Review

“Sweet and Horny”: Biological Activities of the Annonaceae Family

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Review

"Sweet and Horny": Biological Activities of the Annonaceae Family

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Abstract

Natural products are sources of secondary metabolites with various biological activities. This review highlights the promising potential of the Annonaceae family, a large clade of flowering plants with 107 genera and over 2300 species. Known for their vast pharmacological activities, several genera and species within this family are considered excellent sources of bioactive molecules due to the diversity of their secondary metabolites. Chemical investigations have revealed the presence of alkaloids, mainly isoquinolinic alkaloids, phenolic compounds, terpenoids, lactones, and acetogenins. The Annonaceae family exhibits anti-inflammatory, insecticidal, antimicrobial, leishmanicidal, cytotoxic, antitumor, trypanocidal, antioxidant, gastroprotective, and antimalarial activities. However, most studies focus on plant extracts and essential oils, with few isolated molecules and mechanisms of action identified. Investigating the biological activity of isolated compounds is crucial for new drug discovery. This review also compiles important information for the pharmaceutical and agricultural industries.

Keywords: annonaceae; bioactivity; natural products; biological activities

1. Introduction

In addition to carrying out photosynthesis, plants also produce secondary metabolites, chemical molecules that can eventually play a biological role in living beings (Moghadamtousi et al. 2013; Ma et al. 2017). Thus, plants are among the main sources for new therapeutic drug candidates (Newman and Cragg 2016; Aminimoghadamfarouj et al. 2020).

Drugs produced from molecules obtained from plants frequently have important advantages over non-plant based products; they exhibit reduced side effects (as well as excellent efficacy and safety) and increased accessibility, which in turn decreases cost and contributes to more sustainable production process. All of this increases the incentive to search for new plant-based therapeutics (Pan et al. 2013; Chakraborty 2018; Sharifi-Rad et al. 2018; Tekuri et al. 2019; Mohammadi et al. 2020).

The Annonaceae family, first described by Antonie Laurent de Jussieu in 1789, stands out as one of the most anatomically and structurally uniform families (Cronquist 1981; Doyle et al. 2004; Cunha 2009; Silva and Domingues Neta 2011). It is one of the richest families of the Manoliophyta (flowering plant), having 107 genera and roughly 2400 species currently recognized (Guo et al. 2017). The Annonaceae has Pantropical distribution in the world, but requires specific characteristics of soil,

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altitude, temperature and humidity for growth, limiting its distribution to other regions (Popenoe 1921; Encina et al. 2014; Ferreira et al. 2019).

The Annonaceae is rich in fruit species, most of which are edible, making it the target of many studies (Ribeiro et al. 1999; Cunha 2009; Rabêlo 2014). Annonaceae are known for having many bioactive secondary metabolites with vast pharmacological activities. In addition to the classic secondary metabolite classes such as alkaloids, flavonoids, terpenes, etc., Annonaceae are characterized by the presence of isoquinoline alkaloids and acetogenins, a compound class exclusive to this family (Leboeuf et al. 1980; Bermejo et al. 2005; Aminimoghadamfarouj et al. 2011; Cortes et al. 2014). Thus, the Annonaceae family has been massively studied to explore potentially bioactive metabolites.

The objective of this review is to highlight the biological activities recorded by Annonaceae derived compounds and to emphasize the significance of these plants as a source of new therapeutics.

2. Methodology

Information was collected from the literature regarding the biological use of the Annonaceae plants as well as their extracts, essential oils, and secondary metabolites. The articles were collected from Web of Science, PubMed and ScienceDirect using the keywords “Annonaceae”, “Biological activity”, “Activity”, “Pharmacological activities”, and “Biological properties”. Articles were collected through April 2022, and those focusing on synthesis or semi-synthesis, even if inspired by compounds isolated from Annonaceae, were excluded.

3. Results and Discussion

Plants in the Annonaceae family have been widely used in traditional medicine and are well known in the tropical regions of the world. Some traditional uses include the treatment of arthritis, rheumatism, and neuralgia (Cercato et al. 2015), asthma (Auddy et al. 2003; Bhalke and Chavan 2011), wound healing (Tan et al. 2015), cancer (Cascaes et al. 2021), parasitic infections (Moghadamtousi et al. 2015b), as well as fever, diabetes, insomnia, and headaches (Attiq et al. 2017; Cascaes et al. 2021).

As mentioned earlier, the Annonaceae family comprises of approximately 2400 species. Our review includes analysis of about 177 species with proven biological activity, constituting roughly 7.37% of known Annonaceae species. These species are spread across 56 genera, representing 52.33% of all Annonaceae genera. These 56 genera encompass the four subfamilies of Annonaceae (Malmeoideae, Annonoideae, Anaxagoreoidae, and Ambabavioideae), with 8.92% belonging to the Ambavioideae and Anaxagoreoideae subfamilies, which lack tribes. The remaining 91.08% are distributed among seven tribes of Annonoideae and three tribes of Malmeoideae. These data are depicted in a Venn diagram in Figure 1, where the larger square represents the Annonaceae family with its four subfamilies, denoted as circles A, B, C, and D. Within A and B, the Annonoideae and Malmeoideae subfamilies respectively, there are tribes, illustrated by the smaller circles A1 and B1. C represents the Ambavioideae subfamily and D represents the Anaxagoreoideae subfamily. The species examined in the review article are highlighted in red.

The activities listed as “other” include: anti-convulsant activity (Okoye et al. 2013; Moghadamtousi et al. 2015a; Manoj Kumar et al. 2021), anti-*Onchocerca,* (Dikti Vildina et al. 2021), anti-hyperprolactinemic (Yakubu and Fayemo 2021), α-Glucosidase inhibitory (Suthiphasilp et al. 2021), anti-diabetic (Shirwaikar et al. 2004; Kaleem et al. 2008; Mohd et al. 2009; Qi et al. 2010; Basha and Subramanian 2011; Brindis et al. 2013; Ahalya et al. 2014; Florence et al. 2014; Sahu et al. 2016; Calzada et al. 2017, 2019; Coria-Téllez et al. 2018; Taha et al. 2018; Alsenosy et al. 2019; Mazumdar et al. 2021; Chowdhury et al. 2021; Martínez-Solís et al. 2021), antidiarrhea (Owusu et al. 2021), anti-SARS-CoV-2 (Prasad et al. 2021), anti-acetylcholinesterase (Leite et al. 2021), anthelmintic (Nwosu et al. 2022), antischistosoma (Matchi et al. 2022), anti-Platelet aggregation (Yang et al. 2002), apoptosis induction (Chen et al. 2004; Machana et al. 2012; Pumiputavon et al. 2017), testicular function (Abarikwu et al. 2017), anti-HIV (Piacente et al. 1994; Yang-Chang Wu et al. 1996; Chang et al. 1998;

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Wafo et al. 1999; Wu et al. 2003; Ding et al. 2010; Saepou et al. 2010; Hongthong et al. 2016; Silprakob et al. 2018; Yu et al. 2019), antiviral activity (Betancur-Galvis et al. 1999; Paredes et al. 2001; Kanokmedhakul et al. 2006; Paarakh et al. 2009; Gajalakshmi et al. 2012; Gavamukulya et al. 2014; Silva et al. 2016), anxiolytic-like activity (López-Rubalcava et al. 2006; Rejón-Orantes et al. 2011), antidepressant (Martínez-Vázquez et al. 2012), and anti-hypertensive (Nwokocha et al. 2012). Herein, we discuss the studies of the most common biological therapeutic aims of the previous studies.

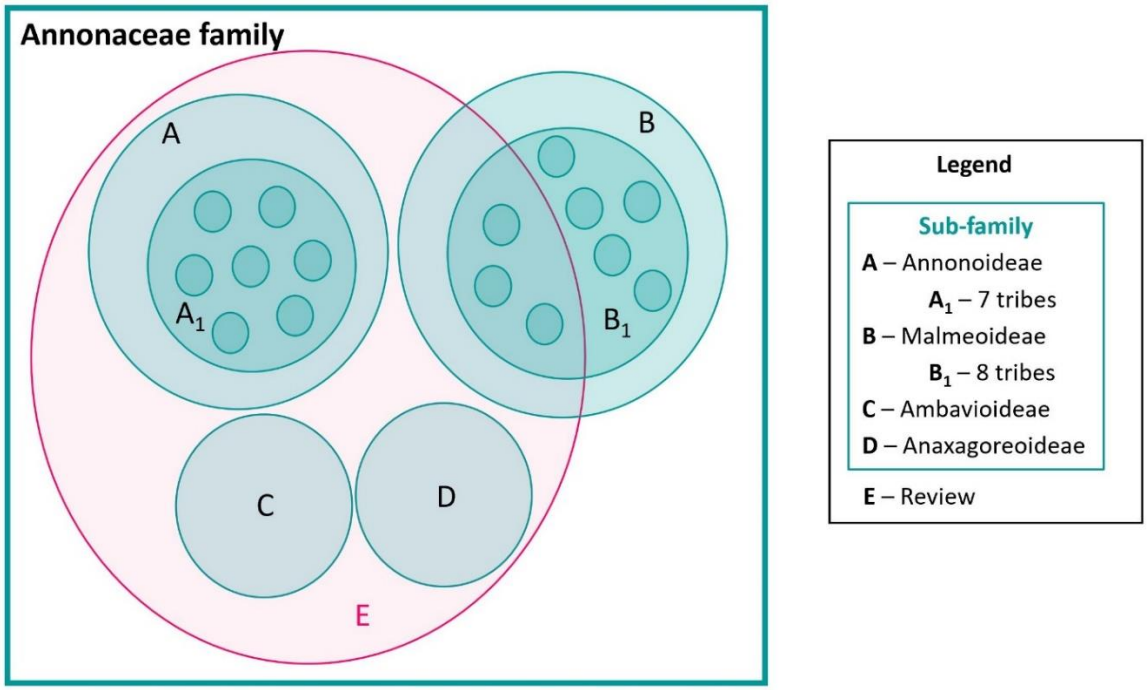
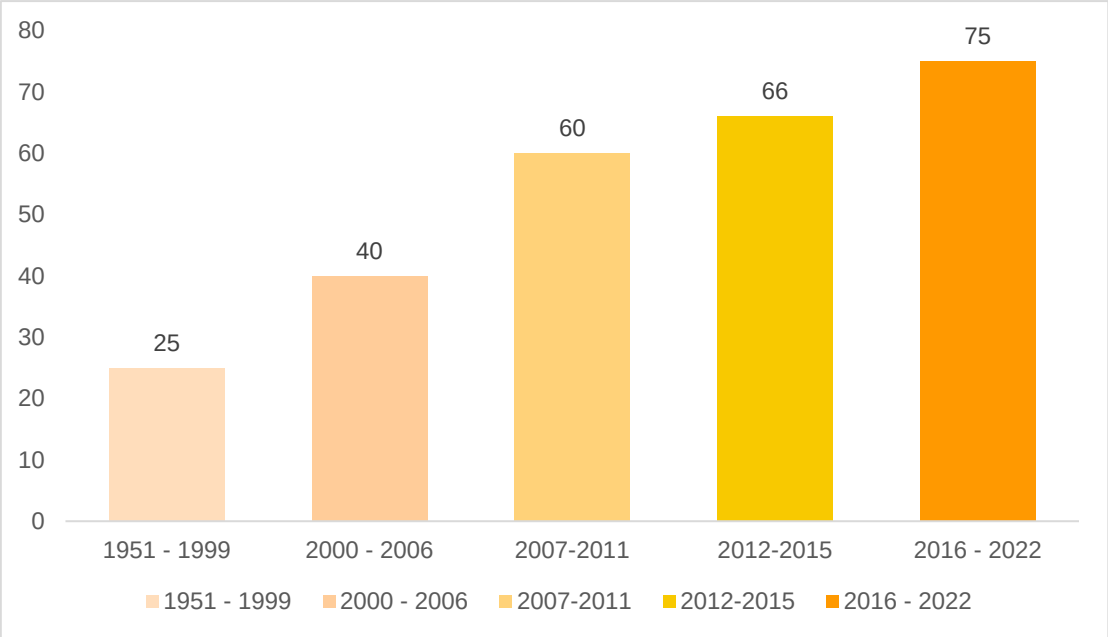


Figure 1. Venn diagram of the subfamilies of species with biological activity reported by the studies covered in this review.

Graph 1 represents the number of articles evaluated in this review grouped by years and in it, one can observe the growth in interest surrounding the Annonaceae family, particularly since 2006 (Menezes et al. 2021). Given the rich structural diversity, it is easy to understand this increase in the search for bioactive Annonaceae-based substances (Menezes et al. 2021).



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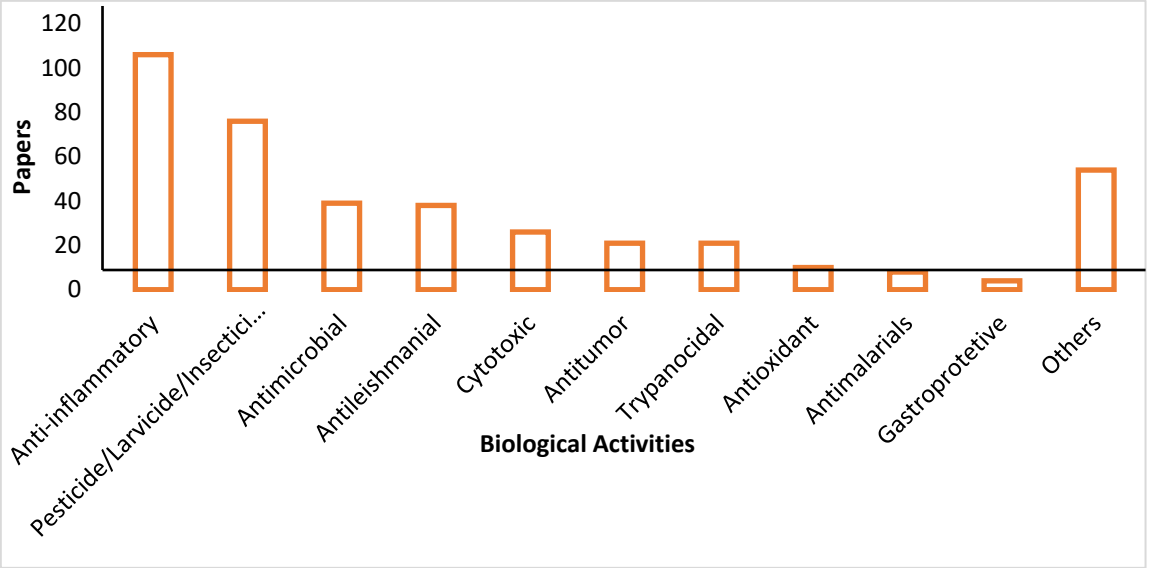
Graph 1. Distribution of papers analyzed in this review over time, based on their year of publication.

Our bibliographic survey on biological activities of the Annonaceae resulted in many published bioactivities for a variety of disease states. Graph 2 depicts the number of articles collected for each disease, and due to their prevalence, the top 10 will be discussed in this review.



Graph 2. Number of articles collected for each biological activity already studied for the Annonaceae.

3.1. Anti-Inflammatory

Inflammation is a physiological response triggered by several factors, such as physical trauma, exposure to allergens, chemical stimuli, infections, etc (Wilson and Trumpp 2006; Guo et al. 2015; Attiq et al. 2017). The inflammatory process can also be initiated by tissue malfunctions or disruptions in homeostasis (Nathan and Ding 2010). In this context, inflammation serves as a protective immune response capable of restoring the body's homeostasis. However, if unregulated, it can become harmful and lead to several diseases, such as autoimmune diseases (rheumatoid arthritis), hypertension , obesity, and cancer, among others (Jachak 2006; Huscher et al. 2009; Nathan and Ding 2010; Attiq et al. 2017).

Inflammation is didactically divided into two phases, the acute phase, and the chronic phase. The acute phase is characterized by the initial stages of inflammation, the emergence of the five cardinal signs of inflammation: pain, heat, redness, swelling, and loss of function (Sedgwick and Lees 1986; Serhan 2010). It also exhibits vasodilation, exudation of protein-rich plasma fluid, and migration of cells to the site of injury. When inflammation is persistent, the chronic phase begins, inducing changes in the composition of infiltrating leukocytes, that is, the replacement of neutrophils with high concentrations of lymphocytes and macrophages (Sherwood and Toliver-Kinsky 2004; Aller et al. 2007). The chronic phase has a prolonged duration, lasting anywhere from several months to years and is associated with blood vessel proliferation, fibrosis, and tissue necrosis. Inflammatory responses tend to present clinically in a progressive way, combining elements of the two phases (Sherwood and Toliver-Kinsky 2004; Fujiwara and Kobayashi 2005).

Several medications such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying anti-rheumatic drugs (DMARDs) are available for the treatment of painful and life-threatening inflammatory conditions (Hoes et al. 2010; Weber and Noels 2011; Attiq et al. 2017). Prolonged use of these drugs can induce toxicity delivering side effects such as uncontrolled hypertension, gastric ulcer, acute kidney failure, liver failure, heart failure, glaucoma, etc (Jachak 2006; Huscher et al. 2009; Attiq et al. 2017). This toxicity remains a major concern with these treatments.

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Attiq, Jalil and Husain, 2017, carried out a literature review study highlighting the great potential of the Annonaceae family in fighting inflammation, pointing out isolated substances as great candidates for possible drugs. The authors further highlight terpenes as a promising secondary metabolite class in anti-inflammatory activity. However, there is still much to be studied in the Annonaceae family, especially in the elucidation of substances with biological potential, given the evidence for extracts with potent anti-inflammatory activity. Due to the abundance of studies discussing this anti-inflammatory potential, data from all these studies are summarized in Table 1, and some are discussed below to highlight the variety and complexity of the inflammatory pathways involved. Overall, these products and their derivatives are shown repeatedly to have significant anti-inflammatory activity, regularly displaying IC_{50} values below that of the therapeutic controls.

Xylopia genus

Xylopia aethiopica is a plant commonly used in African traditional medicine for the healing of wounds, inflammatory disorders, and the treatment of post-natal pain. Based in this traditional knowledge, in 2010 an oil extract from the fruits of *Xylopia aethiopica* was studied by Ezekwesili et al (2010). Specifically, the effects of the oils carbohydrates, glycosides, flavonoids, saponins, tannins and phytosterols on cell membrane stability and prostaglandin synthetase activity were evaluated (Ezekwesili et al. 2010).

The fruit of . *aethiopica* is recognized as a source of unsaturated fatty acid. This was demonstrated by HPLC studies of the lipid extract confirming the presence of palmitic acid (19.21%), palmitoleic acid (0.81%), stearic acid (4.54%), oleic acid (39.12%), linoleic acid (25.98%) and linolenic acid (1.10%). The *X. aethiopica* extract demonstrated the ability to stabilize the erythrocyte membrane, which the authors associated with the stabilization of the lysosomal membrane, a well-known marker of anti-inflammatory potential in drugs. This extract also preserved cellular membrane integrity and acted as a substrate for prostaglandin synthetase, thereby promoting prostaglandin biosynthesis (Ezekwesili et al. 2010).

Xylopic acid is the main compound isolated from the dried fruit of *X. aethiopica*. Anti-inflammatory effects of this acid have been observed specifically in H2S-induced paw edema models, and demonstrate its intervention along the arachidonic acid pathway (Osafo et al. 2016). The same authors found that xylopic acid was effective in suppressing experimentally induced ulcerative colitis by increasing superoxide dismutase (SOD), ascorbate peroxidase (APX), and catalase (CAT) activity (Osafo et al. 2019). These enzymes had been previously identified as prime biomarkers for colon damage, and treatment with xylopic acid treatment resulted in significantly increased expression in the three enzymes at all administered doses (10-100 mg kg^{-1}). Additionally, rats showed reduced mucosal injury, granulomatous inflammation, and cellular proliferation. Finally, the levels of myeloperoxidase (MPO) and malondialdehyde (MDA), both reactive oxygen metabolites (ROMs), were reduced with all treatments of xylopic acid (Osafo et al. 2019). These two compounds are released by immune cells and play an important role in the physiopathology of ulcerative colitis, where upregulation is an indication of oxidative damage and free radical-induced lipid peroxidation (Liu and Wang 2011).

The anti-inflammatory effects of *X. aethiopica* leaves may involve phenolic compounds identified through HPLC-DAD, including cynaroside, rutin, quercitrin, astragalin, and nicotiflorin. O-caffeoylquinic acids and the luteolin monoglycoside cynaroside were also detected in the extract (Macedo et al. 2020).

The anti-inflammatory properties of essential oils obtained from eight batches of *X. aethiopica* fruits from Ghana and Nigeria were obtained by hydrodistillation and tested on RAW 264.7 macrophage cells. The results showed that the oils inhibit NO production in LPS-stimulated RAW264.7 cells concentration-dependently, and better than the control drug, dexamethasone. The oils from Ghana demonstrated better anti-inflammatory effects than those of Nigerian origin, and the authors suggested this was due to the synergistic effects of the 14 different metabolites commonly found in the extract (Alolga et al. 2019).

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Other species of *Xylopia*, including *Xylopia parviflora*, *Xylopia sericea*, and *Xylopia vielana*, have also been investigated. The essential oil from striped African pepper (*Xylopia parviflora*) was studied at different concentrations in RAW 264.7 macrophages stimulated with LPS and shown to decrease NO production by 37% (Woguem et al. 2014). However, a chemical profile of this essential oil (finding mainly β-pinene (34.0%) and α-pinene (10.3%)), does not report any compounds previously identified as anti-inflammatory (Woguem et al. 2014).

An in-silico analysis assessed the anti-inflammatory potential of five guaiane-type sesquiterpene dimers, known as xylopidimers A-E, extracted from *Xylopia vielana*. Molecular docking was performed on the COX-2 protein as anti-inflammatory target (PDB: 1CX2). All the five evaluated dimers showed potent inhibitory activity against COX-2, with binding energy values among -10.51 Kcal/mol and -9.23 Kcal/mol, significantly lower than the controls Ibuprofen and Felbinac (Hassan et al. 2022). Molecular dynamics simulations suggested that these guaiane-type sesquiterpenes allow a ligand-protein stability. This in silico work is one of the few studies that report specific secondary metabolites together with the xylopic acid, since most anti-inflammatory assays for this genus are of the polar extracts.

Annona genus

In a bio-guided fractionation study, the anti-inflammatory activity of the hydromethanolic extracts of the leaves, pulp, and seeds of *Annona cacans* were evaluated in a paw edema model. These compounds inhibited the increase in MPO activity after 6 hrs when compared to both the dexamethasone and control groups (Volobuff et al. 2019).

Similarly, a polyphenol-enriched fraction of *Annona crassiflora* collected in Brazil was studied to evaluate its anti-inflammatory activity. The main components were identified as chlorogenic acid, epi-catechin, procyanidins B2 and C1, quercetin-glucoside, kaempferol, and caffeoyl-glucoside (de Moura et al. 2019). Through ^{1}H NMR studies, kaempferol 3-O-β-glucoside and kaempferol 3-O-β-diglucoside were identified in the extract of *Annona crassiflora* and experimentally determined to inhibit paw edema, reduce myeloperoxidase activity, and reduce the total leukocyte count (Rocha et al. 2016). These results were complimentary to those observed by De Moura et al., 2019, (de Moura et al. 2019)using the polar extracts of this species.

The lyophilized fruit extract of another species of this genus, *Annona muricata,* which is found in different tropical regions and is commonly used in Africa, was studied *in vivo* and found to possesses analgesic and anti-inflammatory activities in various models (Ishola et al. 2014).

Several compounds from *Annona squamosa* L. and *Annona reticulata* L. barks were evaluated *in vivo* by Chavan et al., including a sesquiterpene fraction composed of copaene (35.40%), patchoulane (13.49%) and 1H-cycloprop(e)azulene (22.77%) (Chavan et al. 2012) as well as caryophyllene oxide (Chavan et al. 2010a), 18-acetoxy-ent-kaur-16-ene (Chavan et al. 2011) and saponified petroleum ether extract from the bark of *Annona reticulata L.* bark (Chavan et al. 2010b). All of these compounds exhibited anti-inflammatory activity, with many also demonstrating analgesic effects.

The anti-inflammatory properties of eight ent-kauranes were evaluated using fruits from *Annona glabra*, including three novel compounds: 7β,16α,17-trihydroxy-ent-kauran-19-oic acid, 7β,17-dihydroxy-16α-ent-kauran-19-oic acid 19-O-β-D-glucopyranoside ester, and 7β,17-dihydroxy-ent-kaur-15-en-19-oic acid 19-O-β-D-glucopyranoside ester. All tested ent-kauranes demonstrated greater inhibition of NO production compared to the control, dexamethasone (Nhiem et al. 2015).

Duguetia genus

The essential oil of *Duguetia furfuracea*, consisting of 24 volatile compounds, demonstrated significant inhibition of LPS-induced inducible nitric oxide synthase (iNOS) expression. It also reduced tumor necrosis factor alpha (TNF-α) production and inhibited the recruitment of polymorphonuclear leukocyte*s* (Saldanha et al. 2019). Furthermore, extraction and enrichment of the phenylpropanoids further attenuated the disease states through the same pathways (Saldanha et al. 2020, 2021). Using leaves of this same species, a methanolic extract with high contents of phenols (624.37 mg/g), flavonoids (580.21 mg/g), and flavonols (254.44 mg/g) was obtained and showed significant decrease in inflammation in edema (do Santos et al. 2018).

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Duguetia staudtii is a species found in Africa, mainly in a forest from Sierra Leone to Cameroon. The anti-inflammatory activity of eight compounds (one pachypolignan, one bisnorlignan, four flavonoids, one alkaloid, and one triterpenoid) isolated from *Duguetia staudtii* were evaluated in myeloperoxidase dependent (luminol/zymosan) and independent (lucigenin/PMA) oxidative burst assays. Inhibitory (IC_{50}) values between 6.44 and 14.13 μg/mL were found for pachypodol, kumatakenin, and 5,4′-dihydroxy-3,7,3′,5′-tetramethoxyflavone in macrophages (Ngouonpe et al. 2019).

Polyalthia genus

An extensive review conducted by Yao et al. in 2019 on the *Polyalthia* genus revealed several compounds with potential anti-inflammatory properties. These compounds comprised 16-oxocleroda-3,13-dien-15,16-oic acid and 16-hydroxycleroda-3,13-dien-15,16-olide (clerodane diterpenoids), rutin and quercetin (flavonoids), spinasterol and α-spinasterol (phytosterols), as well as goniothalamin and (−)-5-hydroxygoniothalamin (6S-styrylpyrones). All tested compounds showed IC_{50} values comparable to the positive control. The primary anti-inflammatory mechanisms identified included the inhibition of nuclear factor kappa B (NF-κB), prostaglandins (PGs), pro-inflammatory cytokines, inducible nitric oxide synthase (iNOS), and reactive oxygen species (ROS) (Yao et al. 2019).

Recently, Chen et al., 2021, in a review study of the pharmacological activities of phytochemicals from *Polyalthia,* added new compounds with potential anti-inflammatory activity: polycerasoidol (prenylated benzopyran), 16-Hydroxycleroda-4(18),13-dien-15,16-olide, (-)-3α,16α-dihydroxycleroda-4(18),13(14)Z-dien-15,16-Olide, and (4→2)-abeo-16(R&S)-2,13Z-clerodadien-15,16-olide-3-al. These clerodane compounds, together with dehydrogoniothalamin and the two 6S-styrylpyrones mentioned earlier, were assessed collectively (Chen et al. 2021).

Clerodane diterpenoids were obtained from the methanolic extract of *Polyalthia longifolia and* tested against neutrophil fMLP/CB induced superoxide generation and phorbol 12-myristate 13-acetate (PMA)-induced action. The compound 16-oxocleroda-4(18),13-dien-15,16-olide obtained an IC_{50} value very close to that of the well-known NADPH oxidase inhibitor, diphenyleneiodonium (Chang et al. 2006).

The diterpenoid 16(R&S)-3,13-kolavadien-15,16-olide-2-one, at a concentration of 10μg/mL, showed the lowest IC_{50} value against phorbol 12-myristate 13-acetate (PMA)-induced action. The authors related this action with a critical structural feature, an *E* form double bond at C-13(14) of the 3-ene-clerodane skeleton (Chang et al. 2006). Recently, three of five compounds isolated from a methanolic extract of *Polyalthia longifolia* (16-hydroxy-cleroda-4(18),13-dien-16,15-olide, 3α,16α-dihydroxycleroda-4(18),13(14)Z-dien-15,16-olide, and 16α-hydroxy-cleroda-3,13(14)Z-dien-15,16-olide) exhibited potency as COX-1, COX-2, and 5-LOX inhibitors with IC_{50} values similar or lower to Indomethacin (COX-1 and COX-2) and diclofenac (5-LOX) controls (Nguyen et al. 2020).

Interestingly, these authors performed an in-silico study using the PDB structures of the three proteins: COX-1 (PDB ID: 2OYU), COX-2 (PDB ID: 4COX), and 5-LOX (PDB ID: 3V99), and found a high concurrence with the *in vitro* studies. Two structures, 3α,16α-dihydroxycleroda-4(18),13(14)Z-dien-15,16-olide and 16α-hydroxy-cleroda-3,13(14)Z-dien-15,16-olide, were reported as better inhibitors of COX-1, COX-2, and 5-LOX compared to their respective control drugs (Nguyen et al. 2020).

The anti-inflammatory activity of extracts from other two *Polyalthia* species, *P. simiarum* and *P. suberosa* were evaluated through carrageenan induced paw edema and Xylene-Induced ear edema models, respectively. All three extracts showed significant inhibition at all time points and doses, and acted comparably to the ear edema model control (Yasmen et al. 2018; Kabir et al. 2019).

Others Annonaceae species

Spectroscopic techniques led to the identification of seven compounds from the methanolic extract of *Uvaria flexuosa* leaves, including flexuvaroxepine A, flexuvarin A–D, and flexuvarol A–B, along with four known flavonoids: 6,7-di-O-methyl-baicalein, chrysin, negletein, and 6-hydroxy-5,7-dimethoxy-flavone. In a fMLP/CB model of human neutrophils, both Flexuvarol B and chrysin

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demonstrated greater anti-inflammatory activity compared to the positive control, genistein (Hsu et al. 2016).

In another study, (-) zeylenol, a polyoxygenated cyclohexene derivative, was isolated from the ethyl acetate extract of *U. grandiflora* stems and displayed anti-inflammatory activity in an EPP-induced rat ear edema model. The authors found that (-) zeylenol produced a significant inhibitory effect on the edema formation at all times tested, and the values were similar to those obtained by a dose of 1mg/ear of phenylbutazone, a positive control (Seangphakdee et al. 2013).

An isoquinoline alkaloid, dactyllactone A, was isolated from *Dactylicapnos scandens* and demonstrated a more potent, dose-dependent inhibition of LPS-treated RAW264.7 cells compared to the positive control, without showing cytotoxic effects (Wang et al. 2018).

Additionally, the same researchers isolated two novel aporphines from *Dactylicapnos scandens*, identified as dactylicapnosines A and B, which feature unique five-membered D carbon rings. In LPS-induced RAW 264.7 cells, dactylicapnosine A exhibited anti-inflammatory and analgesic properties by inhibiting the expression of TNF-α, IL-1β, and PGE2. Furthermore, an evaluation of its effect on xylene-induced inflammation in mice, through intraperitoneal injection of dactylicapnosine A (10.2 mg/kg), revealed superior swelling inhibition compared to the positive control Parecoxib (10 mg/kg) (Wang et al. 2020).

In another study, twenty-three chemical components of *Phaeanthus vietnamensis* were isolated, with three being novel. Anti-inflammatory properties of these molecules were evaluated through an assay looking at inhibitory NO production in BV-2 cells. Four compounds displayed significant inhibition, and the IC_{50} of spathulenol was lower than the control. Interestingly, none of the 12 tested compounds displayed cytotoxicity in a cell viability assay (treatment with 20 μM of each compound maintained viability above of 95%) (Nhiem et al. 2017).

The phenolic amide, Melodamide A, along with 12 known compounds was isolated from the leaves of *Melodorum fruticosum*. The inhibitory effects of these compounds were evaluated using a human neutrophil model with fMLP/CB. Melodamide A demonstrated the most potent inhibition of superoxide anion generation induced by fMLP/CB, without causing cytotoxicity (Chan et al. 2013).

To enhance the anti-inflammatory properties of Melodamide A, a series of analogues were synthesized and tested. Among the sixteen analogues, only three with modifications on the A-ring demonstrated inhibitory effects on superoxide anion formation, with IC50 values of 7.49 μM (2-Cl), 5.59 μM (3-F), and 5.19 μM (2-Br). However, none of the analogues exhibited elastase inhibitory activity, leading the authors to conclude that the substitutions on the A-ring did not significantly improve anti-inflammatory activity (Chan et al. 2013).

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Table 1. Summary of anti-inflammatory activity of species of the Annonaceae.

Annonaceae Species	Used Material	Substances/Extracts	Methodology	Inhibition	Ref.
Annona cacans	Leaves Pulp Seeds	Hydromethanolic extract (HME) Ethyl acetate fraction (EAF)	Myeloperoxidase (MPO) activity carrageenan-induced paw oedema	After 6 h, 28% (300 mg/kg HME-Leaves) 53% (100 mg/kg HME-Pulp) 58% (300 mg/kg HME-Pulp) 43% (30 mg/kg EAF), 51% (100 mg /kg EAF)	(Volobuff et al. 2019)
Annona crassiflora	Fruit peel Leaves Leaves Leaves Leaves	Polyphenol-enriched fraction (PEF) Methanolic extract Methanolic extract Methanolic extract Methanolic extract	Wound closure in C57 mice Carrageenan-induced edema MPO activity Total leukocytes Carrageenan-induced leukocyte migration	75% (2% PEF topical) 84%(6% PEF topical) 53% (100mg/kg) 47% (300mg/kg) 60% (100mg/kg) 78% (100mg/kg) 90% (300mg/kg) 43% (300mg/kg)	(de Moura et al. 2019) (Rocha et al. 2016) (Rocha et al. 2016) (Rocha et al. 2016) (Rocha et al. 2016) (Rocha et al. 2016)
Annona glabra	Fruits	7β,16α,17-trihydroxy-ent-kauran-19-oic acid	NO production in LPS-stimulated RAW264.7 cells	IC_{50}= 0.39 ± 0.12 μM	(Nhiem et al. 2015)
	Fruits	16β,17-dihydroxy-ent-kauran-19-al	NO production in LPS-stimulated RAW264.7 cells	IC_{50} = 0.32 ± 0.04 μM	(Nhiem et al. 2015)
Annona muricata	Fruits	Lyophilized extract	Xylene-induced ear edema	34.04% (50μg/mL) 63.83(100μg/mL) 80.85(200μg/mL)	(Ishola et al. 2014)
Annona muricata	Fruits	Lyophilized extract	Cyclooxygenase (COX)-1 activity	39.44% (100μg/mL)	(Ishola et al. 2014)
	Fruits	Lyophilized extract	Cyclooxygenase (COX)-2 activity	55.71% (100μg/mL)	(Ishola et al. 2014)
Annona	Fruits	Lyophilized extract	Cyclooxygenase (COX)-2 activity	55.71% (100μg/mL)	(Ishola et al. 2014)

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Annonaceae Species	**Used Material**	**Substances/Extracts**	**Methodology**	**Inhibition**	**Ref.**
Annona Senegalensis	Seeds	N-cerotoyltryptamine	ROS production in zymosan stimulated human whole blood phagocytes	IC_{50} = 2.7 ± 0.1 µg/mL	(Tamfu et al. 2021)
	Seeds	Methanolic extract	ROS production in zymosan stimulated human whole blood phagocytes	IC_{50} =8.7 ± 10.2 µg/mL	(Tamfu et al. 2021)
	Seeds	Acetogenin	NO production in lipopolysaccharide (LPS) stimulated J774.2 mouse macrophages	IC_{50} = 3.9 ± 0.2 µg/mL	(Tamfu et al. 2021)
Annona squamosa	Bark	Caryophyllene oxide	Carrageenan-induced paw edema	After 2 hours 45% (12.5mg/kg) 51% (25mg/kg)	(Chavan et al. 2011)
	Bark	Sesquiterpene fraction (copaene (35.40%), patchoulane (13.49%) and 1H-cycloprop(e)azulene (22.77%))	Carrageenan-induced paw edema	After 2 hours 38% (12.5mg/kg) 34% (25mg/kg)	(Chavan et al. 2012)
	Bark	18-acetoxy-ent-kaur-16-ene	Carrageenan-induced paw edema	After 2 hours 51.6% (12.5mg/kg) 60.9% (25mg/kg)	(Chavan et al. 2011)
Annona vepretorum	Leaves	Ethanolic extract	leukocyte migration to the peritoneal cavity	62%(25 mg/kg), 76% (50 mg/kg) 98% (100 mg/kg)	(Silva et al. 2015)
	Leaves	Ethanolic extract	Carrageenan-induced paw edema	After 2 hours 58%(25 mg/kg) 45% (50 mg/kg) 72% (100 mg/kg)	(Silva et al. 2015)

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Annona vepretorum	Leaves	Ethanolic extract	Histamine-induced paw edema	After 1 hour >65% (100mg/kg)	(Silva et al. 2015)
Cyathocalyx pruniferus	Leaves	Spathulenol Cyclopropa-azulene Polycarpol Koetjapic acid 2-Octaprenyl-benzoquinone 14-methylloctadec-1-ene 1-Docosene β-Sitosterol	PGE_2	71.4 (IC_{50} = 25.8) 8.6 (IC_{50} = -) 70.1 (IC_{50} = 24.7) 80.4 (IC_{50} = 13.1) 86.1 (IC_{50} = 11.2) 3.5 (IC_{50} = -) 5.8 (IC_{50} = -) 21.6 (IC_{50} = -)	(Attiq et al. 2021)
Annonaceae Species	**Used Material**	**Substances/Extracts**	**Methodology**	**Inhibition**	**Ref.**
Cyathocalyx pruniferus	Leaves	α-Tocopherol 11-prenol Quercetin Epicatechin Chrysin **Indomethacin (Positive control)**	PGE_2	15.9 (IC_{50} = -) 2.1 (IC_{50} = -) 79.8 (IC_{50} = 15.4) 77.3 (IC_{50} =17.3) 73.8 (IC_{50} = 21.8 88.1 (IC_{50} = 11.8)	(Attiq et al. 2021)
Cyathocalyx pruniferus	Leaves	Spathulenol Cyclopropa-azulene Polycarpol Koetjapic acid 2-Octaprenyl-benzoquinone 14-methylloctadec-1-ene 1-Docosene β-Sitosterol α-Tocopherol 11-prenol	COX-2	21.1 (IC_{50} = -) 4.6 (IC_{50} = -) 29.6 (IC_{50} = -) 85.6 (IC_{50} = 8.1) 88.1 (IC_{50} = 6.6) 2.1 (IC_{50} = -) 2.4 (IC_{50} = -) 11.1 (IC_{50} = -) 10.5 (IC_{50} = -)	(Attiq et al. 2021)

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Cyathocalyx pruniferus	Leaves	Quercetin Epicatechin Chrysin **Dexamethasone (Positive control)**	COX-2	3.3 (IC_{50} = -) 80.1 (IC_{50} = 10.3) 74.7 (IC_{50} =12.5) 70.5 (IC_{50} =15.7) 92.8 (IC_{50} = 5.1)	(Attiq et al. 2021)
Duguetia furfuracea	stem bark	Essential oil	LPS-induced paw edema	After two hours 41.67% (3mg/kg) 86.11% (10mg/kg)	(Saldanha et al. 2019)
	stem bark	Essential oil	LPS-induced paw edema	After four hours 45.45% (1mg/kg) 63.64% (3mg/kg) 92.42% (10mg/kg)	(Saldanha et al. 2019)
	Leaves	Methanolic extract	Carrageenan-induced paw edema	After two hours 39% (300mg/kg) 22% (100mg/kg) 17.5% (30mg/kg)	(do Santos et al. 2018)
Annonaceae Species	**Used Material**	**Substances/Extracts**	**Methodology**	**Inhibition**	**Ref.**
Duguetia furfuracea	Leaves	Methanolic extract	Carrageenan-induced paw edema	After four hours 40% (300mg/kg) 25% (100mg/kg)	(do Santos et al. 2018)
	Leaves	Dicentrinone	Carrageenan-induced paw edema	For 100 mg/kg 69.1% (2 hours) 50.4% (4 hours),	(do Santos et al. 2018)
	Leaves	Methanolic extract	Zymosan-induced edema	38.1% (300mg/kg)	(do Santos et al. 2018)
	Leaves	Dicentrinone	Zymosan-induced edema	27.1% (300mg/kg)	(do Santos et al. 2018)

