoa (2009), Tappin *et al*. (2008), Farias *et al*. (2008), Senhorini (2010), Costa-Silva *et al*. (2007), Brito *et al*. (2001), Mendonça *et al*. (2007), Tappin *et al*. (2008), Senhorini (2010), Costa-Silva *et al*. (2007)

Snake bites, scorpions and bees, to combat worms, ringworms, protozoa, leprosy, malaria, arthritis, tetanus, herpes, rheumatism, kidney infection, hepatitis, jaundice and other liver infections, dyspepisia, fatigue muscle, foot pain, colds, flu, cough, psoriasis, scabies, severe ulcers and to cure mumps	Oil	Seed	Pio Correa (1931), Prance & Silva (1975), Berg (1982), Rodrigues (1989), Shanley *et al.* (1998), NatScience (2000), Revilla (2000), Sampaio (2000)
To mummify enemies'heads, to remove ticks and lice, to combating fever, tumors, such as antidiarrheal, antianemic, against bronchitis and respiratory tract infections, analgesic, balsamic	Oil	Seed	Pio Correa (1931), Prance & Silva (1975), Berg (1982), Rodrigues (1989), Shanley *et al.* (1998), NatScience (2000), Revilla (2000), Sampaio (2000)
Analgesic, bronchitis, antipyretic, against infections, respiratory tract infections, bacterial infections, anthelmintic, worms, antidiarrheal, antianemic, against tumors	Oil	Flower	Gomes (2010), Gomes (2010), Gomes (2010), Pessoa (2009), Gomes (2010), Gomes (2010), D'Alessandro (2008), Carvalho (2011), Gomes (2010), Gomes (2010), Gomes (2010), Gomes (2010)
Healing used in general wounds, prevention of skin diseases, insect repellent			Tanaka *et al.* (2012), Tanaka *et al.* (2012), Tanaka *et al.* (2012)

Fonte: Modified and updated from Ministério da Saúde (2015).

Medicinal, Therapeutical and Pharmacological Properties

Studies have reported several properties produced by the seed oil from *C. guianensis* and used in folk medicine, such as treating fever and rheumatism, antiallergic, analgesic, chemotherapeutic, anti-inflammatory effects (Penido & Costa, 2005; Silva *et al.*, 2015) and is effective against arthritis (Costa-Silva *et al.*, 2008). This especie has also acaricidal and insect repellent action (Moit *et al.*, 2004; Farias *et al.*, 2009). The infusion prepared with the bark and flowers of *C. guianensis* is used both as an anthelmintic and wound-healing agent in humans (Carvalho *et al.*, 2012).

Andiroba oil has some proven properties such as acting as an insect repellent (Freire *et al.*, 2006), controlling mites (Farias *et al.*, 2007) and fighting intestinal sepsis (Teixeira *et al.*, 2012). The same has a dark yellow appearance in color and is thick, generally used for lighting and cosmetics in the lotions, shampoos, creams and soaps industry (Tropical Plant Database, 2012).

The plant's oil is also well documented as antiallergic (Penido *et al.*, 2006a), anti-inflammatory (Penido *et al.*, 2006b) and antiplasmodial (Miranda Jr. *et al.*, 2012). In the homeopathic pharmaceutical industry, the oil is marketed in capsule form. It is used for diabetes and rheumatism, as well as in the manufacture of medicinal soaps. In addition, according to popular sellers in the markets, this oil has a supposed sunscreen activity, protecting the skin from sun damage. Therefore, it could be used for the prevention of skin cancer. However, studies have shown that andiroba oil did not show photoprotective activity (Ferrari *et al.*, 2007).

The manufacture of insect repellent candles is done through the remaining residues of oil extraction from the seeds. These are popularly used against *Anopheles* and *Aedes aegypti* mosquitoes, which transmit malaria and dengue, respectively (Mendonça *et al.*, 2005).

The essential oil extracted from *C. guianensis* is used industrially in the production of candles, shampoos, soaps and repellents (Pastore Junior & Borges, 1998; 1999). Studies have reported several effects produced by this plant, such as antiallergic and analgesic (Penido *et al.*, 2006a), acaricidal action (Farias *et al.*, 2009), anti-inflammatory effect (Penido *et al.*, 2006b) and insect repellent action (Miot *et al.*, 2004; Mendonca *et al.*, 2005). In addition, tea made from the *C. guianensis* bark and flowers is used both as an anthelmintic and as a curative agent in humans (Boufleuer, 2004).

According to Henriques & Penido (2014), *C. guianensis* it is used in popular medicine in Brazil and other countries that abandon the Amazon rainforest. Including seed oil, almost all parts of the andiroba tree are used. These parts are used to treat inflammations and infections. Regarding the compounds isolated from *C. guianensis*, they were attributed to the presence of limonoids, which are tetranortriterpenoids. The oil from the seeds of *C. guianensis* contains different tetranorthriterpenoids, including 6α <0215> -acetoxygedunine, 7-deacetoxy-7-oxogedunine, andirobin, gedunine and methyl angolensate.

The oil also contains linoleic acid which lowers cholesterol levels and blood pressure and is beneficial in preventing cancer. In addition, it also contains meliacins, a group of substances that gives the oil a bitter taste and has antimalarial and antiparasitic activities. Also, the limonoids present in the *C. guianensis* oil are anti-inflammatory, insect repellents and anti-tumor properties (Martinborough, 2002; Rain-Tree, 2014).

