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Pharmacological activity and isolated substances from *Carapa guianensis* Aubl.

Jéssica Araújo Marques[1], Daiane Martins[2] and Cleverson Agner Ramos[2]

[1]Escola Superior de Ciências da Saúde - Universidade do Estado do Amazonas - Avenida Carvalho Leal, 1777, Cachoeirinha, Manaus, AM, Brasil – CEP: 69050-010
[2]Faculdade de Ciências Biológicas – Universidade Federal do Amazonas – Avenida General Rodrigo Otávio, 6200, Coroado, Manaus, AM, Brasil – CEP: 69077-000

ABSTRACT

The Carapa guianensis, popularly known the "Andiroba", is a tree that has a considerable importance economic, ecological and ethnopharmacological. Ethnobotanic studies report its medicinal potential, anti-inflammatory, anti-allergic, analgesic, acaricide and other properties, and some of these pharmacological activities have proven. This literature review aims to map the pharmacological activities and compounds isolated from C. guianensis in order to contribute to the further study of their pharmacological potential.

Keywords: *Carapa guianensis*; Andiroba; pharmacological activities; limonoids.

INTRODUCTION

The *Carapa guianensis* Aublis a large tree member of the Meliaceae family, and is popularly known by "Andiroba". Each individual reachs 65 cm in diameter at breast height (DBH) and can reach over 30 m high, with species native to the Brazilian Amazon rainforest [1], also occurring in lowland areas and flooded fields in regions of rivers [2].

With considerable popularity in northern region of Brazil, this species can be found as many popular names like "Angirova", "Andirova", "Carapinha", "Carapa" and "Iandiroba". Its color has reddish patterns and its trunk shows moderately heavy wood. *C. guianensis* is a species of multiple use, from high economic trough ecological importance [3], has an extensive list of benefic applications to Amazon population, contributing in sectors such as shipbuilding, construction, furniture manufacture and in general, cosmetic synthesis and medicinal approach. According to Bausch and Dunisch[4], *C. guianensis* plantation may be recommended in high-quality wood production with an ornamental heartwood. Furthermore, this species is also, described in Database of Aromatic Plants of the Amazon as β-caryophyllene oil components, α -humulene and germacrene D[5]. The trunk core is also used as a fungicide [6].

Regarding to the properties already observed in this species, the extracted oil from their seeds may processed into a byproduct with several medicinal applications including anti-inflammatory [7-9], acaricidal[10], being effective as an insect repellent [11, 12, 9]and the antiallergic activity and analgesic [13, 14]. From the tea prepared by the leaves and bark of "Andiroba" many disease treatments can be performed as anthelmintic treatment [15, 9]. Although the literature suggest a low potential teratogenic [16]such feature can be considered one of the incentives the search for new cosmetics and drugs with represents great value for the pharmaceutical and cosmetic industries, since a estimative of Brazilian consumption reaches approximately 30,000 liters of oil per year, and the annual exportation amounts is near 450,000 liters on average [17].

This review aims in a survey about information of the pharmacological activities of *C. guianensis* described in the literature. Such information will provide a significant data about the main activities found in this species.

EXPERIMENTAL SECTION

The synthesis of this study was performed through surveys of updated information and showed in the form of literature review.

Scientific data were obtained through researches within data sources such as Science Direct, Pubmed, Scielo, Public Domain and SciFinder, using English, Portuguese and Spanish terms. To select relevant studies from those databases the most common keywords used were: "*Carapa guianensis"*, "anti-allergic", "anti-inflammatory", "analgesic", "acaricide", "larvicide", "anti-plasmodial", "anti-inflamatório", "antialérgica", "analgésica", "acaricida", "larvicida" and "antimalárica". The literature review has been conducted by searching published studies on following fields: ethnobotany, phytochemical and pharmacological activities of *Carapa guianensis* with a full qualitative data.

RESULTS AND DISCUSSION

Isolated substances obtained from *C. guianensis*
According to the literature, substances called limonoids were isolated from andiroba tree, belonging to four subclasses: tetranortriterpenoids (TNTP) [13], carapanolides A-X [19-23], andirolides A-Y [24-27], e guianolides A-B [28].

In the group of tetranortriterpenoids, isolated from their seeds have already been structurally characterized in 6 substances: 6a-acetoxigedunine, 7-desacetoxine-7-oxogedunine, andirobin, metilangolensate, 6-Aacetoxiepoxaazadiradione e gedunine (Fig 1) [13]. The authors suggest that these compounds may have biological activity such as anti-allergic activity, anti-inflammatory, analgesic, and antimalarial.

Another study was conducted in order to quantify the limonoids present in the commercial oil of andiroba using CLAE/DAD, their results showed that the limonoid 7-desacetoxina-7-oxogedunina was present as the major component (2,48 mg/g) [18].

Furthermore, several limonoids were isolated from the seeds and they are belonging to the group of carapanolides A-X (Fig. 2)[19-23]. The carapanolides A have moderate activity against leukemia cell lines L1210 (IC50 8,7 µM)[19].The carapanolides C, E and I exhibited moderate activity against leukemia cell lines P388(IC50 of 17,9 µM in C, IC50 of 15,8 µM in I) andL1210 (IC50of 13,3 µM in C, IC50of 18,1 µM in E, IC50 of 16,9 µM in I),while the carapanolides D exhibited a strongly inhibitory effect on the leukemia lines HL-60 (IC50 11,0 µM), the carapanolides F showed inhibitory activity only in cells L1210 (IC50 15,9 µM) and carapanolides I have showed moderate cytotoxic activity on all these cell lines [20]. The carapanolides J, may already be a potential inhibitor of nitric oxide (substance responsible for regulation of blood pressure) [21].

The andirolides A-Y were isolated limonoidsfrom "Andiroba" flowers (Fig. 3)[24-27]. The andirolides A exhibited significant cytotoxic activity against leukemia cell lines P388, HL-60, L1210 and KB (IC50 of 3.3, 19.4, 16.7, 11.4 µM), while the andirolides G (IC50of 14.4, 16.1, 27.0, 29.3 µM) have moderate cytotoxic activity [24].The andirolides H have antimalarial activity against *Plasmodium falciparum* (EC50 4.0x 10^-6) [25]. The andirolides S and T showed significant cytotoxicity to cells lines P388 (IC50 of 1,4 µM in S; 1,8 µM in T) and HL-60 (IC50 of 1,3 µM in S and T) [26].

Substances of guianolides A-B (Fig. 4) were isolated from "Andiroba" seeds and their structures were established by spectroscopic analysis. In a first analysis the guianolides A-B were examined using cell lines P388, HJ-60, L1210, and guianolides A showed low activity against cells lines P388 (IC50 de 33,7 µM), but guianolides B are inactive against all these cell lines [28].

Anti-allergic activity
Anti-allergic potential of the extracted oil from the seeds of *C. guianensis* was evaluated by bioassay. Such bioassay were performed by used of the oil directly and also 6 fractions of tetranortriterpenoids (TNTP) isolated from the seeds. According to the results, the TNT particularly inhibit production of prostaglandin E^2, a characteristic substance found in pulmonary inflammation and antigenic processes. As, decreases the levels of histamine and ovalbumin substances, these are the main substances responsible for anti-allergic processes[8].