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	Leaves	Enriched phenylpropanoid extract	LPS-induced paw edema	After two hours 90.91% (3mg/kg) 92.42% (10mg/kg)	(Saldanha et al. 2021)
Duguetia furfuracea	Leaves	Enriched phenylpropanoid extract	LPS-induced paw edema	After four hours 77.78% (1mg/kg) 77.78% (3mg/kg) 81.48% (10mg/kg)	(Saldanha et al. 2021)
	Leaves	α-asarone	LPS-induced paw edema	After two hours 62.12% (3mg/kg) 69.70% (10mg/kg) 69.70% (30mg/kg)	(Saldanha et al. 2020)
	Leaves	α-asarone	LPS-induced paw edema	After four hours 72.22% (3mg/kg) 81.48% (10mg/kg) 81.48% (30mg/kg)	(Saldanha et al. 2020)
Duguetia moricandiana	Fruits	Discretamine	NO production in LPS-stimulated macrophages	Around 50%. (100 and 200 µg/mL)	(Lemos et al. 2017)
	Fruits	Discretamine	IL-6 production in LPS-stimulated macrophages	74.1% (50µg/mL) 76.6% (100µg/mL) 75.1% (200 µg/mL)	(Lemos et al. 2017)
	Fruits	Discretamine	IL1-b production in LPS-stimulated macrophages	89.4% (50µg/mL) 87.4% (100µg/mL) 71.8% (200 µg/mL)	(Lemos et al. 2017)
Annonaceae Species	**Used Material**	**Substances/Extracts**	**Methodology**	**Inhibition**	**Ref.**
Duguetia moricandiana	Fruits	Discretamine	TNF-α production in LPS-stimulated macrophages	61.0% (50µg/mL) 45.2% (100µg/mL) 52.6% (200 µg/mL)	(Lemos et al. 2017)

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	Fruits	Discretamine	Carrageenan-induced paw edema	After one hour 42% (10mg/kg) 62% (20mg/kg)	(Lemos et al. 2017)
	Fruits	Discretamine	Carrageenan-induced paw edema	After two hours 44% (10mg/kg) 67% (20mg/kg)	(Lemos et al. 2017)
Duguetia moricandiana	Fruits	Discretamine	Carrageenan-induced paw edema	After four hours 59% (5mg/kg) 49% (10mg/kg) 48% (20mg/kg)	(Lemos et al. 2017)
Duguetia staudtii	Stem bark	Pachypodol	Myeloperoxidase dependent (luminol/zymosan) oxidative burst	IC_{50} = 8.32 µg/mL	(Ngouonpe et al. 2019)
	Stem bark	Kumatakenin	Myeloperoxidase dependent (luminol/zymosan) oxidative burst	IC_{50} = 10.64 µg/mL	(Ngouonpe et al. 2019)
	Stem bark	5,4′-dihydroxy-3,7,3′,5′-tetramethoxyflavone	Myeloperoxidase dependent (luminol/zymosan) oxidative burst	IC_{50} = 6.44 µg/mL	(Ngouonpe et al. 2019)
	Stem bark	Pachypodol	Myeloperoxidase independent (lucigenin/PMA) oxidative burst	IC_{50} = 11.04 µg/mL	(Ngouonpe et al. 2019)
	Stem bark	Kumatakenin	Myeloperoxidase independent (lucigenin/PMA) oxidative burst	IC_{50} = 14.13 µg/mL	(Ngouonpe et al. 2019)
	Stem bark	5,4′-dihydroxy-3,7,3′,5′-tetramethoxyflavone	Myeloperoxidase independent (lucigenin/PMA) oxidative burst	IC_{50} = 8.55 µg/mL	(Ngouonpe et al. 2019)
Enicosanthum membranifolium		2β-methoxyhardwickiic acid (-)-Hardwicckiic acid 2β-acetoxyhardwickiic acid 2β-hidroxyhardwickiic acid 15-methozypatagonic acid **Indomethacin**	NO production	IC_{50} µM 65.4 38.9 16.1 82.4 28.9 32.2	(Polbuppha et al. 2022)

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		(Positive control)			
Annonaceae Species	**Used Material**	**Substances/Extracts**	**Methodology**	**Inhibition**	**Ref.**
Isolona dewevrei	Leaves	Essential oil **Nordihydroguaiaretic (Positive control)**	Inhibit lipoxygenases (LOX)	0.0020 (mg/mL) 0.013 (mg/ml)	(Kambiré et al. 2021)
Melodorum fruticosum	Leaves	Melodamide A	Inhibition of superoxide anion generation	IC_{50} = 5.25 μM	(Chan et al. 2013)
	Leaves	Melodamide A derivate (2-Cl)	Inhibition of superoxide anion generation	IC_{50} = 7.49 μM	(Chan et al. 2013)
	Leaves	Melodamide A derivate (3-F)	Inhibition of superoxide anion generation	IC_{50} = 5.59 μM	(Chan et al. 2013)
	Leaves	Melodamide A derivate (2-Br)	Inhibition of superoxide anion generation	IC_{50} = 5.19 μM	(Chan et al. 2013)
Phaeanthus vietnamensis	Leaves	spathulenol	NO production in LPS-stimulated BV2 cells	IC_{50} = 15.7 μM	(Nhiem et al. 2017)
	Leaves	(8R,80R)-bishydrosyringenin	NO production in LPS-stimulated BV2 cells	IC_{50} = 25.3 μM	(Nhiem et al. 2017)
	Leaves	1α*H*,5β*H*-aromandendrane-4α,10α-diol	NO production in LPS-stimulated BV2 cells	IC_{50} = 23.0 μM	(Nhiem et al. 2017)
	Leaves	1β*H*,5β*H*-aromandendrane-4α,10β-diol	NO production in LPS-stimulated BV2 cells	IC_{50} = 22.6 μM	(Nhiem et al. 2017)
Polyalthia longifolia	Seeds	16-oxo-cleroda-3,13(14)*E*-dien-15-oic acid	COX-1, COX-2, and 5-LOX inhibitory activities	62.85% (COX-2) 26.41% (LOX-5)	(Nguyen et al. 2020)
	Seeds	16-hydroxy-cleroda-3,13-dien-15-oic acid	COX-1, COX-2, and 5-LOX inhibitory activities	84.98% (COX-2) 30.51% (LOX-5)	(Nguyen et al. 2020)
	Seeds	16-hydroxy-cleroda-4(18),13-dien-16,15-olide	COX-1, COX-2, and 5-LOX inhibitory activities	82.97% (COX-2) 12.73% (LOX-5)	(Nguyen et al. 2020)
	Seeds	3α,16α-dihydroxy-cleroda-4(18),13(14)*Z*-dien-15,16-olide	COX-1, COX-2, and 5-LOX inhibitory activities	75.14% (COX-2) 14.38% (LOX-5)	(Nguyen et al. 2020)

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Polyalthia longifolia	Seeds	16α-hydroxy-cleroda-3,13(14)Z-dien-15,16-olide	COX-1, COX-2, and 5-LOX inhibitory activities	92.94% (COX-1) 79.41% (COX-2) 16,94% (LOX-5)	(Nguyen et al. 2020)
	Bark	16-oxocleroda-4(18),13-dien-15,16-olide	fMLP/CB induced superoxide generation by neutrophils	IC_{50} = 0.60 mg/mL	(Chang et al. 2006)
Annonaceae Species	**Used Material**	**Substances/Extracts**	**Methodology**	**Inhibition**	**Ref.**
		Diphenyleneiodonium (positive control) 16(R&S)-3,13-kolavadien-15,16-olide-2-one	fMLP/CB induced superoxide generation by neutrophils Phorbol 12-myristate 13 acetate (PMA)-induced action	IC_{50} = 0.11 mg/mL IC_{50} = 10µg/mL	(Chang et al. 2006)
	Stem bark	Ethyl acetate (EA) extract	Carrageenan-induced paw edema	After four hours 27.5%(50mg/kg) 39.1% (100mg/kg)	(Kabir et al. 2019)
	Leaves	Diethyl ether extract	Xylene-induced ear edema	42.70% (200mg/kg) 62.67% (400mg/kg)	(Yasmen et al. 2018)
	Leaves	n-hexane extract	Xylene-induced ear edema	48.54% (200mg/kg) 65.92% (400mg/kg)	(Yasmen et al. 2018)
Polyalthia viridis	Leaves Stem	Leaf Essential oil Stem Essential oil **Butein** (**Positive control**)	NO production in LPS stimulated BV2 cells	80.8 (IC_{50} = 76.7 µg/mL) 87.2 (IC_{50} = 57.6 µg/mL) 91.8 (IC_{50} = 16.1 µg/mL)	(Son et al. 2021)
Uvaria flexuosa	Leaves	Flexuvarol B	Superoxide anion generation assay	IC_{50} = 4.72 mM	(Hsu et al. 2016)
	Leaves	Chrysin	Superoxide anion generation assay	IC_{50} = 2.25 mM	(Hsu et al. 2016)
	Leaves	Flexuvarol B	Elastase release assay	IC_{50} = 5.55 mM	(Hsu et al. 2016)
	Leaves	Chrysin	Elastase release assay	IC_{50} = 2.44 mM	(Hsu et al. 2016)

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Uvaria grandiflora	Stems	(-) zeylenol	EPP-induced rat ear edema	90% (15min) 69% (30min) 52% (1 hour) 52% (2 hours)	(Seangphakdee et al. 2013)
Xylopia aethiopica	Fruits	Methanolic extract	Prostaglandin synthetase activity	-	(Ezekwesili et al. 2010)
	Fruits	Ethanolic extract	Mouse pinnal inflammation in carrageenan-induced paw oedema	23% (30 µg/mL) 62% (300 µg/mL)	(Obiri and Osafo 2013)
Annonaceae Species	**Used Material**	**Substances/Extracts**	**Methodology**	**Inhibition**	**Ref.**
Xylopia aethiopica	Fruits	Extract 30 100 300	Superoxide dismutase (SOD), ascorbate peroxidase (APX), catalase (CAT), myeloperoxidase (MPO) and malondialdehyde (MDA) activity	23.06 40.91 62.83	(Osafo et al. 2016)
	Leaves	Hydroethanolic extract	TNF-α in (Lipopolysaccharide) LPS challenged THP-1-derived macrophages	>90% (500 mg/kg)	(Macedo et al. 2020)
	Leaves	Hydroethanolic extract	Inhibition of IL-6 production, in a LPS challenged THP-1-derived macrophages,	84.6% (250 µg/mL) 96.3% (500 µg/mL)	(Macedo et al. 2020)
	Leaves	Hydroethanolic extract	Interferences of 5-LOX in a LPS challenged THP-1-derived macrophages	IC_{50} = 85 µg/mL	(Macedo et al. 2020)
	Fruits	Essential oil	NO production in LPS-stimulated RAW264.7 cells	-	(Alolga et al. 2019)
Xylopia parviflora	Fruits	Volatile oil	NO production in LPS-stimulated RAW264.7 cells	37% (12µg/mL)	(Woguem et al. 2014)
Xylopia sericea	Leaves	Ethanolic extract	NO production in LPS-stimulated RAW264.7 cells	76%	(Gomes et al. 2022)
	Leaves	Ethanolic extract	IL-6 production in LPS-stimulated RAW264.7 cells	85%	(Gomes et al. 2022)

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3.2. Insecticidal, Larvicidal and Pesticidal

Larvicidal, pesticidal and insecticidal activities are intricately linked, as they are commonly related to the external transmission of diseases or harm to the pestilent being. From now on, we will address the term "insecticide" to refer, in a global way, to larvicidal, insecticidal and pesticidal activities. Compounds classified as insecticides are those capable of killing, attracting and repelling insects (Klocke et al. 1991; Simões et al. 2003; Viegas 2003). However, an ideal insecticide must also be effective at low concentrations, non-toxic to mammals, people, or plants, easy to obtain, handle and apply, economically accessible, and non-cumulative in human and domestic animal adipose tissue (Klocke et al. 1991; Simões et al. 2003; Viegas 2003). All these properties describe a perfect insecticide candidate, which will rarely be found.

The use of plants and their isolated compounds for insecticidal activity has been used since ancient times (Viegas Júnior 2003; Krinski et al. 2014). They were widely used until the 1940s, when synthetic products began to gain space in the market. However, synthetic insecticides are shown to be extremely potent and, on the other hand, are quite unspecific, presenting several toxicity problems (Viegas 2003). In the search for insecticides that have high efficacy, safety, and selectivity, natural products have regained interest. There more than two thousand species of plants recorded in literature to have insecticidal properties. However, few of these species have been used commercially (Ndumu et al. 1999; Simões et al. 2003; Viegas 2003).

It has been found that the use of plant-based secondary metabolites are a low-cost alternative for pest control (Santos et al. 2010; Spletozer et al. 2021). Thus, the search for these compounds has intensified greatly in recent decades, with numerous publications and studies emphasizing the efficacy, along with the economic and ecological advantages of plant-based insecticides (Spletozer et al. 2021).

In this context, the Annonaceae family stands out for its structural variability of secondary metabolites, that are rich in alkaloids and acetogenins (Jossang et al. 1984; Spletozer et al. 2021). Acetogenins, a unique class of natural products found exclusively in Annonaceae, have demonstrated significant promise as prototypes for insecticidal agents (Viegas 2003; Castillo et al. 2010; Spletozer et al. 2021). Studies by Colom et al. (2008) and Alvarez et al. (2007) serve as notable examples of research evaluating the insecticidal potential of acetogenins derived from Annonaceae (Alvarez Colom et al. 2007; Colom et al. 2008).

The review article written by Krinski, Massaroli, and Machado, 2014, presents an analysis of the insecticidal potential of plants from the Annonaceae family, which are found across diverse tropical regions such as Central and South America, Asia and Africa. Despite the potential of Annonaceae as a source of natural insecticides, there is a lack of comprehensive studies on these plants for pest control, which can be partly attributed to the recent discovery of their biocidal properties against insects. However, growing concern about the adverse effects of synthetic insecticides on the environment and human health has prompted a resurgence in studies on botanical insecticides, aiming to obtain compounds that are less environmentally aggressive and avoid insect resistance.

The authors also highlight that Annonaceae metabolites are promising insecticidal substances, especially acetogenins. Approximately 42 species of Annonaceae have been studied for their insecticidal potential, primarily against the main orders of insects considered pests, such as Lepidoptera, Coleoptera, Hemiptera, Diptera, and Blattodea (Krinski et al. 2014).

Although there are promising studies demonstrating the potential of Annonaceae in pest control, further research is needed, especially under field conditions, to validate the results obtained in the laboratory. Additionally, it is essential to isolate the active compounds present in these plants to better understand their mechanisms of action and develop safer and more effective pest control methods (Krinski et al. 2014). Challenges related to the scarcity of plant resources and the lack of standardization and quality control of formulations aside, growing interest in organic products and the environmental impact of synthetic insecticides are driving this search for sustainable alternatives (Krinski et al. 2014).

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Krinski, Massaroli, and Machado, 2014, in their review article, also created a table presenting information about the species of plants from the Annonaceae family studied regarding their insecticidal activity, the genera involved, the insect orders evaluated, and other relevant data for studying the insecticidal potential of these plants.

In this review, we updated the table from Krinski, Massaroli, and Machado, 2014, by adding information about activity values and methods used to evaluate the insecticidal, pesticidal, and larvicidal activity. Despite the plethora of promising results, most studies only assess essential oils, extracts, and fractions. Therefore, research is needed to isolate the secondary metabolites from the species already studied to evaluate them separately and confirm their insecticidal, larvicidal, pesticidal, and cytotoxic potential.

Annona genus

The *Annona* genus is the most extensively studied within the Annonaceae family for pesticide, larvicide, and insecticidal activity. Scientific reports cover 17 *Annona* species, providing evidence of insecticidal activity. Among these species, *A. squamosa, A. muricata, A. coriaceae*, and *A. crassiflora* emerge as the most investigated. The studies encompass a variety of approximately 41 species of insects, with about 14 research efforts specifically aimed at assessing activity against *Aedes aegypti*. These findings underscore the relevance of the genus *Annona* as a potential source of insecticidal and larvicidal compounds, especially concerning the control of disease-transmitting mosquitoes (Kawazu et al. 1989; Sinchaisri et al. 1991; Schmeda-Hirschmann and de Arias 1992; Epino and Chang 1993; Saxena et al. 1993; Monzon et al. 1994; Aku et al. 1998; Alali et al. 1998; Fontana et al. 1998; Guadaño et al. 2000; Kotkar et al. 2002; Leatemia and Isman 2004; LS et al. 2004; Morales et al. 2004; Pérez-Pacheco et al. 2004; Saito et al. 2004; Rao et al. 2005; Bobadilla et al. 2005; Khalequzzaman and Sultana 2006; Rodrigues et al. 2006, 2021; da Silva et al. 2007; de Omena et al. 2007; Henao et al. 2007; Alvarez Colom et al. 2007; Souza, E. M.; Cordeiro, J. R.; Pereira 2007; Coelho et al. 2007; Llanos et al. 2008; Colom et al. 2008; Dadang and Prijono 2009; Guarido 2009; Karunaratne and Arukwatta 2009; Magadula et al. 2009; Oliveira and Pereira 2009; Deshmukhe et al. 2010; Kumar et al. 2010; Araújo 2010; Begum et al. 2010; Toto Blessing et al. 2010; Carneiro 2010; de Cássia Seffrin et al. 2010; Cruz 2011; de Moraes et al. 2011; Kamaraj et al. 2011; Kempraj and Bhat 2011; Sharma et al. 2011; Costa et al. 2012; Dill et al. 2012; González-Esquinca et al. 2012; Kesetyaningsih 2012; Sreeletha and Geetha 2012; Costa, Marilza da Silva, Mônica Josene Barbosa Pereira, Simone Santos de Oliveira, Paulo Teixeira de Souza, Evandro Luiz Dall'oglio 2013; Cruz-Estrada et al. 2013; Allison et al. 2013; Massaroli et al. 2013; Ribeiro et al. 2013; Da Silva et al. 2013b; Krinski and Massaroli 2014).

Others Annonaceae species

Other Annonaceae genera have also been investigated for insecticidal, larvicidal, and pesticidal activity, such as the *Artabotrys* (Kabir 2010), *Asimina* (Mikolajczak et al. 1988), *Cardiopetalum* (Costa, Marilza da Silva, Mônica Josene Barbosa Pereira, Simone Santos de Oliveira, Paulo Teixeira de Souza, Evandro Luiz Dall'oglio 2013), *Dennetia* (Ewete et al. 1996; Okonkwo and Okoye 2001; Akinwumi et al. 2007; Umeotok et al. 2013), *Duguetia* (Rodrigues et al. 2006; Luciana et al. 2013), *Guatteria* (Aciole et al. 2011), *Mikilua* (Odalo et al. 2005), *Oxandra* (Rojano et al. 2007), *Rollinia* (Tolosa et al. 2012), *Uvaria* (Anza et al. 2021) and *Xylopia* genus (Ewete et al. 1996; Rodrigues et al. 2006; Zaridah et al. 2006; Aina et al. 2009). Approximately 11 species of insects have been studied for the insecticidal potential of these genera of Annonaceae.

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Table 2. Summary of insecticidal, pesticidal and larvicidal activity of species of the Annonaceae.

Annonaceae species	Used Material	Substances / Extracts	Insect species (Order)	Methods			Ref.
				Topical (LC_{50} µg/ larva)	Topical (LD_{50} – 95% CL - µg/nymph)	Oral (LC_{50} ppm fresh weight in diet)	
Annona atemoya	Seed	Seed extract	*Trichoplusia ni (Lep.)*	197.67		301.30	(de Cássia Seffrin et al. 2010)
Annona squamosa	Seed	Seed extract	*Trichoplusia ni (Lep.)*	382.37		167.48	(de Cássia Seffrin et al. 2010)
Annona cherimola	Seed	Squamocin Molvizarin Almunequin Itrabin **Deltamethrin (Positive control)**	*Oncopeltus fasciatus*		0.16 0.34 11.23 14.91 7.4		(Colom et al. 2008)
Annona cherimola	Seed	Neoannonin Itrabin Almunequin Asimicin Squamocin Motrilin Cherimolin-1 Cherimolin-2 Tucumanin **Control**	*Spodoptera Frugiperda*	15.5 18.8 19.7 17.3 Instant death 18.0 14.0 17.7 14.7 12.1	10 30 30 30 100 20 0 10 20 10	0.90 0.59 1.10 0.77 0.16 1.19 0.91 0.97 0.81 1.02	(Alvarez Colom et al. 2007)
Annona coriaceae	Seed	Seed Extract	*Aedes aegypti (Dip.)*	0.01	-	-	(Costa et al. 2012)
Annona coriaceae	Seed	100 ppm	*Aedes aegypti* (Dip.)	0.50	3.00	3.5	(Dill et al. 2012)

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		50 ppm DMSO 0.1% **Água (Control)**		0.40 0.30 0.20	6.00 - -	5.5 - -	
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% CL - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Annona coriaceae	Seed	Seed Extract 0 ppm 50 ppm 100 ppm 200 ppm 300 ppm 400 ppm 500 ppm	*Aedes aegypti* (Dip.)	 0.0 0.7 0.7 1.0 2.2 4.5 6.2	 0.0 7.5 7.5 10.0 22.5 45.0 62.5	 10.0 9.25 9.25 9.00 7.75 5.50 3.75	(de Moraes et al. 2011)
Annona coriaceae	Seed	Seed Extract Methanol (des. Hexane) Hexane Dichloromethane Methanol (des. DCM)	*Aedes aegypti* (Dip.)	 0.1 0.1 0.1 0.1	 100.0 100.0 58.75 0.0	 0.007 0.007 0.805 0.0	(Costa, Marilza da Silva, Mônica Josene Barbosa Pereira, Simone Santos de Oliveira, Paulo Teixeira de Souza, Evandro Luiz Dall'oglio 2013)
Annona coriaceae	Seed	Diet	*Anagasta kuehniella* (Lep.)	0.0 2.0	26.3 16.8	71.8 81.9	(Coelho et al. 2007)
Annona coriaceae	Seed	Diet	*Corcyra Cephalonica* (Lep.)	0.0 2.0	23.16 32.25	69.7 49.3	(Coelho et al. 2007)

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Annona coriaceae	Seed	Seed Extract Hexanic 8.0% 4.0% 2.0% 1.0% 0.5% Methanolic 8.0% 4.0%	Dichelops melacanthus (Hem.)		78.00 86.00 68.00 58.00 42.00 96.00		(Souza, E. M.; Cordeiro, J. R.; Pereira 2007)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% CL - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Annona coriaceae	Seed	Seed Extract Methanolic 2.0% 1.0% 0.5% Ethanolic 8.0% 4.0% 2.0% 1.0% 0.5% **Distilled water (Positive Control)**			94.00 94.00 70.00 40.00 100.00 100.00 90.00 84.00 80.00 6.00 4.00 6.00		(Souza, E. M.; Cordeiro, J. R.; Pereira 2007)

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		C 01 C 02			12.00 0.00 2.00		
Annona coriaceae	Seed	Seed Extract Preview 2 Days 5 Days 7 Days **DMSO 20%** **(Positive Control 01)** **Water (Positive Control 02)**	*Euschistus heros* (Hem.)	3.0 4.6 3.4 3.7 3.1, 5.0, 3.4 and 5.0 4.1, 4.4, 2.8 and 5.2	- 8.91 - 26.73 - -		(Da Silva et al. 2013b)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% CL - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Annona coriaceae	Seed	Seed Extract Methanolic 0.5 1.0 2.0 4.0 8.0 DMSO 20% Water	Tuta absoluta (Lep.)	- - - - - - -	8.0 100 100 86.4 86.6 6.6 13.2	- - - - - - -	(da Silva et al. 2007)
Annona cornifolia	Leaves	Leave extract 2.5		-	0.41	-	(Saito et al. 2004)

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		2.0	*Anticarsia gemmantalis* (Lep.)	-	0.38	-	
		1.5		-	-0.10	-	
		1.0		-	-0.25	-	
		0.5		-	0.01	-	
Annona cornifolia	Leaves	Leave extract 2.5	*Spodoptera frugiperda* (Lep.)	-	0.96	-	(Saito et al. 2004)
		2.0		-	0.68	-	
		1.5		-	0.55	-	
		1.0		-	0.66	-	
		0.5		-	0.36	-	
Annona cornifolia	Leaves	Leave extract 2.5	*Spodoptera frugiperda* (Lep.)	-	0.96	-	(Saito et al. 2004)
		2.0		-	0.68	-	
		1.5		-	0.55	-	
		1.0		-	0.66	-	
		0.5		-	0.36	-	
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% CL - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Annona cornifolia	Leaves	Leave extract 2.5	*Spodoptera frugiperda* (Lep.)	-	0.96	-	(Saito et al. 2004)
		2.0		-	0.68	-	
		1.5		-	0.55	-	
		1.0		-	0.66	-	
		0.5		-	0.36	-	

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Annona Crassiflora	Fruits/ Twigs/ Roots	Extract Hexanic SB RW RB Ethanolic RW RB	*Aedes aegypti* (Dip.)	192.57 154.02 264.15 26.89 23.06	- - - - -	- - - - -	(Rodrigues et al. 2006)
Annona Crassiflora	Roots	Extract Root bark Root wood Stem	*Aedes aegypti* (Dip.)	0.71 8.94 16.1	- - -	- - -	(de Omena et al. 2007)
Annona Crassiflora	Seeds	Seeds Extract Methanol (Des. DCM) Hexanic Hydroalcoholic Fraction Ethyl Acetate	*Aedes aegypti* (Dip.)	1.0 1.0 1.0 1.0	0.0 91.25 0.0 0.0	- 0.433 - -	(Costa, Marilza da Silva, Mônica Josene Barbosa Pereira, Simone Santos de Oliveira, Paulo Teixeira de Souza, Evandro Luiz Dall'oglio 2013)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods** **Topical (LC_{50} µg/ larva)**	**Topical (LD_{50} – 95% CL - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	**Ref.**
Annona Crassiflora	Seeds	Fraction Chloroform Crude Methanolic	*Aedes aegypti* (Dip.)	1.0 1.0	0.0 11.25	- 3.189	(Costa, Marilza da Silva, Mônica Josene Barbosa Pereira, Simone Santos de

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							Oliveira, Paulo Teixeira de Souza, Evandro Luiz Dall'oglio 2013)
Annona Crassiflora	Seeds	Seeds Extract 1% 2% 4% **DMSO 40%** **(Positive control)**	*Euschistus heros* (Hem.)	481.50 542.00 372.00 683.00	1.25 1.50 2.00 1.25	353.00 396.00 306.00 309.20	(Oliveira and Pereira 2009)
Annona Crassiflora	Seeds	Seeds Extract Preview 2 Days 5 Days 7 Days **DMSO 20%** **(Positive control 01)** **Water (Positive control 02)**	*Euschistus heros* (Hem.)	2.4 4.1 3.0 4.2 3.1 5.0 3.4 5.0 4.1 4.4 2.8 5.2	17.82 13.04 16.83 - - - - - - - -		(Da Silva et al. 2013b)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% CL - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	

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Annona Crassiflora	Seeds	Seed Extract 24 h 8.0% 4.0% 2.0% 1.0% 0.5% 72 h 8.0% 4.0% 2.0% 1.0% 0.5% 120h 8.0% 4.0% 2.0% 1.0% 0.5% Water + Tween 80 (Positive Control 01) Water (Positive Control 02)	*Tibraca limbativentris* (Hem.)	70.0 64.0 44.0 20.0 6.0 78.0 72.0 54.0 30.0 10.0 81.0 76.0 58.0 34.0 10.0 2.0 4.0 9.0 0.0 2.0 6.0	4.46 3.30	4.34 3.16	(Krinski and Massaroli 2014)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods** **Topical (LC_{50} µg/ larva)**	**Topical (LD_{50} – 95% CL - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	**Ref.**

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Annona dioica	Seeds	Seeds Extract Fraction Dichloromethane Methanol	*Aedes Aegypti* (Dip.)	1.0 1.0	10.00 3.75	2.447 5.196	(Costa, Marilza da Silva, Mônica Josene Barbosa Pereira, Simone Santos de Oliveira, Paulo Teixeira de Souza, Evandro Luiz Dall'oglio 2013)
Annona dioica	Seeds	Seed Extract Topical application method 25 50 100 200 Cantate application method 25 50 100 200	*Rhodnius neglectus* (Hem.)		6.2 85 90 100 88.2 91.6 95.6 96.0		(Carneiro 2010)
Annona diversifolia	Leaves/ Branches	Extract Stem Aqueous Ethanolic Leaf Aqueous Ethanolic	*Anastrepa ludens* (Dip.)	588.685 409.139 >1000 52.0284			(González-Esquinca et al. 2012)
				Methods			

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Annonaceae species	Used Material	Substances / Extracts	Insect species (Order)	Topical (LC_{50} µg/ larva)	Topical (LD_{50} – 95% CL - µg/nymph)	Oral (LC_{50} ppm fresh weight in diet)	Ref.
Annona foetida	Seeds	Seed Extract Methanolic 24h 48h	*Aedes aegypti* (Dip.)	76.15 62.28			(Guarido 2009)
Annona foetida	Seeds	Hexanic 24h 48h Dichloromethanic 24h 48h	*Aedes aegypti* (Dip.)	15.17 6.72 0.73 0.33			(Guarido 2009)
Annona glabra	Seeds	Seed Extract	*Aedes aegypti* (Dip.)	0.06			(de Omena et al. 2007)
Annona montana	Leaves/ Branches	Annonacin *Cis*-annonacin-10-one Densicomacin-1 Gigantetronenin Murihexocin-B Tucupentol **Control**	*Spodoptera frugiperda* (Hem.)	49.20 44.75 60.00 55.20 55.12 59.00 27.12	50 60 40 70 30 30 0.0	50 40 60 30 70 70 10	(Toto Blessing et al. 2010)
Annona mucosa	Fruits and branches	Ethanolic extract Rollinicin Rolliniastacin-1	*Aedes aegypti*	2.60 0.78 0.43		-	(Rodrigues et al. 2021)
Annona mucosa	Fruits and branches	Ethanolic extract Rollinicin	*Aedes albopictus*	0.55 1.13		-	(Rodrigues et al. 2021)

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		Rolliniastacin-1		0.20			
Annona mucosa	Seeds	Seed Extract 0.5 1.0 2.0	*Chrysodeixis includens* (Lep.)		< 55% < 55% < 55%		(Massaroli et al. 2013)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% CL - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Annona mucosa	Seeds	Seed Extract 4.0 8.0	*Chrysodeixis includens* (Lep.)		86.6% 93.3%		(Massaroli et al. 2013)
Annona mucosa	Seeds/ Branches/ Leaves	Extract Seeds 300 mg kg 1500 mg kg Leaves 300 mg kg 1500 mg kg Branches 300 mg kg 1500 mg kg Control	*Sitophilus zeamais* (Col.)	0.80 0.00 36.80 5.60 34.70 39.10 36.90 37.00	98.00 100.00 0.50 61.50 1.50 0.00 0.00 0.00	7.84 1.12 81.97 57.90 83.71 64.97 81.94 81.74	(Ribeiro et al. 2013)
Annona mucosa	Seeds	Seed Extract 24h 8.0% 4.0%	*Timbraca limbativentris* (Hem.)	100.0 92.0 90.0	1.59 1.18	0.49 -0.24	(Krinski and Massaroli 2014)

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		2.0% 1.0% 0.5% 72h 8.0% 4.0% 2.0%		76.0 28.0 100.0 96.0 96.0			
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% LC - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Annona mucosa	Seeds	1.0% 0.5% 120h 8.0% 4.0% 2.0% 1.0% 0.5% **Water + Tween80 (Positive Control 01)** **Water (Positive Control 02)**	*Timbraca limbativentris* (Hem.)	86.0 42.0 100.0 98.0 96.0 88.0 56.0 2.0 4.0 9.0 0.0 2.0 6.0	0.91	-0.76	(Krinski and Massaroli 2014)
Annona muricata	Seeds	Seed Extract	*Aedes aegypti* (Dip.)	236.23	74.68	-	(Morales et al. 2004)
Annona muricata	Seeds	Seed Extract 12h 24h	*Aedes aegypti* (Dip.)	0.18 0.06		0.10 0.05	(Bobadilla et al. 2005)

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		36h 48h		0.04 0.02		0.03 0.01	
Annona muricata	Seeds	Seed Extract	*Aedes aegypti* (Dip.)	900.0		380.0	(Henao et al. 2007)
Annona muricata	Leaves/ Branches	Extract Leaves Ethanolic Aqueous	*Anastrepha ludens* (Dip.)	831.445 >1000	2058.3 3852.6		(González-Esquinca et al. 2012)
Annona muricata	Leaves/ Branches	Stems Ethanolic Aqueous	*Anastrepha ludens* (Dip.)	865.0 >1000	4539 3984.2		(González-Esquinca et al. 2012)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% LC - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Annona muricata	Seed	Seed extract	*Anopheles albimanus* (Dip.)	16.20	0.82		(Morales et al. 2004)
Annona muricata	Seed	Food consumption (%) Low dose Medium dose **Water (Positive Control 01)** **10% Ethanol (Positive Control 02)**	*Anticarsia gemmantallis* (Lep.)		10.0 30.0 0.0 0.0	25.0 29.3 19.9 19.3	(Fontana et al. 1998)
Annona muricata	Seed	Parviflorin Asimicin Sylvaticin	*Blatella germanica* (Blat.)	0.6 1.8 1.5	6 10 8		(Alali et al. 1998)

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		Bullatalicin Annomontacin Gigantetrocin A Cypermethrin Chlorpyrifos Hydramethylnon Propoxur Bendiocarb		6.5 3.6 4.1 0.003 0.3 5.6 39.9 43.2	23 23 34 6 3 12 - -		
Annona muricata	Leaves	Leaves Extract	*Culex Quinquefascintus*	20.87		56.47	(Magadula et al. 2009)
Annona muricata	Seed	Compounds 1 2 Rotenone	*Leptinotarsa dercemlineata* (Col.)		92.18 29.68 100		(Guadaño et al. 2000)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% LC - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Annona muricata	Seeds	Seed Extract	*Plutella xylostella* (Lep.)	43.0	60.0		(Sinchaisri et al. 1991)
Annona muricata	Seeds	Seed Extract Hexanic 24h 48h 72h Ethyl Acetathe 24h	*Sithophillus zeamais* (Col.)	11.447 - - - - -		4.009 3.854 3.760 3.280 2.667 2.542	(Llanos et al. 2008)

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		48h 72h					
Annona muricata	Seeds	Seeds Extract	*Zabrotes subsfasciattus* (Col.)	46.0	39.1	36.4	(Araújo 2010)
Annona reticulata	Seeds	Seed Extract (95% of Methanol) In two periods: 24h and 48h. 1.0 g/l 2.5 g/l 5.0 g/l 7.5 g/l 10.0 g/l 15.0 g/l 20.0 g/l	*Epilachna vigintioctopunctata* (Col.)		(%) 24h and 48h 6.7 - 13.4 40.0 – 53.4 80.0 – 100 100 – 100 100 – 100 100 – 100 100 – 100		(Karunaratne and Arukwatta 2009)
Annona reticulata	Uninformed	Petroleum ether extract Ethanolic extract	*Rhodnius neglectus* (Hem.)		35.0 Not significant		(Schmeda-Hirschmann and de Arias 1992)
Annona reticulata	Seeds	Methanolic extract	*Spodoptera litura* (Lep.)	301.30 (259.15-326.33)	50.0%	167.48 (110.43-383.65)	(de Cássia Seffrin et al. 2010)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% LC - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Annona salzmannii	Barks		*Aedes aegypti* (Dip.)	615.18	(473.71 -981.44)		(Cruz 2011)

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		Hexanic Extract (8,68 g (0,48%) Methanolic Extract 143,29 g (7,96%) $CHCl_3$ alkaloid fraction – FCA		>700.00 163.53	(00.00-00.00) (107.90-238.82) (13.31-19.40) (130.00-218.00) (0.035-0.050)		
Annona salzmannii	Barks	Neutral CHCl3 fraction – FCN caryophyllene oxide Temephos	*Aedes aegypti* (Dip.)	15.92 167.00 0.042			(Cruz 2011)
Annona senegalensis	Root	Root Extract Control	*Callosobruchus maculatus* (Col.)	18.7 4.7	3.7 98.0	0.1 79.5	(Aku et al. 1998)
Annona senegalensis	Fruits	Ethanolic extract	*Culex quinquefascintus* (Dip.)	0.67	23.42	29.78	(Magadula et al. 2009)
Annona senegalensis	Uninformed	Extract	*Sitophilus zeamais* (Col.)	220.71	0.19 – 0.06		(LS et al. 2004)
Annona squamosa	Leaves	Aqueous extract (g/100 ml) 100.0 50.0 25.0 12.5 6.25 3.125 1.5625 **Control**	*Aedes aegypti* (Dip.)	100.0 100.0 83.3 90.0 70.0 76.6 73.3 5.7			(Monzon et al. 1994)
				Methods			

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Annonaceae species	Used Material	Substances / Extracts	Insect species (Order)	Topical (LC_{50} µg/ larva)	Topical (LD_{50} – 95% LC - µg/nymph)	Oral (LC_{50} ppm fresh weight in diet)	Ref.
Annona squamosa	Seeds	Extract (µg/ml) 1	*Aedes albopictus* (Dip.)	388.3	397.4	486.6	(Kempraj and Bhat 2011)
Annona squamosa	Seeds	Extract (µg/ml) 2 4 6 8 10 20	*Aedes albopictus* (Dip.)	231.3 162.3 114.0 64.9 45.6 0.0	240.3 163.8 112.0 72.4 47.8 0.0	268.5 185.4 121.1 84.9 56.3 0.0	(Kempraj and Bhat 2011)
Annona squamosa	Leaves	Ethanol extract (mg/ml) at 24h, 48h and 72h. 5 10 20 30	*Anopheles gambiae* (Dip.)		3.33 (24h) 6.67 (48h) 23.33 (72h) 16.67 (24h) 33.33 (48h) 63.33 (72h) 40.0 (24h) 66.67 (48h) 76.67 (72h) 53.33 (24h) 73.33 (48h) 90.0 (72h)		(Allison et al. 2013)

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Annonaceae species	Used Material	Substances / Extracts	Insect species (Order)	Methods			Ref.
				Topical (LC_{50} µg/ larva)	Topical (LD_{50} – 95% LC - µg/nymph)	Oral (LC_{50} ppm fresh weight in diet)	
Annona squamosa	Leaves	Ethanol extract (mg/ml) at 24h, 48h and 72h. 40	*Anopheles gambiae* (Dip.)		70.0 (24h) 90.0 (48h) 1000 (72h)		(Allison et al. 2013)
Annona squamosa	Whole plant	Extract (ppm) 50 100 150 200	*Anopheles stephensi* (Dip.)	(%) 58 60 70 74	(%) 4 6 16 18	(%) 52 76 86 92	(Saxena et al. 1993)
Annona squamosa	Leaves	Extract (mgl) 500 250 125 62.5 31.25 15.63 7.82	*Anopheles subpictus* (Dip.)		(%) 100 – 0.0 82.6 – 2.46 63.0 – 1.84 48.2 – 4.62 16.4 – 2.04 92.0 – 3.28 4.6 – 4.60		(Kamaraj et al. 2011)
Annona squamosa	Leaves	Ethanolic extract Aqueous extract	*Bemisia tabaci* (Hem.)		100 – 0.0 99.3 – 1.05		(Cruz-Estrada et al. 2013)
Annona squamosa	Seeds	Extract (mg/ml) 0.01 0.03	*Callasobruchus chinensis* (Col.)		(%) 9.66 9.66		(Kotkar et al. 2002)