Therapeutic effect against oral mucositis

As the common and clinically significant response to the effect of anticancer chemotherapy and therapy to oral mucositis has been a challenge for many patients (Cinausero *et al*., 2017). The discontinuation of antineoplastic treatment can occur in extremely severe cases, which can affect the patient's quality of life (Keefe *et al*., 2007, Sonis, 2009). According to Sonis (2013), the stages of mucositis progression are: initiation, positive regulation or activation, signal amplification, ulceration and healing.

For the treatment of oral mucositis, including basic oral care such as combining flossing, use of growth factors and cytokines, use of anti-inflammatory and antimicrobial agents, use of coating agents, anesthetics and analgesics, use of therapies such as laser, light, cryotherapy. With these actions, researchers try to minimize the side effect caused by chemotherapy and/or radiothe-rapy and also by the Multinational Association for the Support of Cancer together with the International Society of Oral Oncology (MASCC/ISOO) there was the recent publication of the Clinical Practice Guidelines for oral mucositis (Lalla *et al*., 2014).

To prevent and treat oral mucositis, phytotherapy is a new line of research that has been extensively studied. Some of the herbal medicines that have already been tested in an oral mucositis model experiment like Chamomile (*Matricaria chamomilla*) (Elad *et al*., 2013), turmeric (*Curcuma longa* L.) (Hawley *et al*., 2014), bee honey (Mardani *et al*., 2016), cumin (*Carum carvi* L.) (Tanideh *et al*., 2013) and marigold (*Calendula officinalis*) (Yarom *et al*., 2013) and all showed significant results. However, needing a more in-depth study of adverse effects, drug interactions and toxicity, in addition to clinical factors, trials as all compounds had limitations (Henriques & Penido, 2014).

Andiroba oil, obtained by processes such as pressing seeds, has been used in traditional medicine for its anti-inflammatory and analgesic activities, both properties are essential in the treatment of oral mucositis. In addition, the plant also has antimicrobial, antiallergic and parasiticidal properties that are effective in skin and muscle disorders (Penido *et al*., 2006).

Those responsible for antiseptic, anti-inflammatory, curative and insecticidal activities in phytotherapeutic studies were the limonoid and triterpene compounds (tetranortriterpenoids), andiroba oil and bark (Nayak *et al*., 2011; Costa-Silva *et al*., 2006). One of the advantages of using phytotherapy is the improvement of symptoms and reduced costs (Tappin *et al*., 2008). Recent experimental studies on the administration of andiroba sseed oil related to the acute and subchronic toxicity of *C. guianesis* concluded that they did not produce toxic effects on rats or offspring (Costa-Silva *et al*., 2006; Miranda Júnior *et al*., 2012). Wanzeler *et al*. (2017) investigated the healing activity of andiroba against oral mucositis induced by 5-fluorouracil in golden Syrian hamsters. As a result, the authors observed that treatment with 100% concentration of andiroba oil reduced the degree of oral mucositis in relation to other groups. Andiroba oil in both concentrations was not cytotoxic, but treatment with 100% andiroba oil showed genotoxic potential. Thus, the authors concluded that the frequent administration of andiroba oil accelerated the healing process in an experimental model of oral mucositis induction using 5-fluorouracil. However, the genotoxicity of andiroba oil in other cellular systems and under other conditions is being tested.

Genotoxic activity

The use of natural products in traditional Brazilian phytomedicine has been widely accepted

and prescribed. This is done mostly in poorer areas, such as the Amazon and the Northeast. Thus, in drug discovery studies, the pharmaceutical potential of Brazilian herbs must be considered (Dutra *et al*., 2016). Unlike allopathy, traditional drug use is apparently considered safe. In most cases, the toxicity of traditional herbal medicines has not been fully assessed, although medicinal plants can be extremely harmful to human health. Plants often used in folk medicine according to some studies have revealed that they are potentially genotoxic (Ananthi *et al*., 2010; Regner *et al*., 2011).

According to Arrebola *et al*. (2012) a genotoxicity study was found for *C. guianensis* seed oil. In this study, Balb/c mice were treated daily for 14 days with seed oil at doses of 400, 1,000 or 2,000mg/kg. The animals were observed twice a day. Then, after sacrificing the animals, the bone marrow of the femur was extracted and evaluated according to the micronucleus cytogenetic technique. According to the aforementioned authors, there were no deaths or clinical symptoms of toxicity during the study. Symptoms were absent as: presence of lesions, respiratory alteration, nervous, cardiovascular, gastrointestinal system, skin condition, hair, coloration of mucous membranes and eyes and presence of polychromatophilic and normochromatophilic erythrocytes. An absence of genotoxic and cytotoxic effects was observed as there was no statistical difference between the treated and control groups regarding the parameters evaluated (Table 2).

Table 2 – Medicinal, therapeutical and pharmacological properties of *Carapa guianensis*.