Another laboratorial tests using fractions containing tetranortriterpenoids (TNTP) isolated from the extracted oil from seeds of *C. guianensis* demonstrate high allergen potential. Regarding such contribution into allergic process, Penido [14],performed methodologies by 6 types of isolated TNTP already structurally characterized as following, 6a-acetoxigedunine, 7-desacetoxina-7-oxogedunine, andirobina, metilangolensate, 6Aacetoxiepoxaazadiradione e gedunine. Applied in biological assays, an intrathoracic injection of ovoalbuminin order to induce pleuritis and antigenic inflammation in mice, followed by ELISA assays and procedure of cytometry fractions flow withdrawn from the body induced with allergies, practices used to assess the levels of antibodies which consist the hyperalgesic response. The results showed to be effective at the inhibition ofthe leukocytes accumulation as well the eosinophils. Futher more, the final conclusion leads that isolates TNTPs as good drug candidates as they effects on the inhibition of eotaxin synthesis and eosinophilia allergic [14].

Ferraris and collaborators [29]have found that TNTP gedunine its allergen because of its ability to modulate T cell activation and trafficking in the airways, because the T cells are involved in allergic processes.

In order to elucidate the mechanisms by which TNTPs exhibit their anti-allergic effects, as well to identify bioactive compounds TNTPs fractions, Ferraris and collaborators[30] demonstrated that TNTPs inhibit the migration of eosinophils, and the activation of lymphocytes T.

Anti-inflammatory activity

Tests made from induction of arthritis also have been made in order the evaluate of TNTPs, isolated from seeds of *C. guianenses*, as an anti-inflammatory substances. The tests that induce arthritis consists on the injection of Zymosan in intra-articular spaces of Swiss mice, and control of inflammation for the following 20 days, established by increasing the diameter of the structures and the presence of estimulated cytokine in the inflammatory process. The later fractions containing TNTP, caused a reduction in cytokine production and inhibition of zymosan-induced arthritis indicating the TNTP as anti-inflammatory potential [8].

Analgesic activity

To evaluate the analgesic activity, Penidoand collaborators[13], have tested the TNTP and the oil from *C. guianenses*, in a role of inhibition the inflammatory fluid in the pulmonary lesions, as well as inhibition of induced edema. TNTP decreases the levels of the substances used in the tests (ovalbumin and histamine), this is considered the main substance in the observed painkillers processes.

Larvicidal activity against *Aedes* mosquitoes.

Evaluation of the larvicidal effect of *C. guianensis* in mosquitoes Silva [31], used “Andiroba” seeds against a sylvatic F1 progeny and a laboratory-colonized population of *Aedesalbopictus* (Skuse).Under these conditions, the results showed a significant mortality.

In another study aiming to determine insecticidal activity of different native medicinal plants in Brazil, the oil extracted from *C. guianenses* showed larvicidal activity against *A. aegypti*[12].

A third study evaluated the larvicidal activity for 2 strains of *A.aegypti*, which are: GCZ strain larvae and Rockefeller lineage larvae. Comparison of the 2 strains of *A. aegypti* in the present study demonstrated significant variation in the susceptibility of larvae to “Andiroba” oil[32].

To evaluated larvicidal activity oil of *C. guianensis* and *Copaifera*sp. Another study evaluated on wild populations of *A.aegypti* larvae. The effectiveness of oils on larval mortality was directly related to the increase of temperature, indicating a potential larvicidal activity in populations of *A. aegypti* from the wild[33].

To evaluate the larvicidal activity of *Azadirachta indica*, *Melaleuca alternifolia*, *Carapa guianensis* essential oils and fermented extract of *Carica papaya* against *A.aegypti.* Were experimented and performed in triplicate, which the larvae were exposed for 24h with the compound of essential oils and fermented extract in different concentrations (50, 25 and 12.5%), which were all effective. Thus, the combination of the three oils and fermented extract can be used in *A. aegypti* Liverpool third larvae stage control programs [34].

Antiplasmodial activity

The antiplasmodial activity of “Andiroba” oil is due to the presence of limonoids, which gedunine has a higher antimalarial potential. This was evaluated using 2 clones of *Plasmodium falciparum*, one having sensitivity to chloroquine (W2) and the other one presenting chloroquine resistance (D6). Their findings showed effective activity even in low concentrations for clone of *P. falciparum* resistant to chloroquine W2(CI5020ng/mL) [35].

Miranda Júnior[36], in the search for new antimalarial activity submitted the crude oil and its fractions to *in vitro* tests with clones of *Plasmodium falciparum* W2 andDd2. In this test, the oil showed antiplasmodial activity at concentrations of 0.82 ng/ml and 8.2 ug/ml, having a inhibition of W2 clone 100% and 71% after 72h exposure Dd2 respectively. For the fraction with the concentration of 3.1 mg/mL to the clone W2,the inhibition was 100% and 82% to Dd2 after 72h exposure. Thus indicating that the activity is time dependent, because the longer exposed to oil, the greater the activity.

Fractions rich in limonoids were submitted to bioassays using W2 and Dd2 strains of *P. falciparum*. The results showed the traditional use of "Andiroba" oil as antimalarial, which additionally showed not be toxic in bioassays conducted on mice [37].

Pereira and collaborators [38] demonstrated that 6α-acetoxigedunine TNTP is a natural product abundant in seeds of *C. guianensis* and exhibit significant anti-malarial properties.

Acaricide activity

To evaluate in vitro effectiveness of the andiroba oil on engorged females of *Boophilus microplus*, which were collected manually from bovines naturally infested there were tested different dilutions of the oil in order to investigate the biological activity of the product. The result have been demonstrated on engorged females by the mortality reduction of the oviposition, in this case, with infertile eggs, revealing the promising use of the phytotherapic product on the control of *B. microplus*[39].

To assess the activity of "Andiroba" oil on engorged female *Rhipicephaluss anguineus* and *Anocent ornitens*, which were manually collected from horses and dogs naturally infested. This test showed similar results to that described above, demonstrating efficacy of 100% on both species in all the dilutions tested. Further more the potential use of "Andiroba" extract against these parasites [10].

For the search to an alternative way to control ticks, the "Andiroba" oil as its potential action on engorged females of *R. sanguineus* were analyzed. The findings has suggested to be a great acaricide, bringing benefits similar to synthetic miticides, but with less risk of contamination to the environment and the health of the host[40].

The acaricide activity was also assessed using an *in vitro* study, applying "Andiroba" four dilutions (100, 50, 25 and 10%) in distilled water on *Felicola subrostratus* (parasitic lice cats). After the test, the insects remained at room temperature and observed by 72 h, presenting 100% mortality of the insects in the first hour at concentrations 100% and 50% and in the third hour at concentrations of 25% and 10%. Based on these results, the use of oil is possible in control of *F. subrostratus*[41].

Roma and collaborators [42, 43]conducted research in order to reiterate the effectiveness of the "Andiroba" oil for the control of engorged females of *R. sanguineus*, indicating its action in inducing apoptotic death of brain nerve tissue parasite.