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		0.05			41.00		
Annona squamosa	Seeds	Extract (mg/ml) 0.07 0.09	*Callasobruchus chinensis* (Col.)		% 81.33 99.00		(Kotkar et al. 2002)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% LC - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Annona squamosa	Seeds	Extract (mg/ml) 0.07 0.09	*Callasobruchus chinensis* (Col.)		% 81.33 99.00		(Kotkar et al. 2002)
Annona squamosa	Seeds	Extract (µg/cm²) Petroleo ether Ethanol Acethone Methanol	*Ceratitis capitata* (Dip.)	(%) 0.031 0.632 0.591 4.038	(%) 198.57 614.26 1000.40 135.25		(Epino and Chang 1993)
Annona squamosa	Seeds	Extract (%) 0.05 0.1 Deltamethrin	*Crocidiolomia pavonana* (Lep.)		10.4 ± 1.2 6.3 ± 2.7 11.0 ± 3.6	32.0 ± 6.9 69.0 ± 4.8 62.4 ± 5.2	(Dadang and Prijono 2009)
Annona squamosa	Seeds	Aqueous extract (25%)	*Culex quinquefasciatus* (Dip.)		33.6%		(Pérez-Pacheco et al. 2004)
Annona squamosa	Leaves	Ethanol extract (mg/ml) at 24h, 48h and 72h.	*Culex quinquefasciatus* (Dip.)		(%) 0.0 (24h) 13.33 (48h)		(Allison et al. 2013)

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		5 10			46.67 (72h) 33.33 (24h) 56.67 (48h) 73.33 (72h)		
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% LC - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Annona squamosa	Leaves	Ethanol extract (mg/ml) at 24h, 48h and 72h. 20 30 40	*Culex quinquefasciatus* (Dip.)		56.67 (24h) 70.0 (48h) 90.0 (72h) 80.0 (24h) 96.67 (48h) 100 (78h) 93.33 (24h) 100 (48h) 1000 (72h)		(Allison et al. 2013)
Annona squamosa	Leaves	Aqueous extract (g/100 ml) 100.0 50.0 25.0 12.5 6.25 3.125 1.5625	*Culex quinquefasciatus* (Dip.)		(%) 100.0 60.0 50.0 36.7 26.7 33.3 10.0		(Monzon et al. 1994)

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Annona squamosa	Leaves	Extract	*Culex quinquefasciatus* (Dip.)	0.64	14.69		(Magadula et al. 2009)
Annona squamosa	Leaves	Methanol Extract (mg/l) 500	*Culex tritaeniorhynchus* (Dip.)		(%) 100.0 ± 00.0		(Kamaraj et al. 2011)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% LC - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Annona squamosa	Leaves	Methanol Extract (mg/l) 250 125 62.5 31.25 15.63 7.82	*Culex tritaeniorhynchus* (Dip.)		(%) 88.4 ± 1.64 52.6 ± 4.63 34.2 ± 2.84 20.6 ± 1.67 12.4 ± 2.45 6.8 ± 1.87		(Kamaraj et al. 2011)
Annona squamosa	Seeds	Diet (µg/2g) 48h	*Drosophila melanogaster* (Dip.)			62.5	(Kawazu et al. 1989)
Annona squamosa	Seeds	Extract (g/l) 1.0 2.5 5.0 10.0 15.0 20.0	*Epilachna vigintioctopunctata* (Col.)	24h and 48h (%) 6.7 and13.4 40.0 and 53.4 80.0 and 53.4 100 and 100 100 100	(%) 64.8 83.4 92.3 95.9 95.9 100.0		(Karunaratne and Arukwatta 2009)

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Annona squamosa	Branches	Extract (%)	*Musca domestica* (Dip.)		41.00		(Sharma et al. 2011)
Annona squamosa	Leaves	Extract (mg/l) 0 200 400 600 800 1000	*Musca domestica* (Dip.)	(%) 100 80 65 50 30 0		(%) 100 62.5 53.85 40.0 33.33 0.0	(Begum et al. 2010)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% LC - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Annona squamosa	Leaves	Extract (% plant poder) 5 10 20	*Oryctes rhinoceros* (Col.)	(%) 10 30 50	(%) 10 20 20		(Sreeletha and Geetha 2012)
Annona squamosa	Leaves	Extract (%) 100 75 50 25 10 5 0.1	*Periplaneta americana* (Blat.)		(%) 80 60 50 20 10 10 0	Average 4.00 ± 0.0 3.00 ± 0.0 2.5 ± 0.71 1.00 ± 0.0 0.5 ± 0.701 0.5 ± 0.701 0.0 ± 0.0	(Kesetyaningsih 2012)

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Annona squamosa	Seeds	Extract (mg/ml) 5 10	*Plutella xylostella* (Lep.)		(%) 46.7 70.0		(Sinchaisri et al. 1991)
Annona squamosa	Seeds	Aqueous extract Larval instar (Time h) **3rd:** 24h 48h 72h **4th:** 24 48 72	*Plutella xylostella* (Lep.)		(%) 5.2 (3.1-8.5); 1.7 (1.3-2.2); 0.9 (0.7-1.2). 8.7 (6.6-11.3); 4.2 (3.5-5.1); 2.0 (1.7-2.4).	(%) 2.5 ± 1.4 10.0 ± 6.8 12.5 ± 6.0 0 1.3 ± 1.3 5.0 ± 2.0	(Leatemia and Isman 2004)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% LC - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Annona squamosa	Seeds	Aqueous extract 1% 5% Control 1 (Acetone) Control 2 (Methanol) Control 3 (Without solvente)	*Sitophilus oryzae* (Col.)		(LD_{50} Min) 23.1 (22.1-23.9) 11.4 (10.7-12.2) 0.0 0.0 0.0	(% min) 39.6±1.4 14.5±1.1 - - -	(Kumar et al. 2010)
Annona squamosa	Seeds	Extract (%) 0.5	*Spodoptera litura* (Lep.)	21.66±1.66	0.0	28.33±1.66	(Deshmukhe et al. 2010)

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Annona squamosa	Seeds	Extract (%) 1 5 10 15 20 25	*Spodoptera litura* (Lep.)	 23.33±1.66 38.33±1.66 48.33±1.66 56.66±1.66 51.66±1.66 61.66±1.66	 0.0 0.0 0.0 0.0 1.66±1.66 1.66±1.66	 33.33±1.66 51.66±1.66 58.33±1.66 78.33±3.33 75.00±0.0 80.00±0.0	(Deshmukhe et al. 2010)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% LC - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Annona squamosa	Seeds	Extract Petroleum ether EtOH Acetone Methanol	*Tribolium castaneum* (Col.)	LD_{50} (µg/cm²) 0.031 0.632 0.591 4.038	95% (Lower and Upper) 0.006 and 0.150; 0.315 and 1.265; 0.285 and 1.224; 1.727 and 9.440.		(Khalequzzaman and Sultana 2006)
Annona squamosa	Seeds	Extracts using two methods of application: Topical (µg/larva) Oral (ppm fresh weight in diet.	*Trichoplusia ni* (Lep.)	301.30 (259.15-326.33)		167.48 (110.43-383.65)	(de Cássia Seffrin et al. 2010)
Annona squamosa	Seeds	Extract (ppm) Hexane extract	*Trogoderma granarium* (Dip.)	(%) 10th day and 15th day		(mg) 10th day and 15th day.	(Rao et al. 2005)

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		250 500 750 1000 1250 1500 Ethyl Acetate extract 50 250 500 750 1000 1250		0.0 and 11.13 4.47 and 11.13 11.13 and 17.8 17.8 and 28.87 48.9 and 53.33 75.33 and 82.2 4.47 and 20.00 24.5 and 33.33 26.7 and 55.53 51.13 and 57.8 64.47 and 80.0 84.5 and 91.13		66.1 and 80.5 75.1 and 84.6 64.9 and 70.9 63.6 and 71.8 64.9 and 70.1 58.3 and 61.5 73.0 and 86.2 65.6 and 73 72.4 and 81.0 62.9 and 69.5 59.8 and 66.0 56.0 and 61.0	
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods** **Topical (LC_{50} µg/ larva)**	**Topical (LD_{50} – 95% LC - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	**Ref.**
Annona squamosa	Seeds	Extract (ppm) Methanol extract 500 750 1000 1250 1500 2000 Acetone control Control	*Trogoderma granarium* (Dip.)	(%) 10th day and 15th day 6.67 and 8.87 13.34 and 17.8 22.2 and 24.47 20.0 and 26.67 48.87 and 57.7 66.67 and 77.7 0.0 and 0.0; 0.0 and 0.0.		(mg) 10th day and 15th day. 78.0 and 96.6 74.1 and 93.1 75.2 and 98.2 74.6 and 92.4 58.0 and 85.0 53.4 and 62.5 100.9 and 150.6. 94.9 and 161.6.	(Rao et al. 2005)

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Artabotrys odoratissimus	Bark	Larval instar and exposure periods (h) Second 12h 24h	*Culex quinquefascintus* (Dip.)	LC_{50} 52.92 42.03	95% (Lower and Upper) 33.59 and 83.87 26.18 and 67.47		(Kabir 2010)
Artabotrys odoratissimus	Bark	Larval instar and exposure periods (h) Third 12h 24h Fouth 12h 24h	*Culex quinquefascintus* (Dip.)	110.03 99.13 170.12 110.41	72.51 and 166.9 60.2 and 163.29 137.6 and 210.26 89.6 and 135.95		(Kabir 2010)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% LC - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Asimina triloba	Roots	Ethanolic extract (Fraction nº.) 017 018 019 020 021 Asimicin	*Acalymma vittatum* (Col.)	LC_{50} (p.p.m.) 7.56 >1000 1.67 0.04 715 0.03			(Mikolajczak et al. 1988)
Cardiopetalum calophyllum	Seeds		*Aedes aegypti* (Dip.)	(%) 5.00	(mg/mL) 1.789		(Costa, Marilza da Silva, Mônica Josene Barbosa

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		Methanolic extract (1.0 mg/mL)					Pereira, Simone Santos de Oliveira, Paulo Teixeira de Souza, Evandro Luiz Dall'oglio 2013)
Dennettia tripetala	Leaves and roots	Ethanol extract (5mL/100g) in 1, 3 and 7 days. 0.0	*Dermestes maculatus* (Col.)		(%) In 1, 3 and 7 days. 0.0 ± 0.0 0.0 ± 0.0 0.0 ± 0.0		(Akinwumi et al. 2007)
Dennettia tripetala	Leaves and roots	Ethanol extract (5mL/100g) in 1, 3 and 7 days. 2.50 5.00	*Dermestes maculatus* (Col.)		(%) In 1, 3 and 7 days. 26.67 ± 0.88 71.67 ± 0.88 100.0 ± 0.0 26.67 ± 0.67 75.0 ± 1.16 100.0 ± 0.0		(Akinwumi et al. 2007)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% LC - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Dennettia tripetala	Leaves and roots	Ethanol extract (5mL/100g) in 1, 3 and 7 days. 7.50 10.0	*Dermestes maculatus* (Col.)		(%) In 1, 3 and 7 days. 48.33 ± 0.88 91.67 ± 0.33 100.0 ± 0.0 51.67 ± 0.66 98.33 ± 0.33		(Akinwumi et al. 2007)

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					100.0 ± 0.0		
Dennettia tripetala	Seeds	Concentration of plant powder/25g fish Extract Untreated control	*Dermestes maculatus* (Col.)	(%) 87.0 100		(g) 0.25 0.50	(Okonkwo and Okoye 2001)
Dennettia tripetala	Uninformed	Extracts (ppm) 0 10 100 1000	*Ostrinia nubialis* (Lep.)	5.79 3.13 3.87 3.84			(Ewete et al. 1996)
Dennettia tripetala	Seeds	Extract (ml/25g) 0.1 0.2 0.3	*Necrobia rufipes* (Col.)		(%) 100 100 100		(Okonkwo and Okoye 2001)
Annonaceae species	**Used Material**	**Substances / Extracts**	**Insect species (Order)**	**Methods**			**Ref.**
				Topical (LC_{50} µg/ larva)	**Topical (LD_{50} – 95% LC - µg/nymph)**	**Oral (LC_{50} ppm fresh weight in diet)**	
Dennettia tripetala	Leaves and roots	Extract (%) at 24h, 48h and 72h. 0%	*Sitophilus zeamais* (Col.)		(%) at 24h, 48h and 72h. 1.83 1.09 1.75		(Umeotok et al. 2013)

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Dennettia tripetala	Leaves and roots	Extract (%) at 24h, 48h and 72h. 1% 5% 10%	*Sitophilus zeamais* (Col.)		(%) at 24h, 48h and 72h. 1.50 2.09 2.58 1.50 2.09 3.08 2.83 3.58 4.67		(Umeotok et al. 2013)
Duguetia furfuraceae	Leaves/barks and roots	Extract	*Aedes aegypti* (Dip.)	(µg/ml) 56.6			(Rodrigues et al. 2006)
Duguetia furfuraceae	Leaves	Extract	*Sitophilus zeamais* (Col.)	(Proportion of insects in the treated area (SDM)) 0.500 (0.113)			(Luciana et al. 2013)
Guatteria blephrophylla	Leaves	Extract (ppm)	*Aedes aegypti* (Dip.)	85.74	(74.05 – 112.78)	4.48±0.89	(Aciole et al. 2011)
Guatteria friesiana	Leaves	Extract (ppm)	*Aedes aegypti* (Dip.)	52.60	(50.11 – 55.17)	6.48±0.55	(Aciole et al. 2011)
Guatteria hispida	Leaves	Extract (ppm)	*Aedes aegypti* (Dip.)	85.74	(74.05 – 112.78)	4.48±0.89	(Aciole et al. 2011)
Mikilua fragans	Aerial parts	Essential oil	*Anopheles gambiae* (Dip.)		RC_{75} ($x10^{-5}$ $mgcm^{-2}$) 481 (11, 145)		(Odalo et al. 2005)
					Methods		**Ref.**

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Annonaceae species	Used Material	Substances / Extracts	Insect species (Order)	Topical (LC_{50} µg/ larva)	Topical (LD_{50} – 95% LC - µg/nymph)	Oral (LC_{50} ppm fresh weight in diet)	
Oxandra cf xylopioides	Leaves	Extract 24h 48h 72h	*Spodoptera frugiperda* (Lep.)		ppm 319.61 311.47 294.13		(Rojano et al. 2007)
Rollinia occidentalis	Seeds	Extract (ppm) 50 100 250	*Spodoptera frugiperda* (Lep.)	(%) 5 35 50	(%) 30 45 50	(%) - 20 -	(Tolosa et al. 2012)
Uvaria scheflerri	Roots	Essential oil 5% 1% 0.5% 0.1	*Anisakis* L_3	- 5 - -			(Anza et al. 2021)
Xylopia aethiopica	Leaves and Roots	Extract Ethanolic Water	*Anopheles gambiae* (Dip.)	LC50 3.57 4.50	(%) 125 (34.72%) 106 (29.44%)		(Aina et al. 2009)
Xylopia aethiopica	Uninformed	Extract (ppm) 0 10 100 1000	Ostrinia nubilalis (Lep.)	(mg) 3.78 3.69 3.87 3.84			(Ewete et al. 1996)

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Annonaceae species	Used Material	Substances / Extracts	Insect species (Order)	Methods			Ref.
				Topical (LC_{50} µg/ larva)	Topical (LD_{50} – 95% LC - µg/nymph)	Oral (LC_{50} ppm fresh weight in diet)	
Xylopia aromatica	Leaves/Barks and Roots	Extract	*Aedes aegypti* (Dip.)	(µg/ml) 384.37			(Rodrigues et al. 2006)
Xylopia caudata	Leaves	Oil	*Aedes aegypti* (Dip.)	29.83 (21.87-37.45)	60.33 (48.04-82.47)	4.19±0.69	(Zaridah et al. 2006)
Xylopia ferruginea	Leaves	Oil	*Aedes aegypti* (Dip.)	74.51 (68.39-86.52)	106.45 (90.23-159.78)	8.27±1.88	(Zaridah et al. 2006)

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3.3. Antimicrobial

Microbial diseases are infections caused by invading microorganisms or imbalances in the individual's microbiota due to low immunity, overpopulation of a certain microorganism, or the presence of bacteria outside its natural habitat. The microbiome of the human body is extremely important, coexisting in a mutual relationship where it protects the host from invading microorganisms. Microorganisms in the microbiota can produce important nutrients, such as the production of vitamin K and B, and contribute to the development of the immune system (Rabêlo et al. 2014; Mendes et al. 2020).

Pathogenic bacteria, those that can cause disease in humans, can be classified into three different groups on account of the composition of their cell wall: Gram-positive bacteria have a thick layer of peptideoglycan on their cell wall and after Gram stain it takes on a violet color; Gram-negative bacteria have a thin layer of peptideoglycan on their cell wall and an outer portion of lipopolysaccharide and lipoproteins so when stained by the Gram method they assume a pink color; and, finally, acid-resistant bacteria, BAARS (acid-resistant bacilli), whose cell wall has complex lipids (mycolic acids) that obtain the primary dye even after subjected to acid-acid discoloration in the Ziehl Neelsen method (Fernandes 2000; Moreira et al. 2015; Mendes 2019).

There are also fungi that are present in the human microbiota and those that can be inhaled, but they do not cause damage to the organism so long as the natural defense barriers are intact. In this way, fungi have almost no infectious power until heavy virulence (Sidrim and Rocha 2004; Gomes et al. 2010; Barros 2014).

The most common bacterial and fungal infections are induced by *Staphylococcus aureus, Staphylococcus epidermides, Escherichia coli, Pseudomonas aeruginosa, Salmonella Typhimarium, Enterococcus faecalis, Klebisiella pneumonieae, Candida krusei, Candida albicans* and *Candida tropicalis* (Fernandes 2000; Moreira et al. 2015).

Infections were commonly fatal until antibiotics were discovered. In addition to being extremely important for the treatment and control of infectious diseases in humans and animals, antibiotics have made it possible to perform complex surgeries, intensive therapy, organ transplants, etc (Acar and Moulin 2012; Andrade 2018).

In the late 1930s, when antibiotics were introduced into therapy, mortality from pneumococcal pneumonia decreased by 20-40%, mortality from pneumococcal bacteremia by 50-80%, and mortality from severe infections such as bacterial meningitis and endocarditis, by 60-75%. Antibiotics have sparked a major revolution in medicine and countless lives have been saved since their discovery (Lepper and Dowling 1951; Breiman et al. 1990; Tomasz 1997; Ortqvist et al. 2005; Davies and Davies 2010; IOM 2010; Andrade 2018).

However, microorganisms have begun to show resistance to antibiotics in the wake of the influx in use. This has increased the spread of antibiotic-resistant bacteria and fungi, as well as the number of deaths from infections (Andrade 2018). According to the World Health Organization (WHO), bacterial and fungal resistance is characterized as a worldwide public health problem, whose simple strategies of combat will not be enough to ameliorate the emergence and spread of resistant infectious organisms (World Health Organization (WHO) 2014; Andrade 2018). Antimicrobial resistance (AMR) is a natural process for microorganisms, but it can be accelerated through the misuse of antibiotics such as the selective, repeated, or incomplete use of some antimicrobial agents (Neill 2016; Andrade 2018; Mendes et al. 2020).

AMR has become a major threat to the health of living beings, making treatment more difficult as well as increasing morbidity and mortality. Bacteria and fungi such as *E. coli, S. aureus, P. aeruginosa,* and *C. albicans* are examples of pathogenic microorganisms that show frequent microbial resistance. In 2020, WHO alerted the world to the shortage of new antimicrobial agents effective against super-resistant bacteria (Barreiras et al. 2020; Mendes et al. 2020; World Health Organization (WHO) 2020). Clinical research focused on the discovery and implementation of new antimicrobial agents has been greatly reduced in recent years. Natural products are rich sources of compounds

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with antimicrobial potential that need to be explored. Thus, the search for new plant-based antimicrobial agents is increasingly frequent (Neill 2016; Andrade 2018; Mendes et al. 2020).

Some species of the Annonaceae family have been studied for their antimicrobial profile against bacteria and fungi pathogenic to humans and plants. Table 3 describes the species of Annonaceae that have been studied for their antimicrobial profile in strains of bacteria and fungi most prevalent in human pathologies: *S. aureus*, *S. epidermides*, *E. coli*, *P. aeruginosa*, *E. faecalis*, *K. pneumonie*, *C. krusei*, *C. albicans* e *C. tropicalis*.

Annona genus

Several species of Annona have been extensively studied for their potential antimicrobial effects. One such species, *A. hypoglauca* Mart., underwent evaluation on two distinct alkaloid fractions. These fractions were assessed for their effectiveness against *S. aureus* (ATCC 29213), E. coli (ATCC 25922), and *E. faecalis* (ATCC 299212). The study revealed that the FA5 fraction, characterized by a higher concentration of isoboldine alkaloid, displayed noteworthy activity against *S. aureus* and *E. faecalis*, demonstrating a remarkable MIC value of 70 μg/mL for both microorganisms. Conversely, the FA6 fraction, enriched with actinodaphine alkaloid, exhibited antimicrobial efficacy against all three microorganisms: *S. aureus*, *E. coli*, and *E. faecalis*, with MIC values of 70 μg/mL, 90 μg/mL, and 80 μg/mL, respectively (Rinaldi et al. 2017).

Moreover, the methanol-methylene chloride extract from the root bark of *A. senegalensis* demonstrated potential antimicrobial activity, particularly against *S. aureus* and *P. aeruginosa*, with MIC values of 8750 μg/mL and 1080 μg/mL, respectively. The F1 subfraction extracted from these samples was found to consist of a diverse range of compounds, including kaur-16-en-19-oic acid, 1-dodecanol, 1-naphthalenemethanol, 6,6-dimethyl-bicyclo[3.1.1]hept-2-ene-2-ethanol, 3,3-dimethyl-2-(3-methylbuta-1,3-dienyl)cyclohexane-1-methanol, and 3-hydroxyandrostan-17-carboxylic acid. Impressively, the F1 subfraction exhibited significant activity against *P. aeruginosa*, with an MIC value of 40 μg/mL (Akah et al. 2012).

The antimicrobial potential of various *Annona* species was investigated by assessing the activity of their leaves. Notably, the essential oil extracted from *A. foetida* exhibited significant antimicrobial properties against *S. aureus* (ATCC 6538) and *C. albicans* (ATCC 10231), demonstrating MIC values of 200 μg/mL and 60 μg/mL, respectively (Costa et al. 2009).

In a parallel study, different samples of dried *A. muricata* leaf powder, varying in granulation, were subjected to evaluation against a range of microorganisms, including *S. aureus* (ATCC 25923), *E. coli* (ATCC 25922), *P. aeruginosa* (ATCC 27853), and *K. pneumoniae* (ATCC 4352). Notably, samples AM3 (with size bands between 0.149 and 0.074) and AM4 (size bands < 0.074) demonstrated the most promising results, with an MIC of 780 μg/mL against *S. aureus*, *E. coli*, and *K. pneumoniae* (de Andrade et al. 2019).

Furthermore, extracts derived from *A. vepretorum* leaves using different organic solvents such as ethanol, hexane, and chloroform were examined for their antimicrobial potential against *S. aureus* (ATCC 25923), *E. coli* (ATCC 25922), *E. faecalis* (ATCC 19433), and *K. pneumoniae* (ATCC 13883). Among these extracts, the hexanic extract exhibited noteworthy activity against *E. coli*, displaying an MIC value of 390 μg/mL (Almeida et al. 2014).

Additionally, a combination of two substances, 11-hydroxy-16-hentriacontanone and 10-hydroxy-hentricontanone, along with the isolated substance palmitone from *A. squamosa* leaves, was assessed for antimicrobial efficacy against *S. aureus* (ATCC 96) and *P. aeruginosa* (ATCC 741). These compounds exhibited notable antimicrobial effects, with palmitone showing a minimum inhibitory concentration (MIC) of 12.5 μg/mL against *S. aureus* and 6.25 μg/mL against *P. aeruginosa* (Shanker et al. 2007).

Guatteria genus

Extensive research has been conducted on numerous species within the Guatteria genus to explore their antimicrobial properties against human pathogens. In particular, the essential oils from the seeds of three species—*Guatteriopsis hispida*, *Guatteriopsis blephaphylla*, and *Guatteriopsis friesiana*—were evaluated for their efficacy against *S. aureus* (ATCC 6538), *S. epidermidis* (ATCC 12228), *E. coli*

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(ATCC 11775), and *P. aeruginosa* (ATCC 133388). Among these, the essential oil from *G. friesiana* proved most effective, with MIC values of 125 μg/mL against *S. aureus*, 100 μg/mL against *S. epidermidis*, and 900 μg/mL against both *E. coli* and *P. aeruginosa*. Isolated compounds from *G. blepharophyla* essential oil, such as β-eudesmol, γ-eudesmol, and α-eudesmol, also showed significant activity. Notably, γ-eudesmol exhibited strong antimicrobial activity against *P. aeruginosa* with an MIC of 300 μg/mL, while α-eudesmol demonstrated potential against both *S. aureus* and *P. aeruginosa*, with MIC values of 250 μg/mL and 200 μg/mL, respectively (Costa et al. 2008).

In a separates studies, essential oils extracted from the leaves of *G. blepharophylla* (synonym Guatteria blepharophylla), *G. costaricensis*, *G. diospyroid*, and *G. oliviformis* were evaluated for their antimicrobial properties against *S. aureus* (ATCC 6538 (Costa et al. 2011c; Alcântara et al. 2017), ATCC 29213(Palazzo et al. 2009)), *E. coli* (ATCC 8739 (Costa et al. 2011c; Alcântara et al. 2017) and ATCC 259222 (Palazzo et al. 2009)), *P. aeruginosa* (ATCC 9027 (Costa et al. 2011c; Alcântara et al. 2017)), and *E. faecalis* (ATCC 29212 (Costa et al. 2011c; Alcântara et al. 2017)). Particularly, *G. blepharophylla* essential oil exhibited promising activity against *S. aureus* and *E. faecalis*, with an MIC of 50 μg/mL. Another significant discovery involved the efficacy of *G. diospyroid* essential oil against *S. aureus*, with an MIC of 312 μg/mL (Palazzo et al. 2009). Additionally, the isomoschatoline alkaloid, isolated from *G. blepharophylla* leaves, displayed significant activity against *C. albicans* (ATCC 10231) with an MIC of 50 μM L-1, surpassing the control compound nystatin, which had an MIC of 54 μM L-1 (Costa et al. 2011c; Alcântara et al. 2017).

Furthermore, the hydroalcoholic extract obtained from *Guatteria citriodora* leaves exhibited potential activity against *S. aureus*, with an MIC of 250 μg/mL, while the alkaloid fraction displayed promising activity against *S. epidermidis* (ATCC 4083) (MIC of 125 μg/mL) (Rabelo et al. 2014). However, the alkaloid fraction derived from the stem bark did not exhibit activity against either *S. aureus* or *S. epidermidis* (Rabelo et al. 2014).

Finally, essential oils extracted from the aerial parts of *G. selewiana*, *G. latifolia*, *G. ferruginea*, *G. australis*, and *G. punctata* were tested against *E. coli* microorganisms (ATCC 11775 (Santos et al. 2017) and CDC-EDL 933-171-0157: H3 (Bay et al. 2019a)), *S. aureus* (ATCC 33591) (Bay et al. 2019a), and *P. aeruginosa* (ATCC 29336) (Bay et al. 2019a). Among these, *G. selewiana*, *G. latifolia*, and *G. ferruginea* exhibited activity against *E. coli* (ATCC 11775), with an MIC of 600 μg/mL (Santos et al. 2017). Conversely, *G. australis* and *G. punctata* did not demonstrate activity against these microorganisms (Santos et al. 2017; Bay et al. 2019a).

Polyalthia genus

The species *P. longifolia* stands out as the most extensively studied within its genus, with antimicrobial activity investigations conducted on extracts derived from its stem bark, roots, and leaves. In stem bark studies, the butanol fraction displayed noteworthy MIC activity levels of 320 μg/mL against *S. aureus* (ATCC 29213 and MRSA 512), as well as *E. coli* (ATCC 29212), and an MIC of 160 μg/mL against *P. aeruginosa*. A compound isolated from the stem bark, 3-o-methyl ellagic acid, exhibited MIC values of 80 μg/mL against *S. aureus* (ATCC 29213), *E. coli*, and *P. aeruginosa*, while it exhibited an MIC of 160 μg/mL against MRSA 512 strains (Jain et al. 2014).

Root-based studies yielded promising results, where three alkaloids—pendulamine A, pendulamine B, and penduline—were isolated, exhibiting intriguing antimicrobial activity against *S. aureus*, *P. aeruginosa*, *S. typhimurium*, and *K. pneumoniae*. Pendulamine A demonstrated an impressive MIC of 0.2 μg/mL against S. aureus, 2 μg/mL against *P. aeruginosa*, 0.02 μg/mL against *S. typhimurium*, and 2 μg/mL against *K. pneumoniae*. Likewise, Pendulamine B was effective against *S. aureus*, *S. typhimurium*, and *K. pneumoniae*, with corresponding MICs of 0.2 μg/mL for both *S. aureus* and *S. typhimurium*, and 2 μg/mL for *K. pneumoniae*. In contrast, the alkaloid penduline exhibited targeted activity solely against *S. aureus*, achieving an MIC of 12.5 μg/mL (Faizi et al. 2003).

Derived from *P. longifolia* leaves, the methanolic extract showcased substantial activity against *S. aureus* and *P. aeruginosa*, with MIC values of 125 μg/mL. Two diterpenes, namely 16(R and S)-hydroxy-cleroda-3,13(14)Z-dien-15,16-olide and 16-oxo-cleroda-3,13(14)E-dien-15-oic acid, were isolated from the leaves. Of these, the diterpene 16(R and S)-hydroxy-cleroda-3,13(14)Z-dien-15,16-

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olide exhibited the most promising antimicrobial activity against *S. aureus*, boasting an MIC of 7.8 µg/mL (Faizi et al. 2008).

Additionally, investigations into the antimicrobial potential of *P. cinnamomea* were conducted. However, the leaf extract did not reveal promising activity against *S. aureus* (ATCC 25923), *S. epidermidis*, *E. coli* (ATCC 10536), or *S. typhimurium* (ATCC 51812) (Mahmud et al. 2018).

Xylopia genus

Antimicrobial investigations have focused on three species within the *Xylopia* genus. *X. staudtii* bark hydroethanol extract revealed notable antimicrobial properties against *E. coli* (ATCC 25922), achieving an MIC of 83.33 µg/mL (Pouofo Nguiam et al. 2021). For both *X. aromatica* and *X. sericea*, the essential oils extracted from their leaves were subjected to analysis. *X. aromatica's* essential oil displayed promising activity against *E. faecalis* (ATCC 29212), registering an MIC of 50 µg/mL (Alcântara et al. 2017). Meanwhile, the essential oil from *X. sericea* exhibited impressive antimicrobial potential against *S. aureus* (ATCC 6538), boasting an MIC of 7.8 µg/mL, and *K. pneumoniae* (ATCC 4552), with an MIC of 12.5 µg/mL (Mendes et al. 2017).

Uvaria genus

Furthermore, antimicrobial investigations extended to three species of *Uvaria*, yielding highly encouraging results. A particularly significant finding was the isolation of the flavonoid 5,7,8-trimethoxyflavone from *U. schefflera* leaves, which exhibited pronounced antimicrobial activity against *E. coli* (ATCC 10418), showing an MIC value of 125 µg/mL (Moshi et al. 2004). Additionally, a mixture of flavonoids, 2',6'-dihydroxy-4'-methoxychalcone and 5,7-dihydroxyflavone, displayed notable antimicrobial activity against *C. albicans*, registering an MIC of 31.2 µg/mL (Moshi et al. 2004).

The methanolic extract from the root bark of *U. tanzaniae* exhibited remarkable antimicrobial activity against *S. aureus* (ATCC 25923), boasting an impressively low MIC of 1.25 µg/mL (Christopher et al. 2018). In a similar vein, the essential oil derived from the leaves of *U. hamiltonii* showcased substantial antimicrobial potential. It displayed noteworthy activities against *S. aureus* (ATCC 25923), *P. aeruginosa* (ATCC 27853), *E. faecalis* (ATCC 29212), and *C. albicans* (ATCC 10231), with MIC values of 20.34 µg/mL, 12.34 µg/mL, 7.99 µg/mL, and 32.57 µg/mL, respectively (Tsiang et al. 2022).

Other species of Annonaceae

Research conducted by Pereira et al., 2016, investigated the antimicrobial properties of *Cleistochlamys kirkii* (Benth) Oliv, a shrub commonly utilized in traditional medicine to treat infectious diseases. From the methanolic extract of *C. kirkii*, the authors isolated nine compounds and assessed their efficacy against six strains of S. aureus, as well as the bacterium E. faecalis. The compound dichamanetin was shown to be highly active against the tested strains and is often more potent than the control antibiotics used in the study. In addition to this substance, the compounds chamanetin, isochamanetin and cleistenolide also showed relevant antibacterial activity against the strains studied. Thus, the authors verified the antibacterial potential of *C. kirkiii* and identified active components as valuable compounds to continue with in antimicrobial studies (Pereira et al. 2016).

In a study conducted by Silva et al. (2015), the polycapol triterpene, a lanostane-type triterpene, was investigated. Polycarpol, which has been isolated from several Annonaceae species including *Unonopsis duckei* R.E. Fr., *Unonopsis floribunda* Diels, *Unonopsis rufescens* (Baill.) R. E. Fr., *Unonopsis stipitata* Diels, *Onychopetalum amazonicum* R.E. Fr., and *Bocageopsis pleiosperma* Maas, demonstrated significant antimicrobial activity. It exhibited MIC values ranging from 25 to 50 µg/mL against *S. aureus*, *S. epidermidis*, and *E. coli* (da Silva et al. 2015).

Numerous species belonging to the Annonaceae family have undergone comprehensive assessments of their essential oils against pathogenic microorganisms. These species include *Bocageopsis multiflora* (Alcântara et al. 2017; Bay et al. 2019a), *Cananga odorata* (Sacchetti et al. 2005), *Cyathocalyx zeylanicus* (Hisham et al. 2012), *Dennetia tripetala* (Oyemitan et al. 2019), *Desmopsis bibacteata* (Palazzo et al. 2009), *Desmopsis macocarpa* (Palazzo et al. 2009), *Desmos chinensis* (Hisham et al. 2012), *Duguetia lanceolata* (Sousa et al. 2012), *Ephedranthus amazonicus* (Alcântara et al. 2017), *Fissistigma kwangsiensis* (Tsiang et al. 2022), *Fusaea longifolia* (Bay et al. 2019a), *Goniothalamus gracilipes*

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(Trieu et al. 2021), and *Unonopsis costaricensis* (Palazzo et al. 2009). Notably, the study involving *Fissistigma kwangsiensis* stands out for its remarkable findings, as the essential oil displayed highly promising activity against *P. aeruginosa* (ATCC 27853), achieving an impressively low MIC of 3.45 μg/mL (Tsiang et al. 2022).

Furthermore, a range of species, including *Goniothalamus longistipetes*, *Mitrephora celebica* (Zgoda-Pols et al. 2002), *Greenwayodendron suaveolens* (Williams et al. 2010; Christopher et al. 2018), *Enantia chlorantha* (Etame et al. 2019), *Cleistopholis patens* (Hu et al. 2006), and *Toussaintia orientalis* Verdc (Samwel et al. 2011), underwent isolation of active compounds from their extracts, with subsequent evaluation of the antimicrobial profiles of these molecules. For example, the diterpene ent-trachyloban-19-oic acid, extracted from *Mitrephora celebica*, showed considerable effectiveness against *S. aureus* (ATCC 43300), with a remarkable MIC of 6.25 μg/mL (Zgoda-Pols et al. 2002).

In addition, the antimicrobial potential of extracts from species such as *Annonidium mannii* (Ngangoue et al. 2020), *Monodora myristica* (Mbosso et al. 2010), *Mitrephora celebica* (Zgoda-Pols et al. 2002), *Greenwayodendron suaveolens* (Williams et al. 2010; Christopher et al. 2018), and *Uvariodendron usabarense* (Christopher et al. 2018) has been evaluated. These collective efforts contribute valuable insights into the rich antimicrobial potential present within the Annonaceae family.

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Table 3. Summary of antimicrobial activity of species of the Annonaceae.