Medicinal, Therapeutical and Pharmacological Properties				
Activity	**Related metabolite**	**Part of the plant used**	**Used form**	**Source in Literature**
Anthemintic and wound-healing agent in humans	Unknown metabolite	Bark and flower	Infusion	Carvalho *et al*. (2012)
Insect repellent, controlling mites, fighting intestinal sepsis	Unknown metabolite	Oil	Seed	Freire *et al*. (2006), Farias *et al*. (2007), Teixeira *et al*. (2012)
Diabetes and rheumatism	Unknown metabolite	Oil	Capsule form	Ferrari *et al*. (2007)
Repellent	Unknown metabolite	Residues from the oil' seeds	Candles	Mendonça *et al*. (2005)
Inflammation and infections	Unknown metabolite	Oil	Seed	Henriques & Penido (2014)
Anthelmintic, curative agent	Unknown metabolite	Bark and flowers	Tea	Boufleur (2004)
Against oral mucositis	Unknown metabolite	Oil	Seed	Wanzeler *et al*. (2017)
Genotoxic activity	Unknown metabolite	Oil	Seed	Arrebola *et al*. (2012)
Anthelmintic activity	Unknown metabolite	Oil	Seed	Carvalho *et al*. (2012)
Healing activity	Taninins, saponins and alkaloids	Oil	Seed	Silva *et al*. (2015), Souza *et al*. (2017)
Tripanocidal effect	Unknown metabolite	Oil	Seed	Baldissera *et al*. (2013)
Leishmanicidal effect	Fatty acids and phenolic compounds	Oil	Seed	Moraes *et al*. (2018), Cunningham *et al*. (1972), Carballeira *et al*. (2012), Rodrigues *et al*. (2014)
Repellent activity	Unknown metabolite	Oil	Seed	Fernandes *et al*. (2016)
Larvicidal effect	Unknown metabolite	Oil	Seed	Silva *et al*. (2006)
Anti-allergic effect	Tetranortri-terpenoid	Oil	Seed	Penido *et al*. (2005)
Anti-inflammatory effect	Tetranortri-terpenoid	Oil	Seed	Penido *et al*. (2006b)
Acaricidal activity	Unknown metabolite	Oil	Seed	Vendramini *et al*. (2012)
Antimalarial activity	6α-aceto-Xygedunin	Oil	Seed	Pereira *et al*. (2014)
Antioxidant activity	Unknown metabolite	Oil	Seed	Milhomem-Paixão *et al*. (2016)
Antitumor activity	Unknown metabolite	Oil	Seed	Porfírio-Dias *et al*. (2020)

Therefore, genotoxicity screening during the pre-clinical evaluation of plant-based extracts or substances is of paramount importance. This screening is intended to verify the mutagenic potential for safety and economy concerns precisely because plants are widely used in medicine and can be a resource for the development of new medicines (Sponchiado *et al*. 2016).

Anthelmintic activity

The *Haemonchus contortus* worm is widely distributed worldwide. It is a gastrointestinal nematode usually found in small ruminants. This parasite generates great economic savings for animal breeders affected by appetite, stomach damage and changes in the total protein content, energy and mineral metabolism (Fox, 1993).

The main method of treatment against this parasite has been the use of anthelmintics. However, the issue of resistance due to the wide and indiscriminate administration of anthelmintics has been a problem. It has been precisely described in the literature by Drudge *et al*. (1964) the first case of resistance to anthelmintics.

As an alternative for the treatment of parasitic infections, there are anthelmintics derived from plants (Akhtar *et al*., 2000). According to Carvalho *et al*. (2012) the action potential of plant extracts on certain diseases and pests has been a good source of knowledge. In this area of study there has been an impressive development related to human and animal health.

Carvalho *et al*. (2012) aimed to evaluate the *in vitro* antiparasitic action of *C. guianensis* against *H. contortus*, and the *in vivo* action against *Strongyloides venezuelensis* in rats.The aforementioned authors obtained no ovicidal or larvicidal activity in the tested concentrations of the oil extracted from the *C. guianensis* seeds (Table 2). There was a difficulty faced in handling this oil in *in vitro* tests with gastrointestinal nematodes was its solubilization. According to the same authors, it would be necessary to increase the amount of solvent. As the parasites are very sensitive, low concentrations were used in the study. It was necessary to increase the concentrations of *C. guianensis* considerably in order to obtain better results in the hatching test of the eggs and the larvae development test to reach the lethal concentration of 50%. Therefore, the standard deviation for *C. guianensis* in the larvae development test showed great variability. *C. guianensis* oil was evaluated and as its main constituents it presented oleic acid (46.8%) and palmitic acid (39.0%).

Healing activity

The healing process is based on a complex sequence of events that causes trauma to repair damaged tissues and occurs similarly in all wounds. Consist of a series of events that are interrelated so that a perfect reconstruction of the tissue occurs. This cascade is coordinated by cells, molecules and biochemical processes. The processes involved in healing can be divided into three overlapping phases, or processes: inflammatory, proliferative or granulation and remodeling or maturation phases (Campos *et al*., 2007; Isaac *et al*., 2010).

The need to find new substances that play an effective role in surgical repair has stimulated the use of herbal medicines in wound healing. Although it is a systemic process with appropriate topical therapy, favorable local conditions are still needed to stimulate the physiological process (Coelho *et al*., 2010).

Brito *et al*. (2001) observed a delay in contraction and epithelialization of wounds when evaluating the effect of andiroba oil in open wounds in rats. The authors suggested a possible anti-inflammatory action resulting in loss during the healing process.

Silva *et al*. (2015) com tested andiroba oil in the healing of rats' colon wounds to verify its healing effect (Table 2). The authors observed that the andiroba group had abscess and infection in 11% of the animals, 5.5% had hematoma, but none had dehiscence or fistula. The treated andiroba groups showed better colorographic healing when compared to the control group.

Despite using andiroba oil in the wild, after suffering damage in the wound healing process and epithelialization in rats' skin wounds (Brito *et al*., 2001), other studies have proven that this oil uses analgesics, antiallergics including inhibiting the formation of edema (Pennaforte, 2003). The antiedema and analgesic effect of andiroba oil is due to a fraction derived from this oil rich in tetranortriterpenoids. This information was confirmed in Switzerland where Penido *et al*. (2005) used C57/BL10 trucks with induced pleurisy and limb edema.