Insecticidal activity

The study by Alessandra and collaborators[44]were have been tested the insecticidal activity of *C. guianenses* on ants of the genera *Atta sexdensrubropilosa*. The ants were taken from laboratory nests distributed in Petri dishes under an artificial diet consisting of glucose and the addition of limonoids for the experimental group, and one diet with glucose and adding solvent to the control group. According to the results, the average survival was 50%, with a moderate insecticidal activity.

Healing activity

In order to evaluate the ethanolic extract obtained from leaves of *C. guianensis* were tested for antibacterial and healing activity using excision and incision in rats. Although the cure rate were measured by the rate of wound contraction, epithelialization period, rupture strength of the skin, weight granulation tissue, there was observed a lack of antibacterial activity, but this extract showed slight healing activity, thus indicating the potential application of *C. guianensis* in wound healing [45].

Using the hydro-alcoholic extract of *C. guianensis* oil in rats male adults (*Rattusnorvegicus albinus* and *Rodentia Mammalia*), Wistar, underwent the same surgical procedure (injury and suture the stomach).It was noted that all animals have been showed good abdominal wound healing of gastric tissue, without infection and dehiscence, demonstrating that the use of hydro-alcoholic extract promoted the healing of the stomach of rats[46].

Anti-trypanosomal activity

In order to investigate the *in vitro* susceptibility of *Trypanosoma evansi* to essential oils of "Andiroba" and "Aroeira", Baldissera and colleagues [47] conducted tests using pure oil in the following concentrations, 0.5%, 1.0% and 2.0% and nanoemulsions oil at the concentrations of 0.5% and 1.0%. After 6hof exposure none of the parasites observed were alive to the essential oil tested, showing a high activity against *T. evansi in vitro*.

Patents

*Carapaguia nense*sas a potential specie to pharmaceutical and biological interest since its various uses have been allowing an obtaintation of some cosmetic and medical patents. Among the cosmetic patent, four were deposited in Brazil by M. de Castro del Castillo, each cosmetic formulated with the oil of "Andiroba": shampoo, conditioner cream, soap and moisturizing [48]. In Japan, there is a patent for a body lotion and the other for preventing gray hair [49, 50]. Among the medicinal patents, a repellent [51] and a pharmaceutical formulation with oil of 'Andiroba" for treating allergic [52] were deposited by FIOCRUZ. In Brazil, it was also deposited 2 topical formulations, an anti-inflammatory [53] and one for the treatment of vitiligo [54].There is a third patent deposited in Brazil it is the repellent action "Andiroba" oil and eucalyptus oil [55].

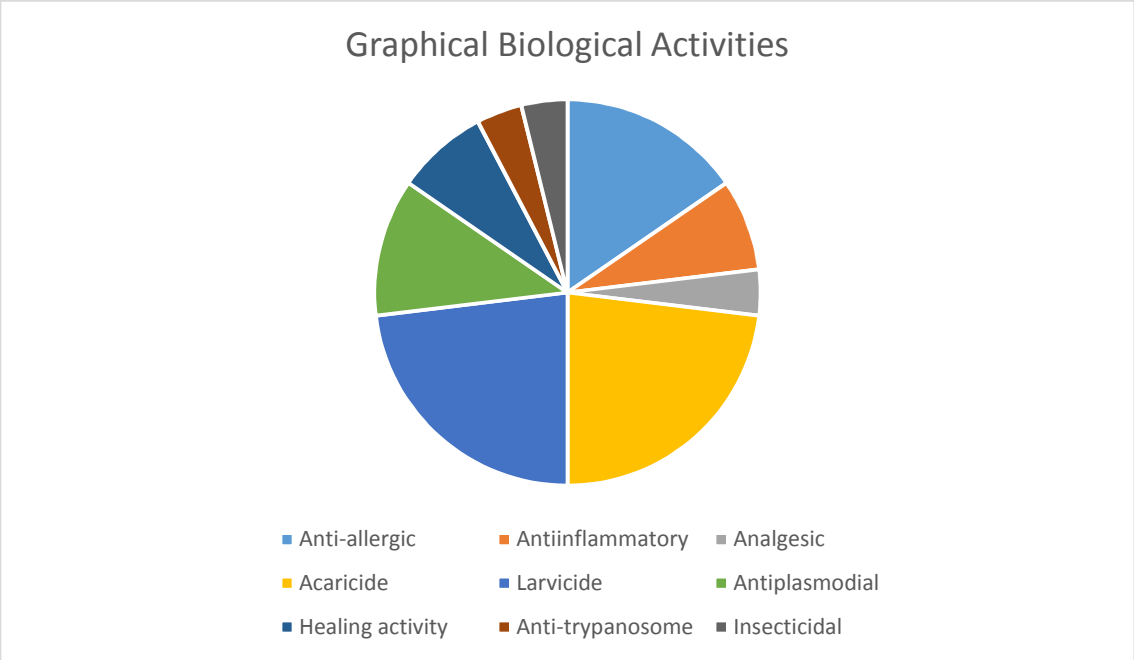
Another patent deposited in various countries, except Brazil, uses the "Andiroba" chestnut extract in topical formulations to prevent cellulite[56, 57].

DISCUSSION

According to the literature, it can be noted that there are numerous articles that testify a popular use of "Andiroba" in pharmaceutical treatments. Graphic 1 quantifies the described items and their perspective activities.

Among the work described, can b observed that isolates fractions of "Andiroba" oil containing tetranortriterpenoids demonstrated high bioactive potential regarding anti-allergic activities, analgesic, anti-inflammatory and anti-malarial drugs, as shown in Table 1.