Annonaceae species	Used Material	Substances/ Extracts	Microorganisms / MIC (µg/mL)									Ref.
			S. aureus	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*E. faecalis*	*K. pneumoniae*	*C. krusei*	*C. albicans*	*C. tropicalis*	
Annona foetida	Leaves	Essential oil **Chloramphenicol** **Nystatin (Positive control)**	ATCC 6538 200 20 -							ATCC 10231 60 - 50		(Costa et al. 2009)
Annona hypoglauca Mart.	Bark	Alkaloid phases FA5 (isoboldine) FA6 (actinodaphnine)	ATCC 29213 70 70		ATCC 25922 - 90		ATCC 299212 70 80					(Rinaldi et al. 2017)
Annona muricata	Leaves	Dried leaf powder: AM0 (Size bands < 2000) AM1	ATCC 25923 3120 1560		ATCC 25922 1560 1560	ATCC 27853 3120 3120		ATCC 4352 3120 3120				(de Andrade et al. 2019)

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		(Size bands between 0.500 and 0.350)										
Annonaceae species	**Used Material**	**Substances/ Extracts**	**Microorganisms / MIC (µg/mL)**									**Ref.**
			S. aureus	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*E. faecalis*	*K. pneumoniae*	*C. krusei*	*C. albicans*	*C. tropicalis*	
Annona senegalensis	Root bark	methanol-methylene chloride extract kaur-16-en-19-oic acid F1 (Subfraction) **Ciprofloxacin** **Gentamicin** **(Positive controls)**	8750 150 - 1.18 0.23			1080 - 40 3.6 0.79						(Akah et al. 2012)
Annona squamosa	Leaves	11-hydroxy-16-hentriacontanona + 10-hydroxy-hentricontanona Palmitone **Ciprofloxacin (positive control)**	MTCC 96 25 12.5 0.78			MTCC 741 25 6.25 0.78						(Shanker et al. 2007)

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Annona vepretorum	Leaves	Crude ethanolic extract Hexanic extract	ATCC 25923 3120 780		ATCC 25922 390 390		ATCC 19433 3120 3120	ATCC 13883 3120 3120				(Almeida et al. 2014)
Annonaceae species	**Used Material**	**Substances/ Extracts**	**Microorganisms / MIC (µg/mL)**									**Ref.**
			S. aureus	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*E. faecalis*	*K. pneumoniae*	*C. krusei*	*C. albicans*	*C. tropicalis*	
Annona vepretorum	Leaves	Chloroform extract	ATCC 25923 1560		ATCC 25922 780		ATCC 19433 12500	ATCC 13883 6250				(Almeida et al. 2014)
Annonidium mannii	Root Bark	Crude extract **Ciproflocaxin (Positive control)**						ATCC 11296 64 2				(Ngangoue et al. 2020)
Bocageopsis pleiosperma Maas	Stem Bark	Polycarpol **Chloramphenicol (Positive control)** **Ketoconazole (Positive control)**	ATCC 6538 25 25 -	ATCC 1228 50 50 -	ATCC 10538 50 50 -	ATCC 27853 - >500 -				ATCC 10231 250 - 12.5		(da Silva et al. 2015)

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Bocageopsis multiflora (Mart.) R.E. Fr	Leaves	Essential oil	ATCC 6538 190		ATCC 8739 1500	ATCC 9027 3000	ATCC 29212 90					(Alcântara et al. 2017)
Annonaceae species	**Used Material**	**Substances/ Extracts**	**Microorganisms / MIC (µg/mL)**									**Ref**
			S. aureus	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*E. faecalis*	*K. pneumoniae*	*C. krusei*	*C. albicans*	*C. tropicalis*	
Bocageopsis multiflora	Aerial parts	Essential oil **TIENAM (Positive control)**	ATCC 33591 4.68 4.68		CDC-EDL 933-171-0157:H3 4.68 1.17	ATCC 29336 4.68 2.34						(Bay et al. 2019a)
Cananga odorata		Essential oil **Thymus vulgaris (reference oil)**								ATCC 48274 170 60		(Sacchetti et al. 2005)
Cleistopholis patens	Leaves	Cleistetroside-8 Cleistetroside-5 Cleistetroside-2 **Vancomycin (positive control)**	ATCC 33591 8 8 0.5 1									(Hu et al. 2006)
	Leaves	Essential oil	ATCC 25923		ATCC 25922	ATCC 37853		ATCC 27853		ATCC 90028		

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Cyathocalyx zeylanicus		**Gentamycin** **Muconazol** **(Positive control)**	250 250 9.0		125 125 12.0	250 250 9.1		250 250 8.0		250 16 4.5		(Hisham et al. 2012)
			Microorganisms / MIC (µg/mL)									
Annonaceae species	**Used Material**	**Substances/ Extracts**	*S. aureus*	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*E. faecalis*	*K. pneumoniae*	*C. krusei*	*C. albicans*	*C. tropicalis*	**Ref.**
Cleistochlamys kirkii (Benth) Oliv.	Root Bark	Chamanetin Isochamanetin Dichamanetin Cleistenolide Acetylmelodorinol **Amoxicillin** **Oxacillin** **Vancomycin** **(Positive control)**	***S. aureus*** MSSA VISA ATCC 6538 CIP 106760 7.5 125 62 62 2 2 30 30 >250 >250 0.2 250 0.2 250	ATCC 43866 15 15 62 2 30 >250 62 250 125 250	ATCC 9144 30 125 250 1 7.5 125 62 250 125 250	FFHB 29593 - 30 4 15 >250 >250 >250 250 250	VRE MRSA HB164 15 30 7.5 30 >250 - - 32	ATCC 700699				(Pereira et al. 2016)

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			0.2 2	0.4 4	0.4	0.8						
Dennetia tripetala Baker f.	Seed	Dried seeds essential oil **Streptomycin** **Acriflavin** **(Positive control)**	NCIB 8586 3.13 - 0.13		NCIB 86 6.25 0.13	NCIB 950 25.0 1.0					NCCYC 6 6.25 - 2.0	(Oyemitan et al. 2019)
Desmopsis bibracteata *Desmopsis macrocarpa*	Leaves Leaves	Essential oil Essential oil	ATCC 29213 625 1250		ATCC 259222 2500 1250							(Palazzo et al. 2009)
Annonaceae species	**Used Material**	**Substances/ Extracts**	**Microorganisms / MIC (µg/mL)**									**Ref.**
			S. aureus	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*E. faecalis*	*K. pneumoniae*	*C. krusei*	*C. albicans*	*C. tropicalis*	
Desmos chinensis	Leaves	Essential oil **Gentamycin** **Muconazol** **(Positive control)**	ATCC 25923 250 250 9.0		ATCC 25922 125 125 12.0	ATCC 37853 250 250 9.1		ATCC 27853 250 250 8.0		ATCC 90028 250 16 4.5		(Hisham et al. 2012)
Duguetia lanceolata	Stem bark	Essential oil (T2) Essential oil (T4)	ATCC 6538 60 125							ATCC 10231 60 100		(Sousa et al. 2012)

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		Chloramphenicol (positive control)	2							15		
Enantia chlorantha	Stem bark	Palmitin **Chloramphenicol (positive control)**	ATCC 25923 32 8		E.C 136 32 32			K.L 128 16 32				(Etame et al. 2019)
Ephedranthus amazonicus R.E. Fr.	Leaves	Essential oil **Chlorhexidine digluconate (Positive controls)**	ATCC 6538 90 6		ATCC 8739 1500 6	ATCC 9027 3000 10	ATCC 29212 190 90					(Alcântara et al. 2017)
Annonaceae species	**Used Material**	**Substances/ Extracts**	**Microorganisms / MIC (µg/mL)**									**Ref.**
			S. aureus	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*E. faecalis*	*K. pneumoniae*	*C. krusei*	*C. albicans*	*C. tropicalis*	
Fissistigma kwangsiensis	Leaves	Essential oil **Nystatine** **Streptomycin** **Cycloheximide (Positive controls)**	ATCC 25923 55.67 - 3.2 -			ATCC 27853 3.45 8.0 - -	ATCC 299212 33.62 2.07 - -			ATCC 10231 16.45 - - 3.2		(Tsiang et al. 2022)

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Fusaea longifolia	Aerial parts	Essential oil **TIENAM (positive control)**	ATCC 33591 37.5 4.68			ATCC 29336 37.5 2.34						(Bay et al. 2019a)
Greenwayodendron suaveolens subs. usambaricum	Root Bark Roots	Methanol extracts Pentacyclindole Polyalthenol **Ciprofloxacin (Positive control)**	ATCC 25923 1000 4 4 2.5									(Christopher et al. 2018) (Williams et al. 2010) (Williams et al. 2010) (Christopher et al. 2018)
Goniothalamus gracilipes	Leaves	Gracilipin C **Streptomycin (Positive control)**	ATCC 25923 32 32									(Trieu et al. 2021)
Annonaceae species	**Used Material**	**Substances/ Extracts**	**Microorganisms / MIC (µg/mL)**									**Ref.**
			S. aureus	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*E. faecalis*	*K. pneumoniae*	*C. krusei*	*C. albicans*	*C. tropicalis*	
Goniothalamus longistipetes	Bark	(+)-altholactone ((2S,3R,3aS,7aS)-3-hydroxy-2-	eMRSA – 15 64 128		NCTC 10418 256 512	NCTC 10662 500 512		NCTC 10662 256 512				(Teo et al. 2020)

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		phenyl-2,3,3a,7a-tetrahydrobenzo-5(4H)-5-one) (2S,3R,3aS,7aS)-3-hydroxy-2-phenyl-2,3,3a,7a-tetrahydrobenzo-5(4H)-5-one) 2,6-dimethoxyisonicotinaldehyde alkenyl-5-hydroxyl-phenyl benzoic acid	128 8-16		256 512	256 128		256 128				
Guatteria blepharophylla	Leaves	Essential oil Isomoschatoline **Chlorhexidine digluconate** **Nystatin (Positive control)**	ATCC 6538 50 - 6		ATCC 8739 1500 - 6	ATCC 9027 1500 - 10	ATCC 29212 50 - 90			ATCC 10231 - 50.81 µM L-1 54 µM L-1		(Costa et al. 2011c; Alcântara et al. 2017)
Annonaceae species	**Used Material**	**Substances/ Extracts**	**Microorganisms / MIC (µg/mL)**									**Ref.**
			S. aureus	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*E. faecalis*	*K. pneumoniae*	*C. krusei*	*C. albicans*	*C. tropicalis*	

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Guatteria costaricensis *Guatteria diospyroides* *Guatteria oliviformis*	Leaves	Essential oil Essential oil Essential oil	ATCC 29213 1250 312 1250		ATC 25922 1250 1250 625							(Palazzo et al. 2009)
Guatteria selowiana *Guatteria latifolia* *Guatteria ferruginea* *Guatteria australis*	Aerial parts Aerial parts Aerial parts Aerial parts	Essential oil Essential oil Essential oil Essential oil **Chloramphenicol (Positive control)**			ATCC 11775 600 600 600 >1000 40							(Santos et al. 2017)
Annonaceae species	**Used Material**	**Substances/ Extracts**	**Microorganisms / MIC (µg/mL)**									**Ref.**
			S. aureus	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*E. faecalis*	*K. pneumoniae*	*C. krusei*	*C. albicans*	*C. tropicalis*	
Guatteria citriodora	Leaves and Stem bark	Crude hydroalcoholic extract of leaves Alkaloid fraction of leaves	250 - - 15.6	ATCC 4083 - 125 - 62.5								(Rabelo et al. 2014)

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		Alkalidic fraction of stem bark **Imipenem (Positive control)**										
Guatteria punctata	Aerial parts	Essential oil **TIENAM (positive control)**	ATCC 33591 - 4.68		CDC-EDL 933-171-0157:H3 - 1.17	ATCC 29336 - 2.34						(Bay et al. 2019a)
Guatteriopsis hispida		Essential oil Oxide caryophyllene	ATCC 6538 >1000 -	ATCC 12228 >1000 -	ATCC 11775 >1000 -	ATCC 133388 >1000 -				ATCC 10231 >1000 600		(Costa et al. 2008)
Annonaceae species	**Used Material**	**Substances/ Extracts**	**Microorganisms / MIC (µg/mL)**									**Ref.**
			S. aureus	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*E. faecalis*	*K. pneumoniae*	*C. krusei*	*C. albicans*	*C. tropicalis*	
Guatteriopsis blepharopylla *Guatteriopsis friesiana*	seed	Essential oil β-eudesmol Y-eudesmol α-eudesmol Essential oil β - pinene α – pinene	ATCC 6538 1000 >1000 600 250 125 - -	ATCC 12228 >1000 600 700 700 100 - -	ATCC 11775 >1000 >1000 >1000 - 900 - -	ATCC 133388 >1000 >1000 300 200 900 - -				ATCC 10231 700 125 500 125 500 100 250		(Costa et al. 2008)

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		(E)-caryophyllene **Chloramphenicol** **Nystatin (Positive control)**	- 20 -	- 40 -	- 40	- 850				- 50		
Mitrephora celebica	Leaves Stem bark Twigs	Crude hydroalcoholic extract of leaves Crude hydroalcoholic extract Crude hydroalcoholic extract *Ent*-trachyloban-19-oic acid	ATCC 43300 >100 12.5 >100 6.25			ATCC 27853 >100 >100 >100 >100						(Zgoda-Pols et al. 2002)
Annonaceae species	**Used Material**	**Substances/ Extracts**	**Microorganisms / MIC (µg/mL)**									**Ref.**
			S. aureus	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*E. faecalis*	*K. pneumoniae*	*C. krusei*	*C. albicans*	*C. tropicalis*	
Mitrephora celebica		*ent*-kaur-16-en-19-oic acid **Gentamycin** **Oxacillin** **Vancomycin**	ATCC 43300 >100 >50 6.2-12.5 0.8			ATCC 27853 >100 0.8 - -						(Zgoda-Pols et al. 2002)

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		(Positive control)										
Monodora myristica	Fruits	Cyclohexane extract Ethyl acetate extract	25 25			25 50		- 50	12.5 12.5	6.3 12.5		(Mbosso et al. 2010)
Polyalthia cinnamomea	Leaves	Leaf extract **Vancomycine** **Streptomicyne** **Kanamycine** **(Positive control)**	ATCC 25923 4000 - 30 -	4000 30 - -	ATCC 10536 1000 - - 30							(Mahmud et al. 2018)
Polyalthia longifolia	Stem bark	Butanol fraction 3-o-methyl ellagic	ATCC 29213/ 512 (MRSA) 320/320 80/160		ATCC 29212 320 80	ATCC 27853 160 80						(Jain et al. 2014)
Annonaceae species	**Used Material**	**Substances/ Extracts**	**Microorganisms / MIC (µg/mL)**									**Ref.**
			S. aureus	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*E. faecalis*	*K. pneumoniae*	*C. krusei*	*C. albicans*	*C. tropicalis*	
Polyalthia longifolia	Stem bark Roots Leaves	**Vancomycin** **Oxacillin** **Ciprofloxacin**	ATCC 29213/ 512 (MRSA)		ATCC 29212 - -	ATCC 27853 - -		2 2 -				(Jain et al. 2014)

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		(Controle positive)	0.25/- -/8.0		0.015	0.25 2		5				(Jain et al. 2014)
		Pendulamine A	-			-						(Jain et al. 2014)
		Pendulamine B	0.2			-						(Faizi et al. 2003)
		Penduline	0.2			5						(Faizi et al. 2003)
		Kanamycin sulfate	12.5 0.31			125 250						(Faizi et al. 2003)
		(Control positive)	125 7.8			500						(Faizi et al. 2003)
		Methanol extract	500									(Faizi et al. 2003)
		16(*R* and *S*)-hydroxy-cleroda-3,13(14)*Z*-dien-15,16-olide										(Faizi et al. 2008)
		16-oxo-cleroda-3,13(14)*E*-dien-15-oic acid										(Faizi et al. 2008)

Annonaceae species	**Used Material**	**Substances/ Extracts**	**Microorganisms / MIC (µg/mL)**									**Ref.**
			S. aureus	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*E. faecalis*	*K. pneumoniae*	*C. krusei*	*C. albicans*	*C. tropicalis*	
Toussaintia orientalis Verdc.	Seeds		ATCC		DSM							(Samwel et al. 2011)
		Toussintine A	25923		1103							
		Toussintine B	-		10							
		Toussintine C	10		20							
		Toussintine D	-		10							
		Toussintine E	5		-							

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		Ampicilin (Positive control)	- 2.5		- 2.5							
Unonopsis duckei R.E. Fr. *Unonopsis floribunda Diels* *Unonopsis rufescens (Baill.)* R.E. Fr. *Unonopsis stipitala* Diels *Onychopetalum amazonicum* R.E. Fr.	Stem Bark	Polycarpol **Chloramphenicol (Positive control)** **Ketoconazole (Positive control)**	ATCC 6538 25 25 -	ATCC 1228 50 50 -	ATCC 10538 50 50 -	ATCC 27853 - >500 -				ATCC 10231 250 - 12.5		(da Silva et al. 2015)
Unonopsis costaricensis	Leaves	Essential oil	ATCC 29213 625		ATCC 25922 1250							(Palazzo et al. 2009)

Annonaceae species	**Used Material**	**Substances/ Extracts**	**Microorganisms / MIC (µg/mL)**									**Ref.**
			S. aureus	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*E. faecalis*	*K. pneumoniae*	*C. krusei*	*C. albicans*	*C. tropicalis*	
Uvaria hamiltonii	Leaves	Essential oil **Nystatine**	ATCC 25923 20.34			ATCC 27853 12.34	ATCC 29212 7.99			ATCC 10231 32.57		(Tsiang et al. 2022)

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		Streptomycin Cycloheximide (Positive controls)	- 1.07 -			8.0 - -	0.48 - -			- - 3.2		
Uvaria schefflera	Leaves	5,7,8-trimetoxiflavona 2′,6′-dihydroxy-4′-methoxychalcone and 5,7-dihydroxyflavone (mixture) **Ampicillin Ketoconazole (positive control)**	NCTC 6571 - 125 0.01		NCTC 10418 125 - 0.25					HG 392 - 31.2 0.125		(Moshi et al. 2004)
Uvaria tanzaniae	Root Bark	Methanol extracts **Ciprofloxacin (Positive control)**	ATCC 25923 1.25 2.5									(Christopher et al. 2018)
		Substances/	**Microorganisms / MIC (µg/mL)**									**Ref.**

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Annonaceae species	**Used Material**	**Extracts**	*S. aureus*	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*E. faecalis*	*K. pneumoniae*	*C. krusei*	*C. albicans*	*C. tropicalis*	
Uvariodendron usambarense	Leaves Stem Bark	Methanol extracts Methanol extracts **Ciprofloxacin (Positive control)**	ATCC 25923 8000 4000 2.5		ATCC 8740 500 - 0.63							(Christopher et al. 2018)
Xylopia staudtii	Bark	Hydroethanolic extract Ciprofloxacin **(Positive control)**			ATCC 25922 83.33 0.97							(Pouofo Nguiam et al. 2021)
Xylopia aromatica (Lam.) Mart.	Leaves	Essential oil **Chlorhexidine digluconate (Positive control)**	ATCC 6538 1200 6		ATCC 8739 3000 6	ATCC 9027 3000 10	ATCC 29212 50 90					(Alcântara et al. 2017)
Xylopia sericea	Fruits	Essential oil **Chloramphenicol Ciprofloxacin**	ATCC 6538 7.8 12.5 0.39		ATCC 10536 1000 6.25 1.56		ATCC 19433 1000 6.25 1.56	ATCC 4552 62.5 12.5 12.5				(Mendes et al. 2017)

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		(positive control)										

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3.4. Leishmanicidal

Leishmaniasis can be caused by any of the 20 species of hemoflagellate protozoa in the genus *Leishmania*. These protozoa are primarily transmitted to humans through the bites of female sandflies belonging to 30 species of *Lutzomyia* (associated with New World Leishmaniasis) and *Phlebotomus* (linked to Old World Leishmaniasis) (López et al. 2009; Brígido et al. 2020). This neglected disease is a public health problem that affects 98 tropical and subtropical countries with approximately 1.7 million cases each year (Lamidi et al. 2005; Ferreira et al. 2017). According to the WHO, it is considered the second most important protozoan public disease, with extensive morbidity and mortality in most developing countries (Lorenzo et al. 2016; Christopher et al. 2018).

Clinically, the disease can affect the skin (cutaneous leishmaniasis), mucosa (mucocutaneous leishmaniasis) and/or organs of the reticulo-endothelial system (visceral leishmaniasis). The forms of the disease are related to the type of parasite and differ in distribution, host and vector involved, incidence and mortality rate (López et al. 2009; Lorenzo et al. 2020).

Since the 1940s, pentavalent antimonial compounds (sodium stibogluconate and meglumine antimoniate) have been the first-line treatment for all forms of leishmaniasis but in cases of therapeutic resistance to these compounds, amphotericin B deoxycholate and liposomal amphotericin B (pentamidine and miltefosine) can be used (Lamidi et al. 2005). However, they are formulations that present high toxicity, high cost and development of parasitic resistance. Therefore, there is an urgent need for new therapies against leishmaniasis (Ferreira et al. 2017).

The lack of effective antiprotozoal drugs has renewed interest in the study of medicinal plants as sources of new therapeutic compounds with stronger activity and fewer side effects (Osorio et al. 2007; Christopher et al. 2018). The literature describes several classes of natural substances with proven leishmanicidal activity in *in vitro* assays on promastigotes and/or amastigotes of *Leishmania* such as terpenes, chalcones, acetogenins, alkaloids, diterpenic acids, quinones and phenolic derivatives (da Silva et al. 2012; Lorenzo et al. 2016, 2020; Ferreira et al. 2017).

The antiprotozoal activity generally reported for the Annonaceae family has been related to the traditional treatment of diseases such as malaria, Chagas disease, sleeping sickness and leishmaniasis (Vila-Nova et al. 2011; De Lima et al. 2012; Musuyu Muganza et al. 2015). A compilation of the leishmanicidal potential of essential oil, extracts, fractions and isolated compounds of species from the Annonaceae family is described in the following sections and in Table 4.

Annona genus

The ethanol extracts from the root barks, stem barks, and stem wood of *A. crassiflora* exhibited activity against *L. donovani* promastigotes, with effective concentrations ranging from 3.7 to 12.4 μg/mL. Additionally, the total alkaloids extracted from the leaves demonstrated activity against *L. chagasi*, with an IC50 value of 24.9 μg/mL (De Mesquita et al. 2005; Brígido et al. 2020). Furthermore, the essential oil derived from the leaves of *A. coriacea* showed anti-leishmanial effects against *L. chagasi* promastigotes (Siqueira et al. 2011).

Acetogenins such as annofolin and annotacin, isolated from *A. cornifolia* seeds, have shown activity against the amastigote forms of *L. amazonensis* with IC_{50} 6.4 and 7.2 μM, respectively (Lima et al. 2014; Brígido et al. 2020). The essential oil, extracts, alkaloid fraction and some compounds (N-hydroxyanno-montine, *O*-methylmoschatolin, liriodenine and annomontine) isolated from bark and leaves of *A. foetida*, showed antileishmanial activity, giving the best results against promastigotes of *L. braziliensis* and *L. guyanensis* (Costa et al. 2009; Brígido et al. 2020).

The hydroalcoholic extract from the leaves of *A. glabra* exhibited activity against *L. amazonensis* promastigotes, with an IC50 of 37.8 μg/mL (Brígido et al. 2020). A study with Annonacin A and Goniothalamicin isolated from *A. glauca* seeds showed activity against the promastigote form of *Leishmania* spp. with IC_{50} 16.75 and 8.37 μM, respectively (Waechter et al. 1998). From the hexanic extract of *A. haematantha* roots, argentilactone was isolated and exhibited *in vitro* activity against various strains of *Leishmania* ssp with IC_{50} value of 10.0 μg/ml (Waechter et al. 1997).

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Various extracts from *A. mucosa* and the alkaloid liriodenine exhibited activity against *L. amazonensis* promastigotes (De Lima et al. 2012; Brígido et al. 2020). Efficacy against *Leishmania* species was also observed in extracts and fractions from the stems of *A. muricata*, which may be attributed to the presence of acetogenins, with increased activity noted following fractionation (Osorio et al. 2007; Vila-Nova et al. 2011; Brígido et al. 2020). Additionally, methanol and aqueous extracts from *A. purpurea* bark and seeds demonstrated significant activity against *L. donovani* promastigotes, while the fraction from the hydroalcoholic leaf extract was effective against *L. panamensis*, exhibiting an IC_{50} of 0.96 μg/mL (Malebo et al. 2013b).

Berbine alkaloids (pessione and spinosine) isolated from the bark and roots of *A. spinescens* were active against *Leishmania* ssp. Promastigotes (Emerson F. Queiroz et al. 1996). A benzylisoquinolinic alkaloid (*O*-methylarmepavine), and a C37 trihydroxy adjacent bistetrahydrofuran acetogenin isolated from leaves of *A. squamosa,* showed activities against promastigote and amastigote forms of *L. chagasi* (Vila-Nova et al. 2011). Ethanolic extracts from the leaves and stem of *A. senegalensis* exhibited activity against *L. donovani* promastigotes, showing IC_{50} values of 10.8 μM for the leaf extract and 27.8 μM for the stem extract (Ohashi et al. 2018; Brígido et al. 2020).

Guatteria genus

The alkaloids xylopine and nornuciferine (extracted from the leaves of *G. amplifolia*) and cryptodorine and nornantenine (from the leaves of *G. dumetorum*) demonstrated significant activity against *L. mexicana* and *L. panamensis promastigotes* (Lorenzo et al. 2016). Essential oil from the leaves of *G. australis* showed activity against *L. infantum* (IC_{50} = 30.71 μg/ml) (Lorenzo et al. 2016).

Bisbenzylisoquinoline alkaloids, including Puertogaline A and B, as well as the derivative Sepeerine, isolated from the stem bark of *G. boliviana,* exhibited moderate inhibition of *Leishmania* spp. promastigotes at a concentration of 100 μg/mL. This level of activity was comparable to that observed with the crude ethanolic extract in the screening assays (Lorenzo et al. 2016).

The branch extract of *G. latifolia* demonstrated notable activity against both *L. amazonensis* promastigotes and intracellular amastigotes and was subsequently fractionated based on in vitro assays. Among the fractions obtained, two alkaloid-rich fractions, GF1 and GF2, exhibited the highest activity against promastigotes, with IC50 values of 25.6 and 16 μg/mL, respectively (Ferreira et al. 2017).

Rollinia genus

The dichloromethane fraction of the stem bark of *R. emarginata* exhibited activity against various *Leishmania* spp. strains. Fractionation of this extract, guided by *in vitro* leishmanicidal activity, resulted in the isolation of five active compounds: four acetogenins (rolliniastatin-1, sylvaticin, squamocin, and rollidecin B) and one oxoaporphine (liriodenin)(Février et al. 1999). Additionally, extracts from the stem of *R. exsucca* and from the stem and leaves of *R. pittieri* demonstrated activity against *Leishmania* spp., with IC_{50} values below 25 μg/mL (Osorio et al. 2007).

Unonopsis genus

Three alkaloids isolated from the dichloromethane extract of the stem bark of *U. buchtienii* exhibited the highest activity against *L. major* and *L. donovani*. The oxoaporphine alkaloids, *O*-methylmoschatoline and lysicamine, had IC_{100} values of 50.0 and 25.0 mg/mL, respectively, and liriodenine, the most active alkaloid had an IC_{100} of 3.12 mg/mL (Waechter et al. 1999).

Alkaloidal fractions extracted from the twigs, bark, and leaves of *U. guatterioides* and *U. duckei* were evaluated for activity against promastigote forms of *L. amazonensis*. All fractions from *U. guatterioides* showed high activity, with IC_{50} values of 1.07, 1.90, and 2.79 mg/mL, respectively. In contrast, only the alkaloidal fraction from the twigs of *U. duckei* did not exhibit any activity (da Silva et al. 2012).

Xylopia genus

The methanol extract from the leaves of *X. aromatica* was active against *Leishmania* spp. Promastigotes, displaying an IC_{50} value of 20.8 μg/ml.(Osorio et al. 2007) The essential oil and eight extracts obtained from leaves and seed of *X. discreta* showed activity against *L. panamensis* promastigotes (López et al. 2009).

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A new *ent*-kaurene diterpene glucoside, 7β-*O*-β-D-glucopyranoside-ent-kaur-16- ene, from the leaves of *X. excellens*, showed high *in vitro* antileishmanial activity (IC_{50} of 15.23 µg/mL) towards promastigote forms of *L. amazonensis*. The dichloromethane extract from roots of *X. parviflora* displayed high inhibitory effects on the growth of amastigote forms of *L. donovani* with IC_{50} value of 5.01 µg/ml (Bapela et al. 2017).

Others Annonaceae species

The azaphenanthrene alkaloids sampangine, imbiline 3, imbiline 1, and eupolaramine, extracted from the roots of *Anaxagorea dolichocarpa*, demonstrated significant activity against the promastigote forms of *L. donovani*, with IC_{50} values of ≤ 24.06 µM (Lorenzo et al. 2016). Furthermore, an aporphine alkaloid (lysicamine) and a bis-aporphine alkaloid (trivalvone) obtained from the leaves of *Annickia kummeriae* showed enhanced effectiveness against the amastigote form of *L. donovani* (Malebo et al. 2013b).

The *Bocageopsis multiflora* essential oil, richer in oxygenated sesquiterpenes, exhibited good activity against the *L. amazonensis* promastigote (IC_{50} =14.6 µg/mL) (Malebo et al. 2013b). The alkaloids duguetine β-N-oxide and dicentrinone isolated from the bark of *Duguetia furfuracea*, presented IC_{50} vlaues of 0.11 and 0.01 µM against the promastigote forms of *L. braziliensis* (da Silva et al. 2009).

The aporphine alkaloid glaucine, extracted from the leaves of *Duguetia lanceolata*, demonstrated effectiveness against *L. infantum* amastigotes. Additionally, an alkaloid-rich fraction containing isocorydine, norglaucine, and N-methyllaurotetanine exhibited activity against promastigotes (da Silva et al. 2009). *Furthermore, the aqueous extract of Enantia chlorantha stem bark and the compound palmatine, isolated from the methanolic bark extract, also showed activity against L. infantum promastigotes* (da Silva et al. 2009).

Extracts, fractions and isolated constituents (polycarpol, dihydropolycarpol and polyathenol) from fruits, leaves, root bark and stem bark of *Greenwayodendron suaveolens* showed *in vitro* activity *against L. infantum* promastigote (da Silva et al. 2009). The crude methanol extract of leaves of *Isolona hexaloba* and the two dichloromethane soluble fractions of the 80% ethanol extracts from root bark and stem bark showed good activity and selectivity against the *L. infantum promastigote, with* IC_{50} values equal to 6.35, 6.96 and 8.0 µg/ml, respectively (Musuyu Muganza et al. 2015).

A new diterpene, (4*S*,9*R*,10*R*) methyl 18-carboxy-labda-8,13(*E*)-diene-15-oate obtained from the stem barks of *Polyalthia macropoda* showed activity against the promastigote *L. donovani.*(Richomme et al. 1991) The methanolic extract of *P. suaveolens* stem bark demonstrated potent antiproliferative activity against *L. infantum* promastigotes (Lamidi et al. 2005).

Acetylene derivatives were isolated from seeds of *Porcelia macrocarpa,* where all isolated compounds demonstrated selectivity towards intracellular amastigotes of *L. infantum*, especially: 3-hydroxy-4-methylene-2-(eicos-11′-yn-19′-enyl)but-2-enolide, 3-hydroxy-4-methylene-2-(octadec-9′-yn-17′-enyl)but-2-enolide and 3-hydroxy-4-methylene-2-(hexadec-7′-yn-15′-enyl)but-2-enolide with IC_{50} values of 9.2, 10.4 and 11.0 µM, respectively and thus indicating superior activity over the positive control miltefosine (IC_{50} of 17.8 µM) (Brito et al. 2021).

An acetylene acetogenin (2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(*n*-eicos-11′-yn-19′-enyl)butanolide was obtained from the seeds of *Porcelia macrocarpa* and showed an IC_{50} value of 29.9 µM against the intracellular amastigote forms of *L. infantum,* whereas the similar compound (2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(*n*-eicos-11′-ynyl)butanolide was inactive. These results suggested that the terminal double bond plays an important role in the activity (Brito et al. 2022).

Three 6-substituted 5,6-dihydro-2H-pyran-2-ones were isolated from leaves of *Raimondia monoica.* All compounds showed activity against *L. panamensis* promastigotes at concentrations ranging between 0.4-10.0 µg/mL (Carmona et al. 2003). Bingervone, a β-triketone derivative, was isolated from the dichloromethane extract of the roots of *Uvaria afzelii,* and showed moderate antileishmanial activities against *L. donovani* and *L. major* promastigotes, with IC_{50} values of 38.9 and 44.4 µM, respectively (Okpekon et al. 2015).

Bioguided-fractionation of a dichloromethane extract of the stems of *Uvaria klaineana* led to isolation of a lactone (klaivanolide), that showed potent *in vitro* antileishmanial activity against both

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sensitive and amphotericin B-resistant promastigote forms of *L. donovani* (IC_{50} values of 1.75 and 3.12 µM, respectively) (Akendengue et al. 2002).

Some studies adopt the following criteria for the evaluation of *in vitro* antiprotozoal screening of extracts, fractions and isolated substances: $IC_{50} \leq 5$ µg/mL: pronounced activity; $5 < IC_{50} \leq 10$ µg/mL: good activity; $10 < IC_{50} \leq 20$ µg/mL: moderate activity; $20 < IC_{50} \leq 40$ µg/mL: low activity; $IC_{50} > 40$ µg/mL: inactive (Musuyu Muganza et al. 2015; Muganza et al. 2016). This should be taken into consideration for the results compiled in Table 4, our summation of published anti-leishmaniasis screening of compounds isolated from Annonaceae plants.

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Table 4. Summary of leishmanicidal activity of species of the Annonaceae.

Annonaceae species	Used Material	Substances/Extracts	*Leishmania* spp.	Parasite form	IC_{50}		Ref.
					µM	µg/ml	
Anaxagorea dolichocarpa	root	Sampangine Imbiline 3 Imbiline 1 EupolaUramine	*L. donovani*	Promastigote	24.06 16.91 18.20 19.90	5.59 5.45 5.32 5.26	(Lorenzo et al. 2016)
Annickia kummeriae	leave	Methanolic extract Lysicamine Trivalvone Palmatine Jatrorrhizine Jatrorrhizinne/Columbamine Palmatine/Tetrahydro-palmetine	*L. donovani*	Amastigote	9.26 5.24 22.13 60.28 19.35 9.88	9.25 2.7 2.9 7.8 20.4 13.1 7.0	(Malebo et al. 2013b)
Annona crassiflora	Stem bark, stem wood, root bark and root wood	Ethanolic extract Stem bark Stem wood Root bark Root wood	*L. donovani*	Promastigote		12.4 8.3 3.7 8.7	(De Mesquita et al. 2005; Brígido et al. 2020)
Annona coriaceae	leave	Essential oil	*L. chagasi*	Promastigote		39.93	(Siqueira et al. 2011)
Annona cornifolia	seed	Annofolin Annotacin Extract	*L. amazonensis*	Amastigote	6.4 7.2	175.0	(Lima et al. 2014; Brígido et al. 2020)

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Annona foetida	bark	Hexane extract Dichlorometahne extract Alkaloid fraction (Dichlorometane extract) Methanolic extract Alkaloid fraction (Methanolic extract) N-hydroxyanno-montine	*L. braziliensis and L. guyanensis*	Promastigote	911.3 and 1577.8	>160.0 and 42.7 23.0 and 2.7 23.0 and 2.7 40.4 and 23.6 24.3 and 9.1 252.7 and 437.5	(Costa et al. 2009; Brígido et al. 2020)
Annonaceae species	**Used Material**	**Substances/Extracts**	***Leishmania* spp.**	**Parasite form**	**IC50**		**Ref.**
					µM	**µg/ml**	
Annona foetida	Bark Leave	O-methylmoschatolin Liriodenine Annomontine Essential oil	*L. braziliensis and L. guyanensis* *L. amazonensis, L. braziliensis, L. chagasi* and *L. guyanensis*	Promastigote	998.35 and 322.7 212.52 and 78.10 >2346.15	320.8 and 103.7 58.5 and 21.5 34.8 and >613.0 16.2, 9.9, 27.2 and 4.1	(Costa et al. 2009; Brígido et al. 2020)
Annona glabra	leave	Hydroalcoolic extrac	*L. amazonensis*	Promastigote		37.8	(Brígido et al. 2020)
Annona glauca	seed	Dichloromethane extract Hexane extract Annonacin A Goniothalamicin Glaucanisin Rolliniastatin-2 Squamocin Glaucafilin Molvizarin	*L. braziliensis, L. amazonensis* and *L. donovani*	Promastigote		**IC100** 25.0 >100.0 10.0 5.0 25.0 25.0 25.0 25.0	(Waechter et al. 1998)
					16.75 8.37 40.13 40.13 40.13 41.88 >168.09		

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		Parviflorin Annonacin			>168.09 21.61	>100.0 >100.0 12.5	
Annona haematantha	root	Argentilactone	*L. donovani, L. major* and *L. amazonensis*	Promastigote	51.47	10.0	(Waechter et al. 1997)
Annona mucosa	Leave Seed	Hexane extract Dichloromethane extrac Methanol extract Hexane extract Methanol extract Liriodenine	*L. amazonensis* and *L. braziliensis*	Promastigote	5.19 and 203.15	24.24 and 65.17 9.32 and 27.42 28.32 and 44.74 44.2 and 170.15 46.54 and 133.8 1.43 and 55.92	(De Lima et al. 2012; Brígido et al. 2020)
Annona muricata	leave	Ethil acetate extract	*L. amazonensis, L. donovani*	Promastigote		25.0	(Osorio et al. 2007; Vila-Nova et al. 2011; Brígido et al. 2020)
Annonaceae species	**Used Material**	**Substances/Extracts**	***Leishmania* spp.**	**Parasite form**	**IC_{50}**		**Ref.**
					µM	**µg/ml**	
Annona muricata	Stem	Hexane extract Methanolic extrac Hexane extract Ethil acetate extract Methanolic extrac	*L. amazonensis, L. brasiliensis and L. donovani*	Promastigote		>100.0 >100.0 98.6 63.2 98.6	(Osorio et al. 2007; Vila-Nova et al. 2011; Brígido et al. 2020)

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	seeds	Annonacinone	*L. chagasi*	Promastigote and Amastigote	63.20 and 22.69	37.6 and 13.5	
			L. donovani, L. mexicana and *L. major*	Promastigote	12.87, 13.44 and 11.29	7.66, 8.00 and 6.72	
	Corossolone	*L. chagasi*	Promastigote and Amastigote	44.74 and 49.57	25.9 and 28.7		
		L. donovani, L. mexicana and *L. major*	Promastigote	32.35, 32.19 and 27.88	18.73, 18.64 and 16.14		
	Scoparone	*L. donovani, L. mexicana* and *L. major*	Promastigote	133.42, 44.18 and 69.69	27.51, 9.11 and 14.37		
Annona purpurea	Bark Seed Leave	Methanolic extract Aqueous extract Hydroalcoolic fraction	*L. donovani* *L. panamensis*	Promastigote		113.24 28.57 289.0 0.961	(Brígido et al. 2020)
Annona spinescens	Bark Root	Annonaine Liriodenine	*L. braziliensis* *L. amazonensis* *L. donovani* *L. braziliensis*	Promastigote	188.45 94.22 376.91 363.29	**IC_{100}** 50.0 25.0 100.0 100.0	(Emerson F. Queiroz et al. 1996)
Annona squamosa	leave	O-methylarmepavine C_{37} trihydroxy adjacent bistetrahydrofuran acetogenin	*L. chagasi*	Promastigote and Amastigote	71.16 and 77.58 42.44 and 40.67	23.3 and 25.4 26.4 and 25.3	(Vila-Nova et al. 2011)
Annona senegalensis	leave Stem	Ethanolic extract	*L. donovani*	Promastigote		10.8 27.8	(Ohashi et al. 2018; Brígido et al. 2020)
Annonaceae species		**Substances/Extracts**	***Leishmania* spp.**	**Parasite form**	**IC_{50}**		**Ref.**

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	Used Material				**µM**	**µg/ml**	
Bocageopsis multiflora	leave	Essential oil	*L. amazonensis*	Promastigote		14.6	(Oliveira et al. 2014)
Duguetia furfuracea	bark	Alkaloid extract Duguetine Duguetine β-N-oxide Dicentrinone N-methyltetrahydropalmatine N-methylglaucine	*L. braziliensis*	Promastigote	16.32 4.32 0.11 0.01 17.03 4.88		(da Silva et al. 2009)
Duguetia lanceolata	leave	Glaucine	*L. infatum*	Amastigote and Promastigote	21.10 and >281.37	7.5 and >100.0	(Dantas et al. 2020)
Enantia chlorantha	stem bark	Aqueous extract	*L. infatum*	Promastigote		10.08	(Olivier et al. 2015)
Guatteria amplifolia	leave	Xylopine Nornuciferine	*L. mexicana* and *L. panamensis*	Promastigote	3.0 and 6.0 14.0 and 28.0		(Montenegro et al. 2003)
Guatteria australis	leave	Essential oil	*L. infatum*	Promastigote		30.71	(Siqueira et al. 2015)
Guatteria boliviana	bark	Ethanolic extract Puertogaline A Puertogaline B Sepeerine	*L. amazonensis, L. braziliensis* and *L. donovani*	Promastigote	177.74 177.74 168.15	100.0 100.0 100.0 100.0	(Mahiou et al. 2000a)
Guatteria dumetorum	leave	Cryptodorine Normantenine	*L. mexicana* and *L. panamensis*	Promastigote	3.0 and 6.0 24.0 and 15.0		(Montenegro et al. 2003)
Guatteria latifolia	branch	Crude extract Buthanolic fraction 1 Buthanolic fraction 2	*L. amazonensis*	Promastigote and Amastigote		51.7 and 30.5 25.6 and 10.4 16.0 and 7.4	(Ferreira et al. 2017)