The analgesic effects of andiroba oil are explained by the blocking of inflammatory mediators (eicosanoids) (Penido *et al*., 2005). Brito *et al*. (2001) had already described a delay in wound healing with the use of andiroba oil. In contrast, the anti-inflammatory action of andiroba oil was attributed to limonoids, tetranortriterpenoids that have the effect of promoting the inhibition of cell influx and edema formation in mice (Penido *et al*., 2005).

According to Araújo *et al*. (2017) observed an advanced epithelialization, fibroblast proliferation and collagen deposition, moderate vascular proliferation and presence of polymorphonuclear cell (PMN) infiltrates and a slight proliferation of mononuclear cells (MN) during histopathological evaluation in wounds treated with ozonized andiroba oil, pure andiroba oil. Thus, it was possible to conclude that both treatments used were beneficial to the control group, showing that the pure and ozonated versions of andiroba oil represent therapeutic alternatives to the treatment of wounds in horses.

The healing process is related to clinical, scientific and economic aspects (Hussni *et al*., 2010) mainly in equine species. These species have a differentiated healing of the skin, with the formation of a granular tissue preventing the normal functions of the animal (Stashak, 1994). Another situation that impairs wound healing is *Diabetes mellitus*. The hyperglycemic state caused by diabetes also determines a state of poor healing. In addition, the ulcers generated can evolve with necrosis and limb amputation. Andiroba oil is already described with great healing potential. Researches that oil effectively participates in wound healing by promoting the formation of granulation, tissue contraction and epithelialization (Burlando & Cornara, 2017; Higuchi *et al*., 2017). According to Souza *et al*. (2017) compared to the control group or andiroba oil showed surprising results, obtaining a lower average of the wound area compared to the control group, mainly macroscopically with a degree of almost total contraction of the incisional wound.

According to Nayak *et al*. (2005), many studies showing the tetraterpenoid and limited effects of *C. guianensis* show the anti-inflammatory effect. However, Souza *et al*. (2017) show that the phytochemical analysis of andiroba by qualitative methods showed the presence of alkaloids, saponins and tannins. According to the same authors, essential oils cause the absence of other components such as triterpenoids and flavonoids. In this way, possibly, constituents such as tannins, saponins and alkaloids can play a role in the wound healing process (Table 2). However, the aforementioned authors claim that more phytochemical studies are needed to isolate the active compounds used by these pharmacological activities.

According to Souza *et al*. (2017) the experimental model demonstrated greater efficacy of topical application of andiroba oil compared to the control group in tissue formation, epithelialization, angiogenesis and collagen deposition in skin lesion. They concluded that there was significant effect in topical application of andiroba oil on wound healing in rats with induced diabetes.

Trypanocidal effect

Baldissera *et al*. (2013) have shown that andiroba oil can be more effective against *Trypanosoma evansi* an important aetiological agent of trypanosomiasis in livestock when encapsulated in nanostructure (Table 2). They tested andiroba oil in nanostructured form in *T. evansi*, a parasite belonging to same family of *Leishmania* (Trypanosomatidae). The authors observed no morphological alterations in the flagellates and reported a significant reduction in the number of live parasites after 1-6h treatment with 0.5% nanoemulsion of andiroba oil.

Leishmanicidal activity

Leishmaniasis caused by the protozoan Leishmania is a widespread parasitic disease throughout the world. *Leishmania* is an obligate intracellular parasite of humans that resides and multiplies in macrophages (Kaye & Scott, 2011; Pace, 2014). The disease manifests itself in several ways: cutaneous, diffuse cutaneous, mucosal and visceral (Okwor & Uzonna, 2016). Each parasite results in a different clinical form, the visceral form is caused by *Leishmania infantum* and the form cutaneous and diffuse cutaneous is caused by *L. amazonensis*. The last form is found in Latin American countries (Pace, 2014). The most of drugs have side effects and there is no vaccine. Another problem is the resistance to classical chemotherapy has become a threat (Okwor & Uzonna, 2016; No, 2016). Therefore newer drug therapies are necessary.

The nanoemulsions as a delivery system for andiroba oils had leishmanicidal effect in intracellular forms and promastigotes. In the author studies, oval cell shape and retracted flagella in *L. amazonensis* and *L. infantum* promastigotes were observed as early as 1h, suggesting that different structures of *Leishmania* should be targets of andiroba (Moraes *et al.,* 2018). It could be suggested that the surfactant coating of the nanoparticles surface may facilitate the penetration of the loaded drug into the parasite because mechanisms of toxicity are not known (Lherm *et al.,* 1987).

According to Moraes *et al*. (2018) did not the constituents of andiroba oil involved in leshmanicidal effect was not identified. However, a series of chemical elements present in andiroba oil, such as fatty acids and phenolic compounds, obtained from other plants had already proved leishmanicidal activity (Table 2) (Cunningham *et al*., 1972; Carballeira *et al*., 2012, Rodrigues *et al*., 2014).

Repelent activity

According to Chagas *et al*. (2003) although the repellency activity be exerted by drugs such as ivermectin, pyrethrin or pyrethroid sprays in which are used to control insects the use of such products leads to the development of resistance to chemical molecules thus bringing harmful effects to the infested bodies. Diseases like myiases occur by the infestation of larvae of flies in tissues of live vertebrate animals (Orfanou *et al*., 2011), generating losses in farm animals (Cramer-Ribeiro *et al*., 2002) and is a common problem in small animal veterinary practice (Cramer-Ribeiro *et al*., 2002; Cardozo & Ramadinha, 2007).