Graphic 1. Index of described activities

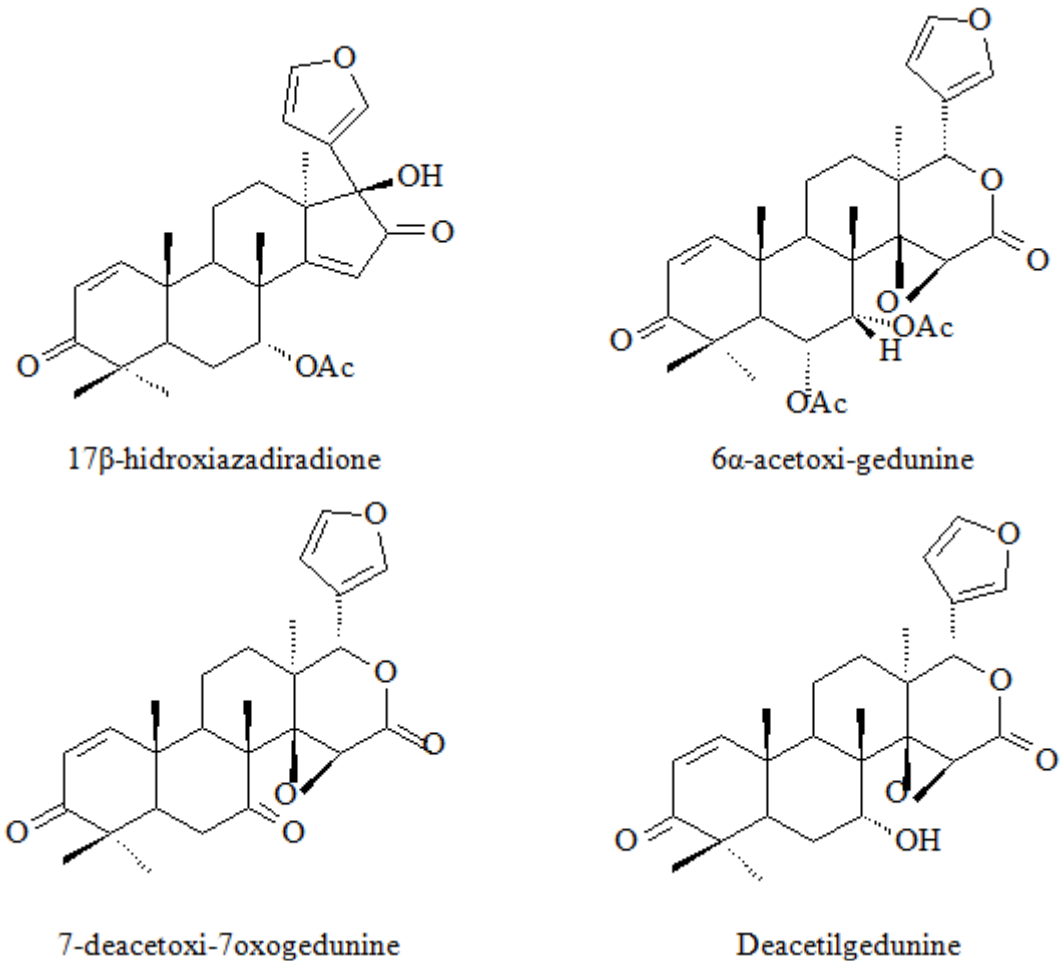


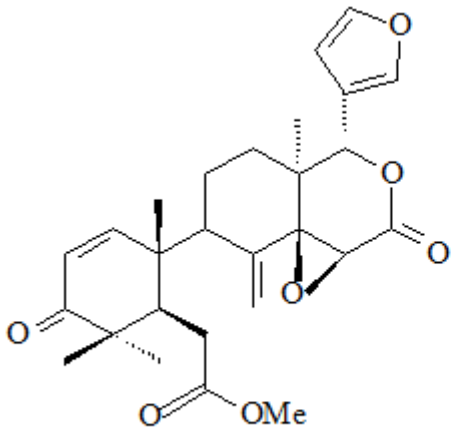
However, other substances extracted from the seeds and andiroba flowers, known as carapanolides, andirolides and guianolides, were discovered recently and preliminary studies have shown positive cytotoxic activity (Table1), thus indicating a need for more studies to prove possible antitumor activities and even a discovery of new pharmacological activities.

Table 1. Classification of substances as the bioactive potential

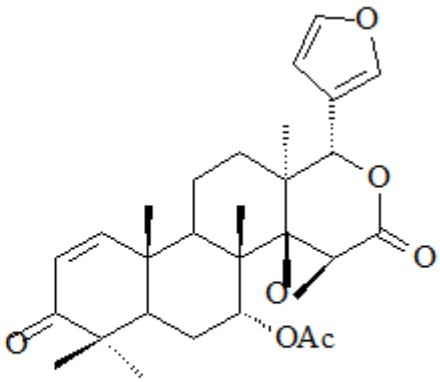
Biologicalactivity	Chemicalclass	Substance	Reference
Anti-allergic/ Antiinflamatory/ Analgesic	TNTP	6a-acetoxigedunine	[13, 8]
Anti-allergic/ Antiinflamatory/ Analgesic	TNTP	7-desacetoxine-7-oxogedunine	[13, 8]
Anti-allergic/ Analgesic	TNTP	Andirobin	[13, 14]
Anti-allergic/ Analgesic	TNTP	Metil angolensate	[13, 14]
Anti-allergic/ Analgesic	TNTP	6Aacetoxiepoxaazadiradione	[13, 14]
Anti-allergic/ Antiinflamatory/ Antiplasmodial/ Analgesic	TNTP	Gedunine	[13, 14, 29, 35]
CytotoxicActivity	Carapanolides	Carapanolides A, C, D, E, F, e I	[19, 20, 21]
Anti-hypertensive	Carapanolides	Carapanolides J	[21]
CytotoxicActivity	Andirolides	Andirolides A, G, S e T	[24, 26]
Antiplasmodial	Andirolides	Andirolides H	[25]
CytotoxicActivity	Guianolides	Guianolides A	[28]

Fig. 1. Tetranortriterpenoids isolated from *C. guianensis*

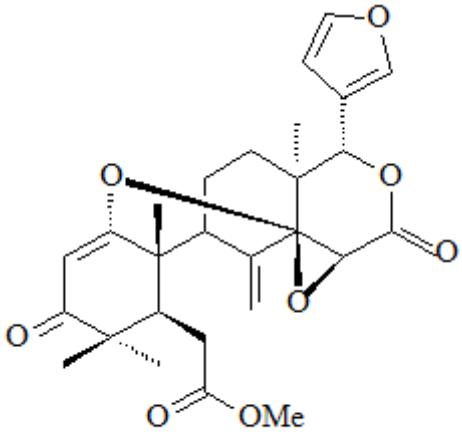




Andirobin

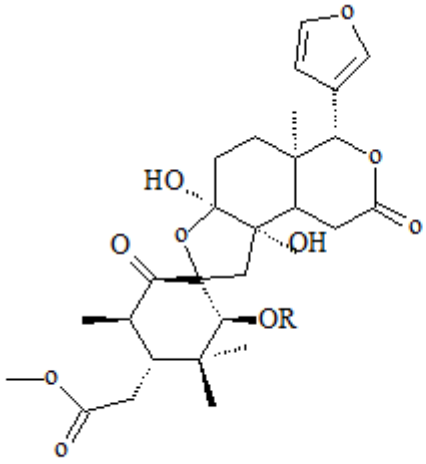


Gedunine

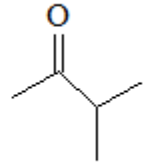


Metil-agolensate

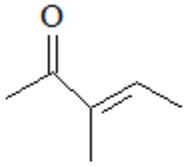
Fig. 2 Carapanolides isolated from *C. Guianensis*