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Greenwayodendron suaveolens	Fruit, leave, root bark and stem bark	Dichlorometahne fraction rich in alkaloids Petroleum ether fraction rich in lipids and waxes Methanolic fraction rich in steroids and terpenes	*L. infatum*	Promastigote		24.05, 34.56, 0.63 and 20.32 24.05, 8.0, 27.27 and 5.04 40.32, 32.46, 7.51 and 6.82	(Muganza et al. 2016)
	Leave, root, stem bark	Crude ethanolic extract				43.07, 8.11 and 24.05	
	Stem bark	Polycarpol Dihydropolycarpol Polyathenol			3.2 8.0 8.1		
Annonaceae species	**Used Material**	**Substances/Extracts**	***Leishmania* spp.**	**Parasite form**	**IC_{50}**		**Ref.**
					µM	**µg/ml**	
Isolona hexaloba	Leave Root bark Stem bark	Aqueous extract Methanolic extract Dichloromethane fraction Dichloromethane fraction	*L. infatum*	Promastigote		2.0 6.35 6.96 8.0	(Musuyu Muganza et al. 2015)
Polyathia macropoda	Stem bark	(4S,9R,1OR) methyl 18-carboxy-labda-8, 1 3(E)-diene-15-oate	*L. donovani*	Promastigote		0.75	(Richomme et al. 1991)
Polyathia suaveolens	stem bark	Methanolic extract	*L. infatum*	Promastigote		1.8	(Lamidi et al. 2005)
Porcelia macrocarpa	Seeds	Docos-13-yn-21-enoic acid 3-hydroxy-4-methylene-2-(eicos-11′-yn-19′-enyl)but-2-enolide 3-hydroxy-4-methylene-2-(octadec-9′-yn-17′-enyl)but-2-enolide	*L. infantum*	Amastigotes	48.5 9.2 10.4 11.0 29.9 17.8		(Brito et al. 2021)

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		3-hydroxy-4-methylene-2-(hexadec-7′-yn-15′-enyl)but-2-enolide (2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(eicos-11′-yn-19′-enyl)butanolide **Miltefosine (positive control)**					
Porcelia macrocarpa	Seeds	(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(*n*-eicos-11′-yn-19′-enyl)butanolide (**1**) (2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(*n*-eicos-11′-ynyl)butanolide (**2**) Mixture of 1 and 2 2:1 1:1 1:2	*L. infantum*	Amastigotes	29.9 Non active 8.4 13.6 19.4		(Brito et al. 2022)
Annonaceae species	**Used Material**	**Substances/Extracts**	***Leishmania* spp.**	**Parasite form**	**IC_{50}**		**Ref.**
					µM	**µg/ml**	
Porcelia macrocarpa	Seeds	(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(*n*-eicosyl)butanolide (**3**)	*L. infantum*	Amastigotes	Non active		(Brito et al. 2022)
Raimondia monoica	leave	(–)-argentilactone (6S)-(50-oxohepten-10E,30Edienyl)-5,6-dihydro-2H-pyran-2-one (6R)-	*L. panamensis*	Promastigote	51.47 9.2 2.03	10.0 1.9 0.42	(Carmona et al. 2003)

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		(50-oxohepten-10Z,30E-dienyl)-5,6-dihydro-2H-pyran-2-one					
Rollinia emarginata	stem bark	Hexanic extract Dichloromethane extract Methanolic extract Rollidecin B Rolliniastatin-1 Lirioresinol B Squamocin Liriodenine Sylvaticin	*L. braziliensis, L. amazonensis* and *L. donovani*	Promastigote	78.25 8.02 >239.0 8.02 18.16 15.65	**IC_{100}** >100.0 100.0 >100.0 50.0 5.0 >100.0 5.0 5.0 10.0	(Février et al. 1999)
Rollinia exsucca	stem	Hexane extract	*L. amazonensis, L. braziliensis* and *L. donovani*	Promastigote		20.8	(Osorio et al. 2007)
Rollina pittieri	leave	Hexane extract Ethyl acetate extract Metanolic extract	*L. amazonensis, L. braziliensis* and *L. donovani*	Promastigote		12.6, 10.7 and 10.7 20.8 19.7, 31.4 and 43.8	(Osorio et al. 2007)
	stem	Hexane extract Ethyl acetate extract				13.5, 15.1 and 15.1 20.8, 25.0 and 19.7	
Unonopsis buchtienii	Stem bark	Petroleum ether extract Dichloromethane extract	*L. major and L. donovani*	Promastigote	155.61 85.82	IC_{100} 50.0 100.0	(Waechter et al. 1999)

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		O-methylmoschatoline Lysicamine Fraction containing Unonopsine				50.0 25.0 25.0	
Annonaceae species	**Used Material**	**Substances/Extracts**	***Leishmania* spp.**	**Parasite form**	**IC_{50}**		**Ref.**
					µM	**µg/ml**	
Unonopsis buchtienii	Stem bark	β-Sitosterol Stigmasterol Liriodenine	*L. major and L. donovani*	Promastigote	>241.13 >242.30 11.33	>100.0 >100.0 3.12	(Waechter et al. 1999)
Unonopsis duckei	Twigs, barks and leaves	Alkaloidal fraction	*L. amazonensis*	Promastigote		155.61, 32.16 and 4.0	(da Silva et al. 2012)
Unonopsis guatteriodes	Twigs, barks and leaves	Alkaloidal fraction	*L. amazonensis*	Promastigote		1.07, 1.90 and 2.79	(da Silva et al. 2012)
Uvaria afzelii	root	Bigervone	*L. donovani and L. major*	Promastigote	38.9 and 44.4		(Okpekon et al. 2015)
Uvaria klaineana	stem	Klaivanolide	*L. donovani*	Promastigote	1.75		(Akendengue et al. 2002)
Xylopia aromatica	leave	Methanolic extract	*L. amazonensis, L. braziliensis* and *L. donovani*	Promastigote		20.8	(Osorio et al. 2007)
Xylopia discreta	Leave	Ethanol extract Ether petroleum extract Acetate extract Methanol extract Essential oil	*L. panamensis* Promastigote			25.0 50.0 50.0 37.5 6.25	(López et al. 2009)
	seed	Ethanol extract				6.25	

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Xylopia excellens	leave	7β-O-β-D-glucopyranoside-ent-kaur-16-ene	*L. amazonensis*	Promastigote	33.74	15.23	(Christopher et al. 2018)
Xylopia parviflora	roots	Dichloromethane extract	*L. donovani*	Amastigote		5.01	(Bapela et al. 2017)

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3.5. Cytotoxic

Cytotoxicity is any form of fatal harm to cells (Costa et al. 2011b). It is said that a cell can be classified as cytotoxic when it has the ability to release harmful substances that culminate in the destruction of other cells (Alberts et al. 2010). Cytotoxic compounds can induce cell death through mechanisms such as necrosis, where there is loss of cell membrane integrity leading to cell death through lysis or rupture (Ferreira et al. 2004); as well as apoptosis, where cell growth is inhibited and there is uncontrolled disruption of cells (Riss and Moravec 2004; Horton and Mathew 2015).

Cytotoxicity tests consist of placing the biological material under study directly or indirectly in contact with a culture of mammalian cells, checking cellular changes by different mechanisms, including the incorporation of vital dyes or the inhibition of the formation of cell colonies (Otręba and Kośmider 2020). The most widely used marker to assess toxicity is cell viability, which can be analyzed with the help of vital dyes, such as neutral red, a water-soluble dye that passes through the cell membrane, settling on the lysosomes (Hadjichristou et al. 2020). The distinction of cell viability is made by measuring the color intensity of the cell culture (Rogero et al. 2003).

Annona genus

Several studies have investigated Annonaceae species in search of novel cytotoxic agents, with a focus on the *Annona* genus, which was the subject of seven studies. Fatope and collaborators, 1996, evaluated the cytotoxic activity of four *ent*-kaurenoid derivatives isolated from *A. senegalensis* stem bark. The brine shrimp lethality test (BST) was conducted according to standard protocols, with LC_{50} values determined for various fractions and isolated compounds obtained from methanolic bark extracts. These fractions were then tested against human solid tumor cell lines including lung carcinoma (A-549), breast carcinoma (MCF-7), colon adenocarcinoma (HT-29), kidney carcinoma (A-498), prostate adenocarcinoma (PC-3), and pancreatic carcinoma (PACA-2), with Adriamycin as a positive control. The 10% aqueous MeOH partitioned fraction from the stem bark chloroform extract exhibited significant lethality in the BST (LC_{50} <1.0 μg/mL) and cytotoxicity against multiple solid tumor cell lines (ED_{50} values of <10-2 μg/mL). *ent*-Kaur-16- en-19-oic acid displayed activity in the BST (LC_{50} 16 μg/mL) and significant selectivity for MCF-7 cells (breast cancer, ED_{50} 1.0 μg/mL) over the other lines tested. Therefore, *ent*-Kaur-16- en-19-oic acid demonstrated noteworthy cytotoxic selectivity, warranting further investigations into the structure-activity relationships of this compound class (Fatope et al. 1996).

Silva et al., 2016, evaluated the cytotoxic activity of select carotenoids, flavonoids, and tannins extracted from the leaves and fruits of *A. squamosa* L. Cytotoxic assays were conducted on Vero cell lines, using the MTT mitochondrial reduction assay to assess cytotoxicity. Additionally, cellular morphological changes were analyzed using May-Grünwald-Giemsa staining. The cytotoxic concentration for 50% of the cell culture (CC_{50}) was calculated. The morphological findings confirmed the apoptotic effects of *A. squamosa* compounds on tumor cells, with signs of apoptosis observed in cells treated with hexane and aqueous extracts. The aqueous extract of the leaves exhibited higher toxicity than the aqueous extract of the seeds, consistent with its tannin content. Generally, hydrophobic extracts showed higher cytotoxicity than hydroalcoholic extracts (Silva et al. 2016).

Lima and colleagues, 2012, evaluated the cytotoxic potential of leaves and seeds of *A. mucosa* against *Leishmania* spp., as well as the oxoaporphine alkaloid liriodenine isolated from leaf dichloromethane extract. The study included *in vitro* evaluations against promastigote and amastigote forms of *Leishmania s*pp., with the main compound, liriodenine, exhibiting significant cytotoxicity against peritoneal macrophages (De Lima et al. 2012).

Volobuff et al., 2019, conducted bio-guided fractionation of *A. cacans* Warm extracts to evaluate antioxidant, antiproliferative, and anti-inflammatory activities. Various assays were employed, including DPPH, ABTS, and β-carotene/linoleic acid methods for antioxidant activity, sulforhodamine B assay for cell proliferation, and measurement of myeloperoxidase (MPO) activity for anti-inflammatory activity. The study isolated four compounds and demonstrated significant antioxidant and antiproliferative activities in pulp extracts, with the ethyl acetate fraction exhibiting

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potent antiproliferative activity against ovarian cancer. Additionally, extracts showed significant inhibition of edema and MPO activity, highlighting the antioxidant and antiproliferative potential of *A. cacans* Warm compounds (Volobuff et al. 2019).

Two distinct studies examined the cytotoxic profile of *A. vepretorum*. In the first study, Silva et al., 2017, assessed cytotoxicity and acute toxicity of leaf extracts from the plant, identifying compounds that exhibited high cytotoxic activity against various tumor cell lines. For instance, the methanolic extract and chloroform extract displayed high cytotoxic activity against the HCT-116 cell line, with cell growth inhibitions of 98.16% and 74.28%, respectively, highlighting the significant cytotoxic potential of *A. vepretorum* extracts (Araújo et al. 2017).

In contrast, Dutra et al., 2014, examined the cytotoxic effects of Ent-kaurane-type diterpenes isolated from the stem bark of *A. vepretorum*. Among the isolated compounds, a novel derivative exhibited the highest tumor inhibition rate, showing the most potent cytotoxic effect on the K562 cell line, with an IC50 of 2.49 μg/mL, thus highlighting the notable cytotoxic potential of this Annona species (Dutra et al. 2014).

Peña-Hidalgo et al., 2021, assessed the cytotoxic activity of alkaloids from *A. crassiflora* leaf extract. The study identified compounds through NMR, IR, and Mass Spectrometry methods, with cytotoxic activity evaluated against HCT-116 and MCF-7 cell lines. However, the observed cytotoxic activity was limited for these cell lines (Peña-Hidalgo et al. 2021).

Xylopia genus

The cytotoxicity of *Xylopia* species has been the focus of several studies, revealing their potential as sources of anticancer agents. Menezes et al., 2016, isolated 19 alkaloids from *X. laevigata* stem extract, including lanuginosine, (+)-xylopine, and (+)-norglaucine, which exhibited potent cytotoxic activity against various tumor cell lines. Notably, lanuginosine and (+)-xylopine both triggered apoptosis, with (+)-xylopine specifically causing G2/M cell cycle arrest in HepG2 cells. These findings underscore *X. laevigata* as a promising reservoir of cytotoxic alkaloids (Menezes et al. 2016).

Anadozie et al., 2021, explored the aqueous extract of *X. aethiopica* fruits, synthesizing gold nanoparticles (AuNPs) and assessing their cytotoxic and antitumor activities. The nanoparticles displayed stability and antioxidant activity, while the extract demonstrated cytotoxicity against breast cancer (MCF-7) and colorectal cancer (MDA-MB and Caco-2 cells), without toxicity to non-cancerous human fibroblastic cells (KMST-6) up to 200 μg/mL. These findings suggest the potential of *X. aethiopica* as a therapeutic agent against breast and colorectal cancer (Anadozie et al. 2021).

In a study by Tavares et al., 2006, two new E*nt*-trachylobane-type diterpenes (3β,5β,16α-trihydroxyhalima-13(14)-en-15,16-olide (**1**) and (-)-8-oxopolyalthiaine(**2**)) from *X. langsdorffiana* stem extract exhibited cytotoxicity against V79 and K562 cells, with compound 1 displaying IC_{50} values of 224 μM and 200 μM, respectively. These results highlight the cytotoxic potential of compounds derived from *X. langsdorffiana* (Tavares et al. 2006).

Bakarnga-Via et al. (2014) evaluated the cytotoxicity of essential oils from various *Xylopi*a species, including *X. aethiopica* and *X. paviflora*, as well as *Monodora myristica*. All the oils exhibited cytotoxic effects against both cancer (MCF-7) and normal epithelial (ARPE-19) cell lines. Notably, certain oils, such as *X. paviflora* from Chad and Cameroon, showed greater selectivity, demonstrating higher cytotoxicity against MCF-7 cells compared to ARPE-19 cells. These results highlight the potential of *Xylopia* essential oils as effective cytotoxic agents against cancer cell (Bakarnga-Via et al. 2014).

Polyalthia genus

Studies focusing on the cytotoxic activity of *Polyalthia* species have revealed their potential as sources of anticancer agents. Suedee et al., 2007, investigated *P. jucunda*, isolating four compounds from the stem bark extract. Among them, 24-methylenelanosta-7,9(11)-dien-3-β,15a-diol displayed significant growth inhibitory effects on various tumor cell lines, including breast adenocarcinoma (MCF-7), lung cancer (NCI-H460), and CNS cancer (SF-268), as well as non-tumor human fetal lung cells (MRC-5), indicating its potential for inducing apoptosis in cancer cells (Suedee et al. 2007).

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Chen et al., 2000, explored *P. longifolia* var Pendula, identifying 20 compounds from the methanolic extract, including two novel compounds. Annonaine exhibited notable inhibitory potential against gastric, colon, and hepatoma cancer cell lines, highlighting its cytotoxic activity (Chen et al. 2000).

Similarly, Chang et al., 2006, investigated *P. longifolia* var Pendula bark extract, isolating 23 compounds, including novel clerodane diterpenes. These compounds demonstrated significant cytotoxicity against hepatoma cell lines (Hep G2 and Hep 3B), suggesting their potential as anticancer agents (Chang et al. 2006).

Tuchinda et al., 2006, evaluated *P. crassa* leaf and branch extracts, isolating 11 compounds, including novel stilide lactone derivatives. Among them, (+)-Crassalactone A exhibited potent cytotoxic activity against various cancer cell lines, including leukemia, epithelial carcinoma, and lung adenocarcinoma cells. Overall, these studies underscore the cytotoxic potential of *Polyalthia* species and their constituents, suggesting their promising role in cancer therapy (Tuchinda et al. 2006).

Guatteria and Desmopsis genus

Costa et al., 2020, and Palazzo et al., 2009, conducted studies focusing on the cytotoxic potential of essential oils from various species of the genera *Guatteria* and *Desmopsis* within the Annonaceae family. In Costa et al.'s study, the essential oil obtained from *G. megalophylla* Diels leaves demonstrated significant cytotoxic activity, especially against HL-60 human promyelocytic leukemia cells, with an IC50 of 12.51 μg/mL. This essential oil also demonstrated anti-leukemic activity *in vivo*, with inhibition rates of the tumor mass ranging from 16.6% to 48.8%. The major constituents identified in this essential oil included spathulenol, γ-muurolene, bicyclogermacrene, β-elemene, and δ-elemene. Similarly, Palazzo et al. evaluated the cytotoxicity of essential oils from species such as *D. bibracteata, D. macrocarpa, G. costaricensis, G. diospyroides, G. oliviformis*, and *Unonopsis costariensis*. These essential oils displayed high cytotoxicity against MDA-MB-231 breast adenocarcinoma cells, with ≥ 99% cell death observed at 100 μg/mL for *D. bibracteata, G. diospyroides, G. oliviformis*, and *U. costariensis*. Moreover, *D. bibracteata* essential oil exhibited 100% kill results against Hs 578T breast ductal carcinoma cells at the same concentration. Notably, germacrene D emerged as a predominant compound in the essential oils of *G. oliviformis* and *U. costariensis*, further emphasizing their cytotoxic potential. These studies underscore the significant cytotoxic activity of essential oils derived from Annonaceae species, particularly against cancer cell lines and highlight their potential as therapeutic agents in cancer treatment (Palazzo et al. 2009; Costa et al. 2020).

Others Annonaceae species

Other studies have viewed other species of Annonaceae that had smaller occurrences; these species include the Milliusa balanceae, Uvaria pandensis, Diclinanona calycina, Neouvaria acuminatissima, Dasymaschalon blumei, Asimina triloba, Artabotrys zeylanicus, Pseuduvaria trimera (Craib), Anaxagorea dolichocarpa and Duguetia chrysocarpa.

Huong et al., 2005, explored the cytotoxicity of a novel flavone named Miliufavol, along with four other known compounds isolated from the leaves and branches of *Miliusa balansae*. Among these compounds, paquipodol exhibited strong cytotoxic activity against KB and Hep-G2 cell lines, with IC50 values of 0.7 mg/mL and 0.55 mg/mL, respectively (Huong et al. 2005).

In another study by Maeda et al., 2022, the methanolic extract of *Uvaria pandensis* Verdc. leaves yielded 12 compounds, including three novel derivatives and two new flavonoids. However, only Pandensenol D and Pandesona A exhibited moderate cytotoxic effects against MCF-7 breast cancer cells, with EC_{50} values greater than 100 μM (Maeda et al. 2022).

Additionally, Costa et al., 2021, investigated the cytotoxic potential of benzylated dihydroflavones and isoquinoline-derived alkaloids from *Diclinanona calycina* bark extract. Dichamanetin and a mixture of uvarinol and isouvarinol demonstrated moderate cytotoxic activity against various cancer cell lines, with IC_{50} values ranging from 9.74 to 25.0 μg/mL. Importantly, they also exhibit low cytotoxicity against non-cancerous cell lines (Costa et al. 2021).

Furthermore, Ik-Soo-Lee et al., 1995, examined labdane-type diterpenes from *Neouvaria acuminatissima* stem bark, revealing broad cytotoxicity from Acuminolide and 17-O-

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Acetylacuminolide across several human cancer cell lines, with ED_{50} values ranging from 10 to 100 µg/mL. However, *in vivo* testing did not yield significant activity (Ik-Soo Lee et al. 1995).

Lastly, Chanakul et al., 2011, explored the cytotoxic potential of *Dasymaschalon blumei* extracts, isolating seven compounds with notable cytotoxic effects against various cancer cell lines. Among these compounds, oxodiscoguattine stood out, exhibiting low ED_{50} values (<19.11 µg/mL) against all tested cell lines (Chanakul et al. 2011).

Woo, Kim, and McLaughlin, 1999, explored the cytotoxicity of compounds from *Asimina triloba* seeds, isolating two novel acetogenins, asitrilobins A and B, which exhibited high potency against the MIA PaCa-2 pancreatic cancer cell line, with ED_{50} values of 3.99x10-5 µg/ml and 2.88x10-4 µg/ml, respectively, significantly outperforming the positive control Adriamycin (Woo et al. 1999).

Additionally, Wijeratne et al., 1995, examined the cytotoxic potential of constituents from *Artabotrys zeylanicus*, highlighting compound N-methoxinorcepharadione A (1) and atherospenine (2), with compound 1 displaying superior inhibitory activity across various cancer cell lines, including RS 322YK (rad52Y), RS 321N, and P-388 (Camptothecin resistant) (Kithsiri Wijeratne et al. 1995).

Sesang et al., 2014, investigated *Pseuduvaria trimera*, isolating two alkaloids, including a novel compound, 8-hydroxyartabonatin C, which demonstrated cytotoxic activity against HepG2 and MDA-MB231 cancer cells, albeit with lower potency compared to Doxorubicin (Sesang et al. 2014).

Lastly, Pinheiro et al., 2016, studied *Anaxagorea dolichocarpa* and *Duguetia chrysocarpa* stem bark extracts, revealing their cytotoxic effects against HCT-116 colon cancer cells, with the hexane extract of *A. dolichocarpa* showing the highest potency, inhibiting cell growth by 89.02% (Pinheiro et al. 2016).

The studies collectively highlight the diverse cytotoxic activities of compounds from Annonaceae species, suggesting their potential as therapeutic agents against various cancer types. Alkaloids, terpenoids, and flavonoids emerge as the most significant contributors to this cytotoxic bioactivity. These findings further emphasize the therapeutic potential of Annonaceae species in combating cancer, as summarized in Table 5, which lists the tested substances and their respective cytotoxic potential.

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Table 5. Summary of cytotoxic activity of species of the Annonaceae.

Annonaceae species	Used material	Substances/ Extracts	Methodology	Cell Proliferation inhibition (%)			Ref.
Anaxagorea dolichocarpa	Stem barks	**Extract** Ad-EtOH (Ethanolic) Ad-Hex (Hexanic) Ad-$CHCl_3$ (Chloroform) Ad-AcOEt (Ethyl acetate)	Human tumor cell lines, including OVCAR-8 (ovarian), SF-295 (brain) and HCT-116 (colon).	**OVCAR-8** 53.94 44.31 52.51 –5.38	**SF-295** 65.49 62.68 58.82 0.09	**HCT-116** 50.19 89.02 67.15 3.40	(Pinheiro et al. 2016)
Annona cacans Warm	The fruits and leaves	PHME-AC (pulp extract) PEAF-AC (ethyl acetate fraction) Acetogenin – PAC-1 **Positive control** **Doxorubicin chloride (0.025–25 lg/mL)**	MCF-7 (breast) OVCAR-3 (ovarian) K-562 (leukemia)	**GI_{50} - lg/mL** **MCF-7** - 11.3 -	 **OVCAR-3** 8.8 5.68 6.4	 **K-562** 6.10 7.84 -	(Volobuff et al. 2019)
Annona crassiflora	Leaves	Crassiflorine Xylopine Stephalagine **Doxorubicin** **(Positive control)**	**Cells line:** HCT-116 – Colon carcinoma MCF-7 – Breast	**IC_{50} µM** **HCT-116** 143.4 30.2 48.5 0.07	 **MCF-7** Not determined 32.9 Not determined 0.15		(Peña-Hidalgo et al. 2021)
Annona Mucosa	Leaves and Fruits	**Fraction** Hexane Extrat (L);	Cytotoxicity was studied after 96 h incubation of peritoneal macrophages with concentrations ranging from 6 to	**Cytotoxicity LC_{50} ($\mu g.mL^{-1}$) + SEMc** 62.63 ± 4.10	**LC_{50}/ IC_{50}** **PH8** 62.63 ± 4.10	 **M2903** 2.58	(De Lima et al. 2012)

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		Dichloromethane extract (L); Methanol extract (L);	100 µg.mL-1 of each extract and liriodenine. Results are expressed as 50% lethal concentrations (LC_{50})	24.07 ± 4.02 29.41 ± 0.89	24.07 ± 4.02 29.41 ± 0.89	2.58 1.03	
Annonaceae species	**Used material**	**Substances/ Extracts**	**Methodology**	**Cell Proliferation inhibition (%)**			**Ref.**
Annona Mucosa	Leaves and Fruits	**Fraction** Hexane extrat (S); Methanol extrat (S); **Compounds** Liriodenine Pentamiddine	Cytotoxicity was studied after 96 h incubation of peritoneal macrophages with concentrations ranging from 6 to 100 µg.mL-1 of each extract and liriodenine. Results are expressed as 50% lethal concentrations (LC_{50})	**Cytotoxicity LC_{50} (µg.mL^{-1}) + SEMc** 262.33 ± 5.81 139.00 ± 3.13 19.11 ± 1.6 51.99 ± 0.58	**LC_{50}/ IC_{50}** **PH8** 262.33 ± 5.81 139.00 ± 3.13 19.11 ± 1.6 51.99 ± 0.58	**LC_{50}/ IC_{50}** **M2903** 5.93 2.98 13.36 742.71	(De Lima et al. 2012)
Annona senegalensis Pers.	The bark	**Fractions** MeOH Extract **Compounds** Adriamicina	BST (brine shrimp lethality test) **Human solid tumor cell lines:** A-549 (lung carcinoma) MCF-7 (breast carcinoma) HT-29 colon (adenocarcinoma) A-498 (kidney carcinoma) PC-3 (prostate adenocarcinoma) PACA-2 (pancreatic carcinoma)	**ED_{50} (µg/mL)** **MeOH Extract** LC_{50} <1,0 <10-2 <10-2 1,0 <10-2 <10-2 <10-2	**ED_{50} (µg/mL)** **Adriamicina** - - $1,85 \times 10^{-1}$ $4,37 \times 10^{-2}$ 1×10^{-2} $2,23 \times 10^{-2}$ $2,05 \times 10^{-2}$		(Fatope et al. 1996)
Anonna squamosa	Mature leaves and fruits	Leaves aqueous extract (LAq)	Vero cell lines, (Vero, ATCC-CL 81) kindly provided by Instituto Butantan (São Paulo, Brazil), were used to perform cytotoxic.	**Cytotoxicity Assays** **Tree Age** 4 14	**Cytotoxicity Assays** **CC_{50} (mg.mL^{-1})** 0.32 0.42		(Silva et al. 2016)

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<table>
<tr><td></td><td></td><td>Seeds aqueous extract (SAq)</td><td></td><td colspan="5">4
14</td><td colspan="2">1.43
1.51</td><td></td></tr>
<tr><td>Annonaceae species</td><td>Used material</td><td>Substances/ Extracts</td><td>Methodology</td><td colspan="7">Cell Proliferation inhibition (%)</td><td>Ref.</td></tr>
<tr><td>Anonna squamosa</td><td>Mature leaves and fruits</td><td>Seeds hexane extract (SHex)</td><td>Vero cell lines, (Vero, ATCC-CL 81) kindly provided by Instituto Butantan (São Paulo, Brazil), were used to perform cytotoxic.</td><td colspan="7">Cytotoxicity Assays
Tree Age | CC50 (mg.mL-1)
4 | 0.49
14 | 0.40</td><td>(Silva et al. 2016)</td></tr>
<tr><td>Annona vepretorum</td><td>Stem bark</td><td>Compounds
ent-3β-hydroxy-kaur-16-en-19-al
ent-3β,19-dihydroxy-kaur-16-eno
ent-3β-hydroxy-kaur-16-eno
ent-3β-acetoxy-kaur-16-eno
ent-3β-hydroxy-kaurenoic acid
Kaurenoic acid
Positive Control
Doxorubicin</td><td>Cytotoxic activities towards tumor and non-tumor cells lines were investigated for compounds 1–6 with Tumor cells: B16-F10, Hep-G2, HL-60, K562 and non-tumor cells: PBMC</td><td colspan="7">IC50 in μg/mL (μM)
B16-F10 | Hep-G2 | HL-60 | K562 | PBMC
21.02 | 15.50 | 9.92 | 2.49 | 7.20
>25 | >25 | >25 | >25 | 8.93
19.12 | 19.38 | 9.86 | 2.94 | 6.49
>25 | >25 | >25 | >25 | >25
>25 | >25 | 24.21 | 20.21 | >25
16.56 | 15.33 | 13.33 | 21.92 | 24.41
2.30 | 0.23 | 0.83 | 0.68 | 5.09</td><td>(Dutra et al. 2014)</td></tr>
<tr><td>Annona vepretorum</td><td>Leaves</td><td>Extract
Av-MeOH
Av-HexC
Av-Hex</td><td>Human tumor cell lines were plated in 96-well plates: HCT-116, SF-295, HL-60, Sarcoma-180.</td><td colspan="7">Cell proliferation inhibition (%)
HCT-116 | SF-295 | HL-60 | Sarcoma-180 | IC50 (μM)
98.16 | 63.98 | 82.23 | 82.34 | 2.81</td><td>(Araújo et al. 2017)</td></tr>
</table>

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			The concentration that caused 50% cell growth inhibition (IC_{50}) was determined from the concentration-response curves by non-linear regression with a confidence interval of 95%.	±0.92 29.96 ±1.60 56.04 ±21.0	±4.84 86.54 ±3.31 65.43 ±6.52	±4.84 17.11 ±7.34 55.85 ±3.56	±1.36 79.43 ±4.39 86.24 ±1.09	±0.41 4.87 ±0.83 45.82 ±9.07	
Annonaceae species	**Used material**	**Substances/ Extracts**	**Methodology**	**Cell Proliferation inhibition (%)**					**Ref.**
Annona vepretorum	Leaves	Av-$CHCl_3$ AV-AcOEt Av-H_2O	Human tumor cell lines were plated in 96-well plates: HCT-116, SF-295, HL-60, Sarcoma-180. The concentration that caused 50% cell growth inhibition (IC_{50}) was determined from the concentration-response curves by non-linear regression with a confidence interval of 95%.	**HCT-116** 74.28 ±0.25 17.8 7±6.45 9.52 ±11.68	**SF-295** 82.05 ±24.67 27.98 ±5.16 6.72 ±1.25	**HL-60** 29.79 ±1.82 68.72 ±38.28 -8.20 ±3.33	**Sarcoma-180** 81.32 ±6.79 63.15 ±6.57 78.57 ±5.91	**IC_{50} (µM)** 2.88 ±1.39 22.82 ±3.76 71.18 ±1.69	(Araújo et al. 2017)

Artabotrys zeylanicus	Not specified	**Compounds** N-methoxynorcepharadione A (1) Atherospennidine (2) **Positive control** Camptothecin	Cytotoxicity assessed by IC_{50} by assay with cells: RS 322YK (rad52Y) RS 321N RS 188N (rad+) P-388 (wild-type) P-388 (Camptothecin resistant)	**IC_{50} (µg/ml)** 1 2.16 1.20 >200 159 1.12		**IC_{50} (µg/ml)** 2 16 27 >50 Not tested Not tested		**IC_{50} (µg/ml)** **Camptothecin** 0.6 - 100 0.012 >20					(Kithsiri Wijeratne et al. 1995)
Asimina triloba	Seeds	Acetogenins 1	Cytotoxicity tests against human tumor cell lines: A-549 (human lung carcinoma), MCF-7 (human	**Human cancer cell line (ED_{50} µg/ml)** **BST LC_{50}**	**A-549**	**MCF-7**	**HT-29**	**A-498**	**PC-3**	**MIA PaCa-2**			(Woo et al. 1999)

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		2 Adramicyn	breast carcinoma), HT-29 (human colon adenocarcinoma), A-498 (human kidney carcinoma), PC-3 (human prostate adenocarcinoma) and MIA PaCa-2 (human pancreatic carcinoma).	0.131 0.00429 Not tested	0.00439 0.00165 0.0174	0.00211 0.00169 0.440	2.09 0.440 0.0116	2.78 2.19 0.0116	2.28 1.06 0.0461	0.00003 9 0.00002 8 0.00781	
Desmopsis bibracteata *Desmopsis macrocarpa*	Leaves	Essential oil	Human MDA-MB-231 breast adenocarcinoma cells and Human Hs 578T breast ductal carcinoma cells.	**% Kill at 100 µg/mL**							(Palazzo et al. 2009)
				MDA-MB-231				**Hs 578T**			
				99.3 (0.7) 53.0 (9.6)				100 8.2 (14.0)			
Annonaceae species	**Used material**	**Substances/ Extracts**	**Methodology**	**Cell Proliferation inhibition (%)**							**Ref.**
Dasymaschalon blumei	The combined leaves and twigs Stems	**Extract:** Acetate de ethyl extract Acetate de ethyl extract **Compounds:** 3,5-diydroxy-2,4-dimethoxyaristolactam Aristolactam BI Goniopedaline Griffithinam Oxodiscoguattine Dicentrinone Duguevalline	Cell culture: P-388 (mouse lymphoid neoplasm), KB (human epidermoid carcinoma in the mouth), Col-2 (human colon cancer), MCF-7 (human breast cancer), Lu-1 (human lung cancer), ASK (rat glioma), Hek 293 (noncancerous human embryonic kidney cell). The Hek 293 cell assay was used as a primary assay for assessing the specificity of an anticancer agent toward cancer cell lines in	**ED50 values (µg/ml)**							(Chanakul et al. 2011)
				P-388	**KB**	**Col-2**	**MCF-7**	**Lu-1**	**ASK**	**Hek 293**	
				<4 <4 2.13 11.18 2.59 13.82 0.60 10.28 9.43	<4 4.12 2.97 - 1.98 - 2.30 4.56 -	17.38 - - - - - 0.91 7.34 -	- - - 3.60 9.45 - 2.74 9.05 19.11	16.46 14.04 - - - - 0.76 4.0 -	- - 3.04 - 12.76 - 2.11 10.20 -	- - 14.75 - 17.97 - 1.6 3.76 -	

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		Positive control Elipticine	comparison with the normal mammalian cell.	0.65	0.62	0.65	0.69	0.17	0.61	0.56	
Diclinanona calycina	Barks	**Compounds** Thalifoline (*S*)-(+)-Reticuline 1*S*,2*R*-Reticuline N$_\beta$-oxide 1*S*,2*S*-Reticuline N$_\alpha$-oxide Bisnorargemonine Isochamanetin Dichamanetin Uvarinol + Isouvarinol **Doxorubicin** **(Positive control)**	**Cancer cells** HL-60 – Human promyelocytic leukemia MCF-7 – Breast adenocarcinoma HepG2 – hepatocellular carcinoma HCT116 – colon carcinoma **Non-cancerous cell:** MRC-5 – Human lung fibroblast	**µM**							(Costa et al. 2021)
				HL-60		**MCF-7**		**HCT116**	**HepG2**	**MRC-5**	
				Not determined Not determined Not determined Not determined Not determined Not determined 15.78 9.74 0.04		Not determined Not determined Not determined Not determined Not determined Not determined 23.59 >25 3.08		>25 >25 >25 >25 >25 18.99 17.31 0.85	20.08 22.54 23.11 >25 >25 19.79 >25 >25 2.05	>25 >25 >25 >25 >25 24.69 >25 >25 3.19	
Annonaceae species	**Used material**	**Substances/ Extracts**	**Methodology**	**Cell Proliferation inhibition (%)**							**Ref.**
				OVCAR-8		**SF-295**		**HCT-116**			
Duguetia chrysocarpa	Stem barks	Dc-EtOH (Ethanolic) Dc-Hex (Hexanic) Dc-CHCl$_3$ (Chloroform)	Human tumor cell lines, including OVCAR-8 (ovarian), SF-295 (brain) and HCT-116 (colon).	49.65 18.39 42.24		43.95 34.84 63.17		60.16 15.61 59.35			(Pinheiro et al. 2016)

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		Dc-AcOEt (Ethyl acetate)		13.01		30.99		9.76					
Guatteria costaricensis *Guatteria diospyroides* *Guatteria oliviformis*	Leaves	Essential oil	Human MDA-MB-231 breast adenocarcinoma cells and Human Hs 578T breast ductal carcinoma cells.	**% Kill at 100 µg/mL**									(Palazzo et al. 2009)
				MDA-MB-231				**Hs 578T**					
				54.6 (5.7) 98.8 (1.2) 100				0 21.1 (8.2) 35.6 (1.9)					
Guatteria megalophylla Diels	Leaves	Essential oil (EO) **Positive Control** Doxorubicin (DOX) 5-Fluorouracil (5-FU)	Toxicity Assays with Human cancer cell lines: HL-60 Promyelocytic leukemia; MCF-7 Breast adenocarcinoma; Cal27 Oral squamous cell carcinoma; HSC-3 Oral squamous cell carcinoma; HepG2 Hepatocellular carcinoma; HCT116 Colon carcinoma and Human non-cancer cell line: MRC-5 Lung fibroblast.	**IC_{50} (µg/mL)**									(Costa et al. 2020)
				HL-60	**MCF-7**	**CAL-27**	**HSC-3**	**Hep-g2**	**HCT116**	**MRC-5**			
				12.51 0.02 1.85	33.45 6.16 10.13	7.58 1.09 2.56	14.90 0.86 1.01	21.62 0.02 13.71	30.07 0.02 0.53	29.85 3.32 5.96			
Miliusa balansae	Leaves and branches	**Flavonoids** Ombuine Crysosplenol B Pachypodol Crysosplenol C **Control** Eliptin (Sigma)	**Cell culture:** **IC_{50} (µg/mL)** - KB (Human Epidermoide Carcinom); - Hep-G2 (Hepatoma G2); - RD (Rhabdosarcoma).	**KB**		**Hep-G2**		**RD**					(Huong et al. 2005)
				> 5 4.6 0.7 4.3 0.002		1.5 0.93 0.55 0.57 0.001		> 5 > 5 3.01 2.09 0.001					

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Annonaceae species	Used material	Substances/ Extracts	Methodology	Cell Proliferation inhibition (%)	Ref.
Neouvaria acuminatissima	Stem bark	**Compounds** Acuminolide (1) 17-*O*-Acetylacuminolide (2) Spiroacuminolide (3) **Positive Control** Doxorubicin	Screened for cytotoxicity against a panel of human cancer cell lines and murine P388 cells, according to established protocols. 14 ED_{50} values of >4 ~tg/ml were regarded as negative. Among the cell lines represented, a human lung cancer cell line (Lul) was used to guide the fractionation against the HT-29 human colorectal and KB human epidermoid carcinoma models, Doxorubicin was run as a positive control.	**ED_{50} Values: tg/ml** Compounds I and 2 were broadly cytotoxic, exhibiting ED_{50} values, ranging from 10 -~ to 10 ° ttg/ml in several cell lines. With the human cell lines, the most potent activity was observed with melanoma (Mel2) (ED_{50}: 0.7 ttg/ml) and prostate (LNCaP) (ED_{50}: 0.8 ~tg/ml) cells for compounds 1 and 2, respectively. Compound 3 was not significantly active for any of the cancer cell lines tested. Acuminolide (1) was inactive when tested in vivo against a HT-29 human colorectal xenograft model in nude mice at 40-60 mg/kg (maximum tolerated dose 70 mg/kg). 17-O-Acetylacuminolide (2) showed no significant activity when tested in vivo against a KB human epidermoid carcinoma murine model at 110 mg/kg.	(Ik-Soo Lee et al. 1995)
Polyalthia crassa	Leaves and twigs	**Compounds** (+)-Crassalactone A (+)-Crassalactone B (+)-Crassalactone C (+)-Crassalactone D Aristolactam AII (+)-tricinnamate **Positive control** Ellipticine	Cytotoxicity assays of compounds 1-4, 10, and 11 were performed employing the colorimetric method.	**Cell line (ED_{50} µg/mL)** **P-388** / **KB** / **Col-2** / **BCA-1** / **Lu-1** / **ASK** 0.18 / 1.7 / 1.9 / 0.92 / 1.9 / 1.6 3.8 / >5 / >5 / >5 / >5 / >5 >5 / >5 / >5 / >5 / >5 / >5 1.1 / 3.3 / 4.0 / 3.2 / >5 / 3.1 2.7 / >5 / >5 / >5 / >5 / >5 3.1 / >5 / >5 / >5 / >5 / >5 0.52 / 0.65 / 0.53 / 0.53 / 0.56 / 0.60	(Tuchinda et al. 2006)
		Compound		**GI_{50} (µM)**	