There are many factors may predispose larval infestation, such as injuries caused by trauma and/or dermatological diseases (Cardozo & Ramadinha, 2007). In this situation, phytotherapy is considered an important alternative in the insects control being relevant to reduce the economic impact (Olivo *et al*., 2008). Generally is used citronella against mosquitoes, flies and ticks as repellent activity of herbal medicines (Olivo *et al*., 2008; Lachange & Grange, 2014). According to Ribas & Carreño (2010), plants like *C. guianensis* has been used as a repellent against mosquitoes. The flies of the *Calliphoridae* family are common agents causing larval infestations in veterinary medicine. Besides that, these species have a particular importance in public health, acting as vectors to other pathogens, aggravated by their synantropic nature (Carvalho & Ribeiro, 2000).

According to Nerio *et al*. (2010), the specific compounds, and their concentration, present in the extract will be influence in the repellent capacity of a given extract. Fernandes *et al*. (2016) related that o petroleum jelly (vaseline) was used to produce the creams used in the study with andiroba seed oil (Table 2). This vehicle has no effect on its own because is a inodorous substance, but probably made it possible by the aggregation of the active substances in the plant extracts. Furthermore, another advantage of the petroleum jelly has been shown to allow a controlled and moderate release of volatile compounds in these extracts, enhancing the period of effect.

According to Fernandes *et al*. (2016) plant based products can be produced at reasonable costs with satisfactory results, as shown in this study. *C. guianensis*'s repellent action on flies of the Calliphoridae family yielded promising results.

Larvicidal effect

Dengue, dengue hemorrhagic fever, yellow fever, zika and chikungunya are important diseases transmitted by vectors such as *Aedes aegypti* L., and which have a major impact in terms of morbidity and mortality for the patient (Gubler, 2002). From December 29, 2019 to April 18, 2020, 603,951 probable cases (incidence rate of 287.4 cases per 100,000 inhabitants) of dengue were reported in Brazil. Regarding chikungunya data, 17,636 probable cases (incidence rate of 8.4 cases per 100 thousand inhabitants) were reported in the country. Regarding Zika data, 2,058 probable cases (incidence rate 1.0 cases per 100 thousand inhabitants) were reported in the country (Ministério da Saúde, 2020). The reduction in the number of vectors is relevant to the degree of epidemic prevention. In addition, these vectors are widely distributed in all regions of Brazil (Silva *et al*., 2006).

Preventive measures such as the elimination or cleaning of water retention containers that serve as larval habitat are paramount for controlling *Ae. aegypti*. Other measures can also be taken, such as the use of repellents, or the application of

chemical insecticides or biological control, such as *Bacillus thuringiensis* subsp. israelensis. The use of organophosphates, such as temephos and fenthion and insect growth regulators, such as diflubenzuron and methoprene, is also a practice for controlling mosquito larvae (Yang *et al*., 2002). However, in Brazil, *Ae. aegypti* has become resistant to organophosphates in several regions (Lima *et al*., 2003; Macoris *et al*., 2003; Braga *et al*., 2004).

Many studies have been carried out to evaluate the insecticidal capacity in plants in order to avoid mosquito resistance to chemical insecticides and to protect the environment and public health. To repel mosquitoes, the Oswaldo Cruz Foundation developed candles containing the essential oil of *C. guianensis* has one with potent insect repellent characteristics (Gilbert *et al*., 1999). These chestnuts (shelled) have a high oil content in terms of weight (56%) (Silveira & Carioca, 2003). *C. guianensis* belongs to the same family as neem, *Azadirachta indica* A. Juss., Considered to be one of the most efficient phytochemical pesticides on the market (Mulla & Su, 1999).

In preliminary studies, Silva *et al*. (2006) found that andiroba grains suffered larvicidal effects on *Aedes albopictus* (Skuse) (Silva *et al*., 2004) and *Ae. aegypti* (Emerick *et al*., 2004). These studies served as a basis for the possibility of using andiroba oil against *Ae. aegypti* larvae. Thus, Silva *et al*. (2006) verified the effect of andiroba oil in two laboratory strains of *Ae. aegypti*.

According to Silva *et al*. (2006), the two laboratory strains of *Ae. aegypti* a significant variation in the susceptibility of larvae to andiroba oil (Table 2). The authors concluded that if there is a greater susceptibility of *Ae. aegypti* populations in the field, andiroba oil should continue to be investigated.

Anti-allergic effect

With a wide range of products with pharmaceutical activity, natural compounds are widely recognized and include great structural diversity. *C. guianensis* is widely used in folk medicine in Brazil and in other countries covering the Amazon rainforest. A plant has several compounds such as triterpenes, tetraterpenes, alkaloids and limonoids. These compounds are standards for all members of the Meliaceae family, andiroba family (Banerji & Nigam 1984).

In order to characterize the chemical composition of the seed extract of *C. guianensis*, Pereira *et al*. (1999) isolated and characterized six different tetranorthriterpenoid compounds: 6a-acetoxygedunine, 7-deacetoxy-7-oxogedunine, andirobin, gedunine, methyl angolensate and 6a -acetoxiepoxy-azadiradione.

Among the most notable properties attributed to ethnopharmacological factors are the analgesic and anti-inflammatory activities attributed to the oil extracted from the seeds of *C. guianensis*, mainly for rheumatic pain and arthritis (Hammer & Johns, 1993; Lorenzi & Matos, 2002).