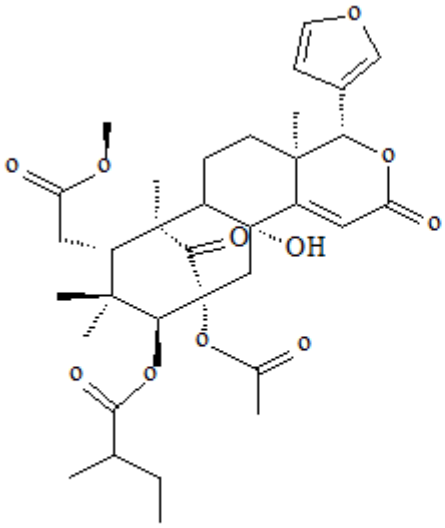
Carapanolides A: R =



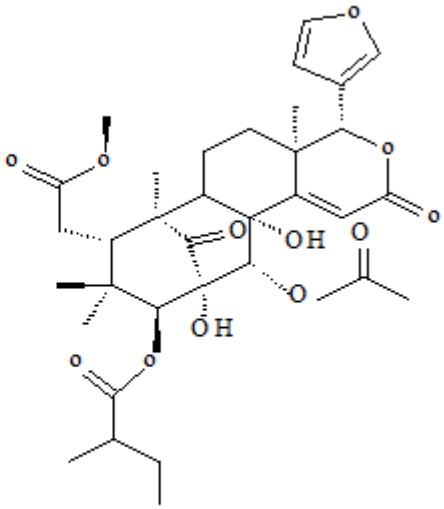
Carapanolides B: R =



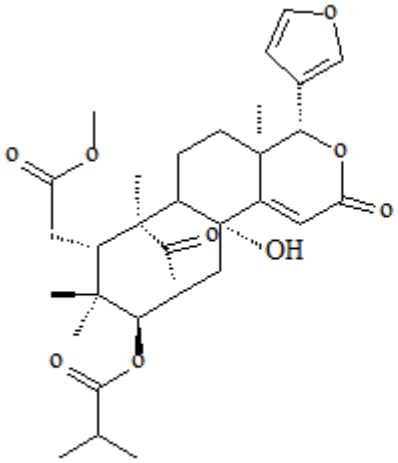
Structure of Carapanolides A and B.



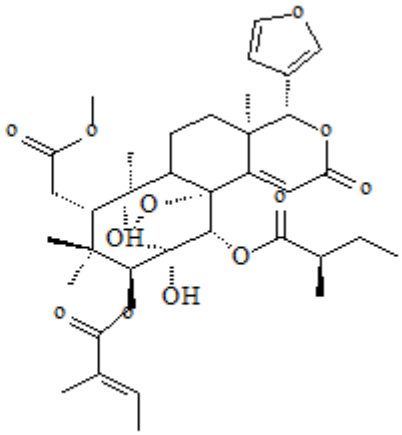
Carapanolides C



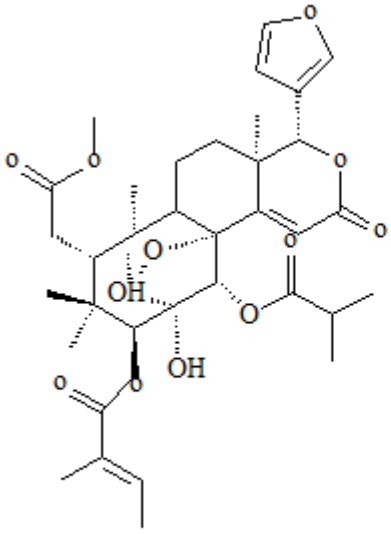
Carapanolides D



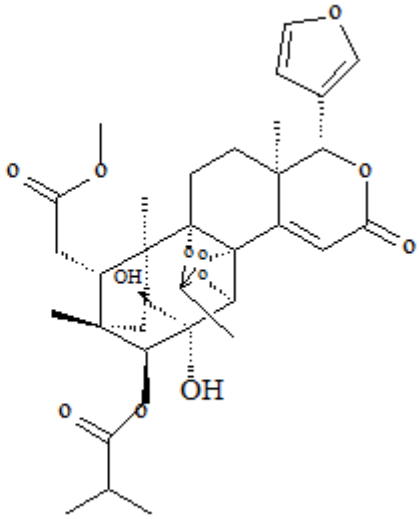
Carapanolides E



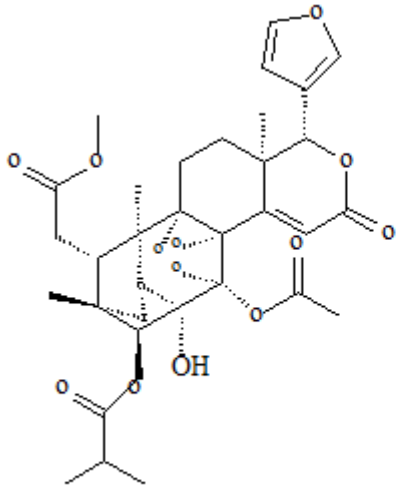
Carapanolides F



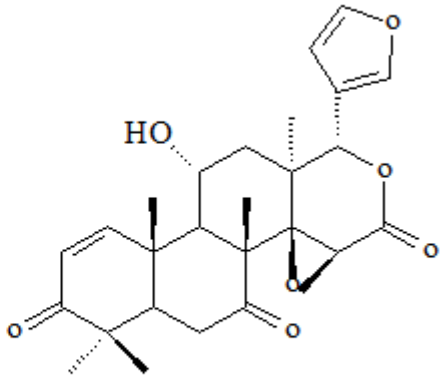
Carapanolides G



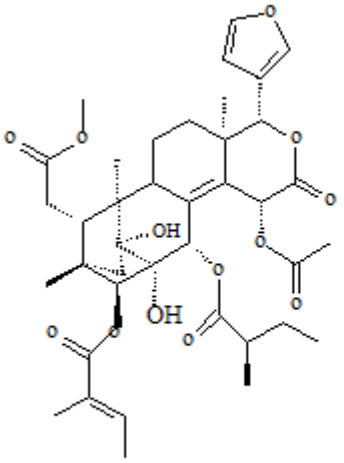
Carapanolides H



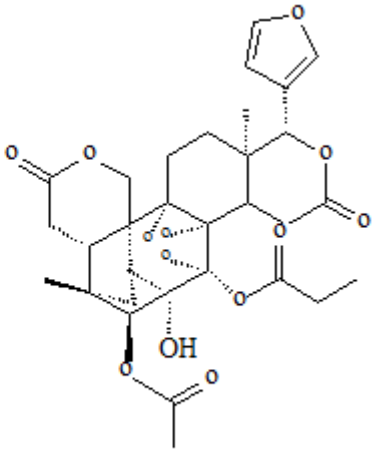
Carapanolides I



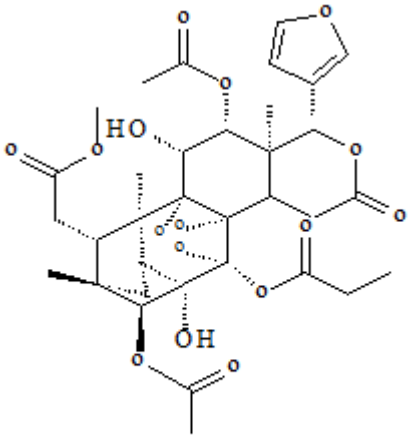
Carapanolides J



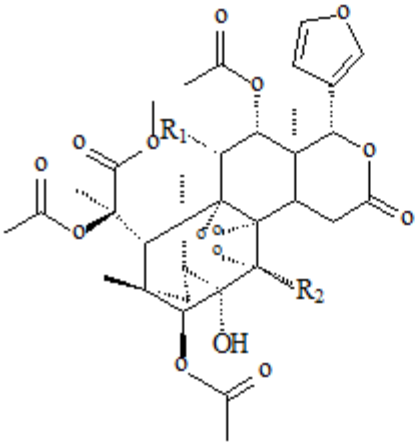
Carapanolides K



Carapanolides L



Carapanolides M



Carapanolideos:

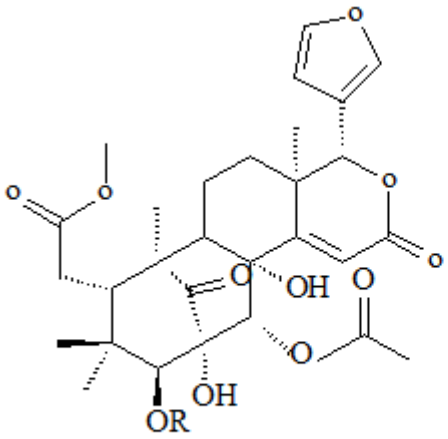
N: R1 = OAc, R2 = 2-methylpropanoyl

O: R1 = OH, R2 = 2-methylpropanoyl

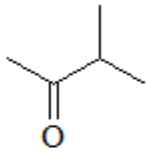
P: R1 = OH, R2 = propanoyl

Q: R1 = H, R2 = propanoyl

Structura of Carapanolides N, O, P and Q.



Carapanolides R: R =



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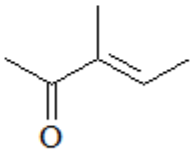
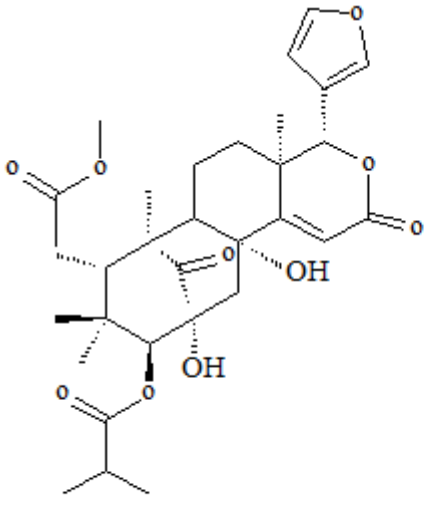
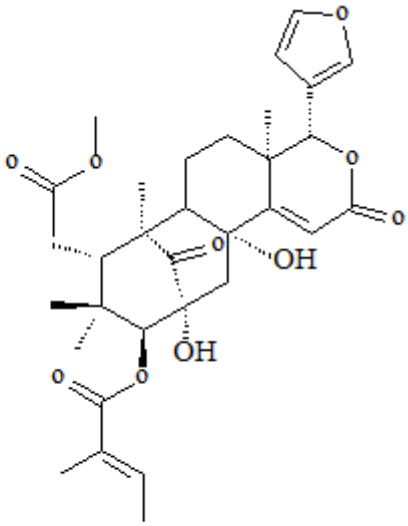


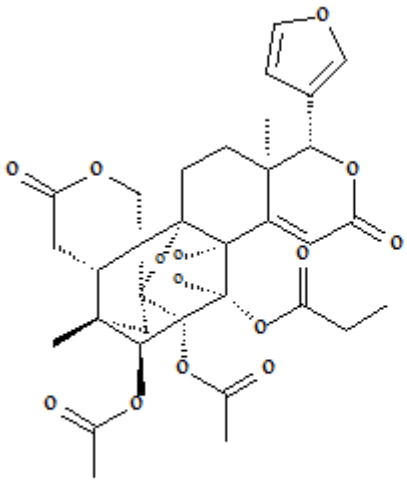
Structure of Carapanolides R and S.