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Polyalthia jucunda	Dried and powdered stem bark.	4-Hydroxy-4,7-dimethyl-α-tetralone 4,5-Dihydroblu- menol A *N-trans*-feruloyltyramine 24–Methy- lenelanosta-7,9(11)-dien-3-β,15α-diol	The effects of compounds on the growth of the human tumor and non–tumor cell lines were evaluated according to the procedure adopted by the National Cancer Institute (USA) for the *in vitro* anticancer drug discovery	**MCF-7** >150 >150 >150 19.3±1.2	**MDA-MB-231** >150 >150 >150 18.8±2.0	**SF-268** >150 >150 >150 21.8±0.6	**NCL-H460** >150 >150 >150 23.0±1.7	**MRC-5** >150 >150 >150 40.3±3.4	(Suede et al. 2007)

Annonacea e species	**Used material**	**Substances/ Extracts**	**Methodology**	**Cell Proliferation inhibition (%)**				**Ref.**
				IC$_{50}$ (μM)				
Polyalthia longifolia var. *pendula*	Leaves	16α-hydroxycleroda3,13-dien-15,16-olide 5-hydroxy-6-Methoxyonychine (-)-anonnaine	Tested against four human cancer cell lines: AGS (gastric cancer cells), DLD1 (colon cancer cells), HepG2 (hepatoma cells), and HA59T (hepatoma cells).	**AGS** 26.9 >30 8.6	**DLD** >30 >30 28.9	**HA597** 23.6 21.7 16.4	**HepG2** >30 >30 20.8	(Chen et al. 2000)
		Compounds		**IC$_{50}$ (μM)**				
Polyalthia longifólia var. *pendula*	The bark samples	16(*R&S*)- 3,13*Z*-kolavadien-15,16-olide-2-one 16-hydroxycleroda- 3,13-dien-15,16-olide 16-hydroxycleroda-4(18),13-dien- 15,16-olide 16-oxocleroda-3,13(14)E-dien-15-oic acid methyl ester	Tested against four human cancer cell lines: MCF-7, MDA-MB-231, Hep-G2, Hep 38.	**MCF-7** 18.28 14.42 10.43 14.34 18.12 11.89 - 10.41	**MDA-MB-231** 4.50 8.29 3.22 13.22 14.67 11.65 - 9.94	**Hep-G2** 2.88 4.42 3.35 - - 2.36 18.33 -	**Hep38** 2.96 2.83 1.97 - - 8.94 15.40 -	(Chang et al. 2006)

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		Solidagonal acid (4→2)-*abeo*- 16(R&S)-2,13*Z*-clerodadien-15,16-olide-3-al labd-13*E*-en-8-ol-15-oic acid Polylongine Liriodenine Lysicamine (+)-Stepharine (−)-Stepholidine *N-trans*-feruloyltyramine *N-trans*-p-coumaroyltyramine **Positive control** Doxorubicin		4.46 8.94 9.40 16.56 25.53 17.35 0.04	10.28 16.75 9.90 - 25.54 - 0.32	- - - - 21.17 - 0.18	- - - - 24.98 - 0.23	

Annonaceae species	**Used material**	**Substances/ Extracts**	**Methodology**	**Cell Proliferation inhibition (%)**				**Ref.**
				IC_{50}				
				HepG2		**MDA-MB231**		
				Mean	**SD**	**Mean**	**SD**	
Pseuduvaria trimera (Craib)	Leaves And twigs	8-hydroxyartabonatine C Ouregidione **Positive control** Doxorubicin	The human hepatocellular carcinoma HepG2 and breast cancer MDA-MB231 cells.	26.36 12.88 2.21	±5.18 ±2.49 ±1.72	64.75 67.06 1.83	±4.45 ±3.5 ±0.09	(Sesang et al. 2014)
Uvaria pandensis	Leaves	Pandensenol D Pandensone A	**Cell culture:** MCF-7 (breast cancer cells)	**EC_{50} (μM)** >523.4				(Maeda et al. 2022)

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		(8′α,9′β-dihydroxy)-3-farnesylindole (6′,7′-dihydro-8′α,9′β-dihydroxy)- 3-farnesylindole		349.8 117.1 >563.4			
Unonopsis costariensis	Leaves	Essential oil	Human MDA-MB-231 breast adenocarcinoma cells and Human Hs 578T breast ductal carcinoma cells.	**% Kill at 100 µg/mL**			(Palazzo et al. 2009)
				MDA-MB-231	**Hs 578T**		
				100	17.3 (10.3)		
Xylopia aethiopica	Fruits	Aqueous extract Aqueous extrat in gold nanoparticles **Positive control** **Fulvestrant** **5-Fluororacil**	**Cell culture:** **IC_{50} (µg/mL)** - MCF-7 (Bresat cancer); - MDA-MB-231; - Caco-2 cells.	**MCF-7**	**MDA-MB-231**	**Caco-2**	(Anadozie et al. 2021)
				171.3 >200 >120 nM -	94.5 141.4 <120 nM -	199.8 >200 - >100	
Xylopia langsdorffiana	Stems	**Compound** ent-7r-Acetoxytrachyloban-18-oic acid	Cytotoxic activity of compound 1 was evaluated against V79 cells and rat hepatocytes using the MTT method.	**IC_{50} (µM)**			(Tavares et al. 2006)
				V79	**K562**		
				224 and 231 µM	200 µM		
Annonaceae species	**Used material**	**Substances/ Extracts**	**Methodology**	**Cell Proliferation inhibition (%)**			**Ref.**
	Fruits	**Essential oil**		**IC_{50} values µL/mL**			

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<table>
<tr><td>Xylopia aethiopica (Dunal) A. Rich; Xylopia paviflora A. Rich (Benth.);</td><td></td><td>Composition: Monoterpenes hydrocarbons; Oxygenated monoterpenes; Sesquiterpene hydrocarbons; Oxygenated sesquiterpenes.</td><td>The cytotoxic activity of all essential oils was evaluated on human breast cancer (MCF-7) and normal epithelial (ARPE-19) cell lines using the MTT assay based on cell viability. Cells were exposed to the oils at concentrations ranging from 0.1 to 2 µL/mL.</td><td colspan="5">The six essential oils exerted cytotoxic activity against cancer (MCF-7) and normal cell lines (ARPE-19), with more pronounced effect on neoplastic cells in most cases. The highest selectivity was obtained with the essential oils of X. parviflora from Chad and Cameroon (5.87 and 5.54) which were more cytotoxic against MCF-7 than against normal cell line (ARPE-19) with IC_{50} values of 0.155 µL/mL and 0.166 µL/mL respectively</td><td>(Bakarnga-Via et al. 2014)</td></tr>
<tr><td rowspan="19">Xylopia laevigata</td><td rowspan="19">Leaves</td><td>Compounds</td><td rowspan="19">B16-F10, HepG2, K562 and HL-60 tumor cell lines were kindly donated by Hospital A.C. Camargo, São Paulo, Brazil. Cell viability was quantified using the Alamar Blue assay.</td><td colspan="5">IC_{50} µg/mL (µM)</td><td rowspan="19">(Menezes et al. 2016)</td></tr>
<tr><td>(-)-Roemerine</td><td>B16-F10</td><td>HepG2</td><td>HL60</td><td>K562</td><td>PBMC</td></tr>
<tr><td>(+)-Anonaine</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr>
<tr><td>Lanuginosine</td><td>18.80</td><td>14.04</td><td>10.09</td><td>10.62</td><td>NA</td></tr>
<tr><td>(+)-Glaucine</td><td>8.46</td><td>3.89</td><td>7.81</td><td>6.61</td><td>24.53</td></tr>
<tr><td>(+)-Xylopine</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr>
<tr><td>Oxoglaucine</td><td>3.77</td><td>1.87</td><td>1.87</td><td>3.12</td><td>4.08</td></tr>
<tr><td>(+)-Norglaucine</td><td>19.14</td><td>NA</td><td>5.90</td><td>12.48</td><td>10.25</td></tr>
<tr><td>(-)-Xylopinine</td><td>8.48</td><td>3.78</td><td>6.84</td><td>7.84</td><td>6.70</td></tr>
<tr><td>(+)-Norpurpureine</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr>
<tr><td>(+)-N-Methyllaurotetanine</td><td>21.08</td><td>NA</td><td>10.11</td><td>16.72</td><td>17.94</td></tr>
<tr><td>(+)-Norpredicentrine</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr>
<tr><td>(+)-Discretine</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr>
<tr><td>(+)-Calycinine</td><td>16.15</td><td>7.89</td><td>12.97</td><td>14.85</td><td>NA</td></tr>
<tr><td>(+)-Laurotetanine</td><td>22.17</td><td>NA</td><td>18.59</td><td>NA</td><td>NA</td></tr>
<tr><td>(+)-Reticuline</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr>
<tr><td>(-)-Corytenchine</td><td>NA</td><td>15.35</td><td>23.81</td><td>NA</td><td>NA</td></tr>
<tr><td>(+)-Discretamine</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td><td>NA</td></tr>
<tr><td>(+)-Flavinantine</td><td>18.80</td><td>14.04</td><td>10.09</td><td>10.62</td><td>NA</td></tr>
</table>

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		Positive Control Doxorubicin		NA 0.08	NA 0.08	NA 0.09	NA 0.15	NA 2.47	

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3.6. NA - Not Active Instead (IC50 > 25µg/mL)Antitumor

Cancer is a heterogeneous disease caused by a series of "genetic" alterations selected clonally in tumor suppressor genes and oncogenes (Aguirre-Ghiso 2007). However, evidence accumulated in recent years indicates that the heterogeneity of tumor cells is partly due to the contributions of "epigenetic" changes in cancer cells (Ducasse and Brown 2006). Thus, it is believed that cancer is the manifestation of genetic and epigenetic changes (Esteller 2008; Ellis et al. 2009). Despite a few examples of genetic inheritance of tumorogenesis, it is believed that most cancers can result from changes that accumulate throughout life due to exposure to various endogenous factors such as nutrients, infections, physical activity, social behavior and other environmental factors (Link et al. 2010).

In Brazil, according to data from the National Cancer Institute (INCA, 2019) the disease is already emerging as the second leading cause of mortality in the country (Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA) 2019). In this way, innumerable anticancer drugs have been introduced in therapy in the last decades, many of which were obtained by plant screening programs. Considering the high incidence of cancer and the toxic effects that antineoplastic drugs have on normal cells, it is important to highlight the role that natural products have played in the search for efficient alternatives for antineoplastic therapy (Zhang et al. 2019; Núcleo de estudos e Pesquisas de Produtos Naturais 2020; Twilley et al. 2020).

Thus, some authors conducted research on species of the Annonaceae family in search of new antitumor agents. The predominant species evaluated include *Annona, Guatteria* and *Xylopia*. Through these studies, the tumor inhibition potential of Annonaceae derived compounds is evident, where the top five studies addressed the action of acetogenins, terpenoids, and alkaloids. Table 6 shows the substances tested in each study as well as their respective antitumor potential.

Annona genus

Rinaldi et al., 2017, discovered that a crude extract of *Annona hypoglauca* Mart., commonly known in Brazil as "beribá," exhibits cytotoxic activity against human cancer cells. Through Gas Chromatography–Mass Spectrometry (GC/MS) analysis, four aporphine alkaloids—actinodaphnine, anonaine, isoboldine, and nornuciferine—were identified as responsible for the antitumoral activity. In cytotoxicity assays, the crude extract demonstrated a lethal effect against breast and colon cancer cells (Rinaldi et al. 2017).

The total alkaloid fraction showed significant cytotoxicity against MCF-7 (–8.90% lethality) and showed cytotoxicity against SF-268 (26.7% growth inhibition), against NCIH461 (29.0% growth inhibition) and against KM-12 (67.6% growth inhibition). Additionally, both the fraction containing Isoboldine and the fraction containing Actinodaphnine displayed activity against the breast cancer cell line. In contrast, alkaloid-free fractions did not demonstrate significant activity against cancer cell lines (Rinaldi et al. 2017).

Chen and colleagues, 2011, examined the antitumor effects of acetogenins (ACGs) derived from the leaves of Annona squamosa Linn. Their study involved using S180 and HepS xenograft-bearing mice to test the antitumor activity. The results demonstrated that some ACGs effectively inhibited tumor growth in a dose-dependent manner, with a particular selectivity for HepS. Among the acetogenins evaluated, adjacent bis-THF ACGs showed greater activity compared to mono-THF and nonadjacent bis-THF ACGs against both HepS and S180. Conversely, nonadjacent bis-THF ACGs were more effective than mono-THF ACGs against S180, while mono-THF ACGs proved more potent than nonadjacent bis-THF ACGs against HepS (Chen et al. 2012).

Additionally, the cytotoxic activity of the fruit pericarp of the same species was investigated using *in vitro* cultures of Dalton's lymphoma cells and HeLa cells. The results revealed that the chloroform extract of *Annona squamosa* pericarp exhibited cytotoxicity against the tested cell lines. The inhibitory concentration required for 50% cytotoxicity (IC_{50}) was also determined. Through bioactivity-directed isolation, two diterpenoids, namely (-)-ent-kaur-16-en-19-oic acid and 16a,17-

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dihydroxy-ent-kauran-19-oic acid, were identified as the compounds responsible for the observed cytotoxic activity (Joy and Remani 2008).

In the volatile oil extracted from fresh leaves of *Annona leptopetala*, spathulenol was found to be the major component, comprising 12.56% of the total. This oil was utilized to assess its antitumor effects through both *in vitro* (using the sulforhodamine B assay) and in vivo (sarcoma 180 murine tumor model) experiments. In the *in vitro* study, the volatile oil demonstrated antitumor activity, particularly against the leukemia cell line (K-562), with a total growth inhibition (TGI) concentration of 0.64 μg/ml when tested up to 250 μg/ml. For the in vivo experiments, the 50% lethal dose in mice was approximately 447.2 mg/kg when administered intraperitoneally. Furthermore, the inhibition rates for Sarcoma 180 tumor growth were 59.29% and 58.77% at doses of 100 and 150 mg/kg intraperitoneally, respectively (Brito et al. 2018).

Leaves of *Annona vepretorum* Mart. were utilized to extract an essential oil, primarily composed of bicyclogermacrene (35.71%), spathulenol (18.89%), (E)-β-ocimene (12.46%), α-phellandrene (8.08%), o-cymene (6.24%), germacrene D (3.27%), and α-pinene (2.18%). The *in vitro* cytotoxicity of the essential oil and some of its major constituents was assessed in tumor cell lines representing different histotypes, using the alamar blue assay. Notably, both the essential oil and spathulenol demonstrated promising cytotoxic effects (Bomfim et al. 2016).

In vivo experiments revealed that the treatment with the essential oil led to a 34.46% inhibition of tumor growth. Prominently, when the essential oil was complexed with β-cyclodextrin in a microencapsulation, there was a significant increase in in vivo tumor growth inhibition, reaching 62.66% (Bomfim et al. 2016).

Among the other *Annona* species highlighted are *Annona muricata* and *Annona crassiflora*. *Annona muricata*, or graviola, boasts over 212 phytochemicals, including annonaceous acetogenins, alkaloids, flavonoids, and sterols. Extensively researched for therapeutic potential, graviola exhibits several biological activities including antitumoral properties. In an in vivo rodent study, *Annona muricata* leaf extract demonstrated a 59.8% inhibition of pancreatic cancer cell growth and metastasis induced by CD18/HPAF cells. The ethanolic extract selectively induced cytotoxicity in three tumor cell lines without affecting normal spleen cells. The extract inhibited EGFR overexpression, EGFR mRNA expression, induced G0/G1 phase cell cycle arrest, and activated caspase-3-mediated apoptosis. In athymic mice, it inhibited MDA-MB-468 tumor growth by 32%, reducing protein expression of EGFR, p-ERK, and p-EGFR. The 80% aqueous ethanol leaf extract suppressed tumor initiation and promotion even at lower dosages, showcasing its multifaceted potential in cancer treatment (Rady et al. 2018).

Using the methanolic extract of *Annona crassiflora,* the antimutagenic evaluation in the micronucleus test showed a damage reduction of 75.00 and 64.58% for the pre-treatment and simultaneous protocols, respectively. The post-treatment protocol enhanced the effects of cyclophosphamide by 45.83%. In contrast, pre-treatment with 15 mg/L of the extract resulted in a significant reduction in the mitotic index, decreasing it by 45.95%. This specific protocol did not effectively reduce MMS-induced toxicity. However, all other protocols and treatments, across various concentrations, led to an increased mitotic index. This implies that the *Annona crassiflora* methanolic extract has the potential to reverse the toxicity induced by MMS treatment in cultures (Rocha et al. 2016).

Xylopia genus

The leaf essential oil of *Xylopia frutescens* contains significant compounds, including (E)-caryophyllene (31.48%), bicyclogermacrene (15.13%), germacrene D (9.66%), δ-cadinene (5.44%), viridiflorene (5.09%), and α-copaene (4.35%), which were identified by GC/FID and GC/MS. *In vitro* cytotoxicity assays conducted on NCI-H358M and PC-3M tumor cells showed that the essential oil had IC_{50} values ranging from 24.6 μg/mL to 40.0 μg/mL. After, the *in vivo* evaluation using Sarcoma 180-bearing mice was performed. The essential oil (dosed at 50 and 100 mg/kg/day) inhibited tumor growth with rates by 31.0–37.5%. Notably, it demonstrated anticancer effects without significant toxicity, presenting a potential alternative for cancer therapy. The essential oil's composition, coupled

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with its *in vitro* and *in vivo* outcomes, underscores its promising role in cancer treatment (Ferraz et al. 2013).

Cavalcanti et al., 2010, explored the genotoxic and mutagenic potential of kaurenoic acid, isolated from dried roots of *Xylopia sericeae* St. Hill, using diverse *in vitro* and in vivo methods. They investigated structure–activity relationships for two natural diterpenoids and three semi-synthetic derivatives of kaurenoic acid. The study unveiled genotoxic and mutagenic effects in human blood cells, yeast, and mice for some compounds, potentially attributed to DNA double-strand breaks or topoisomerase I inhibition. Intriguingly, certain compounds, including kaurenoic acid, exhibited no such effects, pointing to the exocyclic double bond (C16) as the active genotoxic moiety in kaurenoic acid derivatives (Cavalcanti et al. 2010).

The essential oil extracted from the leaves of *Xylopia laevigata* revealed compounds with inhibitory effects against tumor cells in culture, as well as on tumor growth *in vivo*. The essential oil exhibited consistent chemical composition, with major constituents identified as γ-muurolene, δ-cadinene, germacrene, α-copaene, germacrene D, bicyclogermacrene, and (E)-caryophyllene. *In vitro* tests showed that the essential oil has cytotoxicity across tested tumor cell lines, showing consistent profiles without hemolytic or genotoxic effects. After, the *in vivo* studies revealed tumor growth inhibition rates ranging from 37.3% to 42.5%. Essential oil treatment had no significant impact on body weight, organ macroscopy, or blood leukocyte counts (Quintans et al. 2013).

Guatteria genus

Santos et al., 2017, evaluated diverse essential oils extracted from the aerial parts of various *Guatteria* species, including *G. australis*, *G. ferruginea*, *G. latifolia*, and *G. sellowiana*. Following this, they investigated the antiproliferative activity of these extracts on a panel of tumor cell lines, measuring it as the concentration required for complete inhibition of cell growth, expressed as total growth inhibition (TGI) (Santos et al. 2017).

The results showed that while the essential oil from *G. sellowiana* demonstrated limited activity (TGI > 50 μg/ml) against most tumor cell lines, exceptions were observed for leukemia (K562, TGI = 1.1 μg/ml) and ovarian adenocarcinoma (OVCAR-03, TGI = 4.1 μg/ml) cell lines. The essential oils extracted from *G. latifolia, G. ferruginea,* and *G. australis* exhibited pronounced selective effects on OVCAR-03 cells, with TGIs of 1.1, 1.8, and 3.2 μg/ml, respectively. Additionally, they displayed intriguing effects on the multiresistant ovarian adenocarcinoma cell line (NCI-ADR/RES) with TGIs of 10.0, 34.6, and 15.2 μg/ml, respectively (Santos et al. 2017).

Guatteria *elliptica*, another species under examination for its antitumoral properties, underwent assessment using essential oils extracted from leaves sourced from distinct regions in Sao Paulo, Brazil. Notably, the essential oil from Paranapiacaba demonstrated significant antitumor activity against breast (IC_{50} = 7.01 μg/mL) and prostate (IC_{50} = 5.35 μg/mL) cancer cells. Importantly, it exhibited low cytotoxicity towards normal fibroblast cells (IC_{10} = 18.55 μg/mL). Spathulenol, the primary compound isolated from this essential oil, displayed notable efficacy against MCF-7 (5.38 μg/mL and PC-3 (2.25 μg/mL) (Rajca Ferreira et al. 2018).

Mitrephora genus

Bioassay-guided fractionation of *Mitrephora thorelii* led to the discovery of two clerodane-type diterpenes, 6α,16,18-trihydroxycleroda-3(4),13(14)-dien-15,16-olide and 16-hydroxycleroda-3(4),13(14)-dien-15,16-olide. Both compounds exhibited significant inhibitory activity against human hepatoma BEL-7402 cells *in vitro*. Compound 16-hydroxycleroda-3(4),13(14)-dien-15,16-olide demonstrated promising in vivo anti-tumor effects, inhibiting hepatoma H22 growth by 30.7% in mice. *In vitro*, two clerodane-types diterpenes inhibited BEL-7402 cell proliferation with IC_{50} values of 44.6 (6α,16,18-trihydroxycleroda-3(4),13(14)-dien-15,16-olide) and 20.1 μM (16-hydroxycleroda-3(4),13(14)-dien-15,16-olide). The compound 16-hydroxycleroda-3(4),13(14)-dien-15,16-olide, was well-tolerated in mice and represents a potential natural anti-tumor agent (Meng et al. 2007).

Mitrephora glabra stem bark underwent bioactivity-guided fractionation, yielding nine compounds, including three new ent-kaurenoids, five polyacetylenic acids/esters, and the alkaloid liriodenine. Evaluation against cancer cell lines and microorganisms revealed that *ent*-kaurane

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diterpenoids were inactive (IC_{50} >10 μM), contrasting with more potent *ent*-trachylobane diterpenoids from the same plant. Polyacetylenes exhibited varying IC_{50} values (10–40 μM), with the compound methyloropheate displaying no cytotoxicity, suggesting the methyl ester diminished its activity. Notably, the alkaloid liriodenine showed significant cytotoxicity (IC_{50} close to 5 μM) against all tested cell lines (Li et al. 2009).

Others Annonaceae species

Among the other genus of Annonaceae which have showed antitumoral activity are *Asimina, Anaxagorea, Polyalthia, Duguetia* and *Miliusa.* Kim and collaborators, 2005, evaluated the antitumor activity of acetogenins obtained from the leaves of *Asimina triloba* Possessing. The isolated compounds were tested on A-549 (human lung carcinoma), MCF-7 (human breast carcinoma), HT-29 (human colon adenocarcinoma), A-498 (human kidney carcinoma), PC-3 (human prostate adenocarcinoma), and MIA PaCa-2 (human pancreatic carcinoma) cells, with adriamycin as a positive control. The results revealed that asimitrin was selectively cytotoxic against prostate adenocarcinoma (PC3) and 10^4 times more potent than the control. Hydroxytrilobin was equally more active against colon adenocarcinoma (HT-29) than adriamycin. The acetogenins exert their *in vivo* antitumor effects, in part, by inhibiting complex I of the electron transport system in the mitochondria and by blocking the NADH oxidase enzyme particular to the plasma membranes of cancerous cells (Kim et al. 2005).

The antitumor activity of Annonaceae-derived alkaloids was also the objective of Suassuna et al., 2011. In this study, the authors evaluated the activity of alkaloids isolated from the stem bark of *Anaxagorea dolichocarpa*. The alkaloids eupolauramine and sampangine demonstrated strong antitumor activity against K569 cells. In addition, the anticancer potential of *Polyalthia evecta* was evaluated using leaves extracts (Machana et al. 2012). Cytotoxicity against HepG2 and apoptosis induction were systematically examined, unveiling heightened efficacy in 50% ethanol-water crude leaf extract compared to its fractions. Notably, a hexane extract exhibited significant effects, albeit surpassed by the ethanol-water crude leaf extract. The amalgamation of water and hexane extracts demonstrated augmented cytotoxicity and apoptosis induction, presenting a twofold increase in % apoptotic cells compared to the sole hexane extract. The authors suggest the indispensable role of the polar extract fraction in the anticancer activity of the non-polar extract fraction (Lúcio et al. 2011).

The compounds Duguetine and duguetine β-N-oxide displayed significant antitumoral effects across all cell lines when utilizing an alkaloid extract and five isolated alkaloids from the subterranean stem bark of *Duguetia furfuracea*. The alkaloid extract, containing the compounds duguetine and duguetine β-N-oxide, demonstrated notable cytotoxicity against cancer cell lines. These two compounds displayed low IC_{50} values, with duguetine β-N-oxide (IC_{50} 7.27 μM) outperforming duguetine (IC_{50} 12.39 μM) in MDA/MB-435 (da Silva et al. 2009).

Fissistigma cavaleriei (Levl) Rehd underwent a bioassay-guided investigation by Yang et al., 2012. Using the dried roots, they identified an isoindolin derivative displaying antiangiogenic properties, selective COX-2 inhibition, and *in vitro* cytotoxicity against tumor cells. In vivo, this compound effectively hindered S-180 cell growth in mice, synergistically enhancing doxorubicin's antitumor efficacy. The authors propose its role as a multi-target molecule, urging further exploration for its potential as a lead in tumor treatment. Administered at 20 mg/kg, 36 mg/kg, and 64 mg/kg daily, the isoindolin derivative significantly reduced tumor weights in sarcoma 180-bearing mice to 2.33 ± 0.32 g, 1.87 ± 0.22 g, and 1.15 ± 0.11 g, respectively, after an 8-day regimen (Yang et al. 2012).

Finally, a novel compound named Miliufavol, along with known flavones such as ombuine, chrysosplenol B, pachypodol, and chrysosplenol C, was extracted and identified from the leaves and branches of Miliusa balansae. The extraction process involved multiple cycles with MeOH—H2O. The cytotoxic effects of the known compounds were assessed against cancer cell lines KB (human epidermoid carcinoma), Hep-G2, and RD (Rhabdomyosarcoma). Results indicated activity against all three tested cell lines for each of the four compounds. Particularly noteworthy was pachypodol, demonstrating significant potency against two cell lines (KB: 0.7 mg/ml, Hep-G2: 0.55 mg/ml). These findings underscore the remarkable cytotoxic potential of pachypodol and its counterparts (Huong et al. 2005).

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Table 6. Summary of antitumor activity of species of the Annonaceae.

Annonaceae species	Used material	Substances/ Extracts	Methodology	Inhibition				Ref.
				Chromosomal aberrations				
				Treatment	**Damage Reduction Percentages of mitotic index**	**Total** (values compared with the control group)	**Damage Reduction Percentages**	
Annona crassiflora	The leaves	*A. crassiflora* (AC)	To evaluate the antimutagenic/ chemopreventive activity through the Allium cepa test, we used 5, 10, and 15 mg/L of extract, and for the micronucleus test in the peripheral blood, we used the dose of 15 mg/kg.	Mutagenicity AC – 5mg/L AC – 10mg/L AC – 15mg/L Control group (distilled water) **Positive control MMS (Methyl methanesulfonate)** Antimutagenicity AC – 5mg/L Pre-treatment Simple simultaneous Simultaneous with pre-incubation Post-treatment Continuous	 −1.62 −11.35 −29.46 3.51 - −31.35 −44.86 −2.53 −58.38 −37.03 −64.05 −15.95 −35.68	 31 27 34 238 40 - - - 	 - - - - - −66.17 72.72 100.5 89.39 86.36 75.75 33.33 93.93	(Rocha et al. 2016)

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				AC – 10mg/L Pre-treatment Simple simultaneous Simultaneous with pre-incubation				
Annonaceae species	**Used material**	**Substances/ Extracts**	**Methodology**	**Inhibition**				**Ref.**
Annona crassiflora	The leaves	*A. crassiflora* (AC)	To evaluate the antimutagenic/ chemopreventive activity through the Allium cepa test, we used 5, 10, and 15 mg/L of extract, and for the micronucleus test in the peripheral blood, we used the dose of 15 mg/kg.	**Chromosomal aberrations**				(Rocha et al. 2016)
				Treatment	**Damage Reduction Percentages of mitotic index**	**Total** (values compared with the control group)	**Damage Reduction Percentages**	
				AC – 10mg/L Post-treatment Continuous				
				AC – 10mg/L Pre-treatment Simple simultaneous Simultaneous with pre-incubation Post-treatment Continuous	−21.35 −37.03 45.95 −23.78 −16.49 −36.76 −44.59	-	79.79 81.31 69.19 22.22 102.52 84.34 93.43	
	Stem			**MCF-7**	**PC-3**	**NCI-H460**	**KM-12**	**SF-268**	**RPMI-8226**	

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Annona hypoglauca		Crude extract Fraction hexane Dichloromethane/Methanol Fraction ethyl acetate Fraction butanol Total alkaloid fraction	Human tumor cell lines (MCF-7, breast adenocarcinoma; KM-12, colon adenocarcinoma; RPMI-8226, multiple myeloma; PC-3, prostate carcinoma; SF-268 glioblastoma and NCI-H460, non-small lung-cell carcinoma).	−32.80 NI 2.90 Not tested 11.90 −8.90	11.4 77.4 59.6 67.1 46.6 17.04	1.3 48.1 44.9 38.6 65.6 71.7	−2.5 NI NI NI NI 32.4	58.5 NI 93.7 77.4 NI 73.3	17.3 53.5 53.4 NI 83.8 NI	(Rinaldi et al. 2017)
Annonaceae species	**Used material**	**Substances/ Extracts**	**Methodology**	**Inhibition**						**Ref.**
				MCF-7	**PC-3**	**NCI-H460**	**KM-12**	**SF-268**	**RPMI-8226**	
Annona hypoglauca	Stem	Fraction alkaloid 4.4 Fraction alkaloid 5 Fraction alkaloid 9 **Positive control Doxorubicin**	Human tumor cell lines (MCF-7, breast adenocarcinoma; KM-12, colon adenocarcinoma; RPMI-8226, multiple myeloma; PC-3, prostate carcinoma; SF-268 glioblastoma and NCI-H460, non-small lung-cell carcinoma).	Not tested -11.60 -3.10 -16.31	-3.8 Not tested Not tested -50.0	-26.0 Not tested Not tested -46.2	11.7 -14.4 -8.4 -5.1	45.4 Not tested Not tested -34.0	29.7 Not tested Not tested -14.3	(Rinaldi et al. 2017)
Annona leptopetala	Leaves	Essential oil *Annona*	The tumor cell lines used were: U251 – glioma, MCF-	**Total inhibition of cancer cells proliferation (μg/ml)**						
				Cell Lines		**DOX**		**ALO**		

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		leptopetala leaves (ALO) **Doxurubicin (DOX) Positive control**	7 – breast, NCI/ADR-RES - multidrug-resistant ovarian, 786-0 – kidney, NCI-H460 – non-small cell lung cancer, PC-3 – prostate, OVCAR – ovarian, HT29 – colon and K562 – leukemia, and HaCaT human keratinocytes served as the normal cell line. Sarcoma 180 tumor cells were maintained in the peritoneal cavity of Swiss mice.	Glioma (U251) Breast (MCF-7) Ovary Multidrug Resistance Phenotype (NCI-ADR/RES) Kidney (786-O) Lung (NCI-H460) Prostate (PC-3) Ovary (OVCAR) Colon (HT-29)	0.06 0.21 1.35 0.04 0.01 0.27 0.26 0.22	47.23 49.91 >250 101.52 75.53 45.12 >250 75.26	(Brito et al. 2018)

Annonaceae species	**Used material**	**Substances/ Extracts**	**Methodology**	**Inhibition**			**Ref.**
				Total inhibition of cancer cells proliferation (μg/ml)			
				Cell Lines	**DOX**	**ALO**	
Annona leptopetala	Leaves	Essential oil *Annona leptopetala* leaves (ALO) **Doxurubicin (DOX) Positive control**	The tumor cell lines used were: U251 – glioma, MCF-7 – breast, NCI/ADR-RES - multidrug-resistant ovarian, 786-0 – kidney, NCI-H460 – non-small cell lung cancer, PC-3 – prostate, OVCAR – ovarian, HT29 – colon and K562 – leukemia, and HaCaT human keratinocytes	Leukemia (K-562) Skin (line of non-tumor cells) (HaCat)	0.40 0.23	0.64 >250	(Brito et al. 2018)

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<table>
<tr><td></td><td></td><td></td><td>served as the normal cell line. Sarcoma 180 tumor cells were maintained in the peritoneal cavity of Swiss mice.</td><td colspan="4"></td><td></td></tr>
<tr><td>Annona muricata</td><td>Leaf, Seed, Fruit, Pericarp, Twing, Root</td><td>Acetogenins, extracts and fractions</td><td>This current review demonstrates A. muricata's anticancer potential and other health-related benefits by providing insights into its bioactive chemical constituents as well as the in vitro and in vivo studies that have been carried out to elucidate the molecular mechanisms of action of these constituents.</td><td colspan="4">Review Article
Acetogenins or other A. muricata-derived compounds could be tested as monotherapy or as sensitizers in combination with standard cancer treatments for cancer patients.</td><td>(Rady et al. 2018)</td></tr>
<tr><td>Annona squamosa</td><td>Seeds</td><td>Compound Squamostatiin A</td><td>The antitumor activities of 1–5 and standard control taxol against the growth of S180 and HepS in mice were measured by methods reported previously.</td><td colspan="4">Treatment effects of annonaceous acetogenins in the Heps and S180 xenograft tumor model
<table><tr><th rowspan="2">Treatment group</th><th rowspan="2">Dose (μg/kg)</th><th colspan="2">HepS</th><th colspan="2">S180</th></tr><tr><th>Tumor weight (g: mean±SD)</th><th>Inhibition ratio (%)</th><th>Tumor weight (g: mean±SD)</th><th>Inhibition ratio (%)</th></tr><tr><td>Squamostatin A</td><td>15
60</td><td>0.96±0.19
0.79±0.12</td><td>15.0
31.2</td><td>0.36±0.09
0.34±0.10</td><td>52.7
54.2</td></tr></table></td><td>(Chen et al. 2012)</td></tr>
</table>

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<table>
<tr><th>Annonaceae species</th><th>Used material</th><th>Substances/ Extracts</th><th>Methodology</th><th colspan="6">Inhibition</th><th>Ref.</th></tr>
<tr><td rowspan="12">Annona squamosa</td><td rowspan="12">Seeds</td><td rowspan="12">Compounds
Squamostatiin E
4-deoxyannoreticuin
Desacetyluvaricin
Bullatacin
Taxol
Positive control</td><td rowspan="12">The antitumor activities of 1–5 and standard control taxol against the growth of S180 and HepS in mice were measured by methods reported previously.</td><td colspan="6">Treatment effects of annonaceous acetogenins in the Heps and S180 xenograft tumor model</td><td rowspan="12">(Chen et al. 2012)</td></tr>
<tr><td rowspan="2">Treatment group</td><td rowspan="2">Dose (μg/kg)</td><td colspan="2">HepS</td><td colspan="2">S180</td></tr>
<tr><td>Tumor weight (g: mean±SD)</td><td>Inhibition ratio (%)</td><td>Tumor weight (g: mean±SD)</td><td>Inhibition ratio (%)</td></tr>
<tr><td>Control group</td><td></td><td>1.13±0.46</td><td>-</td><td>0.75±0.16</td><td>-</td></tr>
<tr><td>Taxol</td><td>40</td><td>0.43±0.15</td><td>62.2</td><td>0.38±0.12</td><td>48.9</td></tr>
<tr><td>Squamostatin E</td><td>15</td><td>0.75±0.16</td><td>34.2</td><td>0.55±0.10</td><td>27.2</td></tr>
<tr><td>4-deoxyannoreticuin</td><td>60</td><td>0.55±0.18</td><td>51.3</td><td>0.37±0.08</td><td>51.1</td></tr>
<tr><td>Desacetyluvaricin</td><td>15</td><td>0.43±0.12</td><td>61.5</td><td>0.42±0.10</td><td>43.9</td></tr>
<tr><td>Bullatacin</td><td>60</td><td>0.37±0.14</td><td>67.3</td><td>0.39±0.11</td><td>48.3</td></tr>
<tr><td></td><td>15</td><td>0.77±0.18</td><td>32.5</td><td>0.43±0.12</td><td>42.3</td></tr>
<tr><td></td><td>60</td><td>0.33±0.22</td><td>70.9</td><td>0.27±0.08</td><td>63.9</td></tr>
<tr><td></td><td>15</td><td>0.38±0.18</td><td>63.4</td><td>0.26±0.06</td><td>65.8</td></tr>
<tr><td></td><td>60</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td rowspan="2">Annona squamosa</td><td rowspan="2">Fruits</td><td rowspan="2">Compounds
(-)-entkaur-16-en-19-oic acid
(1)</td><td rowspan="2">Cytotoxic activity using in vitro cultures of Dalton’s lymphoma cells as well as HeLa cells. Cytotoxicity was detected by the Trypan blue exclusion test and induction</td><td colspan="6">(%) of cytotoxicity</td><td rowspan="2">(Joy and Remani 2008)</td></tr>
<tr><td colspan="6">There was an increase in the percentage cytotoxicity with increasing concentrations of the fraction containing the compounds. However a slight decrease in activity with increasing incubation time was noted, which implies that the compound has very high cytotoxicity even after 24 h of incubation. Even at a concentration of 1.65 lg/ml, the compounds exhibited more than 50% cytotoxicity after 24 h. The cytotoxic activity for</td></tr>
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<table>
<tr><td></td><td></td><td>16-α,17-dihydroxy-ent-kauran-19-oic acid (2)</td><td>of apoptosis was evaluated by [3-(4,5-Dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide] assay (MTS assay) and DNA ladder assay. The inhibitory concentration required for 50% cytotoxicity (IC_{50}) was also determined.</td><td colspan="5">different time intervals is compared. The highest activity was noted after 24 h, which implies that the efficacy of secondary metabolites as cytotoxic agents at a low dose and a short duration.</td><td></td></tr>
<tr><td>Annonaceae species</td><td>Used material</td><td>Substances/ Extracts</td><td>Methodology</td><td colspan="5">Inhibition</td><td>Ref.</td></tr>
<tr><td rowspan="11">Annona vepretorum</td><td rowspan="11">Leaves</td><td rowspan="11">Essential Oil
Spathulenol
α-Phellandrene
σ- Cymene
α- Pinene
5-Fluorouracil Positive control</td><td rowspan="11">The in vivo antitumour effect was evaluated in C57BL/6 mice inoculated with B16-F10 melanoma. Tumour cells (2 9 106 cells per 500 lL) were implanted subcutaneously into the left hind groin of mice. Animals were euthanized by cervical dislocation, and tumours were excised and weighed. Drug effects are expressed as the per cent inhibition of control.</td><td colspan="5">IC_{50} (µg/mL)</td><td rowspan="11">(Bomfim et al. 2016)</td></tr>
<tr><td>B16-F10</td><td>HepG2</td><td>K562</td><td>HL-60</td><td>PBMCs</td></tr>
<tr><td>9.90</td><td>10.60</td><td>8.43</td><td>6.14</td><td>22.82</td></tr>
<tr><td>7.81-12.55</td><td>8.55-13.26</td><td>5.48-12.97</td><td>4.15-9.12</td><td>19.18-27.15</td></tr>
<tr><td>11.67</td><td>11.19</td><td>3.79</td><td>11.38</td><td>15.59</td></tr>
<tr><td>9.76-13.96</td><td>9.58-13.07</td><td>1.48-9.70</td><td>8.46-15.31</td><td>13.12-18.53</td></tr>
<tr><td>15.44</td><td>17.30</td><td>>25</td><td>20.18</td><td>>25</td></tr>
<tr><td>6.54-36.42</td><td>13.89-21.55</td><td>>25</td><td>16.91-24.08</td><td>>25</td></tr>
<tr><td>>25</td><td>>25</td><td>14.00</td><td>>25</td><td>>25</td></tr>
<tr><td>11.46</td><td>13.05</td><td>10.56-18.55</td><td>14.96</td><td>14.00</td></tr>
<tr><td>5.46-24.04</td><td>9.79-17.38</td><td>0.15</td><td>12.25-18.26</td><td>9.83-23.31</td></tr>
<tr><td>0.68</td><td>0.04</td><td>0.01-1.86</td><td>0.29</td><td></td></tr>
<tr><td>0.21-1.45</td><td>0.01-1.22</td><td></td><td>0.21-0.38</td><td></td></tr>
<tr><td rowspan="2">Asimina triloba</td><td rowspan="2">Seeds</td><td rowspan="2">Compounds Asimitrin</td><td rowspan="2">In vitro cytotoxicity tests against human tumor cell</td><td colspan="5">Human cancer cell line ED50 (µg/mL)</td><td rowspan="2"></td></tr>
<tr><td>Cell lines</td><td colspan="2">Asimitrin</td><td>4-Hydroxytrilobin</td><td>Adriamicyn</td></tr>
</table>