Play an important role in allergic responses and inflammation in inflammatory mediators, including histamine, bradykinin, serotonin, plate-let activation factor and leukotrienes. In addition, they induce an increase in microvascular permeability to plasma proteins, causing edema, as well as infiltration and hyperalgesia (Bilici *et al*., 2001; Zuany-Amorim *et al*., 1994). Penido *et al*. (2005) investigated the anti-allergic and analgesic oil properties and a derived fraction of tetranortriterpenoids (TNTP) obtained from the *C. guianensis* seeds.

The presences of limonoids, which are tetranortriterpenoids in *C. guianensis*, confer medicinal properties to the plant (Banerji & Nigam, 1984). Penido *et al*. (2005) demonstrated that both the oil obtained from the seeds of *C. guianensis* and the TNTP fraction, which contains the set of tetranortriterpenoids, exhibit markers with anti-allergic and anti-hyperalgesic properties in rodents.

The allergic process triggers a rapid increase in histamine, bradykinin and leukotriene levels in bronchoalveolar and nasal lavage washings of sensitized rodents after challenge to the antigen (Shirasaki *et al*., 1989; Mashito *et al*., 1999).

Penido *et al*. (2005) evaluated that the anti-allergic and analgesic factors of a chemically characterized pattern obtained from the *C. guianensis* seeds and its fractions derived from TNTP *in vivo*, including ear and paw edema, pleurisy and thermal hyperalgesia. Thermal hyperalgesia is the exaggerated sensitivity to pain due to the heat generated by the inflammatory reaction caused by an allergy. The authors also investigated the ability of TNTP to influence the effects of various mediators that contribute to inflammatory and allergic processes.

As a result, the aforementioned authors reported that *C. guianensis* oil and TNTP inhibited pleural exudation, paw and ear edema induced by ovalbumin in rats. In addition, TNTP also inhibited histamine-induced paw edema, platelet activation factor and bradykinin. Another effect of TNTP was to inhibit the generation of prostaglandin in the pleural cavity in response to the antigenic challenge. *C. guianensis* oil and TNTP also decreased the ear induced by ovalbumin in rats and the hyperalgesia induced by histamine (Penido *et al*., 2005).

As histamine is an important mediator of allergy causing plasma leakage and edema, it is especially worth noting that the extent and potency of the inhibition provided by TNTP against histamine-induced paw and ear edema, as well as pleural exudation, was similar to that of promethazine, a compound tested with antihistamine reference (Biilici *et al*., 2001; Martins *et al*., 1993). According to Penido *et al*. (2005) in fact, pretreatment with *C. guianensis* or TNTP seed oil inhibited all these effects of histamine very effectively.

Thus, Penido *et al*. (2005) realized how antiallergic properties of TNTP (and perhaps the *C. guianensis* seed oil from which it is derived) can be attributed to the inhibition of pro-inflammatory mechanisms triggered by histamine H1 receptors, platelet activation factor and bradykinin B2, rather than blocking these receivers. However, additional studies must be carried out to fully elucidate the action of TNTP and *C. guianensis* seed oil on these antiallergic mechanisms.

Anti-inflammatory effect

Among the most notable properties of the oil extracted from the seeds of *C. guianensis* attributed to ethnopharmacological research are anti-inflammatory and analgesic activities, mainly for rheumatic pain and arthritis (Hammer & Johns, 1993; Lorenzi & Matos, 2002).

Penido *et al*. (2006) observed in previous studies that *C. guianensis* oil and six different tetranortriterpenoid (TNTP) isolates from that oil had an important antiallergic and analgesic effect related to allergens evoked hyperalgesia in rats due to the blocking of signaling mechanisms and generation of different mediators (Penido *et al*., 2005).

For such studies, the model used to assess the anti-inflammatory effects of different compounds has been zymosan-induced arthritis. An important edema formation is accompanied by a massive infiltration of neutrophils in synovial tissue and inflamed joint fluids after intra-articular treatment with zimosan stimulation. The presence of macrophages and accumulation of lymphocytes characterize the chronic response (Frasnelli *et al*., 2005; Pettipher & Salter, 1996). Joint inflammation is marked by an important generation of mediators. Such mediators contribute to increased microvascular permeability to plasma proteins (and, therefore, edema), as well cellular infiltration and hyperalgesia (Bombini *et al*., 2004; van de Loo *et al*., 1998).

Penido *et al*. (2006) evaluated the anti-inflammatory effects of the effects of TNTP of *C. guianensis* seeds on zimosan-induced arthritis in mice. As a result, the authors demonstrated that a group of six different TNTP inhibited cell flow and edema formation, demonstrating an important anti-inflammatory property. The research was done on a murine model of experimental zimosan-induced arthritis.

The intra-articular injection of zymosan induced a significant increase in the diameter of the knee joint within 6 hours, peaking within 24 hours and remained above control values for 20 days. TNTP administered orally inhibited the increase induced by zymosan in the knee joint, in the leakage of diameter and protein in the synovial cavity within 6h. TNTP also inhibited the influx of leukocytes into synovial space and tissue, as well as into the pleural cavity of mice. The authors came to the conclusion that taken together, these results indicate that TNTP had an important anti-inflammatory effect, inhibiting zymosan-induced arthritis in mice (Table 2).

Acaricidal activity

Ticks cause damage to hosts during the blood feeding process, in addition to vectors of pathogens that affect animals, including humans. In addition, they created one of the most important groups of arthropods in the medical and veterinary field (Walker, 1994).