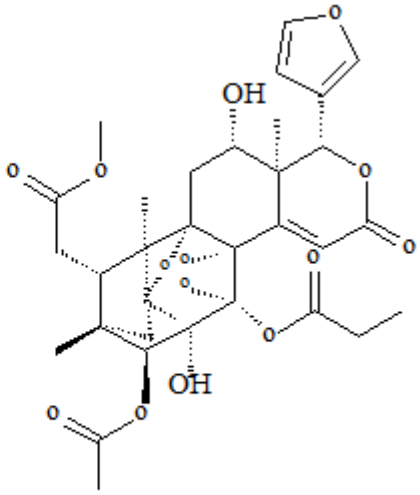
Carapanolides T



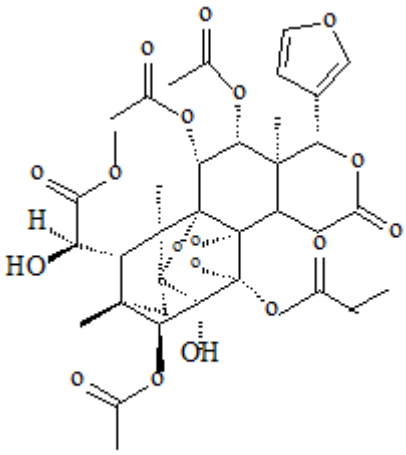
Carapanolides U



Carapanolides V

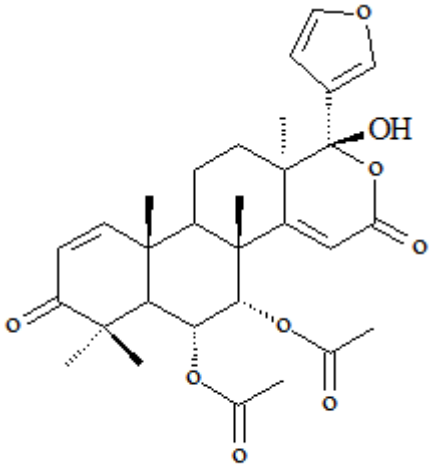


Carapanolides W

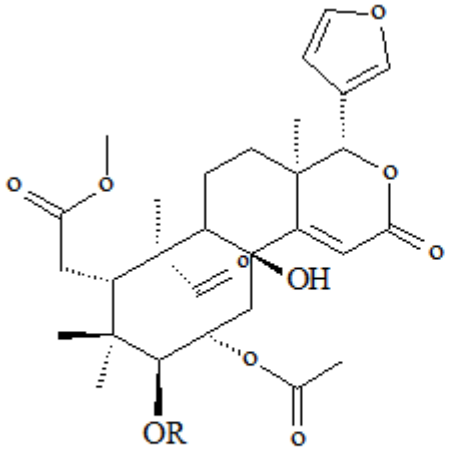


Carapanolides X

Fig. 3 Andirolides isolated from *C. Guianensis*

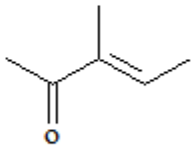


Andirolides A

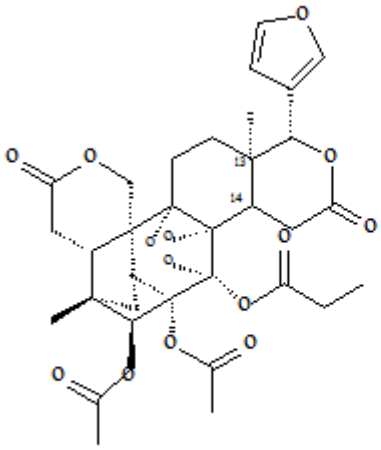


Andirolides B: R = Ac

Andirolides C: R = COCH(CH3)2

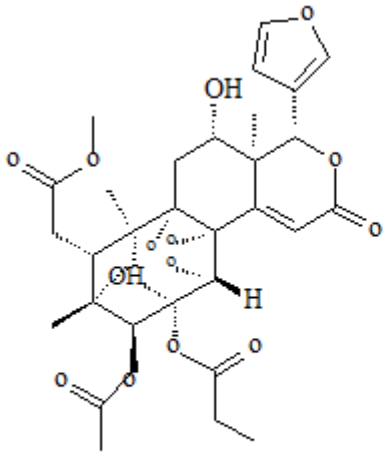
Andirolides D: R = 

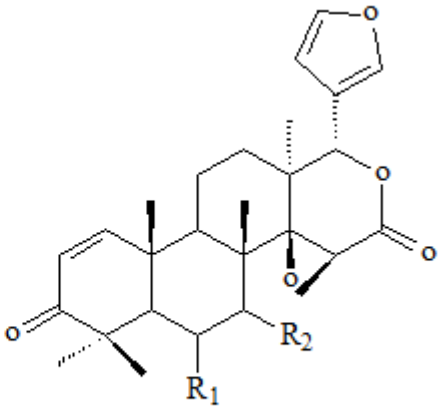
Structure of Andirolides B, C and D.



Andirolides F: R = Δ14, 15 –ene

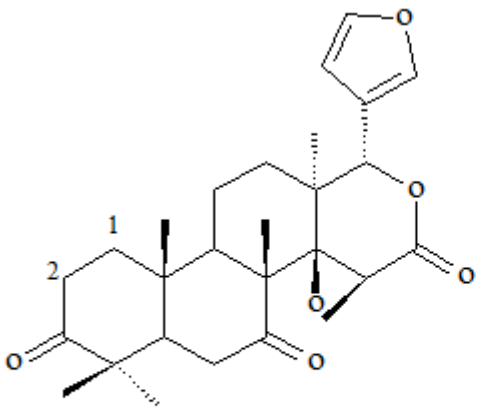
Structure of Andirolides E and F.



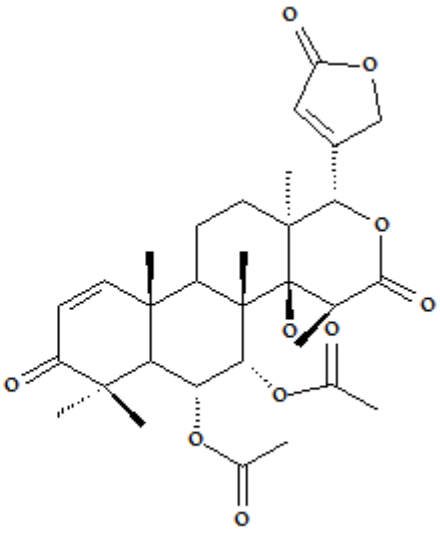


Andirolides G

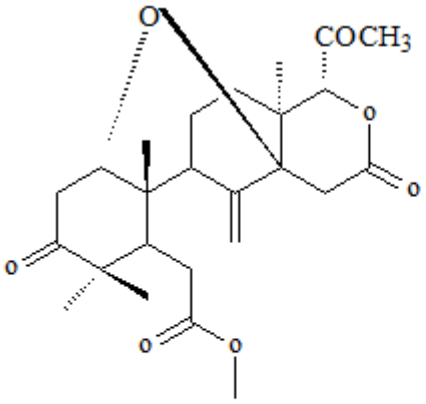
Andirolides H: R1 = α-OAc, R2 = α-OH



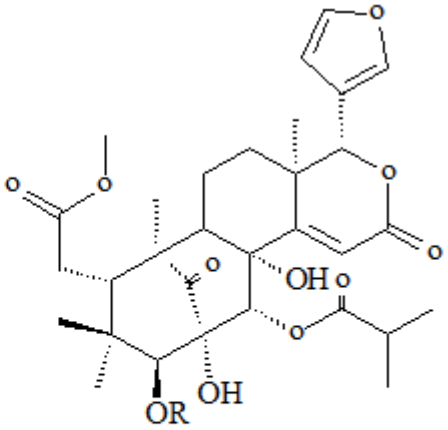
Andirolides I, 1α, 2α-epoxy



Andirolides J



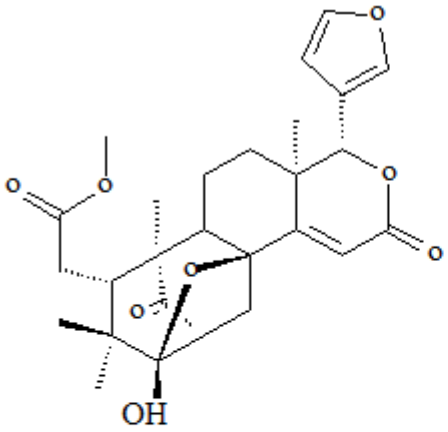
Andirolides K



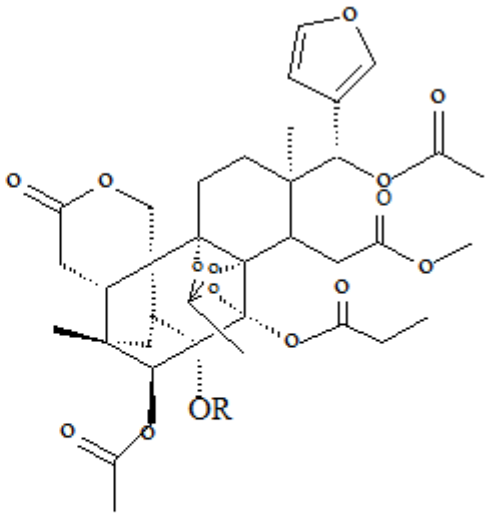
Structure of Andirolideos L and M.

Andirolides L: R = Tig

Andirolides M: R = COCH(CH3)2



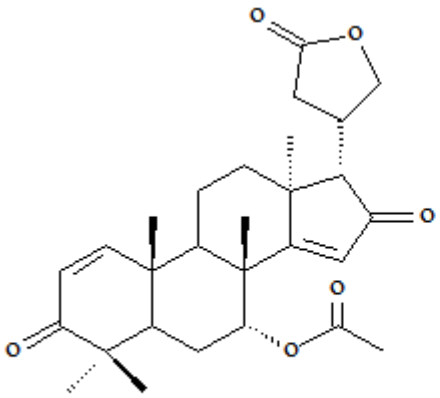
Andirolides N



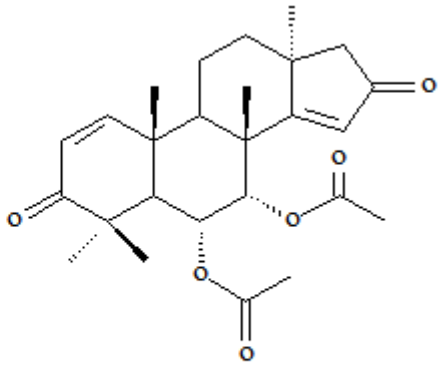
Structure of Andirolides O and P.