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		4-Hydroxytrilobin **Adriamicyn Positive control**	lines s for A-549 (human lung carcinoma),26 MCF-7 (human breast carcinoma),27 HT-29 (human colon adenocarcinoma),28 A-498 (human kidney carcinoma),26 PC-3 (human prostate adenocarcinoma),29 and MIA PaCa-2 (human pancreatic carcinoma)	BST A-549 MCF-7 HT-29 A-498 PC-3 MIA PaCa-2	$2.07x10^{-2}$ 1.19 2.12 $1.19x10^{-4}$ $7.50x10^{-1}$ $1.72x10^{-6}$ $2.11x10^{-4}$	$7.00x10^{-2}$ 1.54 3.79 $1.54x10^{-6}$ $3.62x10^{-2}$ $2.01x10^{-4}$ $2.01x10^{-4}$	NT $6.22x10^{-4}$ $9.53x10^{-1}$ $2.87x10^{-2}$ $2.86x10^{-3}$ $5.77x10^{-2}$ $6.10x10^{-3}$	(Kim et al. 2005)
Annonaceae species	**Used material**	**Substances/ Extracts**	**Methodology**	**Inhibition**				**Ref.**
Anaxagorea dolichocarpa Sprague & Sandwith	The stem bark	Alkaloids Compounds Eupolauramine (1) Sampangine (2)	The cytotoxity was evaluated through the MTT reduction assay, which determines the number of living cells able to reduce the yellow dye 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) to formazan. The determination of the 50% inhibition concentration for cell growth (IC_{50}) of The	**IC_{50} (µg/mL)** The *in vitro* effects of **eupolauramine (1)** and **sampangine (2)** against the K562 cell line were determined in three experiments and in quadruplicate. Both compounds exhibited concentration-dependent inhibitory effect on the proliferation of K562 cells. The IC_{50} values were 18.97 (17.06–21.10) µg/mL and 10.95 (10.15–11.80) µg/mL respectively.				(Lúcio et al. 2011)

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			human leukemic strain K562.				
Duguetia furfuracea	Bark	Duguetine Duguetine β-*N*-oxide Dicentrinone *N*-methyltetrahydropalmatine *N*-methylglaucine Alkaloid Extract **Doxorrubicin Positive control**	The cytotoxic potential of alkaloids was evaluated by the MTT assay. Against three human tumor cell lines: SF-295 (glyoblastoma), HCT-8 (colon cancer) and MDA/MB-435 (melanoma).	**Percentage of inhibition (%)**			(da Silva et al. 2009)
				HCT-8 (%)	**SF-295 (%)**	**MDA/MB-435 (%)**	
				91.1±0.8 92.0±1.0 68.0±0.7 57.6±0.7 45.2±2.1 90.2±1.1 93.3±1.7	86.0±1.1 87.1±0.7 50.3±1.5 39.8±0.7 25.1±2.3 85.1±0.6 92.3±2.2	98.1±0.1 84.5±1.6 37.5±4.0 31.1±0.8 15.1±6.4 99.6±0.4 97.0±1.1	
Annonaceae species	**Used material**	**Substances/ Extracts**	**Methodology**	**Inhibition**			**Ref.**
Fissistigma cavaleriei	The dried roots	5-methoxy-2-methylisoindolin-1-yl, 4-methoxyphenyl **Doxorubicin Positive control**	Evaluation of the antiproliferative effect of compound 1 under study against cells: K562, S-180, A549.	**IC_{50} (mol/L)**			(Yang et al. 2012)
				K562	**S-180**	**A549**	
				$2.54\pm0.22\times10^{-5}$ $1.16\pm0.14\times10^{-6}$	$7.26\pm0.24\times10^{-5}$ $1.61\pm0.11\times10^{-7}$	$8.76\pm0.18\times10^{-5}$ $8.12\pm0.12\times10^{-7}$	

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<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="12">Guatteria autralis
Guatteria ferruginea
Guatteria latifolia
Guatteria sellowiana</td><td rowspan="12">The aerial parts</td><td rowspan="12">Essential Oils (EO)
Doxorubicin Positive control</td><td rowspan="12">The antiproliferative activity of the materials tested was evaluated using eight human tumor cell lines: U251 (central nervous system, CNS, glioma), MCF-7 (breast cancer) NCI-ADR/RES (ovarian tumor with multidrug resistance phenotype), 786-0 (kidney cancer), NCI-H460 (non-small-cell lung cancer), OVCAR-03 (ovarian carcinoma), HT-29 (colorectal cancer), and K562 (leukemia). Using the concentration-response curve for each cell line.</td><td colspan="6">Total growth inhibition (TGI) [µg/ml]</td><td rowspan="12">(Santos et al. 2017)</td></tr>
<tr><td>Cell lines</td><td>EO G. australis</td><td>EO G. ferruginea</td><td>EO G. latifolia</td><td>EO G. sellowiana</td><td>Doxorubicin</td></tr>
<tr><td>U251</td><td>40.4</td><td>36.3</td><td>36.6</td><td>89.1</td><td>2.7</td></tr>
<tr><td>MCF-7</td><td>37.8</td><td>37.6</td><td>47.2</td><td>95.5</td><td>0.88</td></tr>
<tr><td>NCI-ADR/RES</td><td>15.2</td><td>34.6</td><td>10.0</td><td>250</td><td>>25</td></tr>
<tr><td>786-0</td><td>45.6</td><td>50.9</td><td>63.9</td><td>107.8</td><td>3.1</td></tr>
<tr><td>NCI-H460</td><td>49.5</td><td>69.4</td><td>44.9</td><td>82.8</td><td>>25</td></tr>
<tr><td>OVCAR-3</td><td>3.2</td><td>1.8</td><td>1.1</td><td>4.1</td><td>11.7</td></tr>
<tr><td>HT-29</td><td>38.6</td><td>52.7</td><td>39.7</td><td>143.1</td><td>3.6</td></tr>
<tr><td>K562</td><td>86.2</td><td>18.6</td><td>15.6</td><td>1.1</td><td>0.031</td></tr>
<tr><td>HaCat</td><td>48.0</td><td>63.4</td><td>41.0</td><td>75.6</td><td>1.0</td></tr>
<tr><td colspan="4"></td><td colspan="6"></td></tr>
<tr><td>Annonaceae species</td><td>Used material</td><td>Substances/ Extracts</td><td>Methodology</td><td colspan="6">Inhibition</td><td>Ref.</td></tr>
<tr><td rowspan="3">Guatteria elliptica R. E. Fries</td><td rowspan="3">Leaves</td><td rowspan="3">Essential oil Spathulenol</td><td rowspan="3">The antitumor against the normal cell line derived from mouse fibroblasts (BALB/c 3T3, ATCC CCL163) was tested using the MTS method. The IC50</td><td colspan="6">IC₅₀ ± SE (µg/mL)</td><td rowspan="3">(Rajca Ferreira et al. 2018)</td></tr>
<tr><td colspan="3">PC-3</td><td colspan="3">MCF-7</td></tr>
<tr><td colspan="3">5.32 ± 0.35
2.25 ± 0.28</td><td colspan="3">7.01 ± 0.23
5,38 ± 0.20</td></tr>
</table>

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			values were used to determine the median lethal dose (LD50) for cell lines MCF-7 (human breast cancer) and PC-3 (human prostate cancer.				
Miliusa balansae	Leaves and branches	Ombuine Crysosplenol B Pachypodol Crysosplenol C **Eliptin Positive Control**	**Cell culture:** - KB (Human Epidermoide Carcinom); - Hep-G2 (Hepatoma G2); - RD (Rhabdosarcoma).	**IC_{50} (µg/mL)**			(Huong et al. 2005)
				KB	**Hep-G2**	**RD**	
				> 5 4.6 0.7 4.3 0.002	1.5 0.93 0.55 0.57 0.001	> 5 > 5 3.01 2.09 0.001	
Mitrephora glabra	Stem Bark	4-*epi*-kaurenoic acid (**1**) Mitrekaurenone (**2**) Methylmitrekaurenate (**3**) Oropheic acid (**4**) Methyllorophenate (**5**) Octadeca-9,11,13-triynoic acid (**6**)	The cytotoxicity measurements against the KB human oral epidermoid carcinoma: MCF-7 human breast carcinoma, NCI-H460 human large cell lung carcinoma, and SF-268 human astrocytoma.	**IC_{50} µM**			(Li et al. 2009)
				The ent-kaurane diterpenoids (1-3), all were inactive (IC_{50} values >10 µM); the diterpenoids of the ent-trachylobane class, reported previously from the same plant, were more potent in this regard. The polyacetylenes (4 and 6-8) gave IC_{50} values ranging from 10 to 40 µM. However, compound 5 was completely inactive, suggesting that the methyl ester diminishes cytotoxicity. The known alkaloid liriodenine (9) was the most cytotoxic against all four of the cell lines in which it was evaluated (IC_{50} value ~5 µM).			

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<table>
<tr><td></td><td></td><td>Oropheolide (7)
9,10-Dehydrooropheolide (8)</td><td></td><td></td><td></td></tr>
<tr><td>Annonaceae species</td><td>Used material</td><td>Substances/ Extracts</td><td>Methodology</td><td>Inhibition</td><td>Ref.</td></tr>
<tr><td>Mitrephora thorelii</td><td>The aerial parts</td><td>6a,16,18-Trihydroxyclerodа-3(4),13(14)-dien-15,16-olide (1)
16-Hydroxyclerodа-3(4),13(14)-dien-15,16-olide (2)
Cyclophosphamide Positive control</td><td>In vivo evaluation female mice (5–6 weeks old) of Kunming strain were purchased from Shanghai SLAC Laboratory Animal Co. (Shanghai, China). Murine hepatoma H22 is maintained by serial intraperitoneal passage in Kunming mice. H22 cells were subcutaneously implanted into Kunming mice at Diterpenes from M. thorelii 683 1 £ 106 cells/mouse.</td><td>IC₅₀ mM
Compounds 1 and 2 inhibited the proliferation of BEL-7402 cells in vitro with the IC₅₀ values 44.6 and 20.1 mM, respectively. In vivo anti-tumor effect of compound 2 was further evaluated in murine hepatoma H22 model. It was found that compound 2 significantly inhibited the growth of hepatoma H22 with the percentage inhibition of 30.7% (P, 0.05 vs control). The alkylation agent cyclophosphamide served as a positive control (63.8%, P, 0.01 vs control). The mice were well tolerated towards compound 2, and no significant loss of body weight was observed compared with control group (P. 0.05, data not shown).</td><td>(Meng et al. 2007)</td></tr>
<tr><td>Polyalthia evecta</td><td>Leaves</td><td></td><td>Determination the cytotoxicity of the samples in the cell model, neutral red (NR) uptake assay was used for identification of</td><td>% Cytotoxicity
HepG2: 74.6 ± 1.6
Vero: 54.2 ± 15.4
% Apoptotic cells in HepG2: 46.4 ± 2.6</td><td>(Machana et al. 2012)</td></tr>
</table>

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		Hexane fraction (F1) 500 (µg/mL) Chloroform fraction (F2) 500 (µg/mL) Ethylacetate fraction (F3) 500 (µg/mL) Dichloromethane fraction (F4) 500 (µg/mL) Ethanol fraction (F5) 500 (µg/mL)	vital cells. The cytotoxicity assays were performed with HepG2 and Vero cells.	24.3 ± 9.3 29.6 ± 8.8 24.0 ± 7.4 22.7 ± 8.8	2.2 ± 3.8 32.5 ± 8.1 25.5 ± 8.1 7.6 ± 8.3	9.8 ± 4.7 3.2 ± 1.6 2.9 ± 1.1 2.4 ± 1.9	
Annonaceae species	**Used material**	**Substances/ Extracts**	**Methodology**	**Inhibition**			**Ref.**
				% Cytotoxicity		**% Apoptotic cells in HepG2**	
				HepG2	**Vero**		
Polyalthia evecta	Leaves	Methanol fraction (F6) 500 (µg/mL)	Determination the cytotoxicity of the samples in the cell model, neutral red (NR) uptake assay was used for identification of vital cells. The cytotoxicity	9.9 ± 2.5 7.8 ± 2.5 98.9 ± 1.8	12.3 ± 1.3 10.8 ± 0.8 4.0 ± 2.9	4.6 ± 1.6 9.2 ± 2.1 n.d.	(Machana et al. 2012)

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		Water fraction (F7) 500 (µg/mL) Hexane: water (500:100) Hexane: water (500:250) Hexane: water (500:500) Hexane: methanol (500: 100) Hexane: methanol (500: 250) Hexane: methanol (500:500) *P. evecta* crude extract (EW-L) 140 (µg/mL)	assays were performed with HepG2 and Vero cells.	81.8 ± 10.6 100.0 ± 1.0 91.0 ± 6.2 100.0 ± 5.7 100.0 ± 8.9 60.0 ± 4.8 100.0 ± 4.1	43.9 ± 3.3 45.1 ± 4.1 26.9 ± 5.6 36.1 ± 8.0 39.9 ± 3.2 30.2 ± 9.3 37.2 ± 4.2	n.d. 72.7 ± 13.6 n.d. n.d. 54.9 ± 10.8 46.4 ± 2.6 92.8 ± 10.8	

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		P. evecta crude extract (EW-L) 500 (µg/mL)					
Annonaceae species	**Used material**	**Substances/ Extracts**	**Methodology**	**Inhibition**			**Ref.**
Polyalthia evecta	Leaves	Melphalan 76 (µg/mL)	Determination the cytotoxicity of the samples in the cell model, neutral red (NR) uptake assay was used for identification of vital cells. The cytotoxicity assays were performed with HepG2 and Vero cells.	**% Cytotoxicity**		**% Apoptotic cells in HepG2**	(Machana et al. 2012)
				HepG2	**Vero**		
				67.2 ± 3.1	70.3 ± 3.1	41.6 ± 2.1	
Polyalthia longifolia var. *pendula*	Stems	15 compounds isolated were evaluated for cytotoxicity against MCF-7 (human breast carcinoma) and A549 (non-small cell lung cancer) cells with cell viabilities	Cytotoxicity assessment was performed with Human breast carcinoma (MCF-7) cells and non-small cell lung cancer (A549) cells.	**IC_{50} µM**			(Lee et al. 2009)
				Compounds tested, only 16-oxo-cleroda3,13-dien-15-oic acid (8) was cytotoxic against both MCF-7 and A549 cell lines, with IC50 values of 3.7 (0.2 and 3.1 (0.3 µM, respectively. Under the same conditions, the IC50 values of the corresponding positive controls, paclitaxel, and doxorubicin, were 0.0020 (0.0001 and 0.837 (0.034 µM, respectively.			

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<table>
<tr><td></td><td></td><td>assessed using a MTT assay.</td><td></td><td colspan="3"></td><td></td></tr>
<tr><td rowspan="2">*Xylopia frutescens* Aubl.</td><td rowspan="2">Leaves</td><td rowspan="2">Essential oil
Doxorubicin Positive Control</td><td rowspan="2">The in vivo antitumor effect was evaluated using Sarcoma 180 ascites tumor cells. Ten-day-old Sarcoma 180 ascites tumor cells (2 106 cells per 500 ll) were implanted subcutaneously into the left hind groin of mice.</td><td colspan="3">**IC_{50} (µg/mL)**</td><td rowspan="2">(Ferraz et al. 2013)</td></tr>
<tr><td>**OVCAR-8**</td><td>**NCI-H358M**</td><td>**PC-3M**</td></tr>
<tr><td colspan="2"></td><td></td><td>33.9
24.9-46.3
1.2
0.9-1.6</td><td>24.6
14.9-40.7
0.9
0.6-1.3</td><td>40.0
31.3-51.2
1.6
1.1-2.4</td><td></td></tr>
<tr><td rowspan="2">*Xylopia laevigata*</td><td rowspan="2">Leaves</td><td rowspan="2">5% DMSO Essential oil
5-Fluororacil Positive control</td><td rowspan="2">The in vivo antitumor effect was evaluated using sarcoma 180 ascites tumor cells. Ten-day-old sarcoma 180 ascites tumor cells were implanted subcutaneously into the left hind groin of mice.</td><td colspan="3">**Antitumor activity sarcoma 180 ascites tumor cells**</td><td rowspan="2">(Quintans et al. 2013)</td></tr>
<tr><td>**Dose (mg/kg/day)**</td><td>**Tumor (g)**</td><td>**Inhibition (%)**</td></tr>
<tr><td colspan="2"></td><td></td><td>-
50
100
25</td><td>1.97±0.14
1.24±0.09
1.13±0.27
0.63±0.16</td><td>-
37.3
42.5
67.8</td><td></td></tr>
<tr><td>**Annonaceae species**</td><td>**Used materia l**</td><td>**Substances/ Extracts**</td><td>**Methodology**</td><td colspan="3">**Inhibition**</td><td>**Ref.**</td></tr>
<tr><td rowspan="2">*Xylopia sericea*</td><td rowspan="2">Dried roots</td><td rowspan="2">**Compounds** kauren-19-oic acid (KA);</td><td rowspan="2">The human cancer cell-lines used in this work were HL60 and K562 (leukemias), MDA-MB435</td><td colspan="3">Mitotic index, frequency of chromosomal aberrations and numeric changes in human lymphocytes in culture after kaurenoic acid (KA) and their hydrogenated derivative (KAH) treatments.</td><td rowspan="2">(Cavalcanti et al. 2010)</td></tr>
<tr><td>**Substance** | **Treatment**</td><td>**Mitotic index**</td><td>**Aberrant cells**</td></tr>
</table>

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		(−)-kauran-19-oic acid (KAH).	(melanoma) and SF295 (glioblastoma). The growth of tumour cells and PBLs was quantified by the ability of living cells to reduce the yellow dye 3-(4,5-dimethyl-2-thiozolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) to a purple formazan product.			%	Mean±S.E.M	%	Mean±S.E.M	
				MMS (Positive control)	$4x10^{-5}$ M	2.8	2.46±0.3	5.3	6.2±1.8	
					0.1%	2.1	3.86±0.3	8.3	0.46±0.4	
					2.5µg/mL	2.5	4.23±0.1	5.0	0.0	
				DMSO (Vehicle)	5.0 µg/mL	4.1	4.0±0.2	0.7	0.23±0.4	
					10.0 µg/mL	4.0	3.13±0.1	0.0	0.46±0.4	
				KA	30.0 µg/mL	3.5	2.23±0.4	0.7	5.1±0.3	
				KAH	60.0 µg/mL	4.3	1.36±0.3	0.0	5.3±1.2	
					2.5 µg/mL	4.1	4.13±0.2	0.0	0.0	
						4.3		0.0		
						4.0		0.0		
						3.8		0.0		
						4.2		0.0		
						3.3		0.7		
						3.0		0.0		
						3.1		0.7		
						2.3		5.3		
						1.8		4.7		
						2.6		5.3		
						1.3		4.3		
						1.7		5.0		
						1.1		6.2		
						4.4		0.0		
						4.0		0.0		
						4.0		0.0		

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<table>
<tr><th>Annonaceae species</th><th>Used material</th><th>Substances/ Extracts</th><th>Methodology</th><th colspan="6">Inhibition</th><th>Ref.</th></tr>
<tr><td rowspan="14">Xylopia sericea</td><td rowspan="14">Dried roots</td><td rowspan="14">(−)-kauran-19-oic acid (KAH).</td><td rowspan="14">The human cancer cell-lines used in this work were HL60 and K562 (leukemias), MDA-MB435 (melanoma) and SF295 (glioblastoma). The growth of tumour cells and PBLs was quantified by the ability of living cells to reduce the yellow dye 3-(4,5-dimethyl-2-thiozolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) to a purple formazan product.</td><td colspan="6">Mitotic index, frequency of chromosomal aberrations and numeric changes in human lymphocytes in culture after kaurenoic acid (KA) and their hydrogenated derivative (KAH) treatments.</td><td rowspan="14">(Cavalcanti et al. 2010)</td></tr>
<tr><td rowspan="2">Substance</td><td rowspan="2">Treatment</td><td colspan="2">Mitotic index</td><td colspan="2">Aberrant cells</td></tr>
<tr><td>%</td><td>Mean±S.E.M</td><td>%</td><td>Mean±S.E.M</td></tr>
<tr><td rowspan="12">KAH</td><td>5.0 µg/mL</td><td>4.2</td><td>4.0±0.2</td><td>0.0</td><td>0.23±0.4</td></tr>
<tr><td>10.0 µg/mL</td><td>4.1</td><td>3.5±0.4</td><td>0.0</td><td>0.0</td></tr>
<tr><td>30.0 µg/mL</td><td>3.7</td><td>3.43±0.2</td><td>0.0</td><td>0.23±0.4</td></tr>
<tr><td>60.0 µg/mL</td><td>3.5</td><td>3.43±0.3</td><td>0.0</td><td>0.43±0.4</td></tr>
<tr><td></td><td>3.9</td><td></td><td>0.0</td><td></td></tr>
<tr><td></td><td>3.1</td><td></td><td>0.0</td><td></td></tr>
<tr><td></td><td>3.2</td><td></td><td>0.0</td><td></td></tr>
<tr><td></td><td>3.7</td><td></td><td>0.7</td><td></td></tr>
<tr><td></td><td>3.4</td><td></td><td>0.0</td><td></td></tr>
<tr><td></td><td>3.0</td><td></td><td>0.0</td><td></td></tr>
<tr><td></td><td>3.1</td><td></td><td>0.7</td><td></td></tr>
<tr><td></td><td>3.6</td><td></td><td>0.7</td><td></td></tr>
</table>

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3.7. Trypanocidal

Chagas disease (CD) is categorized as a neglected tropical disease, affecting primarily tropical regions that often face insufficient financial support for research and the development of new treatments (Chatelain and Ioset 2011; Chatelain 2015; Armenio et al. 2020; Soerio 2022). The disease came to be known as Chagas disease in honor of Brazilian scientist Carlos Ribeiro Justina das Chagas, who in 1909 first discovered the entry of the monoflagellated protozoan into the bloodstream of human beings through the feces of triatomids. The protozoan was named *Trypanosoma cruzi*, honoring Oswaldo Cruz (Rester 2008; Song et al. 2009; Soerio 2022).

T. cruzi has a complex biological cycle where its intermediate host can be triatomids, insects, and vertebrate animals such as humans, armadillos, bats, paca, porcupine, monkeys, dogs, cats, etc. These hosts can then assume the role of definitive host, and complete the parasite's evolutionary cycle (Chatelain 2015; Oliveira de Souza et al. 2017; Santos et al. 2020).

T. cruzi has different names and morphologies that vary according to the stage they are in. The infecting morphology of the disease is trypomastigotes. They are transmitted through the excreta of the triatomids, and when this hematophagous insect bites to feed, it generates a gateway for the disease-causing agent by defecating on the skin after feeding. The acute phase of CD is recognized when trypomastigotes are found in the host's blood (Sales et al. 2017; Yeung et al. 2021; Santos et al. 2022; Soerio 2022). Amastigotes, characterized by their ability to multiply by binary fission, spherical shape, and absence of flagellum, are the morphological form found in the tissues of infected hosts. They are primarily the heart, colon, and esophagus, and signify the chronic form of CD (Armenio et al. 2020; Santos et al. 2020; Soerio 2022).

CD can also be transmitted through other routes such as blood transfusion or organ transplants, from mother to child during pregnancy or childbirth, contaminated drinking water, laboratory accidents, among others (Armenio et al. 2020; Santos et al. 2020; Soerio 2022). The symptoms of CD vary depending on the phase of the disease. The acute phase is brief and typically presents with few symptoms, while the chronic phase is prolonged and may lead to serious cardiac or digestive complications, potentially resulting in the patient's death (Chatelain and Ioset 2011; Chatelain 2015; Armenio et al. 2020; Soerio 2022).

One of the main causes of heart disease in endemic areas is CD, and it is estimated that more than six million people are infected with *T. cruzi*. These infections occur mainly in the poorest regions of 21 Latin American countries, and it is estimated that 1 million women are infected at their reproductive age (Soerio 2022). According to the WHO 2022,(World Health Organization 2021) and the Drug for Neglected Diseases initiative (DNDi), 2022, it is estimated that more than 75 million people are at risk of acquiring CD, and that 173,000 new cases occur annually with more than 75,000 deaths per year, yet less than 10% of infected people are diagnosed and less than 1% are treated. Compared to other parasitic diseases, CD kills more people each year, and even still treatment represents a great challenge (World Health Organization 2021; DNDi 2022; Soerio 2022).

The treatment of CD is based on only two drugs that have been in clinical use for about 50 years, nifurtimox and benznidazole. Both drugs have low efficacy in the treatment of the chronic phase, are contraindicated during pregnancy, and cause serious side effects. This all leads to a high rate of treatment abandonment by patients, in addition to the fact that these two drugs are ineffective in the treatment of nitroderivative-resistant strains of parasites (Pecoul et al. 2016; Vannier-Santos et al. 2019; Bay et al. 2019b; Armenio et al. 2020; Soerio 2022).

These deficiencies justify the search for new therapeutic options, and once again the search for new molecules from natural products (Armenio et al. 2020; Newman and Cragg 2020; Soerio 2022). In this scenario, the Annonaceae family stands out as a promising source of active substances against *T. cruzi*. Several researchers have been exploring species belonging to this family in search of new compounds with trypanocidal properties.

Some of the most studied species of Annonaceae for trypanocidal activity belong to the *Annona, Guatteria, Xylopia*, and *Duguetia* genera. Studies also highlight classes of secondary metabolites such

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as alkaloids and acetogenins as promising substances for trypanocidal activity. Table 7 describes some species of Annonaceae that have been studied for their trypanocidal activity against different parasitic forms of *T. cruzi* (epimastigote, trypomastigote, and amastigote).

Annona genus

Eight species from the *Annona* genus were examined to assess their potential as trypanocidal agents. *A. amazonica*, *A. cornifolia*, and *A. foetida* were subjected to isolation and investigation of their substances for activity against *T. cruzi*.

Pinheiro et al., 2009, isolated the diterpene Acanthoic acid from *A. amazonica* and assessed its efficacy against the epimastigote form of *T. cruzi*, obtaining an IC_{50} of 59μM. Similarly, Costa et al., 2011, investigated the trypanocidal potential of an alkaloid from *A. against* the epimastigote and trypomastigote stages of *T. cruzi*. The alkaloids liriodenine, O-methylmoschatoline, and annomontine exhibited low activity against the epismastigote form (with IC_{50} values of 645.2, 286.3, and 757.8μM, respectively). However, these alkaloids demonstrated significant activity against the trypomastigote form with IC_{50} values of 14.3, 11.82, and 16.07μM, respectively, and surpassing the positive control, crystal violet (with an IC_{50} of 31.37μM) (Pinheiro et al. 2009; Costa et al. 2011a).

Silva et al., 2009, investigated *A. cornifolia* and isolated acetogenins for evaluation against the amastigote and trypomastigote forms of *T. cruzi*. Three pure acetogenins—squamocin M, annofolin, and annotacin—along with three acetogenin mixtures—4-deoxylongimicin B + folianin, Glaucanisin + parviflorin, and glaucanisin + glaucanetin—displayed potent activity against the analyzed forms of *T. cruzi*, with IC_{50} values ranging from 0.1 to 1.7μM, outperforming the positive control, benznidazole, which had an IC_{50} of 3.8μM. Despite the promising nature of acetogenins, they also exhibited toxicity, with a selectivity index (SI) of 1, whereas the control demonstrated an SI of 625 (Lima et al. 2014).

Three other species of *Annona* had their essential oils (EO) investigated for trypanocidal activity. The species *A. coriaceae*, examined by Siqueira et al., 2011, demonstrated the lowest EO activity against the trypomastigote form, with an IC_{50} of 168.5 μg/ml, compared to the benznidazole control which showed an IC50 of 45.02 mg/ml. In a study conducted by Meira et al., 2015, the EOs of the *A. coriaceae* and *A. vepretorum* species were evaluated against the trypomastigote and epimastigote forms. The EO of *A. vepretorum* proved to be the most active against the trypomastigote form of *T. cruzi*, with an IC_{50} of 11.2 μg/ml, while that of *A. coriaceae* recorded 12.7 μg/ml. The EO of *A. coriaceae* stood out as the most effective against the epimastigote form, with an IC_{50} of 14.9 μg/ml, followed by *A. vepretorum*, with an IC_{50} of 16.2 μg/ml. Benznidazole was used as a control, exhibiting an IC_{50} of 2.7 μg/ml (Siqueira et al. 2011; Meira et al. 2015).

Finally, extracts from two species of *Annona* were analyzed for activity against the epimastigote and amastigote forms of *T. cruzi*. The hexanic and ethyl acetate extracts from the leaves of *A. muricata* were studied by Valencia et al., 2011, with only the ethyl acetate extract being active against the epimastigote form, with an IC_{50} of 40.2 μg /ml (Valencia et al. 2011).

Osorio et al., 2007, investigated the trypanocidal profile of the hexanic and ethyl acetate extracts from the leaves of *A. muricata*, as well as the hexanic, ethyl acetate, and methanolic extracts from the branches of this species. The ethyl acetate extract demonstrated the highest potential, with an IC_{50} of 25 μg/mL for the leaf extract and 63.2 μg/mL for the branch extract (Osorio et al. 2007).

The ethanolic and hexanic extracts from the stem bark, stem wood, root bark, and root wood of *A. crassiflora* were investigated by Mesquita et al., 2005, against the amastigote form of *T. cruzi*. All extracts showed activity, with the ethanolic extract of root bark and the ethanolic extract of root wood being the most promising with IC_{50} values of 5.9 and 9.9 μg/ml, respectively. The results suggest that the roots contain substances with greater potential activity against *T. cruzi* amastigotes (De Mesquita et al. 2005).

Guatteria genus

The genus *Guatteria* has also been thoroughly explored for trypanocidal agents. Extracts from two species, *G. tonduzii* and *G. elliptica*, were examined for their effects on the epimastigote form of *T. cruzi*. The ethanolic extract of *G. elliptica* leaves showed an IC_{50} of 345.1 μg/ml,(Alves et al. 2012) while

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the hexanic extracts from the leaves and branches of *G. tonduzii* were more active, with IC_{50} values of 34 and 25.2 µg/ml, respectively (Valencia et al. 2011).

The essential oils of three *Guatteria* species were also studied. Meira et al., 2017, evaluated the trypanocidal potential of essential oils from the leaves of *G. friesiana* and *G. pogonopus* against the epimastigote and trypomastigote forms of *T. cruzi*. Both essential oils showed activity (IC_{50} values of 11.9 and 28 µg/ml, respectively) (Meira et al. 2017). Another study by Bay et al., 2019a, assessed the essential oil from the aerial parts of *G. punctata* against the trypomastigote and amastigote forms. The essential oil exhibited remarkable efficacy, with an IC_{50} of 0.029 µg/mL, in contrast to benznidazole, which had an IC_{50} of 1 µg/mL as a positive control. The pronounced activity of the *G. punctata* essential oil is credited to its major constituents, (E)-caryophyllene and germacrene D. Published studies indicate that essential oils containing high concentrations of these compounds possess antiprotozoal properties, particularly against *T. cruzi* (Da Silva et al. 2013a; Bay et al. 2019a, b).

Mahiou et al., 2000b, conducted a study in which bisbenzylisoquinoline alkaloids were isolated from the stem bark of *G. boliviana*, and their trypanocidal activity was subsequently evaluated. Eight out of nine isolated alkaloids showed activity against the trypomastigote form of *T. cruzi*, with funiferine being the most promising alkaloid, with an IC_{50} of 47.66 µM (Mahiou et al. 2000b).

Xylopia genus

Research on the *Xylopia* species has explored the trypanocidal properties of both extracts and essential oils. Three different studies examined extracts of *X. aromatica* against the epimastigote and amastigote forms of *T. cruzi*. Osorio et al., 2007, analyzed the hexane, ethyl acetate, and methanol extracts from the leaves and branches of *X. aromatica* against the epimastigote form. The leaf extracts demonstrated superior activity compared to the branch extracts, with the methanolic leaf extract showing the highest efficacy, exhibiting an IC_{50} of 26.1 µg/mL (Osorio et al. 2007). The ethanolic extract of the fruits, investigated by Alves et al., 2012, showed slight activity against the epimastigote form, with an IC_{50} of 253.1 µg/ml (Alves et al. 2012). The hexanic extracts of root wood and root bark of *X. emarginata* were analyzed by Mesquista et al., 2005, against the amastigote form, and both extracts showed activity with IC_{50} values of 21.6 and 23.5 µg/ml, respectively (De Mesquita et al. 2005).

Silva et al., 2013, investigated the leaf essential oils from *X. frutescens* and *X. laevigata* for their activity against the epimastigote and trypomastigote forms. The study revealed that both essential oils were effective against both forms, with a greater potency observed against the trypomastigote form, displaying IC_{50} values of 11.9 and 12.7 µg/mL, respectively (Da Silva et al. 2013a).

Duguetia genus

Mesquita et al.,2005, conducted a study investigating the trypanocidal potential of hexanic and ethanolic extracts derived from stem, root bark, and root wood of *D. furfuracea*. The authors found that these extracts exhibit considerable activity against the amastigote form, with the hexanic extract from the root bark displaying the most potency and boasting an IC_{50} of 6.6 µg/ml (De Mesquita et al. 2005).

In a separate study by Silva et al., 2009, the alkaloid extract and five isolated alkaloids from the bark of the underground stem of *Duguetia furfuracea* were examined for their biological potential against the trypomastigote form of *T. cruzi*. The authors also investigated the potential antitumor and leishmanicidal activity of these molecules. The five isolated alkaloids, duguetine, duguetine B-N-oxide, and dicentrinone, in addition to the alkaloid extract were shown to be active against the trypomastigote forms of *T. cruzi*, with duguetine being the most active (IC_{50} = 11.82 µM) and stronger than the positive control Gentian violet (IC_{50} = 31 µM) (da Silva et al. 2009).

Alkaloids isolated from *D. lanceolata* leaves were examined against both the amastigote and trypomastigote forms of *T. cruzi*. Dantas et al., 2020, observed that only glaucine showed activity against both forms, demonstrating greater efficacy against the amastigote form with an IC_{50} of 28.6 µg/ml. The oxoglaucine + liriodenine alkaloid mixture exhibited activity against trypomastigotes, with an IC_{50} of 83 µg/ml. The other alkaloid mixtures did not demonstrate activity against *T. cruzi* (Dantas et al. 2020).

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Ethanol extracts from the leaves and branches of *D. lanceolata* were investigated by Alves et al., 2012, against the epimastigote form of *T. cruzi*. Both extracts showed activity, and these studies suggested promising activity of the substances present in *D. lanceolata* (Alves et al. 2012).

Bay et al., 2019, carried out a study to evaluate the chemical composition and trypanocidal and antimicrobial activity of four species of Annonaceae: *Bocageopsis multiflora* (MART.) REFR., *Fusaea longifolia* (AUBL.) SAFF., *Duguetia quitarensis* BENTH., and *Guatteria punctata* (AUBL.) RAHOWARD. The four essential oils showed trypanocidal activity, with IC_{50}s of 0.46, 0.26, 0.3 and 0.029 μg/ml respectively. The synergistic action of the substances present in the essential oil should still be considered (Bay et al. 2019a).

Others Annonaceae species

Two separate studies explored the trypanocidal potential of various Colombian plants, including *Desmos panamensis*, *Pseudomalmea boyacana*, *Rollinia exsucca*, and *Rollinia pittieri* from the Annonaceae family. Hexanic, ethyl acetate, and methanolic extracts derived from both the leaves and branches were evaluated for their activity against the epimastigote stage of *T. cruzi*. Among them, the branch extracts of *Desmos panamensis* and *Rollinia pittieri* demonstrated the highest activity, with IC_{50} ranging from 20 to 14 μg/ml (Osorio et al. 2007; Valencia et al. 2011).

Some studies isolated substances and tested them against the trypomastigote form of *T. cruzi*. Armenio et al., 2020, isolated sesquiterpenes from the stem of *Oxandra sessiflora*. All sesquiterpenes showed activity against trypomastigotes, with 4β,10α-dihydroxy-guai-6-eno and 4β,6β,7β,10α-tetrahydroxy-guaiane being the most promising. With IC_{50} values of 16.3 and 17.6 μM, respectively, they performed similarly to the positive control benznidazole (IC_{50} of 16.4 μM) (Armenio et al. 2020). Ngantchou et al., 2009, assessed the efficacy of polycarpol isolated from *Piptostigma preussi*, revealing significant activity with an IC_{50} of 5.114 μM (Ngantchou et al. 2009). Studies by Londero et al., 2018, and Santos et al., 2015, investigated acetylene fatty acid derivatives from flowers and seeds of *Porcelia macrocarpa*. The authors observed that these compounds have activity against trypomastigotes with IC_{50} ranging between 27.6 μM and 59.9 μM. Only isanolic acid did not show activity (Santos et al. 2015; Londero et al. 2018).

The hexanic extract from the stem bark of *Cardiopetalum calophyllum* was analyzed for its potential activity against the amastigote form, which showed activity with an IC_{50} of 60.4 μg/ml (De Mesquita et al. 2005). Extracts from the fruits, leaves, and root bark of *Greenwayodendron suaveolens* were studied for potential activity against *T. cruzi*, and the authors observed that the extracts showed trypanocidal activity. The dichloromethane fraction rich in alkaloids from the root bark was the most active, with an IC_{50} of 0.25 μg/ml (Muganza et al. 2016). Another study investigated the trypanocidal potential of extracts from the leaves, root bark, and stem of *Isolona hexaloba*, and it was observed that most of the extracts showed some trypanocidal activity, with the 80% crude ethanol extract from the leaves displaying an IC_{50} of 8.33 μg/ml (Musuyu Muganza et al. 2015).

These findings collectively support the potential of compounds derived from Annonaceae in combating *T. cruzi*.

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Table 7. Summary of trypanocidal activity of species of the Annonaceae.