The group comprises animals belonging to the order Ixodida subclass Acari, being classified into three families: Ixodidae, Argasidae and

Nutalliellidae (Anderson & Magnarelli, 2008). Mainly parasitizing the domestic dog, Rhipicephalus sanguineus (Latreille, 1806) is found in the family Ixodidae and distributed throughout all continents on the planet. This species causes significant blood loss in the hosts, in addition to being the vector of viruses, bacteria, and protozoa, which cause diseases such as Babesia canis. Some protozoa that act on erythrocytes causing babesiosis or "nambiuvu" (Flechtmann, 1973). Hepatozoon canis is a biopathogen of hepatozoonosis in dogs in Latin America (O'Dwyer & Massard, 2001; Vicent-Johnson *et al*., 1997) and also Ehrlichia canis, which attacks the dog's leukocytes (Davoust, 1993; Simpson *et al*., 1991).

Much research has been done with a view to effective control of ticks as well as new economically viable acaricidal products. Products that at the same time have low toxicity and impact on the environment. Among the alternatives is the use of products from plant extracts, which contain active ingredients with action to control pests (Guerra, 1985). In this sense, andiroba have been recognized as efficient in pest control, mainly due to their repellent action against Arthropoda (Loureiro *et al*., 1979; Martinez, 2002).

The control of ticks is a recurring issue that arouses the interest of researchers and mainly of producers due to serious damage caused by these ectoparasites. The damage generated refers to injuries caused by hosts during blood feeding. In addition, there is the possibility of transmission of pathogens that affect livestock, domestic animals and public health in general (Harwood & James, 1979; Rey, 1973; Freitas *et al*., 2005). To solve this problem, a lot of research is done looking for alternative ways to control ticks. These researches aim to find less toxic methods for the hosts, offering low cost and less environmental impact. One of the alternatives is the use of natural products, extracted from plant extracts as a recognized acaricide or an action repellent (Guerra, 1985).

Few reports are found in the literature on the use of andiroba oil to control ticks. The available data show that this product has an acaricidal potential, in addition to inhibiting the oviposition of *Boophilus microplus*, females of *R. sanguineus* and *Anocentor nitens* (Farias *et al*., 2007; 2009). Vendramini *et al*. (2012) evaluated the action of different concentrations of andiroba seed oil on the oocytes of semi-engorged females of *R. sanguineus*. During the study, there was also the quantification of the reproductive efficiency index through immersion, in addition to histochemical techniques to analyze whether this natural product would be capable of impairing the reproductive success of these species.

The results of the aforementioned authors showed that andiroba oil is a potent natural agent, capable of causing several changes in the oocytes of this species, impairing reproductive success (Table 2). Andiroba oil induced major physiological changes in oocytes at all stages of development, such as drastic reduction of proteins, polysaccharides and lipids in these cells, which are essential components for embryo viability. In addition, the same authors observed that this product stimulates oviposition, mainly in the concentration of 20%. This greater production of eggs represents a defense mechanism developed by the organism to guarantee the reproductive success of the species, even in the presence of the toxic agent. However, the results obtained suggested that the eggs laid were not viable, due to the great changes suffered by the oocytes. Thus, Vendramini *et al*. (2012) showed that the use of andiroba oil would be an alternative way to control ticks, bringing benefits similar to those obtained with the use of synthetic acaricides with less damage to non-target organisms and the environment.

Anti-malarial activity

Malaria, which causes an enormous burden on health with an impact on social and economic development, is considered a serious infectious disease. In Brazil, especially in the Legal Amazon, malaria is considered a serious public health problem. The disease exhibits a wide incidence and debilitating effects due mainly to the environmental conditions conducive to the maintenance of the disease (Tadei *et al*., 2000; Tadei *et al*., 1998).

According to data from the Ministério da Saúde (2019), between 2007 and 2016, malaria cases in Brazil showed a reduction. However, after almost 10 years, malaria had a significant increase in cases in 2017 (53% compared to 2016). In 2018, the country recorded 194,513 reported cases of malaria, a reduction of 1% over the previous year.

The disease is infectious and caused by protozoa of the genus *Plasmodium* and transmitted

to man by female mosquitoes of the genus *Anopheles*. It has symptoms such as acute febrile conditions, caused by four species of plasmodia that can cause the disease: *P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale* (Who, 2020). The question of drug resistance in the treatment against the disease-causing agent is a reality. The presence of chloroquine-resistant *Plasmodium falciparum* (CQR) is now widespread and there are an increasing number of reports of CQR *Plasmodium vivax* worldwide (Who, 2012; Gama *et al*., 2011).

In recent years, attempts have been made to introduce artemisinin-based combination therapy (ACT) as the first line of treatment for *P. falciparum* and for the treatment of CQR *P. vivax*. However, reports by *P. falciparum* show resistance to artemisinin derivatives, increasing interest in lead compounds for the development of a new generation of antimalarial drugs (Who, 2012; Gama *et al*., 2011).

In the past 30 years, natural products are the direct or indirect sources of most of the drugs introduced (Newman & Cragg, 2010). As a rich source of lead compounds, natural plant products are compounds that contain new drugs against parasitic diseases caused by protozoa, such as malaria (Guantai & Chibale, 2011; Schmidt *et al*., 2012).

There are two potent natural antimalarial products from plants: the compound quinine (Achan *et al*., 2011) and an artemisinin. A later development gave rise to synthetic classes of antimalarials quinoline and artemisinin that form the basis of combined artemisinin-based therapy. Artemisinin derivatives (eg, sodium artesunate, art, dihydroartemisinin) and quinolines (like chloroquine and primaquine) are the basis of recurrent treatment of malaria worldwide. For the treatment of malaria in the Amazon region it has a rich tradition of using plants. Various natural products were used and semi-synthetic products were also prepared, exhibiting important antimalarial properties *in vitro* and *in vivo* (Pohlit *et al*., 2013).