Andirolides O: R = Ac

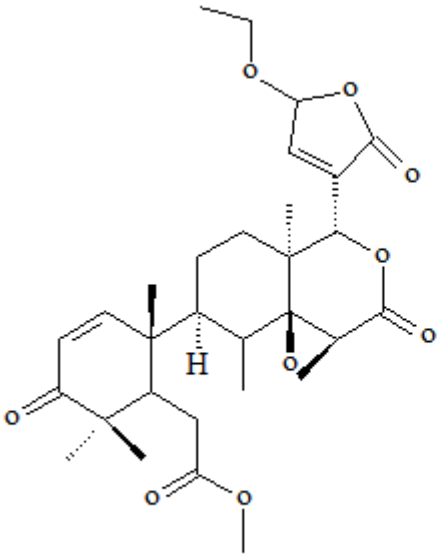
Andirolides P: R = H



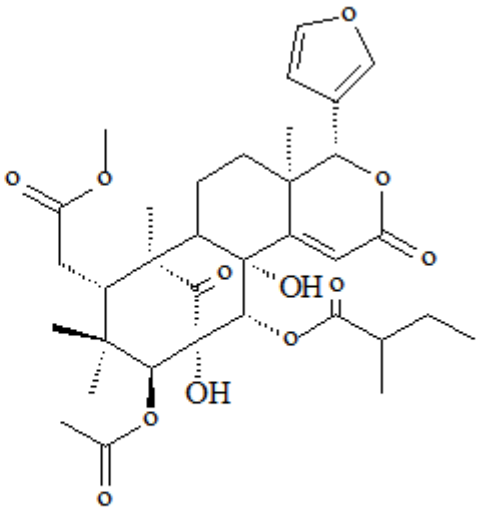
Andirolides Q



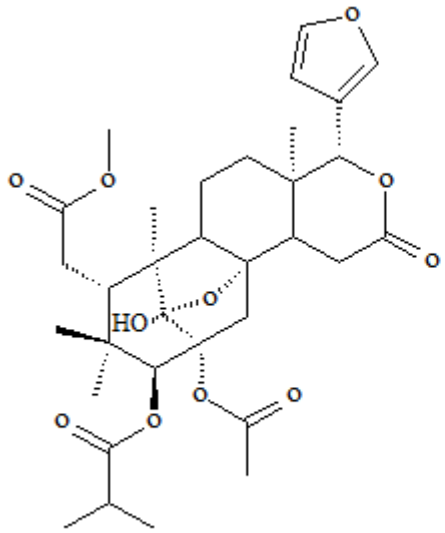
Andirolides R



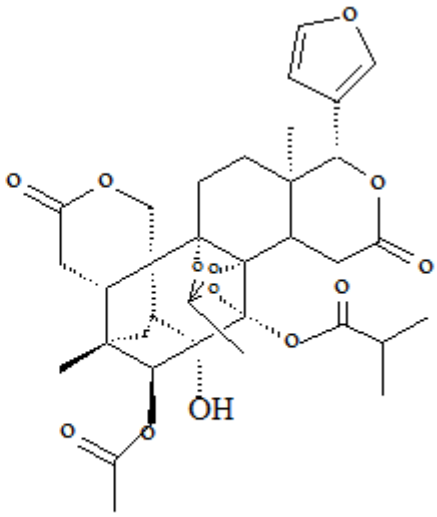
Andirolides S



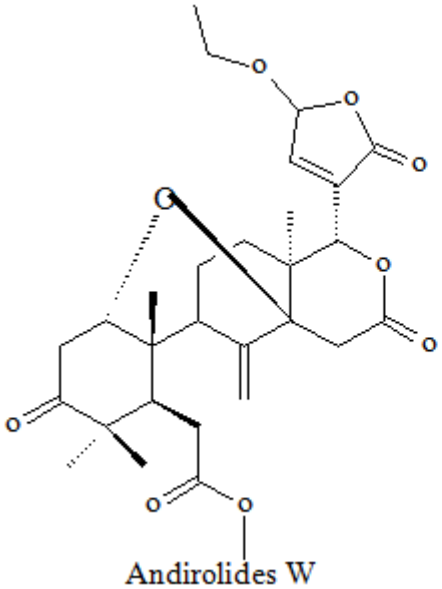
Andirolides T



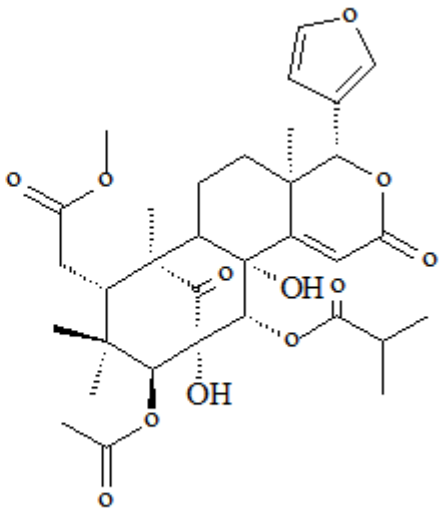
Andirolides U



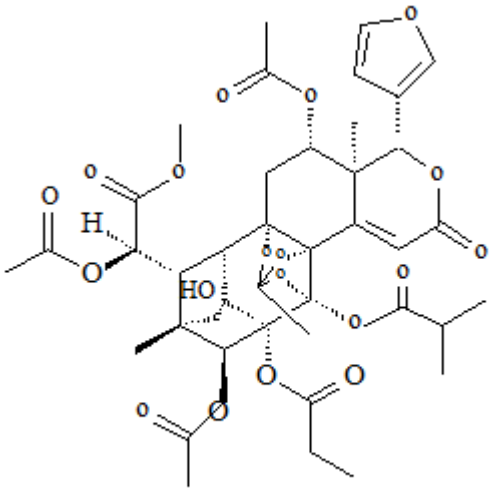
Andirolides V



Andirolides W

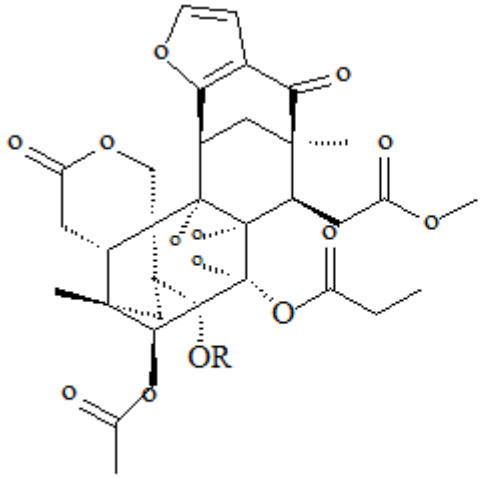


Andirolides X



Andirolides Y

Fig. 4 Guianolides isolated from *C. Guianensis*



Guianolides A: R = Ac

Guianolides B: R = H

Structure of Guianolides A and B.

CONCLUSION

This review had been compiled the most diverse works that described several biological tests, in order to identify different pharmacological activities attributed to the "Andiroba" oil. Such information not only testify or not the folk medicine.

Therefore, had been observed that tetranortriterpenoids are promising molecules in several treatments, presenting a growing need for further studies, these being applied to biological assays.

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