Annonaceae species	Used material	Extracts/ Compounds	Parasite form	*T. cruzi*			Ref.
				IC_{50} µM	IC_{50} µg/ml	SI	
Annona amazonica	Stem bark	Acanthoic acid **Benznidazole** **(Positive control)**	Epimastigote	59 7		5.9	(Pinheiro et al. 2009)
Annona cornifolia	Seed	4-Desoxylongimicin B + Folianin A Squamocin M Annofolin Annotacin Glaucanisin + Parviflorin Glaucanisin + Glaucanetin **Benznidazole** **(Positive Control)**	Amastigote and Trypomastigote	0.12 0.1 0.11 1.7 0.13 1.7 3.8		1 1 1 1 1 1 625	(Lima et al. 2014)
Annona coriaceae	Leaves	Essential oil **Benznidazole** **(Positive control)**	Trypomastigotes		168.5 45.02		(Siqueira et al. 2011)
Annona crassiflora	Stem bark Stem wood Root Bark	Ethanolic extract Ethanolic extract Hexanic extract Ethanolic extract Hexanic extract	Amastigote		14.9 ±2.3 20.5 ±1.1 45.9 ±3.1 5.9 ±1.3 18.6 ±6.8		(De Mesquita et al. 2005)
Annonaceae species	**Used material**	**Extracts/ Compounds**	**Parasite form**	***T. cruzi***			**Ref.**
				IC_{50}	**IC_{50}**	**SI**	

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				µM	µg/ml		
Annona crassiflora	Root wood	Ethanolic extract **Benznidazole** **(Positive control)**	Amastigote		9.9 ±0.5 1.0 ±0.1		(De Mesquita et al. 2005)
Annona foetida	Stem	Liriodenine *O*-methylmoschatoline Annomontine **Benznidazole** **(Positive control)** **Crystal violet** **(Positive control)**	Epimastigote and Trypomastigote	645.2 / 14.53 286.3 / 11.82 757.8 / 16.07 7.6 / - - / 31.37			(Costa et al. 2011a)
***Annona muricata* L.**	Leaves Stems	Hexane extract Ethyl acetate extract Methanol extract Hexane extract Ethyl acetate extract Methanol extract **Benznidazole** **(Positive control)**	Epimastigote		100.0 25.0 40.2 ±11 >100.0 74.9 63.2 98.6 2.0		(Osorio et al. 2007) (Valencia et al. 2011) (Osorio et al. 2007)
Annona squamosa	Leaves	Essential oil **Benznidazole** **(Positive control)**	Trypomastigote Epimastigote		12.7 14.9 2.7		(Meira et al. 2015)
Annona vepretorum	Leaves	Essential oil **Benznidazole** **(Positive control)**	Trypomastigote Epimastigote		11.2 16.2 2.7		(Meira et al. 2015)
Annonaceae species	**Used material**	**Extracts/ Compounds**	**Parasite form**	***T. cruzi***			**Ref.**
				IC_{50}	**IC_{50}**	**SI**	

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				µM	µg/ml		
***Bocageopsis multiflora* (MART.) REFR.**	Aerial parts	Essential oil **Benznidazole** **(Positive control)**	Trypomastigote and Amastigote		0.46 ± 0.07 1	2.9 625	(Bay et al. 2019a)
Cardiopetalum calophyllum	Stem bark	Hexanic extract **Benznidazole** **(Positive control)**	Amastigote		60.4 ±0.1 1.0 ±0.1		(De Mesquita et al. 2005)
***Desmos panamensis* (B.L. Rob) Saff.**	Leaves Stems	Hexane extract Ethyl acetate extract Methanol extract Hexane extract Ethyl acetate extract Methanol extract **Benznidazole** **(Positive control)**	Epimastigote		61.4 10.7 ±3.5 85.6 26 ±13.6 98.6 11.9 ±5.2 98.6 17.7 ±6.4 >100.0 14.5 ±2.7 87.5 18.2 ±3.6 2.0	1.77 1.02 3.36 1.35 2.4 2.86	(Osorio et al. 2007) (Valencia et al. 2011)
Duguetia furfuracea	Stem Root bark Root wood	Hexanic extract Ethanolic extract Hexanic extract Ethanolic extract **Benznidazole** **(Positive control)**	Amastigote		50.0 ±1.6 30.4 ±1.3 6.6 ±0.6 25.6 ±1.5 1.0 ±0.1		(De Mesquita et al. 2005)
Annonaceae species	**Used material**	**Extracts/ Compounds**	**Parasite form**	***T. cruzi***			**Ref.**

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				IC_{50} µM	**IC_{50} µg/ml**	**SI**	
Duguetia furfuracea	Stem bark	Duguetine Duguetine β-*N*-oxide Dicentrinone *N*-methyltetrahydropalmatine *N*-methylglaucine Alkaloid extract **Gentian violet** **(Positive control)**	Trypomastigote	9.32 30.79 18.83 9072 4957 22.44 31			(da Silva et al. 2009)
Duguetia lanceolata	Branches Leaves	Ethanolic extract Ethanolic extract Glaucine Oxoglaucine + liriodenine Oxoglaucine + lanuginosine + dehydroglaucine Norglaucine + Isocorydine + N-methyllaurotetanine **Benznidazole** **(Positive control)**	Epimastigote Trypomastigote / Amastigote		250.2 157.9 46.0/28.6 83/not active >100/not active >100/not active 4.6/1.3 11.77 (epimastigote)	0.21 2.11	(Alves et al. 2012) (Dantas et al. 2020)
***Duguetia quitarensis* BENTH.**	Aerial parts	Essential oil **Benznidazole** **(Positive control)**	Trypomastigote and Amastigote		0.26 ± 0.06 1	2.1 625	(Bay et al. 2019a)
***Fusaea longifolia* (AUBL.) SAFF**	Aerial parts	Essential oil **Benznidazole** **(Positive control)**	Trypomastigote and Amastigote		0.3 ± 0.11 1	3.1 625	(Bay et al. 2019a)
Annonaceae species	**Used material**	**Extracts/ Compounds**	**Parasite form**	***T. cruzi***			**Ref.**

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				IC_{50} µM	IC_{50} µg/ml	SI	
***Greenwayodendron suaveolens* (Engl. & Diels) Verdc. (sin. *Polyalthia suaveolens* Enlg. & Diels)**	Fruits Leaves Root bark	Crude ethanol extract Dichloromethane fraction rich in alkaloids Alkaline aqueous rich in salts e hydrophilic substances Petroleum ether fraction rich in lipids and waxes 90% methanol fraction rich in steroids and terpenes Crude ethanol extract Dichloromethane fraction rich in alkaloids Alkaline aqueous rich in salts e hydrophilic substances Petroleum ether fraction rich in lipids and waxes 90% methanol fraction rich in steroids and terpenes Crude ethanol extract Dichloromethane fraction rich in alkaloids Alkaline aqueous rich in salts e hydrophilic substances Petroleum ether fraction rich in lipids and waxes	Not determined	34.27 14.79 >64.0 7.49 3.58 27.86 31.17 >64.0 8.33 8.06 7.38 0.25 >64.0 7.88 2.11		>1.87 2.34 - 4.07 >17.88 >2.30 >2.05 - 3.84 4.62 1.04 >256.0 - 2.90 13.92	(Muganza et al. 2016)

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		90% methanol fraction rich in steroids and terpenes					
Annonaceae species	**Used material**	**Extracts/ Compounds**	**Parasite form**	***T. cruzi***			**Ref.**
				IC_{50} µM	**IC_{50} µg/ml**	**SI**	
***Greenwayodendron suaveolens* (Engl. & Diels) Verdc. (sin. *Polyalthia suaveolens* Enlg. & Diels)**	Stem bark	Crude ethanol extract Dichloromethane fraction rich in alkaloids Alkaline aqueous rich in salts e hydrophilic substances Petroleum ether fraction rich in lipids and waxes 90% methanol fraction rich in steroids and terpenes		2.0 28.28 >64.0 2.0 2.05		17.94 >2.26 - 8.66 3.64	(Muganza et al. 2016)
Guatteria boliviana	Stem bark	Lanuginosine Pangkorimine Funiferine Tiliageine Antioquine Puertogaline A Puertogaline B Sepeerine Guatteboline	Trypomastigote	>818.8 203.32 47.69 287.66 77.87 242.26 76.13 131.32 100.05			(Mahiou et al. 2000b)
Guatteria elliptica	Leaves	Ethanolic extract **Benznidazole (Positive control)**	Epimastigote		345.1 11.77	0.30	(Alves et al. 2012)

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Guatteria friesiana	Leaves	Essential oil **Benznidazole** **(Positive control)**	Epimastigote / Trypomastigote		11.9 2.7		(Meira et al. 2017)
Guatteria pogonopus	Leaves	Essential oil **Benznidazole** **(Positive control)**	Epimastigote / Trypomastigote		28.0 2.7		(Meira et al. 2017)
Guatteria punctata **(AUBL.) RAHOWARD.**	Aerial parts	Essential oil **Benznidazole** **(Positive control)**	Trypomastigote and Amastigote		0.029 ± 0.014 1	32 625	(Bay et al. 2019a)
Annonaceae species	**Used material**	**Extracts/ Compounds**	**Parasite form**	***T. cruzi***			**Ref.**
				IC_{50} µM	**IC_{50} µg/ml**	**SI**	
Guatteria xf. tonduzii	Leaves Stem	Hexane extract Hexane extract	Epimastigote		34.0 ±17 25.2 ±5.2	0.77 1.09	(Valencia et al. 2011)
Isolona hexaloba	Leaves Root bark Stem bark	Aqueous Extract Dried crude extract 80% crude ethanol extract Dichloromethane fraction rich in alkaloids Alkaline aqueous fraction rich in salts and hydrophilic substances Petroleum ether fraction rich in lipids and waxes 90% methanol fraction rich in steroids and terpenes Aqueous Extract Dried crude extract	Not determined		30.05 33.71 8.33 32.79 >64.00 8.50 16.54 33.07 21.30 34.56 10.34 >64.00 21.71	>2.13 >1.90 3.92 >1.95 - 2.52 >3.87 >1.94 >3.00 >1.85 4.11 - 1.59	(Musuyu Muganza et al. 2015)

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		80% crude ethanol extract Dichloromethane fraction rich in alkaloids Alkaline aqueous fraction rich in salts and hydrophilic substances Petroleum ether fraction rich in lipids and waxes 90% methanol fraction rich in steroids and terpenes Aqueous Extract Dried crude extract 80% crude ethanol extract Dichloromethane fraction rich in alkaloids Alkaline aqueous fraction rich in salts and hydrophilic substances			20.71 - 15.06 34.27 17.55 >64.00	>3.09 - >4.25 >1.87 >3.65 -	
Annonaceae species	**Used material**	**Extracts/ Compounds**	**Parasite form**	***T. cruzi***			**Ref.**
				IC_{50} µM	**IC_{50} µg/ml**	**SI**	
Isolona hexaloba	Stem bark	Petroleum ether fraction rich in lipids and waxes 90% methanol fraction rich in steroids and terpenes **Benznidazole (Positive control)** **Suramine (Positive control)**	Not determined		>64.00 45.02 3.19 -	- >1.42	(Musuyu Muganza et al. 2015)

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Oxandra sessiflora	Stem	4α,10β-aromadendronediol 4β,10α -aromadendronediol 4α,10α-aromadendranediol 1β,6α-dihydroxy-4(15)-eudesmeno 4β,10α-dihydroxy-guai-6-eno 4β,6β,7β,10α-tetrahydroxy-guaiane **Benznidazole** **(Positive control)**	Trypomastigote	23.7 ±3.8 31.7 ±6.9 29.8 ±8.3 47.5 ±5.8 16.3 ±4.7 17.6 ±2.3 16.4 ±0.8			(Armenio et al. 2020)
Piptostigma preussi	-	Polycarpol	Trypomastigote	5.114			(Ngantchou et al. 2009)
Porcelia macrocarpa	Flours Seed	Stearolic acid Santalbic acid 8-hydroxyoctadec-9,11-diynoic Isanolic acid 12,14-octadecadiynoic acid/macrocarpic acid **Benznidazole** **(Positive control)**	Trypomastigote	27.6 59.9 57.3 Not active 38,77 16.4 534.2		>7.2 >3.3 >3.5 - 4.1 >12.2 0.9	(Londero et al. 2018) (Santos et al. 2015)
Annonaceae species	**Used material**	**Extracts/ Compounds**	**Parasite form**	***T. cruzi***			**Ref.**
				IC_{50} µM	**IC_{50} µg/ml**	**SI**	
***Pseudomalmea boyacana* (J.F. Macbr.) L. W. Chatrou.**	Leaves Stems	Hexane extract Ethyl acetate extract Methanol extract	Epimastigote		74.0 89.2 100.0	1.19	(Osorio et al. 2007)

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		Hexane extract Ethyl acetate extract Methanol extract **Benznidazole** **(Positive control)**			15.2 ±3.6 50.4 100.0 87.5 12.8 ±1.3 2.0		(Valencia et al. 2011) (Osorio et al. 2007) (Valencia et al. 2011)
***Rollinia exsucca* (DC. Ex Dunal) A. DC.**	Leaves Stems	Hexane extract Ethyl acetate extract Methanol extract Hexane extract Ethyl acetate extract Methanol extract **Benznidazole** **(Positive control)**	Epimastigote		74.4 98.6 61.4 26.1 18.1 ±7.2 58.3 41.7 ±12 >100.0 2.0		(Osorio et al. 2007) (Valencia et al. 2011) (Osorio et al. 2007) (Valencia et al. 2011) (Osorio et al. 2007)
***Rollinia pittieri* Saff**	Leaves Stems	Hexane extract Ethyl acetate extract Methanol extract Hexane extract Ethyl acetate extract Methanol extract **Benznidazole** **(Positive control)**	Epimastigote		16.5 46.4 ±3.1 20.8 39.8 16.4 20.8 >100.0 2.0		(Osorio et al. 2007) (Valencia et al. 2011) (Osorio et al. 2007)
Annonaceae species	**Used material**	**Extracts/ Compounds**	**Parasite form**	***T. cruzi***			**Ref.**
				IC_{50} µM	**IC_{50} µg/ml**	**SI**	

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***Xylopia aromatica* (Lam.) Mart.**	Leaves Stems	Hexane extract Ethyl acetate extract Methanol extract Hexane extract Ethyl acetate extract Methanol extract **Benznidazole (Positive control)**	Epimastigote		99.2 66.0 26.1 >100.0 58.3 >100.0 2.0		(Osorio et al. 2007)
Xylopia aromatica	Fruits Root wood Root bark	Ethanolic extract **Benznidazole (Positive control)** **Hexanic extract** **Hexanic extract** **Benznidazole (Positive control)**	Epimastigote Amastigote		253.1 11.77 21.6 ±6.0 23.5 ±4.7 1.0 ±0.1	0.39	(Alves et al. 2012) (De Mesquita et al. 2005)
Xylopia emarginata	Leaves	Hexanic extract **Benznidazole (Positive control)**	Amastigote		57.6 ±2.4 1.0 ±0.1		(De Mesquita et al. 2005)
Xylopia frutescens	Leaves	Essential oil **Benznidazole (Positive control)**	Epimastigote / Trypomastigote		20.2 / 11.9 2.8 / 2.8		(Da Silva et al. 2013a)
Xylopia laevigata	Leaves	Essential oil **Benznidazole (Positive control)**	Epimastigote / Trypomastigote		22.2 / 12.7 2.8 / 2.8		(Da Silva et al. 2013a)

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3.8. Antioxidant

Antioxidant compounds have the ability to interfere with oxidation chain reactions that result in the production of toxic compounds, both in the initiation or propagation of these reactions, slowing, neutralizing or preventing actions of oxidizable substrates, and through the inhibition of lipid peroxidation and lipoxygenase (Huber and Rodriguez-Amaya 2008; Silva et al. 2009; Silva 2015).

Antioxidant compounds exert their effects through various mechanisms, including free radical inhibition and metal ion complexation (Pietta 2000; Duarte-Almeida et al. 2006). Free radicals can be acquired exogenously and are also produced endogenously. When in excess the radicals can cause oxidative stress which culminate in the appearance of cardiovascular and neurological diseases, some cancers, cataracts, diabetes, rheumatism, aging of the body, etc (Núñez-Sellés 2005; Prado 2009; Sousa et al. 2011; Silva et al. 2018). Thus, antioxidants bring great benefits to human health by protecting the body from damage caused by free radicals (Oliveira 2015).

Antioxidants can be synthetic or natural. The synthetic ones have greater stability and good efficiency when compared to the natural ones, but the natural ones have less toxicity. In addition to having a greater effect on the oxidation processes, natural antioxidants are generally more sought after than the synthetic ones (Duarte-Almeida et al. 2006; Prado 2009; Silva 2015). For the same reasons, researchers have analyzed the antioxidant potential of Annonaceae species.

Xylopia genus

Several studies have explored the antioxidant properties of Xylopia species, yielding encouraging results. In one such study, Karioti et al., 2004, analyzed the essential oils from different parts of *X. aethiopica* to evaluate their antioxidant activity and determine their main constituents. The findings revealed that the essential oil derived from the leaves displayed the strongest ability to neutralize free radicals (Karioti et al. 2004).

Similarly, Konan et al., 2009, examined the antioxidant activity and chemical composition of essential oils extracted from dried fruits of *X. aethiopica* leaves. Surprisingly, they discovered that the nut oil displayed slightly higher antioxidant activity compared to the essential oil extracted from the leaves (Konan et al. 2009). This contradicted the findings of Karioti et al., 2004, highlighting the variability in antioxidant activity among different parts of the plant.

In another study by Silva et al., 2009, the antioxidant potential of *X. langsdorffiana* was investigated. The authors isolated seven compounds from the leaves and stem bark of the plant, including alkaloids, diterpenes, phaephorbide, and flavonoids. Among these compounds, discretamine, an alkaloid, exhibited exceptional antioxidant activity, with a percentage of activity greater than 90% in the 1,2-diphenyl-2-picryl-hydrazyl (DPPH) free radical scavenging assay (Da Silva et al. 2009).

These studies collectively demonstrate the significant antioxidant potential of Xylopia species, highlighting the importance of further research into their therapeutic applications in combating oxidative stress-related disorders.

Annona genus

Silva et al., 2019, explored the antioxidant potential of *A. nutans*, a species within the Annonaceae family. They conducted comprehensive analyses, including the evaluation of total phenolic content, flavonoids, and tannins, along with quantification of main metabolites using LC-MS. The methanolic fraction of the extract exhibited significant anti-inflammatory effects, reducing paw edema, and inhibiting acute inflammation even six hours after carrageenan injection. Intraperitoneal treatment with the methanolic extract also showed efficacy in reducing inflammation and elicited central antinociceptive effects. Furthermore, the hydromethanolic fraction of *A. nutans* extract demonstrated dose-dependent antioxidant activity comparable to commercial antioxidant BHT. Metabolite analysis identified several compounds contributing to its antioxidant properties, including quercetin derivatives and chlorogenic acid (Silva et al. 2019).

In another study conducted by Leite et al., 2021, the antioxidant potential of extracts from the pulp and seeds of *A. squamosa* L. was evaluated. Chemical profiling revealed the presence of

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anthocyanidins, flavones, flavonols, and alkaloids. Phenol analysis indicated higher levels in the seed extract, while vitamin C content was higher in the pulp extract. Antioxidant activity was assessed using various methods, with the ABTS assay showing the most potent activity for both seed and pulp extracts, with IC_{50} values of 0.14 ± 0.02 and 0.38 ± 0.02 µg/mL, respectively. Additionally, the pulp extract exhibited superior acetylcholinesterase inhibitory activity compared to the seed extract, suggesting potential cognitive benefits. *A. squamosa* emerges as a promising source of antioxidants, further emphasizing its value as a nutritious food source (Leite et al. 2021).

Together, these studies underscore the significant antioxidant potential of *Annona* species, highlighting their possible therapeutic applications in combating oxidative stress-related conditions and promoting overall health and well-being.

Others Annonaceae species

Several studies have investigated the antioxidant activity of various species within the Annonaceae family, shedding light on their potential therapeutic applications. Jain et al., 2014, investigated the chemical profile of the butanolic fraction derived from the hydroalcoholic extract of *P. longifolia* stem bark. They discovered that 3-O-methyl ellagic acid exhibited antioxidant activity with an IC_{50} of 24.28 µg/mL, while the butanolic fraction had an IC50 of 266.59 µg/mL in the DPPH assay (Jain et al. 2014).

Sacchetti et al., 2004, evaluated eleven essential oils, including *Cananga odorata*, to assess their functional ingredients and potential as synthetic preservatives. Among these oils, Cananga odorata oil showed remarkable antioxidant activity, with an activity percentage greater than 75% in the DPPH test (Sacchetti et al. 2005).

Xavier et al., 2016, characterized the chemical composition of the essential oil from the leaves of *Cardiopetalum calophyllum* and evaluated its antioxidant potential. The study demonstrated significant antioxidant activity, with an IC_{50} of 9.66 µg/ml in the DPPH method, validating the antioxidant potential of *C. calophyllum* (Xavier et al. 2016).

Santos et al., 2018, analyzed the methanolic extract of *Duguetia furfuracea* and its fractions for antioxidant and anti-inflammatory potential. The methanolic extract exhibited significant antioxidant activity with an IC_{50} of 22.46 µg/mL in the DPPH assay. Additionally, it showed inhibitory effects on carrageenan-induced edema and leukocyte migration, suggesting its potential in treating inflammatory conditions (do Santos et al. 2018).

A recent study by Nghi et al., 2022, highlighted the antioxidant activity of Rumdul fruit (*Sphaerocoryne affinis*) extract. The aqueous extract showed strong antioxidant capacity with an IC_{50} value of 85.62 ± 1.05 µg/mL in the DPPH assay. The extract also exhibited potential in improving locomotor deficiencies and preventing degeneration of dopaminergic neurons, indicating its promising role in treating Parkinson's Disease (Nghi et al. 2022).

Overall, these studies underscore the significant antioxidant potential of Annonaceae species, suggesting their value as sources of natural antioxidants with potential therapeutic benefits. Table 8 provides a summary of the results discussed in this section.

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Table 8. Antioxidant activity of substances and extracts from species of the Annonaceae.

Annonaceae species	Used material	Substances/ Extracts	IC_{50}	DPPH				Ref.
				%Interaction	%Interaction 20 min	%Interaction 60 min	%Free radical scavenging	
Annona nutans	Leaves	Hydromthanolic fraction	4.89 µg/mL	-	-	-	50.0	(Silva et al. 2019)
Annona squamosa	Seed Pulp	Extract Extract **Vitamin C (positive control)**	0.36 µg/mL 0.83 µg/mL 0.011 µg/mL	-	-	-	-	(Leite et al. 2021)
Cananga Odorata	Essential oil	Essential oil		75.50	-	-	63.80	(Sacchetti et al. 2005)
Cardiopetalum calophyllum	Leaf	Essential oil Quercetin (standard compound)	9.66 µg/mL 3.13 µg/mL	- -	- -	- -	- -	(Xavier et al. 2016)
Duguetia furfuracea	Leaves	Methanolic extract Chloroform fraction Ethyl acetate fraction	22.46 µg/mL 176.88 µg/mL 60.56 µg/mL 28.21 µg/mL	50.0 50.0 50.0 50.0	-	-	-	(do Santos et al. 2018)

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		Hydromethanol fraction						
Polyalthia longifolia	Stem bark	3-*O*-methyl Ellagic Acid	2.5 µg/mL 5 µg/mL 10 µg/mL 20 µg/mL 40 µg/mL 24.28 µg/ml	-	-	-	10.36 28.17 34.83 45.80 69.81 50.00	(Jain et al. 2014)
Annonaceae species	**Used material**	**Substances/ Extracts**	**IC_{50}**	**DPPH**				**Ref.**
				%Interaction	**%Interaction 20 min**	**%Interaction 60 min**	**%Free radical scavenging**	
Sphaerocoryne affinis	Fruit	Rumdul fruit water extract	85.62 µg/mL	-	-	-		(Nghi et al. 2022)
Xylopia aethiopica	Essential oil of leaf, stem bark, roots, and fruits	Leaf oil Leaf oil Root bark oil Stem bark oil Fresh fruit oil Dried fruit oil Dried fruit oil	0.048 g/mL 4.9 mg/mL 0.033 g/mL 0.037 g/mL 0.045 g/mL 0.042 g/mL 4.1 mg/mL	- 50.0 - - - - 50.0	43.8 - 36.5 32.4 85.6 21.2 -	75.9 - 43.2 40.3 85.8 54.8 -	86.8 - 68.4 73.9 66.5 57.2 -	(Karioti et al. 2004) (Konan et al. 2009) (Karioti et al. 2004) (Karioti et al. 2004) (Karioti et al. 2004) (Karioti et al. 2004) (Karioti et al. 2004)

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								(Konan et al. 2009)
Xylopia langsdorffiana	Leaf and stem bark	Discretamine	Concentrations Tested 240 µg/mL 120 µg/mL 60 µg/mL 30 µg/mL	94.25 93.93 91.51 90.05	-	-	-	(Da Silva et al. 2009)

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3.9. Antimalarials

Malaria is an endemic disease in tropical and subtropical areas, occurring mainly in Southeast Asia, the Amazon and Africa (Nascimento et al. 2019; Hammami et al. 2020). Despite numerous efforts to control and eliminate the disease, it is estimated that there were 228 million cases in 2018, with a global mortality rate of up to 30% in severe cases in 2019. Therefore, malaria is considered a public health problem (Talapko et al. 2019; World Health Organization (WHO) 2019; Figueroa-Miranda et al. 2020; Hammami et al. 2020).

The etiological agent of malaria is a Plasmodium protozoan that infects humans (White et al. 2014; Walker et al. 2017; Talapko et al. 2019). This protozoan is an intracellular parasite that can infect red blood cells and some tissues, depending on the species. There are five species that can infect humans, *P. falciparum, P. vivax, P. ovale, P. malarie* e *P. knowlesi* (Vuk et al. 2008; Talapko et al. 2019; World Health Organization (WHO) 2019; Hammami et al. 2020).

The vector, mosquitoes, and parasite have developed resistance to some drugs used for their control and eradication. On top of administration problems, the resistance has made it increasingly difficult to eradicate this disease globally (Asase et al. 2010; Talapko et al. 2019). Thus, research for new drugs and insecticides is still important, as well as studies with the vaccine.

Plants are always an excellent source of new drugs, so the Annonaceae, due to its chemical diversity, can be interesting in the study of new antimalarial drugs. In this sense, several researchers have already analyzed the antimalarial potential of several species of Annonaceae, and the results are described below.

Asase et al., 2010, studied 30 species of plants, belonging to 28 genera and 20 families, used to treat malaria by indigenous communities in the western district of Dangme, Ghana. Five species were described for the first time in the treatment of malaria, including the Annonaceae species *Greenwayodendron sp*. The authors reported that the leaves were boiled, and one cup of this tea was administered three times a day for adults (half a cup for children) until complete recovery (Asase et al. 2010).

Polyathia genus

The dichloromethane extract and two dimeric aporphinoid alkaloids, named bidebiline C and D, obtained from roots of *P. debilis* showed activity against *P. falciparum* (Somdej Kanokmedhakul et al. 2003). The indolosesquiterpene alkaloids, N-acetyl-8α-polyveolinone and N-acetyl-polyveoline, isolated from the stem bark of *P. oliveri*, exhibited moderate antiplasmodial effects against the blood stages of the chloroquine-sensitive *P. falciparum* NF54 strain. (Gbedema et al. 2015).

Fractionation of the ethanolic extract from the stem bark of *P. longifolia* led to the isolation of several compounds through bioassay-guided techniques. This process led to the identification of three clerodane diterpenes (16-hydroxycleroda-3,13-dien-16,15-olide, 16-oxocleroda-3,13E-dien-15-oic acid, and 3,16-dihydroxycleroda-4(18),13(14)Z-dien-15,16-olide), a steroid (β-stigmasterol), and two alkaloids (darienine and stepholidine) with significant antiplasmodial activity. The clerodane diterpenes, in particular, exhibited strong activity against multi-resistant *P. falciparum* K1 strains, with IC_{50} values between 3 and 6 μg/mL. (Gbedema et al. 2015).

Others Annonaceae species

Methanolic extract of the leaves of *Annikia kummeriae* showed strong activity against the multi-resistant strain of *P. falciparum* (K1), with an IC_{50} value of 0.12 μg/mL. Through a biomonitored study four pure alkaloids, lysicamine, trivalvone, palmatine and jatorrizine, were isolated and identified for having strong to moderate activity against *P. falciparum* (IC_{50} ranging from 0.08-2.4 μg/mL) (Malebo et al. 2013a).

Essential oils from the stem bark and leaves of *Cleistopholis patens* and *Uvariastrum pierreanum*, were found to be moderately active against *P. falciparum*. These results indicate that essential oils may offer a promising alternative for the development of new antimalarials (Boyom et al. 2011).

Four essential oils extracted from steam bark of *Xylopia phloiodora*, *Xylopia aethiopica*, *Pachypodanthium confine* and *Hexalobus crispiflorus* were evaluated regarding their anti-plasmodial

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activity against the W2 strain of *P. falciparum*, all oils were active, the most effective was the oil of *H. crispiflorus*, with an IC_{50} of 2 μg/mL (Boyom et al. 2011).

The phytochemical analysis of methanol extracts from the leaves and twigs of *Mitrephora tomentosa* led to the isolation of six polyacetylenic ester-neolignan derivatives, designated mitrephentosins A-F. Among these, mitrephentosins C, E, and F exhibited moderate antimalarial activity, with IC50 values ranging from 13.3 to 24.6 μM, against the *P. falciparum* strains TM4/8.2 and K1CB1 (Boyom et al. 2011).

Significant antiplasmodial activity was noted in the ethyl acetate extracts from the stems of *Rollinia pittieri* and *Pseudomalmea boyacana*. From *R. pittieri*, researchers isolated one oxoaporphinic alkaloid (O-methylmoschatolin) and one 7,7-dimethylaporphinic alkaloid (melosmin). Meanwhile, *P. boyacana* yielded three oxoaporphinic alkaloids (aislamient, liriodenine, and atherospermidin). All isolated alkaloids demonstrated activity, with liriodenine showing the strongest effect against both chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum* (IC_{50} = 8.0-10.0 μg/mL)(Boyom et al. 2011).

The results presented so far reinforce the antiplasmodial activity of substances and extracts of the Annonaceae species, and a table of those tested are elaborated in Table 9.

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Table 9. Antiplasmodial activity of substances and extracts from species of the Annonaceae.

Annonaceae species	Used material	Substances/Extracts	*P. falciparum* (strain) (IC_{50})				Ifβ-h (%) 2mg/ml	Ref.
			F32 (µg/ml)	W2 (µg/ml)	K1 (µg/ml)	NF54 (µM)		
Annickia kummeriae	Leaves	Extract metanolic Lysicamine Trivalvone Palmatine Jatrorrhizine	-	-	0.12 2.4 1.6 0.08 0.24	-	-	(Malebo et al. 2013a)
Cleistopholis patens	Steam bark Leaves	Essential oil		9.19 15.19				(Boyom et al. 2011)
Hexalobus crispiflorus	Stem bark	Essential oil		2.0				(Fekam Boyom et al. 2003)
Mitrephora tomentosa	Leaves and twigs	(-)-(7R,8S)-mitrephentosin C (-)-(7R,8S)-mitrephentosin F **Cyclogunil (Positive control)**			13.3 µM 18.7 µM 5.87 µM			(Wongsomboon et al. 2021)
Pachypodanthium confine	Steam bark	Essential oil		16.6				(Fekam Boyom et al. 2003)
Polyalthia debilis	Roots	dichloromethane extract Bidebiline C			1.35 5.4			(Kanokmedhakul et al. 2003)

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		Bidebiline D			4.1			
Polyalthia longifólia	Steam bark	16-hydroxycleroda-3,13-dien-16,15-olide Acid 16-oxocleroda-3,13E-dien-15-óico			5.33 3.05			(Gbedema et al. 2015)
Annonaceae species	**Used material**	**Substances/Extracts**	***P. falciparum* (strain) (IC_{50})**				**Ifβ-h (%) 2mg/ml**	**Ref.**
			F32 (µg/ml)	**W2 (µg/ml)**	**K1 (µg/ml)**	**NF54 (µM)**		
Polyalthia longifolia	Steam bark	3,16-dihydroxycleroda-4 (18),13 (14) Z-dien-15,16-olida β-Stigmasterol Darienine L-Stepholidine			6.15 63.3 22.05 104.33			(Gbedema et al. 2015)
Polyalthia oliveri	Steam bark	N-acetil-8α-polivolinona N-acetil-polveolina **Chloroquine (Positive Control)**				7.6 29.1 0.006		(Kouam et al. 2014)
Pseudomalmea boyacana		Liriodenina Atherospermidina Isomoschatolina **Chloroquine (Positive control)**	8 – 10 0.01	8.0 0.90			11.4 5.12 2.40 97.0	(Osorio D et al. 2006)
Rollinia pittieri		O-metilmoschatolina Melosmina					98.3 96.4	(Osorio D et al. 2006)

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		Chloroquine (Positive control					97.0	
Uvariastrum pierreanum	Steam bark Leaves	Essential oil		6.08 13.96				(Boyom et al. 2011)
Xylopia phloiodara ***Xylopia aethiopica***	Steam bark	Essential oil		17.9 17.8				(Fekam Boyom et al. 2003)

K1 - multidrug resistant strain, F32 - chloroquine sensitive strain, W2 - chloroquine resistant strain, Ifβ-h - inhibition of β-hematin formation.

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3.10. Gastroprotective

Gastric ulcer (GU) is a very common disease of the digestive system that has a high morbidity and thus is a major public health concern (2016 2017; Zhou et al. 2020). The cause of a GU can be related to several factors, such as for example, the indiscriminate use of non-steroidal anti-inflammatory drugs. This disrupts the protective mechanisms of the gastric mucosa, particularly those associated with prostaglandin levels and antioxidant activity. As a result, the defensive barrier of the gastric mucosa is compromised, leading to the development of gastric ulcers (Franke et al. 2005; Woolf and Rose 2020; Zhou et al. 2020). Oxidative stress induced by ethanol, which generates highly cytotoxic free radicals, has also been linked to GU developement (X et al. 2018; Aziz et al. 2019; Simões et al. 2019; Zhou et al. 2020). Other factors that cause GU are stress and infection by *Helicobacter pylori* bacteria (Tulassay and Herszényi 2010; Montenegro et al. 2014).

Although there are many medications on the market for the treatment of GU, such as antacids, proton pump inhibitors, anticholinergics, cytoprotective agents, etc., the majority of which induce side effects such as hypersensitivity, arrhythmia , impotence, gynecomastia, hematopoietic changes, and hyper gastrinemia, with chronic use (Sheen and Triadafilopoulos 2011; Montenegro et al. 2014; 2016 2017).

Thus, it is necessary to search for new drugs that are less toxic and more effective in the treatment of GU. In this context, plants are an excellent source of new drugs and the Annonaceae stands out for having numerous pharmacological activities, as previously mentioned. The Annonaceae genus which were evaluated include *Annona, Goniothalamus, Polyalthia* and *Xylopia* (Table 10).

Annona genus

In a study conducted by Moghadamtousi et al. (2014) the gastroprotective effects of the ethyl acetate extract from *Annona muricata* leaves (EEAM) were analyzed using the ethanol-induced gastric lesion model in rats. The results indicated a significant reduction in the ulcer injury rate among rats pretreated with oral administration of EEAM, which was comparable to the effect observed with omeprazole in the control group. The authors further concluded that the potential and promising gastroprotective effect of EEAM could be attributed to its suppressive impact on oxidative damage and its conservative effects on gastric wall mucus (Moghadamtousi et al. 2014).

Goniothalamus sp.

The gastroprotective activity of the racemic mixture of goniothalamine (GNT), a lactone naturally occurring in enantiomeric form in plants of the genus *Goniothalamus* (Annonaceae), was evaluated using an ethanol-induced gastric lesion model. The study demonstrated a strong gastroprotective effect of GNT at concentrations of 30 and 60 mg/kg, with an ED_{50} of 18 mg/kg. This activity was found to rely on the generation of sulfhydryl and prostaglandin compounds but was independent of nitric oxide (NO), gastric secretion, and mucus production. The authors proposed that GNT functions as a mild irritant, promoting the production of sulfhydryl and prostaglandin compounds, a process known as adaptive cytoprotection. This suggested mechanism was reinforced by the observation that Michael acceptors, including GNT, are effective inducers of antioxidant responses through mild oxidative stress. The gastroprotective effect of GNT was diminished when pretreatment with N-ethylmaleimide and a NSAID was used, underscoring the critical role of sulfhydryl and prostaglandin compounds in GNT's activity (Vendramini-Costa et al. 2014).

Polyalthia genus

In this sense, some authors have carried out research on some species of the *Polyalthia* genus looking for new gastroprotective agents. Olate et al. (2012), evaluated the gastroprotective potential of 11 amides derived from the diterpene (4S, 9R, 10R) methyl 18-carboxy-labda-8,13 (E) -dien-15-oate (PMD) and its 8 (9) -en isomer [PMD 8 (9) -en], isolated in the species *Polyalthia macropoda*. The gastric lesion model in mice was induced using ethanol/HCl. When administered as a single oral dose of 0.1 mg/kg, compounds 1, 10, and 11 exhibited significant gastroprotective effects, comparable to the reference lansoprazole at 1 mg/kg, with reductions in gastric lesions of 76.7%, 67.7%, and 77.2%, respectively. Compounds 10 and 11 are particularly promising as they demonstrated strong gastroprotective effects without any cytotoxicity (Olate et al. 2012).

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Xylopia genus

Montenegro et al. (2014) investigated the gastroprotective properties of *X. langsdorffiana* A. St.-Hil. & Tul. by analyzing the ethanolic extract (EtOHE) and hexane phase (HexPh) derived from its leaves. The study aimed to assess the gastroprotective efficacy of these extracts and determine their underlying mechanisms of action. They found that both the XL-EtOHE extract and the XL-HexPh phase significantly reduced ulcer formation compared to the negative controls, with the most effective doses being 500 mg/kg for the EtOHE and 250 mg/kg for the HexPh. The authors concluded that the gastroprotective activity is likely due to the involvement of sulfhydryl and nitric oxide (NO) groups, rather than anti-secretory effects or increased mucus production. Additionally, phytochemical analysis of the extracts revealed four major diterpenes, which may contribute to the observed gastroprotective effects of *X. langsdorffiana*. (Montenegro et al. 2014).

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Table 10. Summary of the gastroprotective activity of Annonaceae species.

Annonaceae species	Used material	Substances/Extracts	Methodology	Dose	Ulcer lesion index	%Lesion reduction (gastroprotection)	Ref.
Annona muricata	Leaves	EEAM **Control** **Omeprazole**	Ethanol induced ulcer model	200 mg/kg 400 mg/kg 20 mg/kg	39.0 23.0 9.0	-	(Moghadamtousi et al. 2014)
Goniothalamus sp.	-	Rac-GNT **Control** **Carbenoxolone 200**	Ethanol induced ulcer model	15 mg/kg 30 mg/kg 60 mg/kg 18 mg/kg (ED_{50}) 200mg/kg	**-**	41.7 70.5 86.7 50.0 93.5	(Vendramini-Costa et al. 2014)
Polyalthia macropoda	Stem bark	PMD Amides from PMD 1 10 11 **Control** **Lansoprazole**	Ethanol induced ulcer model	1 mg/kg 5 mg/kg 10 mg/kg 0.1 mg/kg 0.1 mg/kg 0.1 mg/kg 1 mg/kg	20.4 17.7 9.4 10.4 20.8 14.7 13.8	68.3 72.5 85.4 76.7 67.7 77.2 78.6	(Olate et al. 2012)
Xylopia langsdorffiana	Leaves	EtOHE HexPh **Control**	Ethanol induced ulcer model	500 mg/kg 250 mg/kg 500 mg/kg	-	83 81 84	(Montenegro et al. 2014)

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		Carbenoxolone		100 mg/kg		40	

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4. Perspectives

Studies related to natural products are extremely important because they are sources of secondary metabolites that have different biological activities and applications for humans. In this review, the exciting biological potential of the Annonaceae family was highlighted and is extremely promising. These plants continue to be identified as potential therapeutics in many disease states but herein we discussed the most promising to date, the anti-inflammatory, insecticidal, antimicrobial, leishmanicidal, cytotoxic, antitumor, trypanocidal, antioxidant, gastroprotective, and antimalarial activities. Unfortunately, most studies focus on the activities of different plant extracts and essential oils, thus be limited by a lack of isolated molecules and mechanisms of action. The identification of biological activity in isolated compounds is of fundamental importance for the identification of new drugs and pharmaceutical and agricultural production. Where isolated *in vitro* data is available, we encourage researchers to delve deeper into *in vivo* and clinical experiments, for the production and commercialization of new drugs. This review also compiles vital information for the pharmaceutical and agricultural industry.

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