Based on previous information, Pereira *et al*. (2014) evaluated the *in vitro* and *in vivo* anti-malarial activity and cytotoxicity of limonoids isolated from abundant residual pressed seed material (RPSM) of *C. guaianensis*. As a result, the authors were able to evaluate that *in vitro*, among the five compounds tested, the limonoids 1-5 of *C. guianensis* exhibited median concentrations of inhibition. In general, these limonoids were not toxic to normal cells (human fibroblasts MRC-5). *In vivo*, it was observed that two concentrations tested (6α-acetoxygedunin and 7-deacetoxy-7-oxogedunin) in oral doses. It was observed that 6α-acetoxygedunin generated suppressed parasitemia versus untreated controls in 40 and 66%, respectively, showing a clear dose-response. The authors concluded with the study that 6α-acetoxygedunin is an abundant natural product present in seeds of *C. guianensis* that exhibits significant antimalarial properties *in vivo* (Table 2).

Antioxidant activity

Antioxidants are substances that have an inhibitory effect that is triggered by free radicals in the body. They are of great relevance because they inhibit or reduce oxidative processes, mitigating the development of different types of pathology such as Parkinson's, Alzheimer's, multiple sclerosis, cardiovascular diseases, liver diseases and various types of cancer (Santos *et al*., 2008; Abbas *et al*., 2014; Hatamnia *et al*., 2014). For energy production, there is the oxidation process that is fundamental to the organism. However, during this process oxygenated or nitrogenated free radicals are generated. The excess of these radicals in the body generates oxidative stress that can cause damage to cells, since it can cause damage to DNA (Wang *et al*., 2017; Santos *et al*., 2008; Soares *et al*., 2005).

Andiroba oil has in its majority composition essential fatty acids such as oleic, palmitic, stearic and linoleic acids (Martinborough, 2002; Rain-Tree, 2014). Depending on the concentration tested, fatty acids such as oleic, palmitic, stearic and linoleic can cause apoptosis in different cell lines *in vitro* (Mu *et al*., 2001; Lu *et al*., 2003; Cury-Boaventura *et al*., 2004).

Based on this information, Milhomem-Paixão *et al*. (2016) investigate the antioxidant properties of andiroba oil using the comet and micronucleus assays.The authors observed in their results that all three oil samples showed antioxidant activity according to the radical DPPH (2,2-diphenyl-1-picryl-hydrazyl). *In vitro* tests showed that the oil sample from sample 3 from southwestern Amazonia Brazil had a high

antioxidant capacity that can protect biological systems from oxidative stress, although this activity has yet to be demonstrated *in vivo* (Table 2).

They also stated that samples with high and low antioxidant properties showed regional variations, in the northeastern state of Pará, Marajó island and the metropolitan region of Belém, as well as variations within each region. Two commercial samples of andiroba oil (Amazon Ervas and Iana® D'amazônia) were also tested by Milhomem-Paixão et al. (2016) regarding its antioxidant potential. The Iana sample, diluted in mineral oil as indicated on the manufacturer's label, had the lowest antioxidant capacity of all tested samples. The authors concluded that the antioxidant activity of the oil would tend to protect the cell's DNA from oxidation damage. In conclusion, they stated that andiroba oil, used in folk medicine among Amazonian populations, has a low risk of toxicity in the conditions under which it was tested.

Antitumor activity

Since the beginning of the first days of human exposure or use of medicinal plants to cure and treat data on diseases, it is now seen both in developing countries and in countries where conventional medicine prevails in the health system. Spread from generation to generation, a therapeutic adjustment as a basic principle of the plant, as a raw material, is totally safe and effective (Colombo *et al*., 2010; Who, 2000). However, toxicological studies are of great relevance to ensure the safety of herbal medicine (Maciel *et al*., 2002).

Researchers continue to look for less aggressive chemotherapy candidates for the body, as many effective antineoplastic agents have adverse effects (Shivakumar *et al*., 2012). As a good alternative to conventional chemotherapeutic agents, products of natural origin are capable of killing neoplastic cells, generating few side effects. *In vitro* tests using cell culture are done quite frequently in research because their application can decrease and/or replace the test on animals. In addition, these techniques are reproducible, useful and predictive for simple biological systems, and are widely used in toxicological tests (Repetto & Repetto, 1995).

Porfírio-Dias *et al*. (2020) evaluated the cytotoxic, apoptotic and mutagenic potential of andiroba oil in the ACP02 cell line, which is derived from a diffuse-type gastric adenocarcinoma characterized by a poor prognosis and a low response rate to chemotherapy or radiochemotherapy (Schauer *et al*., 2011).

The tests carried out by Porfírio-Dias *et al*. (2020) showed that andiroba oil significantly reduced cell viability only when the highest concentration tested was applied for 48 hours (Table 2). In another test, the apoptosis/necrosis test found that the highest concentration of andiroba oil showed that the induced cells died from apoptosis at 24 and 48 hours. The authors also observed that andiroba oil decreased the viability of ACP02 cells by apoptosis, in this case, without exerting mutagenic effects. The authors suggested that the oil may be useful as an alternative therapeutic agent for primary tumors of stomach cancer.

Conclusion

Despite scientific studies demonstrating genotoxic, healing, trypanocidal, leishmanicidal, repellent, larvicidal, anti-allergic, anti-inflammatory, acaricidal, antimalarial activities as well as antioxidant and antitumor activities of the *Carapa guianensis* 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 to 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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